| BSC_CON_2.04 | Oncology: Molecular Analysis Of Solid Tumors And Hematologic Malignancies | | |
|---|---|---|---|
| **Original Policy Date:** | June 1, 2023 | **Effective Date:** | February 1, 2025 |
| **Section:** | 2.0 Medicine | **Page:** | Page 1 of 62 |

## Example Test Table

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

| Policy Statement Locations | Example Tests (Labs) | Common CPT Codes |
|---|---|---|
| **Molecular Profiling Panel Testing of Solid Tumors and Hematologic Malignancies** | | |
| Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels | FoundationOne CDx (Foundation Medicine) | 0037U |
| | MSK-IMPACT (Memorial Sloan Kettering Medical Center) | 0048U |
| | Oncomap ExTra (Exact Sciences Laboratories, LLC) | 0329U |
| | OnkoSight Advanced Solid Tumor NGS Panel (BioReference Labs) | 81445, 81455, 81457, 81458 |
| | Precise Tumor (Myriad) | |
| | Tempus xT CDx (Tempus) | 0473U |
| | Guardant360 TissueNext (Guardant) | 0334U |
| | PGDx elio tissue complete (Personal Genome Diagnostics, Inc) | 0250U |
| | OmniSeq INSIGHT (Labcorp) | 81459 |
| | Tempus xT with PD-L1 IHC, MMR IHC (Tempus) | |
| | Solid Tumor Expanded Panel (Quest Diagnostics) | 0379U |
| | UW OncoPlex Cancer Gene Panel (University of Washington) | 81459 |
| | Strata Select (Strata Oncology) | 0391U |
| Targeted RNA Fusion Panels | Targeted Solid Tumor NGS Fusion Panel (NeoGenomics) | 81449 |
| Broad RNA Fusion Panels | Tempus xR Whole Transcriptome RNA Sequencing (Tempus) | 81456 |
| | Aventa FusionPlus (Aventa Genomics) | 0444U |
| Broad Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels | FoundationOne Heme (Foundation Medicine) | 81450, 81455 |
| | Tempus xT Hematologic Malignancy (Tempus) | |
| | Neo Comprehensive - Myeloid Disorders (NeoGenomics Laboratories) | |
| | MayoComplete Myeloid Neoplasms, Comprehensive OncoHeme Next-Generation Sequencing, Varies (Mayo Clinic Laboratories) | 81450 |

| Policy Statement Locations | Example Tests (Labs) | Common CPT Codes |
|---|---|---|
| | Onkosight Advanced NGS Myeloid Panel (BioReference Laboratories) | |
| Colorectal Cancer Focused Molecular Profiling Panels | Colon Cancer Mutation Panel (Ohio State University Molecular Pathology Lab) | 81445 |
| | COLONSEQPlus Panel (MedFusion) | 81457 |
| Lung Cancer Focused Molecular Profiling Panels | Oncomine Dx Target Test (Thermo Fisher Scientific) | 0022U |
| | OnkoSight Advanced Lung Cancer NGS Panel (BioReference Laboratories) | 81457 |
| | Lung HDPCR (Protean BioDiagnostics ) | 0478U |
| Cutaneous Melanoma Focused Molecular Profiling Panels | MelanomaSeqPlus (Quest Diagnostics) | 81445 |
| | OnkoSight Advanced Melanoma NGS Panel (BioReference Laboratories) | 81457 |
| Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels | MyAML NGS Gene Panel Assay (Laboratory for Personalized Molecular Medicine) | 0050U |
| | NeoTYPE AML Prognostic Profile (NeoGenomics) | 81450 |
| | LeukoVantage, Acute Myeloid Leukemia (AML) (Quest Diagnostics) | |
| Myeloproliferative Neoplasms (MPNs) Panels | Myeloproliferative Neoplasm, JAK2 V617F with Reflex to CALR and MPL, Varies (Mayo Medical Laboratories) | 81206, 81207, 81208, 81219, 81270, 81279, 81338, 81339 |
| | OnkoSight Advanced NGS JAK2, MPL, CALR Panel (BioReference Laboratories) | |
| **Single Gene Testing of Solid Tumors and Hematologic Malignancies** | | |
| Tumor Specific *BCR/ABL1* Kinase Domain Analysis | ABL1 Kinase Domain Mutation Analysis (NeoGenomics) | 81170 |
| | Onkosight NGS ABL1 Sequencing (BioReference Laboratories) | |
| Tumor Specific *BCR/ABL1* FISH, Qualitative, and Quantitative Tests | BCR-ABL1 Gene Rearrangement, Quantitative, PCR (Quest Diagnostics) | 81206, 81207, 81208 |
| | BCR-ABL1 Transcript Detection for Chronic Myelogenous Leukemia (CML) and Acute Lymphocytic Leukemia (ALL), Quantitative (Labcorp) | |
| | BCR/ABL1 (t9;22)) RNA Quantitative with Interpretation (University of Iowa Hospitals and Clinics - Department of Pathology) | 0016U |
| | MRDx BCR-ABL Test (MolecularMD) | 0040U |
| | Detection by FISH of t(9;22) BCR/ABL (CGC Genetics) | 81479, 88271, 88274, 88275, 88291 |
| | BCR/ABL t(9;22) (NeoGenomics Laboratories) | |
| | BCR ABL Qualitative (Cincinnati Children's Hospital) | |
| Tumor Specific *BRAF* Variant Analysis | BRAF Mutation Analysis (NeoGenomics) | 81210 |
| Tumor Specific *BRCA1/2* Variant Analysis | BRCA1/2 Mutation Analysis, NGS, Tumor (Mayo Clinic Laboratories) | 81162, 81163, 81164, 81165, 81166, 81167, 81216 |

| Policy Statement Locations | Example Tests (Labs) | Common CPT Codes |
|---|---|---|
| | BRCA1/2 Mutation Analysis for Tumors (NeoGenomics Laboratories) | |
| 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 *ESR1* Variant Analysis | ESR1 Mutations Analysis, NGS, Tumor (Mayo Clinic Laboratories) | 81479 |
| Tumor Specific *FLT3* Variant Analysis | FLT3 ITD and TKD Mutation (PCR) (PathGroup) | 81245, 81246 |
| | LeukoStrat CDx FLT3 Mutation Assay (Versiti) | 0023U |
| | FLT3 ITD MRD Assay (Laboratory for Personalized Molecular Medicine) | 0046U |
| Tumor Specific *IDH1* and *IDH2* Variant Analysis | IDH1/IDH2 Mutation Analysis by PCR (NeoGenomics) | 81120, 81121 |
| | IDH1, IDH2, and TERT Mutation Analysis, Next Generation Sequencing, Tumor (IDTRT) (Mayo Clinic) | 0481U |
| Tumor Specific *IGHV* Somatic Hypermutation Analysis | IgVH Mutation Analysis (NeoGenomics) | 81261, 81262, 81263 |
| Tumor Specific *JAK2* Variant Analysis | JAK2 Exon 12 to 15 Sequencing, Polycythemia Vera Reflex, Varies (Mayo Clinic Laboratories) | 0027U |
| | JAK2 Mutation (University of Iowa) | 0017U |
| | JAK2 V617F Mutation Analysis (Quest Diagnostics) | 81270 |
| Tumor Specific *KIT* Variant Analysis | KIT Mutation Analysis (ProPath) | 81272, 81273 |
| | KIT (D816V) Digital PCR in Systemic Mastocytosis (Labcorp) | |
| Tumor Specific *KRAS* Variant Analysis | KRAS Mutation Analysis (NeoGenomics) | 81275, 81276 |
| Tumor Specific *MGMT* Methylation Analysis | MGMT Promoter Methylation -Tumor (Ohio State University Molecular Pathology Laboratory) | 81287 |
| Tumor Specific *MLH1* Methylation Analysis | MLH1 Promoter Methylation Analysis (NeoGenomics) | 81288 |
| Tumor Specific *MPL* Variant Analysis | MPL Mutation Analysis (Quest Diagnostics) | 81338, 81339 |
| Tumor Specific Microsatellite Instability (MSI) Analysis | Microsatellite Instability (MSI) by PCR (NeoGenomics) | 81301 |
| | Microsatellite Instability (MSI) (Quest Diagnostics) | |
| Tumor Specific *NPM1* Variant Analysis | NPM1 MRD Assay (Laboratory for Personalized Molecular Medicine) | 0049U |
| | Onkosight NGS NPM1 Sequencing (BioReference Laboratories) | 81310 |
| Tumor Specific *NRAS* Variant Analysis | NRAS Mutation Analysis (NeoGenomics) | 81311 |
| Tumor Specific *PIK3CA* Variant Analysis | PIK3CA Mutation Analysis (Quest Diagnostics) | 81309 |
| | PIK3CA Mutation Analysis, therascreen - QIAGEN (LabCorp) | 0155U |

| Policy Statement Locations | Example Tests (Labs) | Common CPT Codes |
|---|---|---|
| Tumor Specific *TP53* Variant Analysis | TP53 Mutation Analysis (NeoGenomics Laboratories) | 81352 |
| **HLA Typing for Transplantation** | | |
| HLA Typing for Transplantation | HLA-A,B Intermediate Resolution (Versiti) | 81370, 81371, 81372, 81373 |
| | HLA-B Low Resolution (Versiti) | |
| | HLA-DQB1,DQA1 Intermediate Resolution (Versiti) | 81376 |
| | HLA-A, B, C, DRB1 and DQ High Resolution (Quest) | 81378 |
| | HLA A,B,C Profile (High Resolution) (Labcorp) | 81379 |
| | HLA-A High Resolution (Versiti) | 81380 |
| | HLA High Resolution Panel by NGS (Versiti) | 81378, 81382 |
| **Measureable (Minimal) Residual Disease (MRD) Analysis** | | |
| Hematologic Minimal Residual Disease (MRD) Testing | MyMRD NGS Panel Assay(Laboratory for Personalized Molecular Medicine) | 0171U |
| | ClonoSEQ Assay (Adaptive Biotechnologies) | 0364U |
| Evidence-Based Solid Tumor Minimal Residual Disease (MRD) Testing | Signatera - Residual Disease Test (MRD) - (Natera) | 0340U |
| | Guardant Reveal (Guardant Health) | 81479 |
| | Guardant360 Response (Guardant Health) | 0422U |
| Emerging Evidence Solid Tumor Minimal Residual Disease (MRD) Testing | COLVERA (Clinical Genomics Pathology, Inc.) | 0229U |
| | Invitae Personalized Cancer Monitoring - Baseline Test and Monitoring Test (Invitae) | 0306U, 0307U |
| | Northstar Response (BillionToOne) | 0486U |
| | OptiSeq Colorectal Cancer NGS Panel (DiaCarta Inc.) | 0498U |
| | QuantiDNA Colorectal Cancer Triage Test (DiaCarta Inc.) | 0501U |
| HPV-Related Solid Tumor Minimal Residual Disease (MRD) Testing | NavDx (Naveris) | 0356U |
| **Tumor Mutational Burden (TMB)** | | |
| Tumor Mutational Burden (TMB) | Tumor Mutational Burden (MedFusion) | 81479 |
| **Red Blood Cell Genotyping in Multiple Myeloma** | | |
| Red Blood Cell Genotyping in Multiple Myeloma | PreciseType HEA (Immucor) | 0001U |
| | Navigator ABO Sequencing (Grifols Immunohematology Center) | 0180U |
| | Navigator ABO Blood Group NGS (Grifols | 0221U |

| Policy Statement Locations | Example Tests (Labs) | Common CPT Codes |
|---|---|---|
| | Immunohematology Center) | |
| **Cancer Exome and Genome Sequencing** | | |
| Cancer Exome and Genome Sequencing | Somatic Whole Genome Sequencing (Praxis Genomics) | 0297U |
| | Cancer Whole Exome Sequencing with Transcriptome (Columbia University - Personalized Genomic Medicine) | 81415, 81416, 81425, 81426 |
| | Tempus xE (Tempus AI, Inc) | |
| | EXaCT-1 Whole Exome Testing (Weill Cornell Medicine) | 0036U |
| **Genetic Testing to Confirm the Identity of Laboratory Specimens** | | |
| Genetic Testing to Confirm the Identity of Laboratory Specimens | know error DNA Specimen Provenance Assay (DSPA) (Strand Diagnostics, LLC) | 81265, 81266, 81479 |

## Policy Statement

**Molecular Profiling Panel Testing of Solid Tumors and Hematologic Malignancies**
**Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels**

I. Tumor-type agnostic solid tumor molecular profiling panels (0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U, 0473U, 81445, 81455, 81457, 81458, 81459) may be considered **medically necessary** when:
   A. The member meets **both** of the following:
      1. The member has a diagnosis of:
         a. Recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, **OR**
         b. Histiocytosis**, OR**
         c. Non-small cell lung cancer (NSCLC) regardless of stage, **OR**
         d. Resectable or borderline resectable pancreatic adenocarcinoma, **OR**
         e. Central nervous system tumor, **AND**
      2. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy), **OR**
   B. The member meets **one** of the following:
      1. The member has a diagnosis of uterine neoplasm, **AND**
         a. The member is undergoing initial evaluation, **OR**
      2. The member has a gastrointestinal stromal tumor, **AND**
         a. The tumor is negative for *KIT* and *PDGFRA* mutations.

II. Repeat testing via a tumor-type agnostic solid tumor molecular profiling panel (0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U, 0473U, 81445, 81455, 81457, 81458, 81459) may be considered **medically necessary** when:
   A. The member has progression of **any** of the following:
      1. Advanced or metastatic non-small cell lung cancer (NSCLC), **OR**
      2. Advanced or metastatic gastric adenocarcinoma, **OR**
      3. Metastatic prostate cancer.

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

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

**Targeted RNA Fusion Panels**

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

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

**Broad RNA Fusion Panels**

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

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

**Broad Molecular Profiling Panels For Hematologic Malignancies and Myeloid Malignancy Panels**

VIII. Broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) may be considered **medically necessary** when **any** of the following are met:
   A. The member is undergoing evaluation for acute myeloid leukemia (AML), **OR**
   B. The member has newly diagnosed acute lymphoblastic leukemia (ALL), **OR**
   C. The member has newly diagnosed myelodysplastic syndrome (MDS), **OR**
   D. The member has suspected myelodysplastic syndrome (MDS) **AND**
      1. Other causes of cytopenia(s) have been ruled out, **OR**
   E. The member is suspected to have a myeloproliferative neoplasm (MPN), **AND any** of the following
      1. This is the member's initial genetic evaluation for suspected MPN, **OR**
      2. Previous results of *JAK2*, *CALR*, and *MPL* analysis were negative, **OR**
   F. The member has a diagnosis of chronic myelogenous leukemia (CML), **AND any** of the following:
      1. There has been progression to accelerated or blast phase, **OR**
      2. Results of *BCR-ABL1* kinase domain mutation analysis were negative.

IX. Repeat broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) may be considered **medically necessary** when:
   A. The member has myelodysplastic syndrome (MDS), **AND**
      1. The member has relapsed after allo-HCT [hematopoietic cell transplant], **OR**
   B. The member has acute lymphoblastic leukemia (ALL), **AND**

1. The member is showing evidence of symptomatic relapse after maintenance therapy, **OR**

C. The member has acute myeloid leukemia (AML), **AND**
1. The member has relapsed or refractory disease or progression on treatment.

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

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

**Colorectal Cancer Focused Molecular Profiling Panels**

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

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

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

**Lung Cancer Focused Molecular Profiling Panels**

XIII. Lung cancer focused molecular profiling panels (0022U, 81457) may be considered **medically necessary** when:
A. The member has a diagnosis of **any** of the following:
1. Advanced (stage IIIb or higher) or metastatic lung adenocarcinoma, **OR**
2. Advanced (stage IIIb or higher) or metastatic large cell lung carcinoma, **OR**
3. Advanced (stage IIIb or higher) or metastatic squamous cell lung carcinoma, **OR**
4. Advanced (stage IIIb or higher) or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **AND**
B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy).

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

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

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

**Cutaneous Melanoma Focused Molecular Profiling Panels**

XVI. Cutaneous melanoma focused molecular profiling panels (81445, 81457) **may be** considered **medically necessary** when **all** of the following are met:
A. The member has a diagnosis of **one** of the following:
1. Stage III melanoma or higher, **OR**
2. Recurrent melanoma, **AND**
B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy), **AND**
C. **One** of the following:
1. The member has not had previous somatic testing via a multigene cancer panel for the same primary melanoma diagnosis, **OR**

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

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

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

**Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels**

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

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

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

**Myeloproliferative Neoplasms (MPNs) Panels**

XX. Myeloproliferative neoplasm (MPN) molecular profiling panels (81206, 81207, 81208, 81219, 81270, 81279, 81338, 81339) may be considered **medically necessary** when **both** of the following criteria are met:
A. The member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), **AND**
B. The panel includes, at a minimum, testing of the following genes: *JAK2*, *CALR*, and *MPL*.

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

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

XXII. Tumor specific *BCR/ABL1* kinase domain analysis (81170) in hematologic malignancies may be considered **medically necessary** when **both** of the following criteria are met:
A. The member has a diagnosis of **any** of the following:
1. Chronic myeloid leukemia (CML), **OR**
2. Ph-positive acute lymphocytic leukemia (ALL), **AND**
B. The member has **any** of the following:
1. Inadequate initial response to TKI therapy, **OR**
2. Loss of response to TKI therapy, **OR**
3. Disease progression to the accelerated or blast phase, **OR**
4. Relapsed/refractory disease.

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

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

4. B-cell lymphoma, **OR**

C. The member is undergoing monitoring of disease progression or for minimal residual disease (MRD) monitoring using a quantitative test only for **any** of the following:
1. Acute lymphoblastic leukemia (ALL), **OR**
2. Acute myeloid leukemia (AML), **OR**
3. Chronic myelogenous leukemia (CML), **OR**
4. B-cell lymphoma.

**Tumor Specific *BRAF* Variant Analysis**

XXIV. Tumor specific *BRAF* variant analysis (81210) in solid tumors and hematologic malignancies may be considered **medically necessary** when:
A. The member has a diagnosis of **any** of the following:
1. Suspected or proven metastatic colorectal cancer, **OR**
2. Advanced or metastatic non-small-cell lung cancer (NSCLC), **OR**
3. Stage III or stage IV cutaneous melanoma, **OR**
4. Indeterminate thyroid nodules requiring biopsy, **OR**
5. Anaplastic thyroid carcinoma, **OR**
6. Locally recurrent, advanced and/or metastatic papillary thyroid cancer, **OR**
7. Locally recurrent, advanced and/or metastatic follicular thyroid cancer, **OR**
8. Locally recurrent, advanced and/or metastatic Hurthle cell thyroid carcinoma, **OR**
9. Low-grade glioma or pilocytic astrocytoma, **OR**
10. Resectable or borderline resectable or locally advanced /metastatic pancreatic adenocarcinoma, **OR**
11. Metastatic small bowel adenocarcinoma, **OR**
12. Locally advanced, recurrent or metastatic esophageal or esophagogastric junction cancer, **OR**
13. Locally advanced, recurrent or metastatic gastric cancer, **OR**

B. The member is being evaluated for **any** of the following:
1. Hairy cell leukemia (for individuals without cHCL [classical hairy cell leukemia] immunophenotype), **OR**
2. Histiocytosis (Langerhans cell histiocytosis or Erdheim-Chester disease).

**Tumor Specific *BRCA1/2* Variant Analysis**

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

**Tumor Specific *CALR* Variant Analysis**

XXVI. Tumor specific *CALR* variant analysis (81219) may be considered **medically necessary** when:
A. The member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), **OR**
B. The member is suspected to have a myelodysplastic syndrome (MDS).

**Tumor Specific *CEBPA* Variant Analysis**

XXVII. Tumor specific *CEBPA* variant analysis (81218) in hematologic malignancies may be considered **medically necessary** when:
A. The member is undergoing evaluation for acute myeloid leukemia (AML).

**Tumor Specific *EGFR* Variant Analysis**

XXVIII. Tumor specific *EGFR* variant analysis (81235) in solid tumors may be considered **medically necessary** when **any** of the following:

A. The member has a diagnosis of:
   1. Stage IB or higher lung adenocarcinoma, **OR**
   2. Stage IB or higher large cell lung carcinoma, **OR**
   3. Stage IB or higher squamous cell lung carcinoma, **OR**
   4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS).

**Tumor Specific *ESR1* Variant Analysis**

XXIX. Tumor specific *ESR1* variant analysis (81479) in solid tumors is considered **medically necessary** when:
   A. The member is **one** of the following:
      1. Pre- menopausal female receiving ovarian ablation or suppression, **OR**
      2. Postmenopausal female, **OR**
      3. Adult male, **AND**
   B. The member has a diagnosis of ER-positive and *HER2*-negative breast cancer, **AND**
   C. The member has disease progression after one or two prior lines of endocrine therapy, including one line containing a *CDK4/6* inhibitor.

**Tumor Specific *FLT3* Variant Analysis**

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

**Tumor Specific *IDH1* and *IDH2* Variant Analysis**

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

**Tumor Specific *IGHV* Somatic Hypermutation Analysis**

XXXII. Tumor specific *IGHV* somatic hypermutation analysis (81261, 81262, 81263) in hematologic malignancies may be considered **medically necessary** when:
   A. The member is undergoing work up for or has a diagnosis of **any** of the following:
      1. Chronic lymphocytic leukemia (CLL), **OR**
      2. Small lymphocytic leukemia (SLL), **OR**
      3. Primary cutaneous B-cell lymphoma, **OR**
      4. B-cell lymphoma.

**Tumor Specific *JAK2* Variant Analysis**

XXXIII. Tumor specific *JAK2* variant analysis (0017U, 0027U, 81270) in solid tumors or hematologic malignancies may be considered **medically necessary** when **any** of the following are met:
   A. The member is suspected to have a myeloproliferative neoplasm (MPN) (example: polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), **OR**
   B. The member has acute lymphoblastic leukemia (ALL), **OR**
   C. The member is suspected to have a myelodysplastic syndrome (MDS).

**Tumor Specific *KIT* Variant Analysis**

XXXIV. Tumor specific *KIT* variant analysis (81272, 81273) in solid tumors or hematologic malignancies may be considered **medically necessary** when **any** of the following are met:

A. The member is being evaluated for systemic mastocytosis, **OR**
B. The member has a diagnosis of acute myeloid leukemia (AML), **OR**
C. The member has stage IV cutaneous melanoma, **OR**
D. The member has a suspected or confirmed gastrointestinal stromal tumor (GIST).

**Tumor Specific *KRAS* Variant Analysis**

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

**Tumor Specific *MGMT* Methylation Analysis**

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

**Tumor Specific *MLH1* Methylation Analysis**

XXXVII. Tumor specific *MLH1* promoter methylation analysis (81288) in solid tumors may be considered **medically necessary** when:
A. The member has a diagnosis of **any** of the following:
1. Colorectal cancer, **OR**
2. Endometrial (uterine) cancer, **AND**
B. Previous tumor testing showed loss of *MLH1* on immunohistochemistry analysis.

**Tumor Specific *MPL* Variant Analysis**

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

**Tumor Specific Microsatellite Instability (MSI) Analysis**

XXXIX. Tumor specific microsatellite instability (MSI) analysis (81301) in solid tumors may be considered **medically necessary** when:
A. The member has a diagnosis of **any** of the following:
1. Colorectal cancer, **OR**
2. Endometrial cancer, **OR**
3. Gastric cancer, **OR**
4. Esophageal and esophagogastric junction cancer, **OR**
5. Recurrent, progressive or metastatic cervical carcinoma, **OR**
6. Testicular cancer with progression after high dose chemotherapy or third-line therapy, **OR**
7. Unresectable or metastatic gallbladder cancer, **OR**
8. Unresectable or metastatic intrahepatic or extrahepatic cholangiocarcinoma, **OR**

9. Unresectable or metastatic breast cancer, **OR**
10. Small bowel adenocarcinoma, **OR**
11. Resectable, borderline resectable, or metastatic pancreatic cancer, **OR**
12. Metastatic occult primary, **OR**
13. Recurrent, progressive or metastatic squamous cell carcinoma of the vulva**, OR**
14. Metastatic chondrosarcoma, **OR**
15. Metastatic chordoma, **OR**
16. Widely metastatic Ewing sarcoma, **OR**
17. Metastatic osteosarcoma, **OR**
18. Recurrent or metastatic vaginal cancer, **OR**
19. Recurrent ovarian cancer

**Tumor Specific *NPM1* Variant Analysis**

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

**Tumor Specific *NRAS* Variant Analysis**

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

**Tumor Specific *PIK3CA* Variant Analysis**

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

**Tumor Specific *TP53* Variant Analysis**

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

**HLA Typing For Transplantation**

XLIV. HLA typing for transplantation (81370, 81371, 81372, 81373, 81376, 81378, 81379, 81380, 81382) may be considered **medically necessary** when the member meets the following:
   A. The member is being considered for **any** of the following:
      1. Recipient of bone marrow transplantation, **OR**
      2. Donor for bone marrow transplantation, **OR**
      3. Recipient of solid organ transplantation, **OR**
      4. Donor for solid organ transplantation.

XLV. HLA typing for transplantation (81370, 81371, 81372, 81373, 81376, 81378, 81379, 81380, 81382) is considered **investigational** for all other indications.

**Measurable (Minimal) Residual Disease (MRD) Analysis**
**Hematologic Minimal Residual Disease (MRD) Testing**

XLVI. Measurable (minimal) residual disease (MRD) analysis (0171U, 0364U) in bone marrow or peripheral blood may be considered **medically necessary** when:
   A. The member has a diagnosis of **any** of the following:

1. Acute Lymphocytic Leukemia (ALL), **OR**
2. Multiple Myeloma, **OR**
3. Chronic Lymphocytic Leukemia (CLL).

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

XLVII. Minimal residual disease (MRD) analysis for solid tumors using cell free DNA (0340U, 0422U, 81479) with sufficient evidence of clinical utility and validity may be considered **medically necessary** when:
- A. The identification of recurrent, refractory, or progressive disease will require a change in management, **AND**
- B. The member is not undergoing concurrent molecular laboratory testing for surveillance or monitoring for recurrent, refractory, or progressive disease, **AND**
- C. The member meets **one** of the following:
  1. The member is currently being treated for cancer, **AND**
     a. The test has not previously been done for this cancer diagnosis, **OR**
     b. There is a clinical suspicion that the molecular profile of the member's tumor has changed, **OR**
  2. The member is not currently being treated for their cancer, **AND**
     a. The test has not been done in the past 12 months, **OR**
     b. There is a clinical suspicion for tumor recurrence, **AND**
- D. The member meets **one** of the following:
  1. The member is being tested via Guardant360 Response or Guardant Reveal and has one of the following:
     a. Metastatic colon cancer, **OR**
     b. Colon cancer at any stage, **AND**
        i. The member is being monitored for response to immune checkpoint inhibitor therapy, **OR**
  2. The member is being tested via Signatera and has one of the following:
     a. Metastatic colon cancer, **OR**
     b. Muscle invasive bladder cancer, **OR**
     c. Metastatic breast cancer, **OR**
     d. Any solid tumor, **AND**
        i. The member is being monitored for response to immune checkpoint inhibitor therapy.

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

**Emerging Evidence Solid Tumor Minimal Residual Disease (MRD) Testing**

XLIX. Minimal residual disease (MRD) analysis (0229U, 0306U, 0307U) with insufficient evidence of clinical validity using solid tumor tissue is considered **investigational**.

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

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

2. The member is not currently being treated for HPV-driven oropharyngeal cancer, **AND**
   a. The test has not been done in the past 12 months.

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

**Tumor Mutational Burden (TMB)**

LII. Tumor mutational burden (TMB) testing (81479) may be considered **medically necessary** when:
   A. The member has a diagnosis of:
      1. Recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, **AND**
      2. The member has had progression of the cancer following prior treatment, **AND**
      3. The member has no remaining satisfactory treatment options, **AND**
      4. The member does not have central nervous system cancer.

**Red Blood Cell Genotyping In Multiple Myeloma**

LIII. Red blood cell genotyping (0001U, 0180U, 0221U) in individuals with multiple myeloma may be considered **medically necessary** when:
   A. The member has a diagnosis of multiple myeloma, **AND**
   B. The member is currently being treated or will be treated with **either** of the following:
      1. Daratumumab (Darazalex), **OR**
      2. Isatuximab (Sarclisa).

**Cancer Exome And Genome Sequencing**

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

**Genetic Testing To Confirm The Identity Of Laboratory Specimens**

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

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

## Policy Guidelines

**Definitions**

1. **Tumor mutational burden**: A measurement of mutations carried by tumor cells and is a predictive biomarker that is being studied to evaluate its association with response to immunotherapy.
2. **Advanced cancer**: Cancer that is unlikely to be cured or controlled with treatment. The cancer may have spread from where it first started to nearby tissue, lymph nodes, or distant parts of the body. Treatment may be given to help shrink the tumor, slow the growth of cancer cells, or relieve symptoms.
3. **Myeloproliferative Neoplasms:** Rare overlapping blood diseases in which the bone marrow makes too many red blood cells, white blood cells, or platelets. There are seven subcategories of myeloproliferative neoplasms:
   - Chronic myeloid leukemia (CML)
   - Polycythemia vera (PV)
   - Primary myelofibrosis (PMF)
   - Essential thrombocytopenia (ET)
   - Chronic neutrophilic leukemia

- Chronic eosinophilic leukemia
- Chronic eosinophilic leukemia-not otherwise specified
- MPN, unclassifiable (MPN-U)

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

**Coding**
See the Codes table for details.

## Description

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

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

While the primary goal of the molecular analysis of solid tumors and hematologic malignancies is to identify biomarkers that diagnose or to give prognostic and treatment selection information, this testing also has the potential to uncover clinically relevant germline variations that are associated with a hereditary cancer susceptibility syndrome, and other conditions, if confirmed to be present in the germline. Providers should communicate the potential for these incidental findings with their patients prior to somatic mutation profiling. Clinical decision making should not be made based on variants of uncertain significance. 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.

In addition to evaluating tumors for driver mutations, molecular testing can also be useful in identifying other valuable information such as tumor mutational burden (TMB), microsatellite instability (MSI) and gene fusions. Testing to identify these tumor characteristics can be performed for many different types of tumors (tumor agnostic) and can be helpful in predicting tumor response to specific treatments such as immunotherapy. It is also possible to analyze complete tumor DNA via exome or genome sequencing; this is an area of ongoing research to determine the best use of the potentially large volume of information available from this technology.

Information from tumor molecular testing can also be useful for monitoring measurable (minimal) residual disease (MRD) in both solid tumors and hematologic malignancies. These tests can be used to determine disease recurrence or relapse after treatment in addition to monitoring disease progression or response to various cancer treatments. This is also an area of active research to determine the clinical utility and validity of this testing across multiple tumor types.

## Related Policies

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

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

## Benefit Application

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

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

## Regulatory Status

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

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

## Rationale

**Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines on Breast Cancer (4.2024) recommend comprehensive somatic testing to aid in clinical management of patients with recurrent/stage IV breast cancer. (p. BINV-18)

The NCCN guideline on Occult Primary (1.2025) 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 somatic tumor profiling 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 (7.2024) has several recommendations regarding biomarker testing:

- For stage IV / advanced or metastatic disease, broad molecular profiling is recommended to be performed for adenocarcinoma, large cell, or NSCLC not otherwise specified. NCCN recommends consideration of broad molecular profiling for squamous cell carcinoma of the lung (p. NSCL-14, NSCL-19).
- Generally, it is recommended that broad, panel-based genomic profiling be performed via NGS when feasible. NCCN defines broad molecular profiling as a panel which includes all the following biomarkers in either one assay or several smaller assays: *EGFR, ALK, KRAS, ROS1, BRAF, NTRK1/2/3*, *MET*ex14 skipping, *RET, ERBB2 (HER2),* and *PD-L1*. (p. NSCL-19 and NSCL-H 1 and 2 of 8)
- Repeat somatic genetic testing can be helpful to aid in deciding next therapeutic steps when a patient's tumor shows evidence of progression on first-line therapy. Broad genomic profiling may be the best testing method to ensure all possible therapeutic biomarkers are analyzed. (p. NSCL-H 7 of 8)

The NCCN guideline for Colon Cancer (4.2024) recommends all patients with metastatic colorectal cancer have molecular testing which should be done via a broad panel to identify rare and actionable alterations including fusions (p. COL-2). l. Testing can be performed on the primary tumor and/or metastases. (p. COL-B 4 of 10)

The NCCN guideline for Gastric Cancer (2.2024) recommends consideration of NGS testing during the workup for gastric cancer (p. GAST-1). NGS testing can be considered in place of sequential testing for individual biomarkers if there is limited tissue or traditional biopsy cannot be done in patients with inoperable locally advanced, recurrent or metastatic adenocarcinoma of the stomach considering an FDA approved therapy. (p. GAST-B 5 of 6) 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 (3.2024) recommends that patients with recurrent disease undergo comprehensive tumor

molecular analysis to identify alterations that would be amenable to targeted therapeutics that have tumor specific or tumor-agnostic benefit. (p OV-6) These guidelines also recommend that molecular testing be performed on the most recent tumor tissue available. (p. OV-B, 1 of 3)

The NCCN guideline for Pancreatic Adenocarcinoma (3.2024) recommends tumor/somatic molecular profiling to identify targetable alterations for patients with locally advanced or metastatic disease and recommends consideration of this testing for patients with resectable or borderline resectable disease who are candidates for systemic therapy. Testing can include but is not limited to fusions (*ALK, NRG1, NTRK, ROS1, FGFR2, RET*), mutations (*BRAF, BRCA1/2*, *KRAS*, *PALB2)*, amplifications (*HER2*), MSI, tumor mutational burden and mismatch repair deficiency. (p. PANC-1A, PANC-F, 1 of 12)
The NCCN guideline for Prostate Cancer (4.2024) recommends consideration of somatic multigene tumor testing to identify alterations in HRR genes in addition to MSI and TMB testing for patients with metastatic prostate cancer. NCCN recommends consideration of this testing in patients with regional prostate cancer. The guidelines also recommend that repeat tumor profiles can be considered at the time of progression of disease. (p. PROS-C, 2 of 2)

The NCCN guideline for Histiocytic Neoplasms (2.2024) recommends molecular mutation profiling in the work-up/evaluation of Langerhans Cell Histiocytosis (LCH), Erdheim-Chester Disease (ECD) and Rosai-Dorfman Disease (RDD) for prognostic and treatment information. (p. HIST-C, 1 of 5)
The NCCN guideline for Uterine Neoplasms (2.2024) recommends comprehensive molecular profiling, in the initial evaluation of uterine neoplasms. This can be done on the initial biopsy or the hysterectomy specimen. (p. ENDO-A 2 of 4)

NCCN guidelines for Ampullary Adenocarcinoma (2.2024) recommend somatic molecular profiling to identify uncommon and potentially actionable mutations including fusions, amplifications, MSI, dMMR, and TMB for patients with locally advanced or metastatic disease who are candidates for systemic therapy. (p. AMP-6)

NCCN guidelines for Gastrointestinal Stromal Tumors (2.2024) recommend molecular testing for a suspected or confirmed gastrointestinal stromal tumor when systemic therapy is being considered. (p. GIST-1) If testing does not show a KIT or PDGFRA mutation, NGS testing is recommended to look for alternative driver mutations that will identify targeted therapy options. (p. GIST-B)

NCCN guidelines for Central Nervous System Cancers (2.2024) recommend next-generation sequencing in the pathologic workup of CNS tumors, since there are now multiple prognostic and diagnostic biomarkers that should be tested to aid in treatment decisions. (p. BRAIN-E 2 of 9)

*Food and Drug Administration (FDA)*
The FoundationOne CDx test has been approved by the FDA as a companion diagnostic test for several therapies, including some that are indicated for early stage non-small cell lung cancer diagnoses.

**Targeted RNA Fusion Panels**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines for Acute Lymphoblastic Leukemia (2.2024) and Pediatric Acute Lymphoblastic Leukemia (5.2024) recommends comprehensive testing during the diagnostic workup by next generation sequencing for gene fusions and pathogenic mutations, especially for Ph-like ALL, which is associated with recurrent gene fusions in the tyrosine kinase pathways. (p. ALL-1, p. PEDALL-1)
Per the NCCN Biomarker Compendium, testing for gene fusions involving *ABL1*, *ABL2*, *CRLF2*, *CSF1R*, *EPOR*, *JAK2*, or *PDGFRB* and mutations involving *FLT3*, *IL7R*, *SH2B3*, *JAK1*, *JAK3*, and *JAK2* (in combination with *CRLF2* gene fusions) is recommended for this indication.

NCCN guidelines for Central Nervous System Cancers (2.2024) recommends *NTRK* fusion and *BRAF* fusion testing for glioblastoma, and *ZFTA* and YAP1 fusion testing for ependymomas by RNA sequencing for prognostication and treatment options. (p. BRAIN-E, 2, 5-6 of 9)

NCCN guidelines for Non-Small Cell Lung Cancer (7.2024) recommend consideration of, RNA-based NGS testing for patients who don't have identifiable driver oncogenes via broad panel testing to maximize detection of fusion events as fusions involving *ROS1*, *MET* and *RET* have better detection using RNA based methods. (p. NSCL-H, 2, 4, 5 of 8)

NCCN guidelines for Soft Tissue Sarcoma (2.2024) state that while morphologic diagnosis remains the preferred method of sarcoma diagnosis, molecular genetic testing using NGS based methods including DNA and RNA sequencing is an ancillary approach that can be helpful depending on type of tumor. (p. SARC-C, 1 of 4)

NCCN guidelines for Histiocytic Neoplasms (2.2024) recommends a gene fusion assay in the workup for Langerhans Cell Histiocytosis, (p. LCH-2), Erdheim-Chester Disease, (p. ECD-2) and Rosai-Dorfman Disease. (p. RDD-2) RNA-based molecular panels including fusion testing should cover *BRAF*, *ALK*, and *NTRK1* rearrangements.

NCCN guidelines for Gastrointestinal Stromal Tumors (2.2024) state that all GIST without a *KIT* or *PDGFRA* mutation should be tested for alternative driver mutations, specifically *BRAF*, *NF1*, *NTRK*, and *FGFR* fusions, which may be detected by NGS to identify potential targeted treatments. (p. GIST-B)

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

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

### Broad RNA Fusion Panels

The NCCN guidelines for Acute Lymphoblastic Leukemia (2.2024) recommend comprehensive testing by next-generation sequencing (NGS) for gene fusions and pathogenic mutations at the time of diagnosis. (p. ALL-1)

The NCCN guidelines for Pediatric Acute Lymphoblastic Leukemia (6.2024) recommend testing for potentially actionable or prognostic mutations and gene fusions via next generation sequencing (NGS) or alternative methods at the time of diagnosis. (p. PEDALL-1)

### Broad Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels

*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines for Acute Myeloid Leukemia (3.2024) recommends molecular testing via multiplex gene panels and targeted analysis by next generation sequencing for adult patients for purposes of prognostication, therapy, and ongoing management. (p.EVAL-1, EVAL-1A)

The NCCN guidelines for Acute Lymphoblastic Leukemia (2.2024) recommend that patients diagnosed with acute lymphoblastic leukemia should undergo molecular characterization of their disease, including comprehensive testing for gene fusions and pathogenic mutations. (p. ALL-1) Additionally, patients who are undergoing surveillance after maintenance therapy and are showing evidence of symptomatic relapse should undergo repeat testing. (p. ALL-8)

The NCCN guidelines for Myelodysplastic Syndromes (3.2024) recommends the following:

- During the initial evaluation of suspected myelodysplasia in patients with cytopenia, genetic testing should be performed on bone marrow or peripheral blood for somatic mutations in genes associated with myelodysplastic syndromes. (p. MDS-1, MDS-1A) Cytopenia should be present for 4-6 months and other underlying causes should be ruled out. (p. MS-3)
- Repeat molecular testing if a patient has relapsed after allo-HCT [hematopoietic cell transplant]. (p. MDS-7 and MDS-7A)

The NCCN guidelines for Myeloproliferative Neoplasms (1.2024) recommend molecular testing on blood or bone marrow for patients suspected of having a myeloproliferative neoplasm. This testing can be done in a stepwise manner, or as an NGS multigene panel that includes JAK2, CALR and MPL. Once a diagnosis is confirmed, additional testing for somatic mutations is recommended for prognostication. (p. MPN-1)

The NCCN guidelines for Chronic Myeloid Leukemia (2.2024) recommends consideration of testing for myeloid mutations for patients with advanced phase CML who are in either accelerated or blast phase (CML-1). NCCN recommends consideration of panel testing for myeloid mutations in patients on TKI therapy who have progressed to accelerated or blast phase if they lack a *BCR-ABL1* kinase domain mutation. (p. CML-E)

**Colorectal Cancer Focused Molecular Profiling Panels**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guideline for Colon Cancer (4.2024) recommends all patients with suspected or proven metastatic colorectal cancer have tumor genotyping for *KRAS, NRAS, BRAF* individually or as part of an NGS panel. (p. COL-B, 4 of 10) This testing can be performed on the primary colorectal cancers and/or the metastasis.

**Lung Cancer Focused Molecular Profiling Panels**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guideline for Non-Small Cell Lung Cancer (7.2024) recommends molecular testing for patients with advanced or metastatic disease and when feasible, testing be performed via a broad, panel-based approach, most typically performed by NGS. (p. NSCL-19) This can be a single assay or a combination of assays and tiered approaches are also acceptable. Additionally, patients with stages IB-IIIA or IIIB[T3,N2] are recommended to have testing for PD-L1, EGFR and ALK if perioperative systemic therapy is being considered. (p. NSCL-E, 1 of 5) In some clinical scenarios it is necessary to do rapid testing which can be followed up with broad testing (p. NSCL-H, 1 of 8, NSCL-H 2 of 8)

**Cutaneous Melanoma Focused Molecular Profiling Panels**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines for Cutaneous Melanoma (2.2024) recommend molecular testing of *BRAF* for stage III disease, and *KIT* for stage IV disease, or clinical recurrence. (p. ME-6, ME-9, ME-18, ME-18A, ME-C 4 of 8) NCCN recommends consideration of broader genomic profiling especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial. Single gene or small multigene panels are acceptable (p. ME-C, 3 of 8). Repeat testing using the same approach following progression on targeted therapy (*BRAF*- or *KIT*-directed therapy) does not appear to have clinical utility. (p. ME-C 5 of 8)

**Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines for Acute Myeloid Leukemia (3.2024) recommends molecular testing via multiplex gene panels and targeted analysis by next generation sequencing for adult patients for purposes of prognostication, therapy, and ongoing management. (p. EVAL-1, EVAL-2A)

**Myeloproliferative Neoplasms (MPNs) Panels**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines on Myeloproliferative Neoplasms (1.2024) recommend molecular testing in the workup phase for myeloproliferative neoplasms. Molecular testing using a multi-gene NGS panel that includes at least *JAK2, MPL* and *CALR* can be used as an alternative to stepwise single gene testing. (p. MPN-1)

**Tumor Specific *BCR/ABL1* Kinase Domain Analysis**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines on Chronic Myeloid Leukemia (2.2024) outline recommended methods for diagnosis and treatment management of chronic myelogenous leukemia, including *BCR/ABL1* tests for diagnosis and monitoring. *BCR/ABL1* kinase domain mutation analysis is recommended, among other times, when patients are in chronic phase CML and show loss of hematologic or complete cytogenetic response to TKI therapy or have 1-log increase in BCR::ABL1 transcripts with loss of major molecular response. Additionally, this test is recommended with disease progression to accelerated phase or blast phase. (p. CML-E)

The NCCN guidelines for Acute Lymphoblastic Leukemia (2.2024) recommend *ABL1* kinase domain mutation testing for patients with relapsed/refractory, Philadelphia chromosome positive (Ph+) B-ALL. (p. ALL-9) Similar recommendations are made in the NCCN guidelines for Pediatric Acute Lymphoblastic Leukemia (5.2024). (p. PEDALL-9)

**Tumor Specific *BCR/ABL1* FISH, Qualitative and Quantitative Tests**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines on Pediatric Acute Lymphoblastic Leukemia (6.2024) recommend reverse transcriptase-polymerase chain reaction (RT-PCR) testing for *BCR::ABL1* (quantitative or qualitative) in B-ALL including determination of transcript size (i.e., p190 vs. p210). (p. PEDALL-1) Additionally, reverse transcriptase quantitative PCR assay of BCR::ABL1 is used to assess minimal residual disease. (p. PEDALL-I, 1 of 2)

The NCCN guidelines on Acute Lymphoblastic Leukemia (2.2024) recommend reverse transcriptase polymerase chain reaction (RT-PCR) testing for *BCR::ABL1* in B-ALL (quantitative or qualitative), including determination of transcript size (i.e., p190 vs. p210). (p. ALL-1) Additionally, reverse transcriptase quantitative PCR (RT-qPCR) assays for BCR::ABL1 are used to monitor minimal residual disease. (p. ALL-F)

The NCCN guidelines on B-cell Lymphomas (2.2024) include PCR for *BCR-ABL* as one of the essential steps in diagnostic testing for lymphoblastic lymphoma. (p. BLAST-1)

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

The NCCN guidelines for Acute Myeloid Leukemia (3.2024) recommend molecular testing to assist with prognostication of AML in the evaluation and initial workup for suspected AML. (p. EVAL-1) AML with *BCR-ABL1* rearrangement is listed as having a poor/adverse outcome. (p. AML-A)

The NCCN guidelines for Chronic Myeloid Leukemia (2.2024) recommend quantitative RT-PCR testing on blood for *BCR/ABL1* for patients undergoing work-up for CML. NCCN also recommends consideration of qualitative RT-PCR for the detection of atypical BCR::ABL1 transcripts. (p. CML-1)

**Tumor Specific *BRAF* Variant Analysis**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines on Thyroid Carcinoma (3.2024) recommend molecular diagnostic testing for evaluating FNA results that are suspicious for follicular cell neoplasms or AUS/FLUS. The guideline

also recommends that individuals with anaplastic thyroid cancer and/or locally recurrent, advanced and/or metastatic papillary, follicular or oncocytic carcinoma undergo molecular testing including *BRAF, NTRK, ALK, RET* and tumor mutational burden if not previously done. (p. ANAP-1, p. PAP-10, p. FOLL-9, p. ONC-9)

The NCCN guideline on Hairy Cell Leukemia (2.2024) recommends molecular testing for *BRAF* V600E as a useful part of diagnostic work-up for individuals that do not have cHCL [classical hairy cell leukemia] immunophenotype. (p. HCL-1)

The NCCN guideline on Cutaneous Melanoma (2.2024) recommends *BRAF* mutation testing in patients with stage IIIB or higher cutaneous melanoma if adjuvant therapy or clinical trials are being considered (p. ME-4) and recommends consideration of testing if stage IIIA. (p. ME-5).

The NCCN guideline on Central Nervous System Cancers (2.2024) recommends *BRAF* fusion and/or mutation testing in patients with gliomas to help characterize the tumor and guide treatment decisions (p. BRAIN-E, 5 of 9).

The NCCN guidelines for Non-Small Cell Lung Cancer (7.2024) recommend molecular testing including *BRAF* analysis for advanced or metastatic adenocarcinoma, large cell, NSCLC not otherwise specified, or squamous cell carcinoma and consideration of molecular testing for squamous cell carcinoma of the lung. (p. NSCL-19)

The NCCN guidelines for Colon Cancer (4.2024) recommends *BRAF* mutation testing (among other genetic testing) for suspected or proven metastatic adenocarcinoma. (p. COL-2)
NCCN guidelines for Histiocytic Neoplasms (2.2024) recommends *BRAF* V600E testing (IHC or PCR) from biopsy tissue during the workup for Langerhans cell histiocytosis or Erdheim-Chester disease. (p. LCH-2, ECD-2)

NCCN guidelines for Pancreatic Adenocarcinoma (3.2024) recommend testing for potentially actionable somatic findings including *BRAF* mutations for resectable or borderline resectable disease when systemic therapy is being considered (p. PANC-F, 1 of 12) as well as in locally advanced/metastatic disease. (p. PANC-1A)

NCCN guidelines for Small Bowel Adenocarcinoma (4.2024) recommend *BRAF* V600E testing for metastatic adenocarcinoma. (p. SBA-5)

NCCN guidelines for Esophageal and Esophagogastric Junction Cancers (4.2024) recommend biomarker testing for patients with locally advanced, recurrent or metastatic esophageal or esophagogastric junction cancer and lists BRAF V600E mutation as a targeted biomarker. (p. ESOPH-B, 3 and 5 of 6)

NCCN guidelines for Gastric Cancer (2.2024) recommend biomarker testing for patients with locally advanced, recurrent or metastatic gastric cancer and lists BRAF V600E mutation as a targeted biomarker. (p. GAST-B, 3 and 5 of 6)

**Tumor Specific *BRCA1/2* Variant Analysis**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guideline on Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer (3.2024) recommends that all patients with ovarian cancer, fallopian tube cancer or primary peritoneal cancer should have somatic testing of *BRCA1* and *BRCA2* if not previously done to inform maintenance therapy. (p. OV-1)

The NCCN guideline on Prostate Cancer (4.2024) recommends tumor testing for BRCA1 and BRCA2 (among other HRR genes) in patients with metastatic prostate cancer and consideration of testing in patients with regional or castration sensitive metastatic prostate cancer. (p. PROS-C, 2 of 2)
The NCCN guideline on Pancreatic Adenocarcinoma (3.2024) recommends molecular profiling of tumor tissue for patients with resectable, borderline resectable, or locally advanced/metastatic disease who are candidates for systemic therapy. Testing can include but not be limited to: fusions (*ALK*, *NRG1*, *NTRK*, *ROS1*, *FGFR2*, and *RET*), mutations (*BRAF*, *BRCA1/2*, *KRAS*, and *PALB2*), etc. (p. PANC-1 and PANC-1A, p. PANC-F, 1 of 12)

*American Society of Clinical Oncology (ASCO)*
ASCO (2020) published the following recommendations for somatic and germline genetic testing for women diagnosed with ovarian cancer:

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

**Tumor Specific *CALR* Variant Analysis**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines on Myeloproliferative Neoplasms (1.2024) recommend that molecular testing for *CALR* mutations in initial work-up for all patients with suspected MPN. 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. (p. MPN-1)
The NCCN guidelines for Myelodysplastic Syndromes (3.2024) recommend genetic testing for somatic mutations in genes associated with MDS, which includes CALR. (p. MDS-1, MDS-C 2 of 3)

**Tumor Specific *CEBPA* Variant Analysis**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines on Acute Myeloid Leukemia (3.2024) recommend that molecular testing be part of the evaluation for AML for all patients and list a variety of gene mutations that are associated with specific prognoses and may guide medical decision making while other mutations may have treatment implications. Presently this includes c-*KIT, FLT-ITD, FLT-TKD, NPM1, CEBPA, IDH1/IDH2, RUNX1, ASXL1,* and *TP53*. (p. EVAL-1, EVAL-2A)

**Tumor Specific *EGFR* Variant Analysis**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines on Non-Small Cell Lung Cancer (7.2024) recommend that molecular testing for *EGFR* mutations should be performed when neoadjuvant TKI therapy or nivolumab is a consideration for NSCLC stage IB–IIIA, IIIB [T3,N2]. (p. NSCL-E, 1 of 5) Testing should also be performed for advanced or metastatic disease preferably by broad molecular profiling. (p. NSCL-19)

**Tumor Specific *ESR1* Variant Analysis**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines on Breast Cancer (4.2024) recommend that premenopausal females being treated with ovarian suppression or ablation, or postmenopausal females, or adult males, with ER-positive, HER2-negative, *ESR1*-mutation positive breast cancer that have progressed following one or two lines of endocrine therapy, including one line containing a CDK4/6 inhibitor, be considered for treatment with Elacestrant. Testing for *ESR1* mutations should occur at progression following the endocrine therapy. (p. BINV-Q 6 of 14)

### Tumor Specific *FLT3* Variant Analysis

*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines on Acute Myeloid Leukemia (3.2024) recommend molecular testing be part of the evaluation for AML and list a variety of gene mutations that 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*. (p. EVAL-1, EVAL-2A)

NCCN guidelines for Acute Lymphoblastic Leukemia (2.2024) and Pediatric Acute Lymphoblastic Leukemia (5.2024) indicate that comprehensive testing for gene fusions and pathogenic mutations using NGS sequencing is recommended for molecular prognostic risk stratification and that *FLT3* mutations confer poor or unfavorable risk. (p. ALL-1, ALL-3, PEDALL-1, PEDALL-A, 1 of 2)

The NCCN guidelines on Myelodysplastic Syndromes (3.2024) recommends that during initial evaluation for suspected myelodysplasia, genetic testing for somatic mutations in genes associated with myelodysplastic syndromes should be done, which includes *FLT3.* (p. MDS-1, MDS-C, 1 of 3)
NCCN guidelines for Myeloproliferative Neoplasms (1.2024) recommends molecular testing via NGS panel for mutational prognostication in patients with confirmed MPN diagnosis. (p. MPN1) Based on NGS panel results (e.g., if NGS shows particular mutations such as *IDH1*, *IDH2*, or *FLT3*), low intensity or targeted therapy can be considered. (p. MS-30)

### Tumor Specific *IDH1* and *IDH2* Variant Analysis

*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines on Acute Myeloid Leukemia (3.2024) recommend molecular testing during the initial evaluation for AML and list IDH1 and IDH2 as genes to be included in analysis for prognosis and treatment decision making. (p. EVAL-1, 2A)

The NCCN guideline on Central Nervous System Cancers (2.2024) recommends *IDH* mutation testing (*IDH1* and *IDH2*) for the work-up for all gliomas. (p. BRAIN-E 2 of 9)

### Tumor Specific *IGHV* Somatic Hypermutation Analysis

*National Comprehensive Cancer Network (NCCN)*
The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma guidelines (3.2024) recommend molecular testing for the immunoglobulin heavy chain variable region gene (*IGHV*) as it is useful for prognostic and/or therapy determination. (p. CSLL-1)

The NCCN B-cell Lymphomas guidelines (2.2024) recommend molecular analysis to detect Ig gene rearrangements (IGHV) during the diagnostic workup for B Cell lymphomas. Testing should be done on an excisional or incisional biopsy. (p. DIAG-1, MS-3,4).

The NCCN Primary Cutaneous Lymphomas guidelines (2.2024) recommend consideration of flow cytometry or IGH gene rearrangement studies for patients with primary cutaneous B-cell lymphoma to determine B-cell clonality, if adequate biopsy material is available. (p. CUTB-1)

### Tumor Specific *JAK2* Variant Analysis

*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines on Myeloproliferative Neoplasms (1.2024) recommend molecular testing for *JAK2* mutations in the initial work-up for all patients with suspected MPN. They further recommend that if testing for *JAK2* mutations is negative, additional testing of *MPL* and *CALR* mutations should be performed. Alternatively, molecular testing using a multi-gene NGS panel that includes *JAK2, MPL* and *CALR* can be used as part of the initial work-up in all patients. (p. MPN-1)

The NCCN guidelines on Acute Lymphoblastic Leukemia (2.2024) and Pediatric Acute Lymphoblastic Leukemia (5.2024) recommend cytogenetic and molecular prognostic risk stratification for B-ALL

using comprehensive NGS testing. (p. ALL-1, PEDALL-1) gene fusions and mutations that activate tyrosine kinase pathways are associated with Ph-like ALL and an unfavorable prognosis; these include 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). (p. MS-7, PEDALL-A 2 of 2)

The NCCN guidelines for Myelodysplastic Syndromes (3.2024) recommend genetic testing for somatic mutations in genes associated with MDS, which includes JAK2. (p. MDS-1, MDS-C 2 of 3)

**Tumor Specific *KIT* Variant Analysis**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guideline on Cutaneous Melanoma (2.2024) recommends testing for *BRAF* and *KIT* gene mutations in all patients with stage IV melanoma as this could impact treatment options. (p. ME-9) Molecular testing should be done to confirm KIT IHC results (p. ME-C, 3 of 8). They further recommend that if feasible, broader genomic profiling with NGS panels be performed in individuals with stage IV or recurrent melanoma especially if the test results could guide future treatment options. (p. ME-C, 4 of 8)

NCCN guidelines for Gastrointestinal Stromal Tumors (2.2024) recommend *KIT* mutation analysis to aid in diagnosis of and treatment selection for a gastrointestinal stromal tumor. (p. GIST-B)
The NCCN guidelines on Acute Myeloid Leukemia (3.2024) recommend molecular testing during the evaluation for AML for genes associated with prognosis or treatment options, including c-KIT. (p. EVAL-1, EVAL-2A)

The NCCN guidelines for Systemic Mastocytosis (3.2024) recommends that all patients presenting with signs or symptoms of mastocytosis undergo molecular testing for *KIT* mutations. (p. SM-1)

**Tumor Specific *KRAS* Variant Analysis**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guideline on Colon Cancer (4.2024) recommends that all patients with metastatic colorectal cancer have tumor testing for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations individually or as part of an NGS panel as this can inform treatment. Testing can be done on the primary tumor or the metastasis. (p. COL-B 4 of 10)

The NCCN guideline on Non-Small Cell Lung Cancer (7.2024) recommends molecular testing including *KRAS* for patients with advanced or metastatic adenocarcinoma, large cell, or NSCLC and recommends consideration of molecular testing for squamous cell carcinoma of the lung. Testing should be done via broader molecular profiling but concurrent or sequential testing is acceptable. (p. NSCL- 19)

NCCN guidelines for Pancreatic Adenocarcinoma (3.2024) indicate that testing for potentially actionable somatic findings including *KRAS* should be considered for resectable or borderline resectable disease when systemic therapy is being considered (p. PANC-F, 1 of 12) as well as in locally advanced/metastatic disease. (p. PANC-1A)

NCCN guidelines for Biliary Tract Cancers (3.2024) recommend molecular testing for KRAS variant G12C in unresectable or metastatic biliary tract cancers including gallbladder, intrahepatic cholangiocarcinoma or extrahepatic cholangiocarcinoma. (p. BIL-B, 2 of 8)

**Tumor Specific *MGMT* Methylation Analysis**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guideline for Central Nervous System Cancers (2.2024) recommends *MGMT* promoter methylation testing for all high-grade gliomas (grade 3 and 4). *MGMT* promoter methylation is used for risk stratification in clinical trials and can be helpful with treatment decisions for older adults.

Patients with glioblastoma that is not *MGMT* promoter methylated benefit less from treatment with temozolomide (TMZ) compared to those whose tumors are methylated. (p. BRAIN-E, 3 of 9)

### Tumor Specific *MLH1* Methylation Analysis

*National Comprehensive Cancer Network (NCCN)*
The NCCN guideline on Genetic/Familial High-Risk Assessment: Colorectal (2.2023) recommends germline testing for Lynch syndrome or tumor testing for *MLH1* methylation in patients with colorectal or endometrial (uterine) cancer with tumors that show abnormal *MLH1* IHC. Hypermethylation of the *MLH1* promoter in these tumors has been associated with sporadic cancer, and not Lynch syndrome. If germline testing is done and is negative for Lynch syndrome pathogenic mutations, tumor *MLH1* methylation testing is recommended. (p. LS-A 2 of 9)

### Tumor Specific *MPL* Variant Analysis

*National Comprehensive Cancer Network (NCCN)*
The NCCN guideline on Myeloproliferative Neoplasms (1.2024) recommends molecular testing (blood or bone marrow) for patients with suspicion of myeloproliferative disease. Testing can be done in a stepwise fashion or via a multigene panel that includes *JAK2*, *CALR* and *MPL*. (p. MPN-1)

The NCCN Myelodysplastic Syndromes guidelines (3.2024) recommend genetic testing for somatic mutations in genes associated with MDS, which includes MPL. (p. MDS-1, MDS-C 2 of 3)

### Tumor Specific Microsatellite Instability (MSI) Analysis

*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines for Colon Cancer (4.2024) recommend determination of tumor MMR or MSI in all individuals with newly diagnosed colorectal cancer. (p. COL-B 4 of 10)

The NCCN guidelines for Uterine Neoplasms (2.2024) recommend MSI (among other studies) for patients undergoing initial evaluation for known or suspected uterine malignancy. (p. UN-1, ENDO-A 2 of 4, UTSARC-A 1 of 8))

The NCCN guideline on Gastric Cancer (2.2024) recommends MSI testing for all newly diagnosed gastric cancers. (p. GAST-1)

The NCCN guideline on Esophageal and Esophagogastric Junction Cancer (4.2024) recommends MSI by PCR or NGS for all patients with newly diagnosed esophageal and EGJ cancers. (p. ESOPH-1)
The NCCN guidelines for Cervical Cancer (3.2024) recommend MSI testing for patients with progressive, recurrent, or metastatic cervical carcinoma. (p. CERV-A 1 of 7)

The NCCN guideline for Testicular Cancer (1.2024) recommends MSI testing in individuals with pure seminoma or nonseminoma testicular cancer who have had progression after high-dose chemotherapy or third line therapy. (p. SEM-7, NSEM-10)

The NCCN guidelines for Biliary Tract Cancers (3.2024) recommends MSI testing for unresectable or metastatic gallbladder cancer or unresectable or metastatic intrahepatic cholangiocarcinoma or extrahepatic cholangiocarcinoma. (p. BIL-B, 2 of 8)

The NCCN guidelines for Breast Cancer (4.2024) recommend MSI testing for patients with recurrent unresectable or metastatic breast cancer considering a targeted therapy. (p. BINV-Q, 6 of 14)

The NCCN guidelines for Small Bowel Adenocarcinoma (4.2024) recommend universal MSI testing for all patients with newly diagnosed small bowel adenocarcinoma. (p. SBA-B)

The NCCN guidelines for an Occult Primary (1.2025) recommend MSI testing as part of work-up for patients with a suspected metastatic malignancy of unknown or uncertain etiology. (p. OCC-1)

The NCCN guidelines for Pancreatic Adenocarcinoma (3.2024) recommend MSI (among other studies) for patients with metastatic pancreatic cancer (p. PANC-1A) or resectable or borderline resectable disease when systemic therapy is being considered. (p. PANC-F, 1 of 12)

NCCN guidelines for Vulvar Cancer (4.2024) recommend consideration of MSI testing for recurrent, progressive or metastatic squamous cell carcinoma of the vulva. (p. VULVA-A, 2 of 4)

NCCN guidelines for Bone Cancer (2.2024) recommend consideration of testing for TMB and MMR/MSI to inform treatment options for metastatic chondrosarcoma, (p. CHON-4), metastatic chordoma (p. CHOR-3), widely metastatic Ewing sarcoma (p. EW-3), and metastatic osteosarcoma. (p. OSTEO-3)

NCCN guidelines for Vaginal Cancer (1.2025) recommend consideration of MSI testing for recurrent or metastatic vaginal cancer. (p. VAG-5-6, VAG-A 2 of 2)

NCCN guidelines for Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer (3.2024) recommend MSI testing as part of the molecular tumor workup for recurrent primary ovarian cancer at any stage. (p. OV-6, p. OV-B 1 of 3)

**Tumor Specific *NPM1* Variant Analysis**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines on Acute Myeloid Leukemia (3.2024) recommend molecular testing during the evaluation for AML for genes associated with prognosis or treatment options, including NPM1. (p. EVAL-1, EVAL-2A)

**Tumor Specific *NRAS* Variant Analysis**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guideline on Colon Cancer (4.2024) recommends that all patients with metastatic colorectal cancer should have tumor testing for *RAS* (*KRAS* and *NRAS*) and *BRAF* mutations individually or as part of an NGS panel. Testing can be done on the primary tumor or the metastasis. (p. COL-B 4 of 10)

**Tumor Specific *PIK3CA* Variant Analysis**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines on Breast Cancer (4.2024) recommends molecular testing for PIK3CA mutations in patients with recurrent or stage IV HR-positive/HER2-negative breast cancers (p. BINV-Q, 6 of 14) to identify candidates for Alpelisib or Capivasertib + fulvestrant.

**Tumor Specific *TP53* Variant Analysis**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines on Acute Myeloid Leukemia (3.2024) recommend molecular testing during the evaluation for AML for genes with prognostic or treatment implications, including TP53. (p. EVAL-1, EVAL-2A)

The NCCN guidelines on B-cell Lymphoma (2.2024) recommend *TP53* mutation analysis for patients with a diagnosis of mantle cell lymphoma in order to direct treatment selection, as patients with a *TP53* mutation have been associated with poor prognosis when treated with conventional therapy. (p. MANT-1)

The NCCN guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (3.2024) recommend *TP53* sequencing analysis to inform prognosis and therapeutic options for patients diagnosed with CLL/SLL or upon progression or recurrence. (p. CSLL-1, CSLL-4A)

### HLA Typing for Transplantation

*UpToDate: Human leukocyte antigens (HLA): A roadmap*
For patients who are undergoing or being evaluated for hematopoietic stem cell transplantation, full HLA typing is required.

*UpToDate: Donor selection for hematopoietic cell transplantation*
HLA typing is an important part of the process in achieving a successful hematopoietic cell transplantation (HCT). Matching HLA class I (-A, -B, -C) and class II (-DRB1 and -DQB1) haplotypes in both the candidate and donor is recommended to increase success of allogeneic HCT.

*NMDP, formerly known as the National Marrow Donor Program and Be The Match*
"These guidelines were developed jointly by NMDP and the American Society for Transplantation and Cellular Therapy (ASTCT). The guidelines are based on current clinical practice, medical literature, National Comprehensive Cancer Network (NCCN) Guidelines for the treatment of cancer and evidence-based reviews."

"If allogeneic transplant is potentially indicated, you should perform HLA typing of the patient and potential family donors at diagnosis. In addition, a preliminary unrelated donor search of the NMDP Registry should be completed."

*Organ Procurement and Transplantation Network (OPTN)*
The OPTN (effective date: 4/2/2024) includes a section titled "Requirements for Performing and Reporting HLA Typing", in which it states:
"Laboratories must perform HLA typing on a kidney, kidney-pancreas, pancreas, or pancreas islet candidate and report results for HLA A, B, Bw4, Bw6, and DR to the transplant program prior to registration on the waiting list." (p. 52)

Additionally, the document states:
"Laboratories performing histocompatibility testing for kidney transplants or multi-organ transplants in which a kidney is to be transplanted must perform a final crossmatch and report the results to the Transplant Program before transplant. (p. 55)

*Tait, et al*
In 2013, Tait et al. created a list of technical test recommendations for pre and post solid organ transplantation. Per the article:
"HLA typing of donor and recipient must be performed at a level required for accurate antibody interpretation. When a patient is sensitized, precise characterization of HLA antibodies and complete HLA typing of the donor pretransplantation must be performed." (p. 37)
Of note, there is no mention of performing HLA Typing post-transplantation.

## MEASUREABLE (MINIMAL) RESIDUAL DISEASE (MRD) ANALYSIS

### Hematologic Minimal Residual Disease (MRD) Testing

*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines for Acute Lymphoblastic Leukemia (2.2024) recommend baseline flow cytometric and/or molecular characterization of leukemic clone(s) to be used in subsequent minimal/measurable residual disease (MRD) analysis. (p. ALL-1) After treatment induction, MRD is recommended to determine consolidation therapy. (p. ALL-5)

The NCCN guidelines for Multiple Myeloma (4.2024) recommend consideration of a baseline clone identification and storage of an aspirate sample for MRD testing by NGS in the initial diagnostic workup (p. MYEL-1) or prognostication during follow up after primary treatment. (p. MYEL-4)
The NCCN guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (3.2024) recommend minimal residual disease testing at the end of treatment for CLL/SLL as an important

predictor of treatment effectiveness. MRD evaluation can be done using flow cytometry, PCR or NGS assay. (p. CSLL-E, 2 of 2)

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

*Centers for Medicare and Medicaid Services*

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

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

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

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

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

### Emerging Evidence Solid Tumor Minimal Residual Disease (MRD) Testing

Tests that have limited established clinical utility or validity as defined in the Concert policy for General Approach to Genetic and Molecular testing do not meet the threshold for coverage. Evidence for validity may include a Technology Assessment conducted by an independent third party (e.g. MolDx Tech, ECRI, Optum Genomic) and/or evidence-based guidelines published by professional societies. Such evidence was not identified for the tests referenced by this policy.

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

*Centers for Medicare and Medicaid Services*

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

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

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

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

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

**Tumor Mutational Burden (TMB)**
*National Comprehensive Cancer Network (NCCN)*
The NCCN guidelines for Breast Cancer (4.2024) recommend tumor mutation burden (TMB) testing for patients with recurrent unresectable or stage IV disease for whom pembrolizumab is being considered for treatment. (p. BINV-Q, 6 of 14)

The NCCN guidelines for Biliary Tract Cancers (3.2024) recommend tumor mutational burden testing for unresectable or metastatic gallbladder cancer, intrahepatic cholangiocarcinoma, and extrahepatic cholangiocarcinoma. (p. BIL-B, 2 of 8)

The NCCN guidelines for Occult Primary Cancers (1.2025) recommends consideration of tumor mutational burden testing for patients with suspected metastatic malignancy of uncertain pathology. (p. OCC-1)

The NCCN guidelines for Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer (3.2024) recommend tumor analysis, including tumor mutational burden, for recurrent ovarian/Fallopian tube/primary peritoneal cancer. (p. OV-B 1 of 3)

The NCCN guidelines for Pancreatic Adenocarcinoma (3.2024) recommend testing of tumor mutational burden for patients with resectable, borderline resectable, or locally advanced and metastatic pancreatic cancer who are candidates for systemic therapy. (p. PANC-1A, PANC-F, 1 of 12)
The NCCN guidelines for Prostate Cancer (4.2024) recommend somatic testing for tumor mutational burden for patients with metastatic castration-resistant prostate cancer. (p. PROS-15)

The NCCN guidelines for Testicular Cancer (1.2024) recommend tumor mutational burden testing for patients with pure seminoma or nonseminoma testicular cancer who have experienced disease progression after high-dose chemotherapy or third-line therapy. (p. SEM-7, NSEM-10)

The NCCN guidelines for Uterine Neoplasms (2.2024) recommend consideration of tumor mutational burden testing for patients with endometrial cancer (p. ENDO-A 2 of 4). The guidelines also recommend tumor mutational burden testing be done for patients with uterine sarcoma. (p. UTSARC-A 1 of 8)

NCCN guidelines for Ampullary Adenocarcinoma (2.2024) recommend tumor/somatic molecular profiling, including tumor mutational burden, for patients with locally advanced/metastatic disease who are candidates for systemic therapy. (p. AMP-3)

NCCN guidelines for Bone Cancer (2.2024) recommend consideration of testing for TMB and MMR/MSI to inform treatment options for metastatic chondrosarcoma, (p. CHON-4), metastatic chordoma (p. CHOR-3), widely metastatic Ewing sarcoma (p. EW-3), and metastatic osteosarcoma. (p. OSTEO-3)

NCCN guidelines for Esophageal and Esophagogastric Junction Cancers (4.2024) recommend molecular testing (IHC, FISH, PCR, NGS) for identification of biomarkers for which targeted therapies are approved. Tumor mutational burden is a biomarker for which testing should be done. (p. ESOPH-B, 5 of 6)

NCCN guidelines for Gastric Cancer (2.2024) recommend molecular testing (IHC, FISH, PCR, NGS) for identification of biomarkers for which targeted therapies are approved. Tumor mutational burden is a biomarker for which testing should be done. (p. GAST-B, 5 of 6)

NCCN guidelines for Head and Neck Cancers (4.2024) recommends that NGS profiling and other appropriate biomarker testing should be done to assess tumor mutational burden (TMB), among other biomarkers, prior to treatment for metastatic salivary gland tumors. (p. SALI-4)

NCCN guidelines for Neuroendocrine and Adrenal Tumors (2.2024) recommends TMB testing for locally advanced unresectable or metastatic, extra pulmonary poorly differentiated neuroendocrine carcinoma, large or small cell carcinoma and mixed neuroendocrine-non-neuroendocrine neoplasm (p. PDNEC-1A) and recommends consideration of TMB testing for adrenocortical carcinoma. (p. AGT-5)

NCCN guidelines for Thyroid Carcinoma (3.2024) state that genomic testing to identify actionable mutations including tumor mutational burden (TMB) should be done for patients with locally recurrent, advanced and/or metastatic papillary (p. PAP-10), follicular (p. FOLL-9) or oncocytic carcinoma (p. ONC-9) that is not amenable to RAI therapy, and for patients with stage IVC anaplastic carcinoma. (p. ANAP-3)

NCCN guidelines for Vulvar Cancer (4.2024) recommend consideration of tumor mutational burden (TMB) testing in the pathologic assessment for squamous cell carcinoma of the vulva. (p. VULVA-A, 2 of 4)

NCCN guidelines for Small Bowel Adenocarcinoma (4.2024) recommend consideration of tumor mutational burden testing for metastatic adenocarcinoma. (p. SBA-5)

NCCN guidelines for Vaginal Cancer (1.2025) recommend consideration of tumor mutational burden testing for recurrent or metastatic vaginal cancer. (p. VAG-5-6, VAG-A. 2 of 2)

*Food and Drug Administration (FDA)*
Per the FDA label for KEYTRUDA (pembrolizumab) injection:
"Tumor Mutational Burden-High (TMB-H) Cancer for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options. Limitations of Use: The safety and effectiveness of KEYTRUDA in pediatric patients with TMB-H central nervous system cancers have not been established."

### Red Blood Cell Genotyping in Multiple Myeloma

*Association for the Advancement of Blood and Biotherapies*
The AABB (Association for the Advancement of Blood and Biotherapies; formerly known as the American Association of Blood Banks) published Association Bulletin #16-02 on January 15 2016 (updated April 2023) recommending consideration of baseline phenotype and genotype prior to initiation of anti-CD38 monoclonal antibody treatment (daratumumab or isatuximab) 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.

## References

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 7.2024. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 4.2024. http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf
3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal. Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf
4. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 4.2024. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
5. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer, Including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 3.2024. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf
6. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes. Version 3.2024 https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf
7. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 3.2024. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf
8. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastrointestinal Stromal Tumors (GISTs). Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/gist.pdf

9. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cutaneous Melanoma. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf
10. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Acute Myeloid Leukemia. Version 3.2024. https://www.nccn.org/professionals/physician_gls/pdf/aml.pdf
11. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Systemic Mastocytosis. Version 3.2024. https://www.nccn.org/professionals/physician_gls/pdf/mastocytosis.pdf
12. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Myeloproliferative Neoplasms. Version 1.2024 https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf
13. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma. Version 3.2024 https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf
14. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Uterine Neoplasms. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf
15. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Chronic Myeloid Leukemia. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/cml.pdf
16. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Pediatric Acute Lymphoblastic Leukemia. Version 6.2024. https://www.nccn.org/professionals/physician_gls/pdf/ped_all.pdf
17. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Acute Lymphoblastic Leukemia. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/all.pdf
18. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in B-Cell Lymphomas. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf
19. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Hairy Cell Leukemia. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/hairy_cell.pdf
20. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Central Nervous System Cancers. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/cns.pdf
21. Konstantinopoulos PA, Norquist B, Lacchetti C, et al. Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(11):1222-1245. doi:10.1200/JCO.19.02960
22. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 4.2024. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
23. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf
24. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancer. Version 4.2024. https://www.nccn.org/professionals/physician_gls/pdf/esophageal.pdf
25. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Chronic Lymphocytic Leukemia/Small Lymphocytic Leukemia. Version 3.2024. https://www.nccn.org/professionals/physician_gls/pdf/cll.pdf
26. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer. Version 3.2024. https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf

27. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Biliary Tract Cancers. Version 3.2024. https://www.nccn.org/professionals/physician_gls/pdf/btc.pdf
28. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Occult Primary (Cancer of Unknown Primary [CUP]). Version 1.2025. https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf
29. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Testicular Cancer. Version 1.2024. https://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf
30. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. Version 4.2024. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf
31. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Small Bowel Adenocarcinoma. Version 4.2024. https://www.nccn.org/professionals/physician_gls/pdf/small_bowel.pdf
32. National Comprehensive Cancer Network. Biomarker Compendium. https://www.nccn.org/professionals/biomarkers/content/. Accessed 04/01/2024.
33. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Primary Cutaneous Lymphomas. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf
34. Association for the Advancement of Blood and Biotherapies Association Bulletin #16-02: Mitigating the Anti-CD38 Interference with Serologic Testing. (2016, January 15). https://www.aabb.org/docs/default-source/default-document-library/resources/association-bulletins/ab16-02.pdf
35. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Histiocytic Neoplasms. Version 2.2024 https://www.nccn.org/professionals/physician_gls/pdf/histiocytic_neoplasms.pdf
36. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Soft Tissue Sarcoma. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf
37. Chakravarty D, Johnson A, Sklar J, et al. Somatic Genomic Testing in Patients With Metastatic or Advanced Cancer: ASCO Provisional Clinical Opinion [published correction appears in J Clin Oncol. 2022 Jun 20;40(18):2068]. J Clin Oncol. 2022;40(11):1231-1258. doi:10.1200/JCO.21.02767
38. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Vulvar Cancer. Version 4.2024. https://www.nccn.org/professionals/physician_gls/pdf/vulvar.pdf
39. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ampullary Adenocarcinoma. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/ampullary.pdf
40. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Bone Cancer. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/bone.pdf
41. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Head and Neck Cancers. Version 4.2024. https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf
42. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors. Version 2.2024. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf
43. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Vaginal Cancer. Version 1.2025. https://www.nccn.org/professionals/physician_gls/pdf/vaginal.pdf

44. Merck & CO, Inc. KEYTRUDA (pembrolizumab). U.S. Food and Drug Administration. Website: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125514s071s090lbl.pdf. Accessed 4/24/2024.
45. Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. MolDX: Minimal Residual Disease Testing for Cancer (L38779). Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38779
46. Centers for Medicare & Medicaid Services. Medicare Coverage Database: Billing and Coding: MolDX: Minimal Residual Disease Testing for Solid Tumor Cancers (A58376). Available at: https://www.cms.gov/medicare-coverage-database/view/article.aspx?articleId=58376
47. Viatte, MD, PhD, et al. Human leukocyte antigens (HLA): A roadmap. In: UpToDate, Connor RF (ed), Wolters Kluwer (Accessed on May 8, 2024). https://www.uptodate.com/contents/human-leukocyte-antigens-hla-a-roadmap
48. Negrin, R.S., MD, et al. Donor selection for hematopoietic cell transplantation. In: UpToDate, Connor, RF (ed), Wolters Kluwer (Accessed May 8, 2024). https://www.uptodate.com/contents/donor-selection-for-hematopoietic-cell-transplantation
49. 2024 CONSULTATION GUIDELINES Recommended Timing for Transplant Consultation. Published jointly by NMDPSM and the American Society for Transplantation and Cellular Therapy (ASTCT). Available at: https://bethematchclinical.org/transplant-indications-and-outcomes/referral-timing-guidelines/
50. Tait BD, Süsal C, Gebel HM, et al. Consensus guidelines on the testing and clinical management issues associated with HLA and non-HLA antibodies in transplantation. *Transplantation*. 2013;95(1):19-47. doi:10.1097/TP.0b013e31827a19cc
51. "Requirements for Performing and Reporting HLA Typing" OTPN (Effective Date: 4/2/2024). Available at: https://optn.transplant.hrsa.gov/media/eavh5bf3/optn_policies.pdf
52. FoundationOne CDx Technical Information (PMA approval number: P170019). US Food and Drug Administration. Website: https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170019C.pdf. Accessed 08/12/2024.

## Documentation for Clinical Review

**Please provide the following documentation:**

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

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

- Results/reports of tests performed

## Coding

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

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

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

| Type | Code | Description |
|---|---|---|
| | 0050U | Targeted genomic sequence analysis panel, acute myelogenous leukemia, DNA analysis, 194 genes, interrogation for sequence variants, copy number variants or rearrangements |
| | 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 |
| | 0229U | BCAT1 (Branched chain amino acid transaminase 1) and IKZF1 (IKAROS family zinc finger 1) (e.g., colorectal cancer) promoter methylation analysis |
| | 0250U | Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden |
| | 0306U | Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis, cell-free DNA, initial (baseline) assessment to determine a patient-specific panel for future comparisons to evaluate for MRD |
| | 0307U | Oncology (minimal residual disease [MRD]), next-generation targeted sequencing analysis of a patient-specific panel, cell-free DNA, subsequent assessment with comparison to previously analyzed patient specimens to evaluate for MRD |
| | 0329U | Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations |
| | 0334U | Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffin[1]embedded (FFPE) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden |
| | 0340U | Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next-generation sequencing of the patient's tumor and germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate |
| | 0356U | Oncology (oropharyngeal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence |
| | 0364U | Oncology (hematolymphoid neoplasm), genomic sequence analysis using multiplex (PCR) and next-generation sequencing with algorithm, quantification of dominant clonal sequence(s), reported as presence or |

| Type | Code | Description |
|---|---|---|
| | | absence of minimal residual disease (MRD) with quantitation of disease burden, when appropriate |
| | 0379U | Targeted genomic sequence analysis panel, solid organ neoplasm, DNA (523 genes) and RNA (55 genes) by next-generation sequencing, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability, and tumor mutational burden |
| | 0391U | Oncology (solid tumor), DNA and RNA by next-generation sequencing, utilizing formalin-fixed paraffin-embedded (FFPE) tissue, 437 genes, interpretive report for single nucleotide variants, splicesite variants, insertions/deletions, copy number alterations, gene fusions, tumor mutational burden, and microsatellite instability, with algorithm quantifying immunotherapy response score |
| | 0409U | Oncology (solid tumor), DNA (80 genes) and RNA (36 genes), by next-generation sequencing from plasma, including single nucleotide variants, insertions/deletions, copy number alterations, microsatellite instability, and fusions, report showing identified mutations with clinical actionability |
| | 0422U | Oncology (pan-solid tumor), analysis of DNA biomarker response to anti-cancer therapy using cell-free circulating DNA, biomarker comparison to a previous baseline pre-treatment cell-free circulating DNA analysis using next-generation sequencing, algorithm reported as a quantitative change from baseline, including specific alterations, if appropriate |
| | 0444U | Oncology (solid organ neoplasia), targeted genomic sequence analysis panel of 361 genes, interrogation for gene fusions, translocations, or other rearrangements, using DNA from formalin-fixed paraffin-embedded (FFPE) tumor tissue, report of clinically significant variant(s) ***(Code effective 4/1/2024)*** |
| | 0450U | Oncology (multiple myeloma), liquid chromatography with tandem mass spectrometry (LC-MS/MS), monoclonal paraprotein sequencing analysis, serum, results reported as baseline presence or absence of detectable clonotypic peptides ***(Code effective 7/1/2024)*** |
| | 0451U | Oncology (multiple myeloma), LC-MS/MS, peptide ion quantification, serum, results compared with baseline to determine monoclonal paraprotein abundance ***(Code effective 7/1/2024)*** |
| | 0467U | Oncology (bladder), DNA, next-generation sequencing (NGS) of 60 genes and whole genome aneuploidy, urine, algorithms reported as minimal residual disease (MRD) status positive or negative and quantitative disease burden ***(Code effective 7/1/2024)*** |
| | 0473U | Oncology (solid tumor), next-generation sequencing (NGS) of DNA from formalin-fixed paraffin-embedded (FFPE) tissue with comparative sequence analysis from a matched normal specimen (blood or saliva), 648 genes, interrogation for sequence variants, insertion and deletion alterations, copy number variants, rearrangements, microsatellite instability, and tumor-mutation burden ***(Code effective 7/1/2024)*** |
| | 0478U | Oncology (non-small cell lung cancer), DNA and RNA, digital PCR analysis of 9 genes (EGFR, KRAS, BRAF, ALK, ROS1, RET, NTRK 1/2/3, ERBB2, and MET) in formalin-fixed paraffin-embedded (FFPE) tissue, interrogation for single-nucleotide variants, insertions/deletions, gene rearrangements, and reported as actionable detected variants for therapy selection ***(Code effective 10/1/2024)*** |

| Type | Code | Description |
|---|---|---|
| | 0481U | IDH1 (isocitrate dehydrogenase 1 [NADP+]), IDH2 (isocitrate dehydrogenase 2 [NADP+]), and TERT (telomerase reverse transcriptase) promoter (e.g., central nervous system [CNS] tumors), next-generation sequencing (single-nucleotide variants [SNV], deletions, and insertions) ***(Code effective 10/1/2024)*** |
| | 0486U | Oncology (pan-solid tumor), next-generation sequencing analysis of tumor methylation markers present in cell-free circulating tumor DNA, algorithm reported as quantitative measurement of methylation as a correlate of tumor fraction***(Code effective 10/1/2024)*** |
| | 0498U | Oncology (colorectal), next-generation sequencing for mutation detection in 43 genes and methylation pattern in 45 genes, blood, and formalin-fixed paraffin-embedded (FFPE) tissue, report of variants and methylation pattern with interpretation ***(Code effective 10/1/2024)*** |
| | 0501U | Oncology (colorectal), blood, quantitative measurement of cell-free DNA (cfDNA) |
| | 0511U | Oncology (solid tumor), tumor cell culture in 3D microenvironment, 36 or more drug panel, reported as tumor-response prediction for each drug ***(Code effective 10/1/2024)*** |
| | 0523U | Oncology (solid tumor), DNA, qualitative, next-generation sequencing (NGS) of single-nucleotide variants (SNV) and insertion/deletions in 22 genes utilizing formalin-fixed paraffin-embedded tissue, reported as presence or absence of mutation(s), location of mutation(s), nucleotide change, and amino acid change ***(Code effective 1/1/2025)*** |
| | 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 |
| | 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 |

| Type | Code | Description |
|---|---|---|
| | 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) |
| | 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 |

| Type | Code | Description |
|---|---|---|
| | 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) |
| | 81370 | HLA Class I and II typing, low resolution (e.g., antigen equivalents); HLA-A, -B, -C, -DRB1/3/4/5, and -DQB1 |
| | 81371 | HLA Class I and II typing, low resolution (e.g., antigen equivalents); HLA-A, -B, and -DRB1 (e.g., verification typing) |
| | 81372 | HLA Class I typing, low resolution (e.g., antigen equivalents); complete (i.e., HLA-A, -B, and -C) |
| | 81373 | HLA Class I typing, low resolution (e.g., antigen equivalents); one locus (e.g., HLA-A, -B, or -C), each |
| | 81376 | HLA Class II typing, low resolution (e.g., antigen equivalents); one locus (e.g., HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each |
| | 81378 | HLA Class I and II typing, high resolution (i.e., alleles or allele groups), HLA-A, -B, -C, and -DRB1 |
| | 81379 | HLA Class I typing, high resolution (i.e., alleles or allele groups); complete (i.e., HLA-A, -B, and -C) |
| | 81380 | HLA Class I typing, high resolution (i.e., alleles or allele groups); one locus (e.g., HLA-A, -B, or -C), each |
| | 81382 | HLA Class II typing, high resolution (i.e., alleles or allele groups); one locus (e.g., HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each |
| | 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, |

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

## Policy History

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

| Effective Date | Action |
|---|---|
| 06/01/2023 | New policy (combined policies 2.04.115, 2.04.124, and 2.04.60). |
| 07/01/2023 | Administrative update. Policy statement and guidelines updated. |
| 09/01/2023 | Administrative update. Policy statement and guidelines updated. |
| 11/01/2023 | Coding Update. |
| 03/01/2024 | Coding Update. |
| 05/01/2024 | Coding Update. |
| 07/01/2024 | Annual review. Policy statement, guidelines and literature updated. |
| 09/01/2024 | Coding Update. |
| 11/01/2024 | Coding Update. |
| 02/01/2025 | Annual review. Policy statement, guidelines and literature updated.<br>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 | |
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| **BEFORE**<br>Red font: Verbiage removed | **AFTER**<br>Blue font: Verbiage Changes/Additions |
| **Oncology: Molecular Analysis Of Solid Tumors And Hematologic Malignancies BSC_CON_2.04**<br><br>**Policy Statement:**<br>**Molecular Profiling Panel Testing of Solid Tumors and Hematologic Malignancies**<br>**Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels**<br>I. Tumor-type agnostic solid tumor molecular profiling panels (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U) may be considered **medically necessary** when:<br>A. The member has a diagnosis of:<br>1. Recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, **OR**<br>2. Histiocytosis**, OR**<br>3. Non-small cell lung cancer (NSCLC) regardless of stage, **AND**<br>B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy), **OR**<br>C. The member has a diagnosis of uterine neoplasm, **AND**<br>1. The member is undergoing initial evaluation, **OR**<br>D. The member has resectable or borderline resectable pancreatic adenocarcinoma, **AND**<br>1. The member is being considered for systemic therapy.<br><br>II. Repeat testing via a tumor-type agnostic solid tumor molecular profiling panel (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U) may be considered **medically necessary** when:<br>A. The member has progression of **any** of the following: | **Oncology: Molecular Analysis Of Solid Tumors And Hematologic Malignancies BSC_CON_2.04**<br><br>**Policy Statement:**<br>**Molecular Profiling Panel Testing of Solid Tumors and Hematologic Malignancies**<br>**Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels**<br>I. Tumor-type agnostic solid tumor molecular profiling panels (0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U, 0473U, 81445, 81455, 81457, 81458, 81459) may be considered **medically necessary** when:<br>A. The member meets **both** of the following:<br>1. The member has a diagnosis of:<br>a. Recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, **OR**<br>b. Histiocytosis**, OR**<br>c. Non-small cell lung cancer (NSCLC) regardless of stage, **OR**<br>d. Resectable or borderline resectable pancreatic adenocarcinoma, **OR**<br>e. Central nervous system tumor, **AND**<br>2. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy), **OR**<br>B. The member meets **one** of the following:<br>1. The member has a diagnosis of uterine neoplasm, **AND**<br>a. The member is undergoing initial evaluation, **OR**<br>2. The member has a gastrointestinal stromal tumor, **AND**<br>a. The tumor is negative for *KIT* and *PDGFRA* mutations.<br><br>II. Repeat testing via a tumor-type agnostic solid tumor molecular profiling panel (0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U, 0473U, 81445, 81455, 81457, 81458, 81459) may be considered **medically necessary** when:<br>A. The member has progression of **any** of the following: |

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| 1. Advanced or metastatic non-small cell lung cancer (NSCLC), **OR**<br>2. Advanced or metastatic gastric adenocarcinoma, **OR**<br>3. Metastatic prostate cancer.<br><br>III. Tumor-type agnostic solid tumor molecular profiling panels (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U) are considered **investigational** for all other indications.<br><br>**Note**: Additional codes representing additional IHC and/or cytogenetics analyses may be billed alongside the PLA or GSP codes.<br><br>**Targeted RNA Fusion Panels**<br>IV. RNA specific fusion panels with 5-50 genes performed on peripheral blood, bone marrow or solid tumors (81449, 81451) may be considered **medically necessary** when **any** of the following are met:<br>A. The member has a diagnosis of or is undergoing workup for **any** of the following:<br>1. Adult or pediatric acute lymphoblastic leukemia (ALL)<br>2. Glioma<br>3. Histiocytosis<br>4. Sarcoma<br>B. The member has a gastrointestinal stromal tumor, **AND**<br>1. The tumor is negative for *KIT* and *PDGFRA* somatic mutations<br>C. The member has non-small cell lung cancer, **AND**<br>1. DNA based NGS tumor profiling was negative for actionable mutations<br>D. The member has a metastatic or advanced solid tumor, **AND any** of the following:<br>1. There is a fusion-targeted therapy with regulatory approval for that cancer type<br>2. DNA-based panel testing was negative for oncogenic driver mutations. | 1. Advanced or metastatic non-small cell lung cancer (NSCLC), **OR**<br>2. Advanced or metastatic gastric adenocarcinoma, **OR**<br>3. Metastatic prostate cancer.<br><br>III. Tumor-type agnostic solid tumor molecular profiling panels (81445, 81455, 81457, 81458, 81459, 0037U, 0048U, 0250U, 0329U, 0334U, 0379U, 0391U) are considered **investigational** for all other indications.<br><br>**Note**: Additional codes representing additional IHC and/or cytogenetics analyses may be billed alongside the PLA or GSP codes.<br><br>**Targeted RNA Fusion Panels**<br>IV. RNA specific fusion panels with 5-50 genes performed on peripheral blood, bone marrow or solid tumors (81449) may be considered **medically necessary** when **any** of the following are met:<br>A. The member has a diagnosis of, or is undergoing workup for **any** of the following:<br>1. Adult or pediatric acute lymphoblastic leukemia (ALL), **OR**<br>2. Glioma, **OR**<br>3. Histiocytosis, **OR**<br>4. Sarcoma, **OR**<br>B. The member has a gastrointestinal stromal tumor, **AND**<br>1. The tumor is negative for *KIT* and *PDGFRA* somatic mutations, **OR**<br>C. The member has non-small cell lung cancer, **AND**<br>1. DNA based NGS tumor profiling was negative for actionable mutations, **OR**<br>D. The member has a metastatic or advanced solid tumor, **AND any** of the following:<br>1. There is a fusion-targeted therapy with regulatory approval for that cancer type, **OR**<br>2. DNA-based panel testing was negative for oncogenic driver mutations. |

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| V. RNA specific fusion panels (81449, 81451) are considered **investigational** for all other indications. | V. RNA specific fusion panels (81449) are considered **investigational** for all other indications. |
| **Broad RNA Fusion Panels**<br>VI. RNA fusion panels tests with 51 or more genes utilizing RNA analysis alone (81456, 0444U) may be considered **medically necessary** when:<br>A. The member has a diagnosis of adult or pediatric acute lymphoblastic leukemia (ALL). | **Broad RNA Fusion Panels**<br>VI. RNA fusion panels tests with 51 or more genes utilizing RNA analysis alone (0444U, 81456) may be considered **medically necessary** when:<br>A. The member has a diagnosis of adult or pediatric acute lymphoblastic leukemia (ALL). |
| VII. RNA fusion panel tests with 51 or more genes utilizing RNA analysis alone (81456, 0444U) are considered **investigational** for all other indications. | VII. RNA fusion panel tests with 51 or more genes utilizing RNA analysis alone (0444U, 81456) are considered **investigational** for all other indications. |
| **Broad Molecular Profiling Panels For Hematologic Malignancies and Myeloid Malignancy Panels**<br>VIII. Broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) may be considered **medically necessary** when **any** of the following are met:<br>A. The member has blood work (CBC) and bone marrow evaluation which are consistent with acute myeloid leukemia (AML)<br>B. The member has newly diagnosed acute lymphoblastic leukemia (ALL)<br>C. The member has newly diagnosed myelodysplastic syndrome (MDS)<br>D. The member has suspected myelodysplastic syndrome (MDS) **AND**<br>1. Other causes of cytopenia(s) have been ruled out<br>E. The member is suspected to have a myeloproliferative neoplasm (MPN), **AND any** of the following:<br>1. This is the member's initial genetic evaluation for suspected MPN | **Broad Molecular Profiling Panels For Hematologic Malignancies and Myeloid Malignancy Panels**<br>VIII. Broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) may be considered **medically necessary** when **any** of the following are met:<br>A. The member is undergoing evaluation for acute myeloid leukemia (AML), **OR**<br>B. The member has newly diagnosed acute lymphoblastic leukemia (ALL), **OR**<br>C. The member has newly diagnosed myelodysplastic syndrome (MDS), **OR**<br>D. The member has suspected myelodysplastic syndrome (MDS) **AND**<br>1. Other causes of cytopenia(s) have been ruled out, **OR**<br>E. The member is suspected to have a myeloproliferative neoplasm (MPN), **AND any** of the following:<br>1. This is the member's initial genetic evaluation for suspected MPN, **OR** |

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| 2. Previous results of *JAK2*, *CALR*, and *MPL* analysis were negative<br>F. The member has a diagnosis of chronic myelogenous leukemia (CML), **AND any** of the following:<br>1. There has been progression to accelerated or blast phase<br>2. Results of *BCR-ABL1* kinase domain mutation analysis were negative. | 2. Previous results of *JAK2*, *CALR*, and *MPL* analysis were negative, **OR**<br>F. The member has a diagnosis of chronic myelogenous leukemia (CML), **AND any** of the following:<br>1. There has been progression to accelerated or blast phase, **OR**<br>2. Results of *BCR-ABL1* kinase domain mutation analysis were negative. |
| IX. Repeat broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) may be considered **medically necessary** when:<br>A. The member has myelodysplastic syndrome (MDS), **AND**<br>1. The member has relapsed after allo-HCT [hematopoietic cell transplant], **OR**<br>B. The member has acute lymphoblastic leukemia (ALL), **AND**<br>1. The member is showing evidence of symptomatic relapse after maintenance therapy, **OR**<br>C. The member has acute myeloid leukemia (AML), **AND**<br>1. The member has relapsed or refractory disease or progression on treatment. | IX. Repeat broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) may be considered **medically necessary** when:<br>A. The member has myelodysplastic syndrome (MDS), **AND**<br>1. The member has relapsed after allo-HCT [hematopoietic cell transplant], **OR**<br>B. The member has acute lymphoblastic leukemia (ALL), **AND**<br>1. The member is showing evidence of symptomatic relapse after maintenance therapy, **OR**<br>C. The member has acute myeloid leukemia (AML), **AND**<br>1. The member has relapsed or refractory disease or progression on treatment. |
| X. Broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) are considered **investigational** for all other indications. | X. Broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood (81450, 81455) are considered **investigational** for all other indications. |
| **Note:** If a multigene panel is performed, appropriate panel codes should be used. These clinical criteria are not intended to address liquid biopsies. | **Note:** If a multigene panel is performed, appropriate panel codes should be used. These clinical criteria are not intended to address liquid biopsies. |
| **Colorectal Cancer Focused Molecular Profiling Panels**<br>XI. Colorectal cancer focused molecular profiling panels (0111U, 81445, 81457) in solid tumors may be considered **medically necessary** when: | **Colorectal Cancer Focused Molecular Profiling Panels**<br>XI. Colorectal cancer focused molecular profiling panels (81445, 81457) in solid tumors may be considered **medically necessary** when: |

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| A. The member has suspected or proven metastatic colorectal cancer, **AND**<br>B. The panel contains, at a minimum, the following genes: *KRAS, NRAS, BRAF.* | A. The member has suspected or proven metastatic colorectal cancer, **AND**<br>B. The panel contains, at a minimum, the following genes: *KRAS, NRAS, BRAF.* |
| XII. Colorectal cancer-focused molecular profiling panels (0111U, 81445, 81457) are considered **investigational** for all other indications. | XII. Colorectal cancer-focused molecular profiling panels (81445, 81457) are considered **investigational** for all other indications. |
| **Note:** If a panel is performed, appropriate panel codes should be used. | **Note:** If a panel is performed, appropriate panel codes should be used. |
| **Lung Cancer Focused Molecular Profiling Panels** | **Lung Cancer Focused Molecular Profiling Panels** |
| XIII. Lung cancer focused molecular profiling panels (0022U, 81457) may be considered **medically necessary** when:<br>A. The member has a diagnosis of **any** of the following:<br>1. Advanced (stage IIIb or higher) or metastatic lung adenocarcinoma<br>2. Advanced (stage IIIb or higher) or metastatic large cell lung carcinoma<br>3. Advanced (stage IIIb or higher) or metastatic squamous cell lung carcinoma,<br>4. Advanced (stage IIIb or higher) or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **AND**<br>B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy). | XIII. Lung cancer focused molecular profiling panels (0022U, 81457) may be considered **medically necessary** when:<br>A. The member has a diagnosis of **any** of the following:<br>1. Advanced (stage IIIb or higher) or metastatic lung adenocarcinoma, **OR**<br>2. Advanced (stage IIIb or higher) or metastatic large cell lung carcinoma, **OR**<br>3. Advanced (stage IIIb or higher) or metastatic squamous cell lung carcinoma, **OR**<br>4. Advanced (stage IIIb or higher) or metastatic non-small cell lung cancer (NSCLC) not otherwise specified (NOS), **AND**<br>B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy). |
| XIV. Repeat lung cancer-focused molecular profiling panels (0022U, 81457) may be considered **medically necessary** when the member has progression on targeted therapy for non-small cell lung cancer. | XIV. Repeat lung cancer-focused molecular profiling panels (0022U, 81457) are considered **medically necessary** when the member has progression on targeted therapy for non-small cell lung cancer. |
| XV. Lung cancer-focused molecular profiling panels (0022U, 81457) are considered **investigational** for all other indications. | XV. Lung cancer-focused molecular profiling panels (0022U, 81457) are considered **investigational** for all other indications. |
| **Note:** If a panel is performed, appropriate panel codes should be used. | **Note:** If a panel is performed, appropriate panel codes should be used. |

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| **Cutaneous Melanoma Focused Molecular Profiling Panels**<br>XVI. Cutaneous melanoma focused molecular profiling panels (81445, 81457) may be considered **medically necessary** when **all** of the following are met:<br>A. The member has a new diagnosis of stage IV melanoma or has recurrent melanoma<br>B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy)<br>C. **One** of the following:<br>1. The member has not had previous somatic testing via a multigene cancer panel for the same primary melanoma diagnosis<br>2. The member **has** had previous somatic testing via a multigene cancer panel for a primary melanoma diagnosis, and has a **new** primary melanoma diagnosis for which this testing is being ordered.<br><br>XVII. Cutaneous melanoma focused molecular profiling panels (81445, 81457) are considered **investigational** for all other indications.<br><br>**Note:** If a panel is performed, appropriate panel codes should be used. | **Cutaneous Melanoma Focused Molecular Profiling Panels**<br>XVI. Cutaneous melanoma focused molecular profiling panels (81445, 81457) **may be** considered **medically necessary** when **all** of the following are met:<br>A. The member has a diagnosis of **one** of the following:<br>1. Stage III melanoma or higher, **OR**<br>2. Recurrent melanoma, **AND**<br>B. The member is seeking further cancer treatment (e.g., therapeutic chemotherapy), **AND**<br>C. **One** of the following:<br>1. The member has not had previous somatic testing via a multigene cancer panel for the same primary melanoma diagnosis, **OR**<br>2. The member **has** had previous somatic testing via a multigene cancer panel for a primary melanoma diagnosis, and has a **new** primary melanoma diagnosis for which this testing is being ordered.<br><br>XVII. Cutaneous melanoma focused molecular profiling panels (81445, 81457) are considered **investigational** for all other indications.<br><br>**Note:** If a panel is performed, appropriate panel codes should be used. |
| **Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels**<br>XVIII. Acute myeloid leukemia focused molecular profiling panels (0050U, 81450) for the diagnosis or evaluation of acute myeloid leukemia (AML) may be considered **medically** necessary when:<br>A. The member has a suspected or confirmed diagnosis of acute myeloid leukemia (AML).<br><br>XIX. Acute myeloid leukemia focused molecular profiling panels (0050U, 81450) for the diagnosis or evaluation of acute myeloid leukemia (AML) are considered **investigational** for all other indications. | **Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels**<br>XVIII. Acute myeloid leukemia focused molecular profiling panels (0050U, 81450) for the diagnosis or evaluation of acute myeloid leukemia (AML) may be considered **medically** necessary when:<br>A. The member has a suspected or confirmed diagnosis of acute myeloid leukemia (AML).<br><br>XIX. Acute myeloid leukemia focused molecular profiling panels (0050U, 81450) for the diagnosis or evaluation of acute myeloid leukemia (AML) are considered **investigational** for all other indications. |

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| **Note:** If a multigene panel is performed, appropriate panel codes should be used. | **Note:** If a multigene panel is performed, appropriate panel codes should be used. |
| **Myeloproliferative Neoplasms (MPNs) Panels**<br>XX. Myeloproliferative neoplasm (MPN) molecular profiling panels (81206, 81207, 81208, 81219, 81270, 81279, 81338, 81339) may be considered **medically necessary** when **both** of the following criteria are met:<br>A. The member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia)<br>B. The panel does not include genes other than *JAK2*, *CALR*, *MPL*, and *BCR/ABL1*. | **Myeloproliferative Neoplasms (MPNs) Panels**<br>XX. Myeloproliferative neoplasm (MPN) molecular profiling panels (81206, 81207, 81208, 81219, 81270, 81279, 81338, 81339) may be considered **medically necessary** when **both** of the following criteria are met:<br>A. The member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), **AND**<br>B. The panel includes, at a minimum, testing of the following genes: *JAK2*, *CALR*, and *MPL*. |
| XXI. Myeloproliferative neoplasm (MPN) molecular profiling panels (81206, 81207, 81208, 81219, 81270, 81279, 81338, 81339) are considered **investigational** for all other indications. | XXI. Myeloproliferative neoplasm (MPN) molecular profiling panels (81206, 81207, 81208, 81219, 81270, 81279, 81338, 81339) are considered **investigational** for all other indications. |
| **Single-Gene Testing Of Solid Tumors And Hematologic Malignancies**<br>**Tumor Specific *BCR/ABL1* Kinase Domain Analysis**<br>XXII. Tumor specific *BCR/ABL1* kinase domain analysis (81170) in hematologic malignancies may be considered **medically necessary** when **both** of the following criteria are met:<br>A. The member has a diagnosis of chronic myeloid leukemia (CML) or Philadelphia Ph-like acute lymphocytic leukemia (ALL)<br>B. The member has **any** of the following:<br>1. Inadequate initial response to TKI therapy<br>2. Loss of response to TKI therapy<br>3. Disease progression to the accelerated or blast phase<br>4. Relapsed/refractory disease. | **Single-Gene Testing Of Solid Tumors And Hematologic Malignancies**<br>**Tumor Specific *BCR/ABL1* Kinase Domain Analysis**<br>XXII. Tumor specific *BCR/ABL1* kinase domain analysis (81170) in hematologic malignancies may be considered **medically necessary** when **both** of the following criteria are met:<br>A. The member has a diagnosis of **any** of the following:<br>1. Chronic myeloid leukemia (CML), **OR**<br>2. Ph-positive acute lymphocytic leukemia (ALL), **AND**<br>B. The member has **any** of the following:<br>1. Inadequate initial response to TKI therapy, **OR**<br>2. Loss of response to TKI therapy, **OR**<br>3. Disease progression to the accelerated or blast phase, **OR**<br>4. Relapsed/refractory disease. |
| **Tumor Specific *BCR/ABL1* FISH, Qualitative, or Quantitative Tests** | **Tumor Specific *BCR/ABL1* FISH, Qualitative, or Quantitative Tests** |

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| XXIII. Tumor specific *BCR/ABL1* FISH, qualitative, or quantitative tests (0016U, 0040U, 81206, 81207, 81208, 88271, 88274, 88275, 88291, 81479) in hematologic malignancies may be considered **medically necessary** when **any** of the following are met:<br>A. The member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia)<br>B. The member is undergoing diagnostic workup for **any** of the following:<br>1. Acute lymphoblastic leukemia (ALL)<br>2. Acute myeloid leukemia (AML)<br>3. Chronic myeloid leukemia (CML)<br>4. B-cell lymphoma<br>C. The member is undergoing monitoring of disease progression or for minimal residual disease (MRD) monitoring using a quantitative test only for **any** of the following:<br>1. Acute lymphoblastic leukemia (ALL)<br>2. Acute myeloid leukemia (AML)<br>3. Chronic myelogenous leukemia (CML)<br>4. B-cell lymphoma. | XXIII. Tumor specific *BCR/ABL1* FISH, qualitative, or quantitative tests (0016U, 0040U, 81206, 81207, 81208, 81479, 88271, 88274, 88275, 88291) in hematologic malignancies may be considered **medically necessary** when **any** of the following are met:<br>A. The member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), **OR**<br>B. The member is undergoing diagnostic workup for **any** of the following:<br>1. Acute lymphoblastic leukemia (ALL), **OR**<br>2. Acute myeloid leukemia (AML), **OR**<br>3. Chronic myeloid leukemia (CML), **OR**<br>4. B-cell lymphoma, **OR**<br>C. The member is undergoing monitoring of disease progression or for minimal residual disease (MRD) monitoring using a quantitative test only for **any** of the following:<br>1. Acute lymphoblastic leukemia (ALL), **OR**<br>2. Acute myeloid leukemia (AML), **OR**<br>3. Chronic myelogenous leukemia (CML), **OR**<br>4. B-cell lymphoma. |
| **Tumor Specific *BRAF* Variant Analysis**<br>XXIV. Tumor specific *BRAF* variant analysis (81210) in solid tumors and hematologic malignancies may be considered **medically necessary** when:<br>A. The member has a diagnosis of **any** of the following:<br>1. Suspected or proven metastatic colorectal cancer,<br>2. Advanced or metastatic non-small-cell lung cancer (NSCLC)<br>3. Stage III or stage IV cutaneous melanoma<br>4. Indeterminate thyroid nodules requiring biopsy<br>5. Anaplastic thyroid carcinoma or<br>locally recurrent, advanced and/or metastatic papillary, | **Tumor Specific *BRAF* Variant Analysis**<br>XXIV. Tumor specific *BRAF* variant analysis (81210) in solid tumors and hematologic malignancies may be considered **medically necessary** when:<br>A. The member has a diagnosis of **any** of the following:<br>1. Suspected or proven metastatic colorectal cancer, **OR**<br>2. Advanced or metastatic non-small-cell lung cancer (NSCLC), **OR**<br>3. Stage III or stage IV cutaneous melanoma, **OR**<br>4. Indeterminate thyroid nodules requiring biopsy, **OR**<br>5. Anaplastic thyroid carcinoma, **OR**<br>6. Locally recurrent, advanced and/or metastatic papillary thyroid cancer, **OR** |

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| follicular<br><br>or Hurthle cell thyroid carcinoma<br>6. Low-grade glioma or pilocytic astrocytoma<br>7. Resectable or borderline resectable or locally advanced/metastatic pancreatic adenocarcinoma<br><br>8. Metastatic small bowel adenocarcinoma | 7. Locally recurrent, advanced and/or metastatic follicular thyroid cancer, **OR**<br>8. Locally recurrent, advanced and/or metastatic Hurthle cell thyroid carcinoma, **OR**<br>9. Low-grade glioma or pilocytic astrocytoma, **OR**<br>10. Resectable or borderline resectable or locally advanced/metastatic pancreatic adenocarcinoma, **OR**<br>11. Metastatic small bowel adenocarcinoma, **OR**<br>12. Locally advanced, recurrent or metastatic esophageal or esophagogastric junction cancer, **OR**<br>13. Locally advanced, recurrent or metastatic gastric cancer, **OR** |
| B. The member is being evaluated for **any** of the following:<br>1. Hairy cell leukemia (for individuals without cHCL [classical hairy cell leukemia] immunophenotype)<br>2. Histiocytosis (Langerhans cell histiocytosis or Erdheim-Chester disease). | B. The member is being evaluated for **any** of the following:<br>1. Hairy cell leukemia (for individuals without cHCL [classical hairy cell leukemia] immunophenotype), **OR**<br>2. Histiocytosis (Langerhans cell histiocytosis or Erdheim-Chester disease). |
| **Tumor Specific *BRCA1/2* Variant Analysis**<br>XXV. Tumor specific *BRCA1/2* variant analysis (81162, 81163, 81164, 81165, 81166, 81167, 81216) in solid tumors may be considered **medically necessary** when:<br>A. The member has a diagnosis of **any** of the following:<br>1. Ovarian, fallopian tube and/or primary peritoneal cancer<br>2. Metastatic prostate cancer<br>3. Resectable, borderline resectable, or locally advanced/metastatic pancreatic cancer. | **Tumor Specific *BRCA1/2* Variant Analysis**<br>XXV. Tumor specific *BRCA1/2* variant analysis (81162, 81163, 81164, 81165, 81166, 81167, 81216) in solid tumors may be considered **medically necessary** when:<br>A. The member has a diagnosis of **any** of the following:<br>1. Ovarian, fallopian tube and/or primary peritoneal cancer, **OR**<br>2. Metastatic prostate cancer, **OR**<br>3. Resectable, borderline resectable, or locally advanced/metastatic pancreatic cancer. |
| **Tumor Specific *CALR* Variant Analysis**<br>XXVI. Tumor specific *CALR* variant analysis (81219) may be considered **medically necessary** when:<br>A. The member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia). | **Tumor Specific *CALR* Variant Analysis**<br>XXVI. Tumor specific *CALR* variant analysis (81219) may be considered **medically necessary** when:<br>A. The member is suspected to have a myeloproliferative neoplasm (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), **OR** |

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| | B. The member is suspected to have a myelodysplastic syndrome (MDS). |
| **Tumor Specific *CEBPA* Variant Analysis**<br>XXVII. Tumor specific *CEBPA* variant analysis (81218) in hematologic malignancies may be considered **medically necessary** when:<br>A. The member has cytogenetically normal acute myeloid leukemia (AML). | **Tumor Specific *CEBPA* Variant Analysis**<br>XXVII. Tumor specific *CEBPA* variant analysis (81218) in hematologic malignancies may be considered **medically necessary** when:<br>A. The member is undergoing evaluation for acute myeloid leukemia (AML). |
| **Tumor Specific *EGFR* Variant Analysis**<br>XVIII. Tumor specific *EGFR* variant analysis (81235) in solid tumors may be considered **medically necessary** when:<br>A. The member has a diagnosis of **any** of the following:<br>1. Stage IB or higher lung adenocarcinoma<br>2. Stage IB or higher large cell lung carcinoma<br>3. Stage IB or higher squamous cell lung carcinoma<br>4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS). | **Tumor Specific *EGFR* Variant Analysis**<br>XXVIII. Tumor specific *EGFR* variant analysis (81235) in solid tumors may be considered **medically necessary** when **any** of the following:<br>A. The member has a diagnosis of:<br>1. Stage IB or higher lung adenocarcinoma, **OR**<br>2. Stage IB or higher large cell lung carcinoma, **OR**<br>3. Stage IB or higher squamous cell lung carcinoma, **OR**<br>4. Stage IB or higher non-small cell lung cancer (NSCLC) not otherwise specified (NOS). |
| **Tumor Specific *ESR1* Variant Analysis**<br>XXIX. Tumor specific *ESR1* variant analysis (81479) in solid tumors may be considered **medically necessary** when **all** of the following are met:<br>A. The member is a postmenopausal female or adult male<br>B. The member has a diagnosis of ER-positive and HER2-negative breast cancer<br>C. The member has disease progression after one or two prior lines of endocrine therapy, including one line containing a CDK4/6 inhibitor. | **Tumor Specific *ESR1* Variant Analysis**<br>XXIX. Tumor specific *ESR1* variant analysis (81479) in solid tumors is considered **medically necessary** when:<br>A. The member is **one** of the following:<br>1. Pre- menopausal female receiving ovarian ablation or suppression, **OR**<br>2. Postmenopausal female, **OR**<br>3. Adult male, **AND**<br>B. The member has a diagnosis of ER-positive and *HER2*-negative breast cancer, **AND**<br>C. The member has disease progression after one or two prior lines of endocrine therapy, including one line containing a *CDK4/6* inhibitor. |
| **Tumor Specific *FLT3* Variant Analysis** | **Tumor Specific *FLT3* Variant Analysis** |

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| XXX. Tumor specific *FLT3* variant analysis (81245, 81246, 0023U, 0046U) in hematologic malignancies may be considered **medically necessary** when:<br>A. The member has suspected or confirmed acute myeloid leukemia (AML), **OR**<br>B. The member has a diagnosis of **any** of the following:<br>1. Acute lymphocytic leukemia (ALL)<br>2. Myelodysplastic syndrome (MDS),<br>3. Myeloproliferative neoplasm. | XXX. Tumor specific *FLT3* variant analysis (0023U, 0046U, 81245, 81246) in hematologic malignancies may be considered **medically necessary** when:<br>A. The member has suspected or confirmed acute myeloid leukemia (AML), **OR**<br>B. The member has a diagnosis of<br>1. Acute lymphocytic leukemia (ALL), **OR**<br>2. Myelodysplastic syndrome (MDS), **OR**<br>3. Myeloproliferative neoplasm. |
| **Tumor Specific *IDH1* and *IDH2* Variant Analysis**<br>XXXI. Tumor specific *IDH1* and *IDH2* variant analysis (81120, 81121) in solid tumors or hematologic malignancies may be considered **medically necessary** when:<br>A. The member has a diagnosis of:<br>1. Glioma, **OR**<br>2. Acute myeloid leukemia (AML). | **Tumor Specific *IDH1* and *IDH2* Variant Analysis**<br>XXXI. Tumor specific *IDH1* and *IDH2* variant analysis (81120, 81121) in solid tumors or hematologic malignancies may be considered **medically necessary** when:<br>A. The member has a diagnosis of:<br>1. Glioma, **OR**<br>2. Acute myeloid leukemia (AML). |
| **Tumor Specific *IGHV* Somatic Hypermutation Analysis**<br>XXXII. Tumor specific *IGHV* somatic hypermutation analysis (81261, 81262, 81263) in hematologic malignancies may be considered **medically necessary** when:<br>A. The member has a diagnosis of **any** of the following:<br>1. Chronic lymphocytic leukemia (CLL)<br>2. Small lymphocytic leukemia (SLL)<br>3. Primary cutaneous B-cell lymphoma<br>4. Mantle cell lymphoma<br>5. Post-transplant lymphoproliferative disorder. | **Tumor Specific *IGHV* Somatic Hypermutation Analysis**<br>XXXII. Tumor specific *IGHV* somatic hypermutation analysis (81261, 81262, 81263) in hematologic malignancies may be considered **medically necessary** when:<br>A. The member is undergoing work up for or has a diagnosis of **any** of the following:<br>1. Chronic lymphocytic leukemia (CLL), **OR**<br>2. Small lymphocytic leukemia (SLL), **OR**<br>3. Primary cutaneous B-cell lymphoma, **OR**<br>4. B-cell lymphoma. |
| **Tumor Specific *JAK2* Variant Analysis**<br>XXIII. Tumor specific *JAK2* variant analysis (81270, 0017U, 0027U) in solid tumors or hematologic malignancies may be considered **medically necessary** when **any** of the following are met:<br>A. The member is suspected to have a myeloproliferative neoplasm (MPN) (example: polycythemia vera, essential | **Tumor Specific *JAK2* Variant Analysis**<br>XXXIII. Tumor specific *JAK2* variant analysis (0017U, 0027U, 81270) in solid tumors or hematologic malignancies may be considered **medically necessary** when **any** of the following are met:<br>A. The member is suspected to have a myeloproliferative neoplasm (MPN) (example: polycythemia vera, essential |

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| thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia)<br>B. The member has acute lymphoblastic leukemia (ALL)<br>C. The member is suspected to have a myelodysplastic syndrome (MDS). | thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), **OR**<br>B. The member has acute lymphoblastic leukemia (ALL), **OR**<br>C. The member is suspected to have a myelodysplastic syndrome (MDS). |
| **Tumor Specific *KIT* Variant Analysis**<br>XXIV. Tumor specific *KIT* variant analysis (81272, 81273) in solid tumors or hematologic malignancies may be considered **medically necessary** when **any** of the following are met:<br>A. The member is suspected to have, or is being evaluated for systemic mastocytosis<br>B. The member has a diagnosis of acute myeloid leukemia (AML)<br>C. The member has stage IV cutaneous melanoma, **OR**<br>D. The member has a suspected or confirmed gastrointestinal stromal tumor (GIST). | **Tumor Specific *KIT* Variant Analysis**<br>XXIV. Tumor specific *KIT* variant analysis (81272, 81273) in solid tumors or hematologic malignancies may be considered **medically necessary** when **any** of the following are met:<br>A. The member is being evaluated for systemic mastocytosis, **OR**<br>B. The member has a diagnosis of acute myeloid leukemia (AML), **OR**<br>C. The member has stage IV cutaneous melanoma, **OR**<br>D. The member has a suspected or confirmed gastrointestinal stromal tumor (GIST). |
| **Tumor Specific *KRAS* Variant Analysis**<br>XXV. Tumor specific *KRAS* variant analysis (81275, 81276) in solid tumors may be considered **medically necessary** when **any** of the following criteria are met:<br>A. The member has suspected or proven metastatic colorectal cancer<br>B. The member is undergoing workup for metastasis of non-small cell lung cancer<br>C. The member has resectable, borderline resectable, or locally advanced/metastatic pancreatic adenocarcinoma. | **Tumor Specific *KRAS* Variant Analysis**<br>XXV. Tumor specific *KRAS* variant analysis (81275, 81276) in solid tumors may be considered **medically necessary** when **any** of the following criteria are met:<br>A. The member has suspected or proven metastatic colorectal cancer, **OR**<br>B. The member is undergoing workup for metastasis of non-small cell lung cancer, **OR**<br>C. The member has resectable, borderline resectable, or locally advanced/metastatic pancreatic adenocarcinoma, **OR**<br>D. The member has unresectable or metastatic gallbladder cancer, **OR**<br>E. The member has unresectable or metastatic intrahepatic or extrahepatic cholangiocarcinoma. |
| **Tumor Specific *MGMT* Methylation Analysis**<br>XXVI. Tumor specific *MGMT* promoter methylation analysis (81287) in solid tumors may be considered **medically necessary** when: | **Tumor Specific *MGMT* Methylation Analysis**<br>XXVI. Tumor specific *MGMT* promoter methylation analysis (81287) in solid tumors may be considered **medically necessary** when: |

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| A. The member has a diagnosis of **any** of the following:<br>1. High grade (stage III or IV) anaplastic oligodendroglioma<br>2. High grade (stage III or IV) anaplastic astrocytoma<br>3. High grade (stage III or IV) anaplastic glioma<br>4. High grade (stage III or IV) glioblastoma. | A. The member has a diagnosis of **any** of the following:<br>1. High grade (stage III or IV) anaplastic oligodendroglioma, **OR**<br>2. High grade (stage III or IV) anaplastic astrocytoma, **OR**<br>3. High grade (stage III or IV) anaplastic glioma, **OR**<br>4. High grade (stage III or IV) glioblastoma. |
| **Tumor Specific *MLH1* Methylation Analysis**<br>XXVII. Tumor specific *MLH1* promoter methylation analysis (81288) in solid tumors may be considered **medically necessary** when:<br>A. The member has a diagnosis of colorectal cancer or endometrial (uterine) cancer, **AND**<br>B. Previous tumor testing showed loss of *MLH1* on immunohistochemistry analysis. | **Tumor Specific *MLH1* Methylation Analysis**<br>XXVII. Tumor specific *MLH1* promoter methylation analysis (81288) in solid tumors may be considered **medically necessary** when:<br>A. The member has a diagnosis of **any** of the following:<br>1. Colorectal cancer, **OR**<br>2. Endometrial (uterine) cancer, **AND**<br>B. Previous tumor testing showed loss of *MLH1* on immunohistochemistry analysis. |
| **Tumor Specific *MPL* Variant Analysis**<br>XVIII. Tumor specific *MPL* variant analysis (81338, 81339) in hematologic malignancies may be considered **medically necessary** when:<br>A. The member is suspected to have a myeloproliferative neoplasm (MPN) (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia). | **Tumor Specific *MPL* Variant Analysis**<br>XXVIII. Tumor specific *MPL* variant analysis (81338, 81339) in hematologic malignancies may be considered **medically necessary** when:<br>A. The member is suspected to have a myeloproliferative neoplasm (MPN) (i.e., polycythemia vera, essential thrombocythemia, primary myelofibrosis, and chronic myeloid leukemia), **OR**<br>B. The member is suspected to have a myelodysplastic syndrome (MDS). |
| **Tumor Specific Microsatellite Instability (MSI) Analysis**<br>XXIX. Tumor specific microsatellite instability (MSI) analysis (81301) in solid tumors may be considered **medically necessary** when:<br>A. The member has a diagnosis of **any** of the following:<br>1. Colorectal cancer<br>2. Endometrial cancer<br>3. Gastric cancer<br>4. Esophageal and esophagogastric junction cancer<br>5. Recurrent, progressive or metastatic cervical carcinoma | **Tumor Specific Microsatellite Instability (MSI) Analysis**<br>XXXIX. Tumor specific microsatellite instability (MSI) analysis (81301) in solid tumors may be considered **medically necessary** when:<br>A. The member has a diagnosis of **any** of the following:<br>1. Colorectal cancer, **OR**<br>2. Endometrial cancer, **OR**<br>3. Gastric cancer, **OR**<br>4. Esophageal and esophagogastric junction cancer, **OR**<br>5. Recurrent, progressive or metastatic cervical carcinoma, **OR** |

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| 6. Testicular cancer (nonseminoma) with progression after high dose chemotherapy or third-line therapy<br>7. Unresectable or metastatic gallbladder cancer<br>8. Unresectable or metastatic intrahepatic or extrahepatic cholangiocarcinoma<br>9. Unresectable or metastatic breast cancer<br>10. Small bowel adenocarcinom<br>11. Resectable, borderline resectable, or metastatic pancreatic cancer<br>12. Metastatic occult primary<br>13. Recurrent, progressive or metastatic squamous cell carcinoma of the vulva. | 6. Testicular cancer with progression after high dose chemotherapy or third-line therapy, **OR**<br>7. Unresectable or metastatic gallbladder cancer, **OR**<br>8. Unresectable or metastatic intrahepatic or extrahepatic cholangiocarcinoma, **OR**<br>9. Unresectable or metastatic breast cancer, **OR**<br>10. Small bowel adenocarcinoma, **OR**<br>11. Resectable, borderline resectable, or metastatic pancreatic cancer, **OR**<br>12. Metastatic occult primary, **OR**<br>13. Recurrent, progressive or metastatic squamous cell carcinoma of the vulva**, OR**<br>14. Metastatic chondrosarcoma, **OR**<br>15. Metastatic chordoma, **OR**<br>16. Widely metastatic Ewing sarcoma, **OR**<br>17. Metastatic osteosarcoma, **OR**<br>18. Recurrent or metastatic vaginal cancer, **OR**<br>19. Recurrent ovarian cancer |
| **Tumor Specific *NPM1* Variant Analysis**<br>XL. Tumor specific *NPM1* variant analysis (81310, 0049U) in hematological malignancies may be considered **medically necessary** when:<br>A. The member has cytogenetically normal acute myeloid leukemia (AML). | **Tumor Specific *NPM1* Variant Analysis**<br>XL. Tumor specific *NPM1* variant analysis (0049U, 81310) in hematological malignancies may be considered **medically necessary** when:<br>A. The member has cytogenetically normal acute myeloid leukemia (AML). |
| **Tumor Specific *NRAS* Variant Analysis**<br>XLI. Tumor specific *NRAS* variant analysis (81311) in solid tumors may be considered **medically necessary** when:<br>A. The member has suspected or proven metastatic colorectal cancer. | **Tumor Specific *NRAS* Variant Analysis**<br>XLI. Tumor specific *NRAS* variant analysis (81311) in solid tumors may be considered **medically necessary** when:<br>A. The member has suspected or proven metastatic colorectal cancer. |
| **Tumor Specific *PIK3CA* Variant Analysis**<br>XLII. Tumor specific *PIK3CA* variant analysis (81309, 0155U) in solid tumors may be considered **medically necessary** when **either** of the following are met: | **Tumor Specific *PIK3CA* Variant Analysis**<br>XLII. Tumor specific *PIK3CA* variant analysis (0155U, 81309) in solid tumors may be considered **medically necessary** when: |

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| A. The member has a diagnosis of recurrent or stage IV, HR positive, HER2 negative invasive breast cancer<br>B. The member has a diagnosis of uterine rhabdomyosarcoma. | A. The member has a diagnosis of recurrent or stage IV, HR positive, HER2 negative invasive breast cancer. |
| **Tumor Specific *TP53* Variant Analysis**<br>XLIII. Tumor specific *TP53* variant analysis (81352) in bone marrow or peripheral blood may be considered **medically necessary** when **either** of the following are met:<br>A. The member has a diagnosis of **any** of the following:<br>1. Acute myeloid leukemia (AML)<br>2. Chronic lymphocytic leukemia (CLL)<br>3. Small lymphocytic leukemia (SLL)<br>B. The member is undergoing diagnostic workup for mantle cell lymphoma (MCL). | **Tumor Specific *TP53* Variant Analysis**<br>XLIII. Tumor specific *TP53* variant analysis (81352) in bone marrow or peripheral blood may be considered **medically necessary** when **either** of the following are met:<br>A. The member has a diagnosis of **any** of the following:<br>1. Acute myeloid leukemia (AML), **OR**<br>2. Chronic lymphocytic leukemia (CLL), **OR**<br>3. Small lymphocytic leukemia (SLL), **OR**<br>B. The member is undergoing diagnostic workup for mantle cell lymphoma (MCL). |
| | **HLA Typing For Transplantation**<br>XLIV. HLA typing for transplantation (81370, 81371, 81372, 81373, 81376, 81378, 81379, 81380, 81382) may be considered **medically necessary** when the member meets the following:<br>A. The member is being considered for **any** of the following:<br>1. Recipient of bone marrow transplantation, **OR**<br>2. Donor for bone marrow transplantation, **OR**<br>3. Recipient of solid organ transplantation, **OR**<br>4. Donor for solid organ transplantation.<br><br>XLV. HLA typing for transplantation (81370, 81371, 81372, 81373, 81376, 81378, 81379, 81380, 81382) is considered **investigational** for all other indications. |
| **Measurable (Minimal) Residual Disease (MRD) Analysis**<br>**Hematologic Minimal Residual Disease (MRD) Testing**<br>XLIV. Measurable (minimal) residual disease (MRD) analysis (0171U, 0364U) in bone marrow or peripheral blood may be considered **medically necessary** when:<br>A. The member has a diagnosis of **any** of the following:<br>1. Acute Lymphocytic Leukemia (ALL) | **Measurable (Minimal) Residual Disease (MRD) Analysis**<br>**Hematologic Minimal Residual Disease (MRD) Testing**<br>XLVI. Measurable (minimal) residual disease (MRD) analysis (0171U, 0364U) in bone marrow or peripheral blood may be considered **medically necessary** when:<br>A. The member has a diagnosis of **any** of the following:<br>1. Acute Lymphocytic Leukemia (ALL), **OR** |

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| 2. Multiple Myeloma<br>3. Chronic Lymphocytic Leukemia (CLL) | 2. Multiple Myeloma, **OR**<br>3. Chronic Lymphocytic Leukemia (CLL). |
| **Evidence-Based Solid Tumor Minimal Residual Disease (MRD) Testing** | **Evidence-Based Solid Tumor Minimal Residual Disease (MRD) Testing** |
| XLV. Measurable (minimal) residual disease (MRD) analysis (0340U, 0422U, 81479) with sufficient evidence of clinical utility and validity using solid tumor tissue may be considered **medically necessary** when **all** of the following are met:<br>A. The member has a personal history of metastatic colorectal or breast cancer, or muscle invasive bladder cancer<br>B. The identification of recurrence or progression of disease will require a change in management<br>C. The member is not undergoing concurrent surveillance or monitoring for recurrence or progression by any other method,<br>D. The member meets **one** of the following:<br>1. The member is currently being treated for cancer, **AND**<br>a. The test has not previously been done for this episode of cancer<br>2. The member is not currently being treated for their cancer, **AND**<br>a. The test has not been done in the past 12 months, **OR**<br>3. The member is being monitored for response to immune checkpoint inhibitor therapy, **AND**<br>a. The test has not previously been ordered for this episode of cancer, **AND**<br>b. The member has **either** of the following:<br>i. Colorectal cancer, for which Guardant360 Response is being performed, **OR**<br>ii. Any solid tumor, for which Signatera is being performed. | XLVII. Minimal residual disease (MRD) analysis for solid tumors using cell free DNA (0340U, 0422U, 81479) with sufficient evidence of clinical utility and validity may be considered **medically necessary** when:<br>A. The identification of recurrent, refractory, or progressive disease will require a change in management, **AND**<br>B. The member is not undergoing concurrent molecular laboratory testing for surveillance or monitoring for recurrent, refractory, or progressive disease, **AND**<br>C. The member meets **one** of the following:<br>1. The member is currently being treated for cancer, **AND**<br>a. The test has not previously been done for this cancer diagnosis, **OR**<br>b. There is a clinical suspicion that the molecular profile of the member's tumor has changed, **OR**<br>2. The member is not currently being treated for their cancer, **AND**<br>a. The test has not been done in the past 12 months, **OR**<br>b. There is a clinical suspicion for tumor recurrence, **AND**<br>D. The member meets **one** of the following:<br>1. The member is being tested via Guardant360 Response or Guardant Reveal and has one of the following:<br>a. Metastatic colon cancer, **OR**<br>b. Colon cancer at any stage, **AND**<br>i. The member is being monitored for response to immune checkpoint inhibitor therapy, **OR**<br>2. The member is being tested via Signatera and has one of the following:<br>a. Metastatic colon cancer, **OR**<br>b. Muscle invasive bladder cancer, **OR** |

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| | c. Metastatic breast cancer, **OR**<br>d. Any solid tumor, **AND**<br>i. The member is being monitored for response to immune checkpoint inhibitor therapy. |
| XLVI. Measurable (minimal) residual disease (MRD) analysis (0340U, 0422U, 81479) with sufficient evidence of clinical utility and validity using solid tumor tissue is considered **investigational** for all other indications where clinical utility and validity have not been demonstrated. | XLVIII. Minimal residual disease (MRD) analysis (0340U, 0422U, 81479) with sufficient evidence of clinical utility and validity using solid tumor tissue is considered **investigational** for all other indications where clinical utility and validity have not been demonstrated. |
| | **Emerging Evidence Solid Tumor Minimal Residual Disease (MRD) Testing**<br>XLIX. Minimal residual disease (MRD) analysis (0229U, 0306U, 0307U) with insufficient evidence of clinical validity using solid tumor tissue is considered **investigational**. |
| **HPV-Related Solid Tumor Measurable (Minimal) Residual Disease (MRD) Testing**<br>XLVII. Measurable (minimal) residual disease analysis (0356U) using tumor tissue from HPV-related head and neck cancers may be **medically necessary** when **all** of the following are met:<br>A. The member has a personal history of HPV-driven oropharyngeal cancer<br>B. The identification of recurrence or progression of disease will require a change in management<br>C. The member is not undergoing concurrent surveillance or monitoring for recurrence or progression by any other method,<br>D. The member meets **one** of the following:<br>1. The member is currently being treated for HPV-driven oropharyngeal cancer, **AND**<br>a. The test has not previously been done for this episode of cancer, **OR**<br>2. The member is not currently being treated for HPV-driven oropharyngeal cancer, **AND**<br>a. The test has not been done in the past 12 months. | **HPV-Related Solid Tumor Minimal Residual Disease (MRD) Testing**<br>L. Minimal residual disease analysis for HPV-related head and neck cancers using cell-free DNA (0356U) may be **medically necessary** when **all** of the following are met:<br>A. The member has a personal history of HPV-driven oropharyngeal cancer, **AND**<br>B. The identification of recurrence or progression of disease will require a change in management, **AND**<br>C. The member is not undergoing concurrent surveillance or monitoring for recurrence or progression by any other method, **AND**<br>D. The member meets **one** of the following:<br>1. The member is currently being treated for HPV-driven oropharyngeal cancer, **AND**<br>b. The test has not previously been done for this episode of cancer, **OR**<br>2. The member is not currently being treated for HPV-driven oropharyngeal cancer, **AND**<br>a. The test has not been done in the past 12 months. |

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| LVIII. Measurable (minimal) residual disease analysis (0356U) using tumor tissue from HPV-related head and neck cancers is considered **investigational** for all other indications.<br><br>**Tumor Mutational Burden (TMB)**<br>XLIX. Tumor mutational burden (TMB) testing (81479) may be considered **medically necessary** when:<br>A. The member has a diagnosis of **any** of the following:<br>1. Recurrent or metastatic breast cancer<br>2. Unresectable or metastatic gallbladder cancer<br>3. Unresectable or metastatic extrahepatic or intrahepatic cholangiocarcinoma<br>4. Suspected metastatic malignant occult primary tumor<br>5. Recurrent ovarian/fallopian tube/primary peritoneal cancer<br>6. Resectable or borderline resectable or metastatic or advanced pancreatic adenocarcinoma<br>7. Metastatic castration-resistant prostate cancer<br>8. Progression of testicular cancer (nonseminoma) after high dose chemotherapy or third line therapy<br>9. Endometrial carcinoma or uterine sarcoma<br>10. Locally advanced/metastatic ampullary adenocarcinoma<br>11. Metastatic chondrosarcoma<br>12. Metastatic chordoma<br>13. Widely metastatic Ewing sarcoma<br>14. Metastatic osteosarcoma<br>15. Metastatic esophageal or esophagogastric junction cancer<br>16. Gastric cancer<br>17. Metastatic salivary gland tumor<br>18. Adrenocortical carcinoma<br>19. Extrapulmonary poorly differentiated neuroendocrine carcinoma<br>20. Neuroendocrine large or small cell carcinoma<br>21. Mixed neuroendocrine-non-neuroendocrine neoplasm | LI. Minimal residual disease analysis (0356U) using tumor tissue from HPV-related head and neck cancers is considered **investigational** for all other indications.<br><br>**Tumor Mutational Burden (TMB)**<br>LII. Tumor mutational burden (TMB) testing (81479) may be considered **medically necessary** when:<br>A. The member has a diagnosis of:<br>1. Recurrent, relapsed, refractory, metastatic, or advanced stages III or IV cancer, **AND**<br>2. The member has had progression of the cancer following prior treatment, **AND**<br>3. The member has no remaining satisfactory treatment options, **AND**<br>4. The member does not have central nervous system cancer. |

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| 22. Structurally persistent/recurrent locoregional or distant metastatic papillary thyroid carcinoma<br>23. Structurally persistent/recurrent locoregional or distant metastatic follicular thyroid carcinoma<br>24. Structurally persistent/recurrent locoregional or distant metastatic oncocytic thyroid carcinoma<br>25. Stage IV anaplastic carcinoma<br>26. Vulvar squamous cell carcinoma<br>27. Metastatic small bowel adenocarcinoma. | |
| **Red Blood Cell Genotyping In Multiple Myeloma**<br>L. Red blood cell genotyping (0001U, 0180U, 0221U) in individuals with multiple myeloma may be considered **medically necessary** when **both** of the following are met:<br>A. The member has a diagnosis of multiple myeloma<br>B. The member is currently being treated or will be treated with Daratumumab (DARA). | **Red Blood Cell Genotyping In Multiple Myeloma**<br>LIII. Red blood cell genotyping (0001U, 0180U, 0221U) in individuals with multiple myeloma may be considered **medically necessary** when:<br>A. The member has a diagnosis of multiple myeloma, **AND**<br>B. The member is currently being treated or will be treated with **either** of the following:<br>1. Daratumumab (Darazalex), **OR**<br>2. Isatuximab (Sarclisa). |
| **Cancer Exome And Genome Sequencing**<br>LI. Cancer exome and genome sequencing in solid tumors and hematologic malignancies (0036U, 0297U, 81415, 81416, 81425, 81426) is considered **investigational**. | **Cancer Exome And Genome Sequencing**<br>LIV. Cancer exome and genome sequencing in solid tumors and hematologic malignancies (0036U, 0297U, 81415, 81416, 81425, 81426) is considered **investigational**. |
| **Genetic Testing To Confirm The Identity Of Laboratory Specimens**<br>LII. Genetic testing to confirm the identity of laboratory specimens (e.g., ToxProtect®, know error®) (0007U, 81265, 81266, 81479), when billed separately, is considered **investigational** because it is generally considered to be an existing component of the genetic testing process for quality assurance. | **Genetic Testing To Confirm The Identity Of Laboratory Specimens**<br>LV. Genetic testing to confirm the identity of laboratory specimens (e.g., know error) (81265, 81266, 81479), when billed separately, is considered **investigational** because it is generally considered to be an existing component of the genetic testing process for quality assurance. |