Concert Genetics Oncology: Hematologic Malignancies

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Coding implications
Revision Log

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

OVERVIEW

This policy addresses the use of diagnostic testing related to malignancies of the hematologic system.

While the primary goal of this testing is to identify biomarkers that diagnose cancer, or 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.

For additional information see the Rationale section.

POLICY REFERENCE TABLE

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2024, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only and may not support medical necessity. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

The tests, CPT codes, and ICD codes referenced in this policy are not comprehensive, and their inclusion does not represent a guarantee of coverage or non-coverage. Please see the Concert Platform for additional registered tests.

> **NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis. The non-covered codes will only be denoted in the table below and not throughout the policy. Please only reference the policy reference table for covered and non-covered codes.**

CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Molecular Profiling Panels for Hematologic Malignancies			
Broad RNA Fusion Panels for Hematologic Malignancy	Tempus xR Whole Transcriptome RNA Sequencing (Hematologic Malignancy) (Tempus AI, Inc)	81456*, C00-C80	1, 2
Broad Molecular Profiling Panels For Hematologic Malignancies and Myeloid Malignancy Panels	FoundationOne Heme (Foundation Medicine)	81450*, 81455*, C91, C92, D46.9	2, 3, 4, 5, 6
	Tempus xT Hematologic Malignancy (Tempus)		
	Neo Comprehensive - Myeloid Disorders (NeoGenomics Laboratories)		
	MayoComplete Myeloid Neoplasms, Comprehensive OncoHeme Next-Generation Sequencing, Varies (Mayo Clinic Laboratories)		
	Onkosight Advanced NGS Myeloid Panel (BioReference Laboratories)		
Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels	MyAML NGS Gene Panel Assay 0050U* - (Laboratory for Personalized Molecular Medicine)	0050U*, 81450*, C92, D47	4
	NeoTYPE AML Prognostic Profile (NeoGenomics)		
	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, D47	5

CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
	OnkoSight Advanced NGS JAK2, MPL, CALR Panel (BioReference Laboratories)		
Measurable (Minimal) Residual Disease (MRD) Analysis for Hematologic Malignancies			
Hematologic Minimal Residual Disease (MRD) Testing	MyMRD NGS Gene Panel Assay - 0171U* (Laboratory for Personalized Molecular Medicine)	0171U*, 0364U*, 0450U*, 0451U*, C91, R71, R79	2, 8, 9
	ClonoSEQ Tracking (MRD) Assay - 0364U* (Adaptive Biotechnologies)		
	M-inSight® Patient Definition Assay - 0450U (Corgenix Clinical Laboratory)		
	M-inSight® Patient Follow-Up Assessment - 0451U* (Corgenix Clinical Laboratory)		
Single Gene Testing for Hematologic Malignancies			
Tumor Specific *BCR-ABL1* Kinase Domain Analysis	ABL1 Kinase Domain Mutation Analysis (NeoGenomics)	81170, C91, C92	2, 6
	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, 0016U*, 0040U*, 81479, 88271, 88274, 88275, 88291, C83, C85,	1, 2, 4, 5, 6
	BCR-ABL1 Transcript Detection for Chronic Myelogenous Leukemia		

CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
	(CML) and Acute Lymphocytic Leukemia (ALL), Quantitative (Labcorp)	C91.00 - C91.02, C92.0 - C92.12, D45, D47, D47.1, D47.3, D69.3	
	BCR/ABL1 (t9;22)) RNA Quantitative with Interpretation - 0016U (University of Iowa Hospitals and Clinics - Department of Pathology)		
	MRDx BCR-ABL Test - 0040U (MolecularMD)		
	Detection by FISH of t(9;22) BCR/ABL (CGC Genetics)		
	BCR/ABL t(9;22) (NeoGenomics Laboratories)		
	BCR ABL Qualitative (Cincinnati Children's Hospital)		
Tumor Specific *CALR* Variant Analysis	Calreticulin (CALR) Mutation Analysis (Quest Diagnostics)	81219*, C94, D47.1	3, 5
Tumor Specific *CEBPA* Variant Analysis	CEBPA Mutation Analysis (Labcorp)	81218*, C92	4
Tumor Specific *FLT3* Variant Analysis	FLT3 ITD and TKD Mutation (PCR) (PathGroup)	81245*, 81246*, 0023U*, 0046U*, C92	1, 2, 3, 4, 5
	LeukoStrat CDx FLT3 Mutation Assay - 0023U (Versiti)		
	FLT3 ITD MRD Assay - 0046U (Laboratory for Personalized Molecular Medicine)		
Tumor Specific *IDH1* and *IDH2* Variant Analysis (Hematologic)	IDH1/IDH2 Mutation, Blood/Bone marrow (Cleveland Clinic Laboratories)	81120*, 81121*, C92, D47	4

CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Tumor Specific *IGHV* Somatic Hypermutation Analysis	IgVH Mutation Analysis (NeoGenomics)	81261*, 81262*, 81263*, C83, C91, D47.Z1	7, 9, 10
Tumor Specific *JAK2* Variant Analysis	JAK2 Exon 12 to 15 Sequencing, Polycythemia Vera Reflex, Varies - 0027U (Mayo Clinic Laboratories)	0027U*, 0017U*, 81270*, C91, C92, C94, D45, D47.1, D47.3, D75.81	3, 5
	JAK2 Mutation - 0017U (University of Iowa)		
	JAK2 V617F Mutation Analysis (Quest Diagnostics)		
Tumor Specific *MPL* Variant Analysis	MPL Mutation Analysis (Quest Diagnostics)	81338, 81339, D45, D47.1, D47.3, D75.81	5
Tumor Specific *NPM1* Variant Analysis	NPM1 MRD Assay - 0049U (Laboratory for Personalized Molecular Medicine)	0049U*, 81310*, C92	4
	Onkosight NGS NPM1 Sequencing (BioReference Laboratories)		
Tumor Specific *TP53* Variant Analysis	TP53 Mutation Analysis (NeoGenomics Laboratories)	81352, C92, R71, R79	4, 7, 9
Cytogenetic Testing for Hematologic Malignancies			
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) FISH Panel Analysis	FISH for Chronic Lymphocytic Leukemia (Cleveland Clinic Laboratories)	88271, 88274, 88275, 88291, C91, C94, C95, Z85.6	7

CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
	FISH, B-Cell Chronic Lymphocytic Leukemia Panel (Quest Diagnostics)		
Multiple Myeloma FISH Panel Analysis	Oncology FISH Analysis - Multiple Myeloma FISH Panel (Baylor Genetics, LLC)	88237, 88271, 88275, 88291, C90	8
	Multiple Myeloma (MM) Profile, FISH (Labcorp)		
Tumor Specific *PML/RARA* Gene Rearrangement (Qualitative FISH and PCR)	FISH, APL, PML/RARA, Translocation 15, 17 (Quest Diagnostics)	81315*, 81316*, 88271, 88274, 88275, 88291, C91, C92, C93, C94, C95	4
	PML/RARA t(15;17) (NeoGenomics Laboratories)		
Red Blood Cell Genotyping in Multiple Myeloma			
Red Blood Cell Genotyping in Multiple Myeloma	PreciseType HEA - 0001U (Immucor)	0001U*, 0180U*, 0221U*, C90.0, R71, R79	11
	Navigator ABO Sequencing - 0180U (Grifols Immunohematology Center)		
	Navigator ABO Blood Group NGS - 0221U (Grifols Immunohematology Center)		

RELATED POLICIES

This policy document provides criteria for hematologic malignancy molecular diagnostics. Please refer to:

- ***Oncology Testing: Solid Tumor Molecular Diagnostics*** for criteria related to molecular profiling of a known or suspected cancer (e.g. broad molecular profiling, including Minimal Residual Disease (MRD) Testing, Tumor Mutational Burden (TMB), and cytogenetic / fusion testing).
- ***Oncology Testing: Hereditary Cancer Susceptibility*** for criteria related to genetic testing for hereditary cancer predisposition syndromes.
- ***Oncology Testing: Cancer Screening and Surveillance*** for criteria related to screening and biomarker cancer tests.
- ***Oncology Testing: Algorithmic Assays*** for criteria related to gene expression profiling and tumor biomarker tests with algorithmic analyses.
- ***Specialty Testing: Multisystem Genetic Conditions*** for criteria related to diagnostic tests for genetic disorders that affect multiple organ systems (e.g. whole exome and genome sequencing, chromosomal microarray, and multigene panels for broad phenotypes).
- ***General Approach to Laboratory Testing*** for criteria related to hematologic malignancies, including known familial variant testing, that is not specifically discussed in this or another non-general policy.

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CRITERIA

It is the policy of Louisiana Healthcare Connections that the specific genetic testing noted below is **medically necessary** when meeting the related criteria:

MOLECULAR PROFILING PANELS FOR HEMATOLOGIC MALIGNANCIES

Broad RNA Fusion Panels for Hematologic Malignancy

I. RNA fusion panel tests with 51 or more genes utilizing RNA analysis alone that are performed on hematologic malignancies are considered **medically necessary** when:

   A. The member/enrollee is undergoing diagnostic workup for adult or pediatric acute lymphoblastic leukemia (ALL).

II. Current evidence does not support RNA fusion panel tests with 51 or more genes utilizing RNA analysis alone that are performed on hematologic malignancies for all other indications.

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Broad Molecular Profiling Panels For Hematologic Malignancies and Myeloid Malignancy Panels

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

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

III. Current evidence does not support broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood 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.

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Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels

I. Acute myeloid leukemia focused molecular profiling panels for the diagnosis or evaluation of acute myeloid leukemia (AML) are considered **medically necessary** when:
   A. The member/enrollee has a suspected or confirmed diagnosis of acute myeloid leukemia (AML).

II. Current evidence does not support acute myeloid leukemia focused molecular profiling panels for the diagnosis or evaluation of acute myeloid leukemia (AML) for all other indications.

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

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Myeloproliferative Neoplasms (MPNs) Panels

I. Myeloproliferative neoplasm (MPN) molecular profiling panels are considered **medically necessary** when:
   A. The member/enrollee is suspected to have a myeloproliferative neoplasm (MPN), **AND**
   B. The panel includes, at a minimum, testing of the following genes: *JAK2*, *CALR*, and *MPL*.

II. Current evidence does not support myeloproliferative neoplasm (MPN) molecular profiling panels for all other indications.

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MEASURABLE (MINIMAL) RESIDUAL DISEASE (MRD) ANALYSIS FOR HEMATOLOGIC MALIGNANCIES

Hematologic Minimal Residual Disease (MRD) Testing

I. Measurable (minimal) residual disease (MRD) analysis in bone marrow or peripheral blood is considered **medically necessary** when:
   A. The member/enrollee has a diagnosis of:
      1. Acute Lymphocytic Leukemia (ALL), **OR**
      2. Multiple Myeloma, **OR**
      3. Chronic Lymphocytic Leukemia (CLL), **AND**
         a) The member/enrollee has completed treatment.

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SINGLE GENE TESTING FOR HEMATOLOGIC MALIGNANCIES

Tumor Specific *BCR-ABL1* Kinase Domain Analysis

I. Tumor specific *BCR-ABL1* kinase domain analysis in hematologic malignancies is considered **medically necessary** when:
   A. The member/enrollee 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/enrollee 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.

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

I. Tumor specific *BCR-ABL1* FISH, qualitative, or quantitative tests in hematologic malignancies are considered **medically necessary** when:
   A. The member/enrollee is suspected to have a myeloproliferative neoplasm (MPN), **OR**

B. The member/enrollee is undergoing diagnostic workup for:
    1. Acute lymphoblastic leukemia (ALL), **OR**
    2. Acute myeloid leukemia (AML), **OR**
    3. Chronic myeloid leukemia (CML), **OR**
    4. Lymphoblastic leukemia, **OR**
C. The member/enrollee is undergoing monitoring of disease progression or for minimal residual disease (MRD) monitoring using a quantitative test only for:
    1. Acute lymphoblastic leukemia (ALL), **OR**
    2. Acute myeloid leukemia (AML), **OR**
    3. Chronic myeloid leukemia (CML).

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Tumor Specific *CALR* Variant Analysis

I. Tumor specific *CALR* variant analysis is considered **medically necessary** when:

A. The member/enrollee is suspected to have a myeloproliferative neoplasm (MPN), **OR**
B. The member/enrollee is suspected to have a myelodysplastic syndrome (MDS).

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Tumor Specific *CEBPA* Variant Analysis

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

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Tumor Specific *FLT3* Variant Analysis

I. Tumor specific *FLT3* variant analysis in hematologic malignancies is considered **medically necessary** when:
    A. The member/enrollee has suspected or confirmed acute myeloid leukemia (AML), **OR**
    B. The member/enrollee has a diagnosis of:
        1. Acute lymphocytic leukemia (ALL), **OR**
        2. Myelodysplastic syndrome (MDS), **OR**

3. Myeloproliferative neoplasm (MPN).

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Tumor Specific *IDH1* and *IDH2* Variant Analysis (Hematologic)

I. Tumor specific *IDH1* and *IDH2* variant analysis in hematologic malignancies is considered **medically necessary** when:
   A. The member/enrollee has a diagnosis of acute myeloid leukemia (AML).

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Tumor Specific *IGHV* Somatic Hypermutation Analysis

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

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Tumor Specific *JAK2* Variant Analysis

I. Tumor specific *JAK2* variant analysis in hematologic malignancies is considered **medically necessary** when:
   A. The member/enrollee is suspected to have a myeloproliferative neoplasm (MPN), **OR**
   B. The member/enrollee has acute lymphoblastic leukemia (ALL), **OR**
   C. The member/enrollee is suspected to have a myelodysplastic syndrome (MDS).

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Tumor Specific *MPL* Variant Analysis

I. Tumor specific *MPL* variant analysis in hematologic malignancies is considered **medically necessary** when:

A. The member/enrollee is suspected to have a myeloproliferative neoplasm (MPN), **OR**
B. The member/enrollee is suspected to have a myelodysplastic syndrome (MDS).

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Tumor Specific *NPM1* Variant Analysis

I. Tumor specific *NPM1* variant analysis in hematological malignancies is considered **medically necessary** when:
   A. The member/enrollee is undergoing evaluation for acute myeloid leukemia (AML).

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Tumor Specific *TP53* Variant Analysis

I. Tumor specific *TP53* variant analysis in bone marrow or peripheral blood is considered **medically necessary** when:
   A. The member/enrollee has a diagnosis of:
      1. Acute myeloid leukemia (AML), **OR**
      2. Chronic lymphocytic leukemia (CLL), **OR**
      3. Small lymphocytic leukemia (SLL), **OR**
   B. The member/enrollee is undergoing diagnostic workup for mantle cell lymphoma (MCL).

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CYTOGENETIC TESTING FOR HEMATOLOGIC MALIGNANCIES

Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) FISH Panel Analysis

I. Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) FISH panel analysis in peripheral blood or bone marrow is considered **medically necessary** when:
   A. The member/enrollee is undergoing initial diagnostic workup for chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).

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Multiple Myeloma FISH Panel Analysis

I. Multiple myeloma FISH panel analysis of bone marrow is considered **medically necessary** when:
   A. The panel includes analysis for del(13), del(17p13), t(4;14), t(11;14), t(14;16), t(14;20), 1q21 gain/amplification, and del(1p), **AND**
   B. The member/enrollee is undergoing initial diagnostic workup for multiple myeloma.

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Tumor Specific *PML/RARA* Gene Rearrangement (Qualitative FISH and PCR)

I. *PML/RARA* rearrangement analysis via fluorescent in situ hybridization (FISH) in peripheral blood or bone marrow is considered **medically necessary** when:
   A. The member/enrollee is undergoing initial diagnostic work up for acute myeloid leukemia (AML).

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RED BLOOD CELL GENOTYPING IN MULTIPLE MYELOMA

Red Blood Cell Genotyping in Multiple Myeloma

I. Red blood cell genotyping in individuals with multiple myeloma is considered **medically necessary** when:
   A. The member/enrollee has a diagnosis of multiple myeloma, **AND**
   B. The member/enrollee is currently being treated or will be treated with an anti-CD38 monoclonal antibody.

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RATIONALE

Broad RNA Fusion Panels for Hematologic Malignancy

The NCCN guidelines for Acute Lymphoblastic Leukemia (3.2024) 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 (2.2025) 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).

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Broad Molecular Profiling Panels For Hematologic Malignancies and Myeloid Malignancy Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Acute Myeloid Leukemia (1.2025) recommends molecular testing via multiplex gene panels and targeted analysis by next generation sequencing for adult patients for purposes of prognostication, therapy, ongoing management (p. EVAL-1, EVAL-2A), and in the presence of relapsed or refractory disease after completion of consolidation (p. AML-8, AML-J 1 of 2).

The NCCN guidelines for Acute Lymphoblastic Leukemia (3.2024) 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 (2.2025) recommends molecular testing during the initial evaluation of suspected myelodysplasia in patients with cytopenia. Testing should be performed on bone marrow or peripheral blood for somatic mutations in genes associated with myelodysplastic syndromes (p. MDS-1, MDS-1A).

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 (2.2024) 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 (3.2025) 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).

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Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Acute Myeloid Leukemia (1.2025) 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).

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Myeloproliferative Neoplasms (MPNs) Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Myeloproliferative Neoplasms (2.2024) 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).

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Hematologic Minimal Residual Disease (MRD) Testing

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Acute Lymphoblastic Leukemia (3.2024) recommend minimal residual disease (MRD) testing at numerous time points including prior to induction, following consolidation therapy, for serial monitoring, and as needed based on regimen and risk factors. MRD may also be used at baseline if needed for characterization of the leukemic clone to be used in subsequent MRD analysis (p. ALL-1, ALL-F).

The NCCN guidelines for Multiple Myeloma (1.2025) 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),prognostication during follow up after primary treatment (p. MYEL-4), and as part of response assessment after suspected complete response following each stage of treatment and prior to starting a new therapy (p. MYEL-E 1 of 3, MYEL-E 3 of 3).

The NCCN guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (1.2025) 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).

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Tumor Specific *BCR-ABL1* Kinase Domain Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Chronic Myeloid Leukemia (3.2025) 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 (3.2024) 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 (2.2025) (p. PEDALL-9).

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

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Pediatric Acute Lymphoblastic Leukemia (2.2025) recommend quantitative or qualitative reverse transcriptase-polymerase chain reaction (RT-PCR) testing for *BCR-ABL1* in B-ALL to determine transcript size (p. PEDALL-1). Additionally, reverse transcriptase quantitative PCR assay of *BCR-ABL1* is used to assess minimal residual disease (p. PEDALL-J, 1 of 2).

The NCCN guidelines on Acute Lymphoblastic Leukemia (3.2024) recommend reverse transcriptase polymerase chain reaction (RT-PCR) testing for *BCR-ABL1* in B-ALL (quantitative or qualitative), including determination of transcript size (ie, 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 for Myeloproliferative Neoplasms (2.2024) 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 (1.2025) recommend molecular testing to assist with prognostication of AML in the evaluation and initial workup for suspected AML (p.

EVAL-1). The NCCN guidelines also recommend confirmation of remission and ongoing monitoring for recurrence by PCR (p. APL-5).

The NCCN guidelines for Chronic Myeloid Leukemia (3.2025) 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). The NCCN guidelines also recommend confirmation of remission and ongoing monitoring for recurrence by PCR (p.CML-6).

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Tumor Specific *CALR* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Myeloproliferative Neoplasms (2.2025) 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 (2.2025) recommend genetic testing for somatic mutations in genes associated with MDS, which includes CALR. (p. MDS-1, MDS-C 2 of 3).

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Tumor Specific *CEBPA* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Acute Myeloid Leukemia (1.2025) 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).

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Tumor Specific *FLT3* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Acute Myeloid Leukemia (1.2025) 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 (3.2024) and Pediatric Acute Lymphoblastic Leukemia (2.2025) 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 (2.2025) 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 (2.2024) 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).

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Tumor Specific *IDH1* and *IDH2* Variant Analysis (Hematologic)

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Acute Myeloid Leukemia (1.2025) 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).

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Tumor Specific *IGHV* Somatic Hypermutation Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma guidelines (1.2025) 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 (3.2024) 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 (3..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).

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Tumor Specific *JAK2* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Myeloproliferative Neoplasms (2.2024) recommend molecular testing for *JAK2* mutations in the initial work-up for all patients with suspected MPN. The NCCN guidelines on Acute Lymphoblastic Leukemia (3.2024) and Pediatric Acute Lymphoblastic Leukemia (2.2025) 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 (2.2025) recommend genetic testing for somatic mutations in genes associated with MDS, which includes JAK2 (p. MDS-1, MDS-C 2 of 3).

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Tumor Specific *MPL* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guideline on Myeloproliferative Neoplasms (2.2024) 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 (2.2025) recommend genetic testing for somatic mutations in genes associated with MDS, which includes MPL (p. MDS-1, MDS-C 2 of 3).

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Tumor Specific *NPM1* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Acute Myeloid Leukemia (3.20241.2025) recommend molecular testing during the evaluation for AML for genes associated with prognosis or treatment options, including *NPM1* (p. EVAL-1, EVAL-2A).

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Tumor Specific *TP53* Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines on Acute Myeloid Leukemia (1.2025) 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 (3.2024) recommend *TP53* mutation analysis for patients with a diagnosis of mantle cell lymphoma in order to direct treatment selection, as patients with a *TP53* mutation have been associated with poor prognosis when treated with conventional therapy (p. MANT-1).

The NCCN guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (1.2025) 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).

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Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) FISH Panel Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma guidelines (1.2025) recommend FISH testing including r +12; del(11q); del(13q); del(17p) during the diagnostic workup for CLL/SLL and states this is “informative for prognostic and/or therapy determination” (p. CSLL-1, CSLL-A). Ruling out mantle cell lymphoma via FISH for t(11;14); t(11q;v) is recommended during the diagnostic workup when the initial diagnosis was made by flow cytometry (CSLL-1).

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Multiple Myeloma FISH Panel Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Multiple Myeloma guidelines (1.2025) recommend FISH testing during the initial workup of multiple myeloma for prognostic purposes. The recommended FISH testing includes: del(13), del (17p13), t(4;14), t(11;14), t(14;16), t(14:20), 1q21 gain/1q21 amplification, 1p deletion (p. MYEL-1).

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Tumor Specific *PML/RARA* Gene Rearrangement (Qualitative FISH and PCR)

National Comprehensive Cancer Network (NCCN)

NCCN Acute Myeloid Leukemia guidelines (1.2025) state that many different types of gene mutations are associated with specific prognoses, helping to guide medical management decisions, and/or may indicate that specific therapeutic agents are useful. Therefore, all patients with AML should be tested for these mutations (p. EVAL-1). The discussion section of this guideline states that *PML-RAR* alpha is included in this group of genetic markers that should be tested in all patients (p. MS-4).

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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 2024) recommending consideration of baseline phenotype and genotype prior to initiation of anti-CD38 monoclonal antibody treatment 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. 3).

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DEFINITIONS

1. A **Myeloproliferative Neoplasm (MPN)** is a rare blood disease in which the bone marrow makes too many red blood cells, white blood cells, or platelets.There are seven subcategories of myeloproliferative neoplasms:

    a. Chronic myeloid leukemia (CML)
    b. Polycythemia vera (PV)
    c. Primary myelofibrosis (PMF)
    d. Essential thrombocytopenia (ET)
    e. Chronic neutrophilic leukemia
    f. Chronic eosinophilic leukemia
    g. Chronic eosinophilic leukemia-not otherwise specified
    h. MPN, unclassifiable (MPN-U)

2. A **Myelodysplastic Syndrome (MDS)** is a disorder 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:

    a. MDS with multilineage dysplasia (MDS-MLD)
    b. MDS with single lineage dysplasia (MDS-SLD)
    c. MDS with ring sideroblasts (MDS-RS)
    d. MDS with excess blasts (MDS-EB)
    e. MDS with isolated del(5q)
    f. MDS, unclassifiable (MDS-U)

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Reviews, Revisions, and Approvals	Revision Date	Approval Date	Effective Date
Converted corporate to local policy	12/23	2/27/24	
Semi-annual review. In Broad RNA Fusion Panels, now ***COVERED***, for acute lymphoblastic leukemia. In Tumor-Type Agnostic Solid Tumor Molecular Profiling Panels, minor expansion of criteria to be consistent with guidelines (added several tumor types for coverage). In Tumor Specific BCR/ABL1 FISH, Qualitative, and Quantitative Tests, criteria set name changed (formerly "Tumor Specific BCR/ABL1 Quantitation and Breakpoint Analysis"). Criteria updated to include indication for diagnostic testing. In Tumor Mutational Burden (TMB), minor expansion of criteria to be consistent with guidelines (added several tumor types for coverage). In Colorectal Cancer Focused Molecular Profiling Panels, clinical criteria updated to be consistent with guidelines. In Tumor Specific *BRAF* Variant Analysis, minor expansion of criteria to be consistent with guidelines (added several tumor types for coverage). In Tumor Specific *BRCA1/2* Variant Analysis, clarification requirements for pancreatic cancer diagnosis to better align with guidelines. In Tumor Specific *CALR* Variant Analysis, clarification of criteria wording to be more clear/streamlined. In Tumor Specific *FLT3* Variant Analysis, minor expansion of criteria to be consistent with guidelines (added tumor type for coverage). In Tumor Specific *KRAS* Variant Analysis, minor expansion of criteria to be consistent with guidelines (added several tumor types for coverage). In Tumor Specific Microsatellite Instability (MSI) Analysis, minor expansion of criteria to be consistent with guidelines (added tumor type for coverage). Clarified qualifying stages of other cancers to be consistent with guidelines. In Overview and Clinical Considerations, policy overview updated to include information from the Clinical Considerations section, which has been consolidated into the Overview section. Minor rewording for clarity throughout. Coding, reference-table, background and references updated.	06/24	9/4/24	10/4/24

Reviews, Revisions, and Approvals	Revision Date	Approval Date	Effective Date
Semi-annual review. Updated title to reflect V1.2025. Solid Tumor Minimal Residual Disease (MRD) Testing criteria: RETIRED criteria and developed two criteria sets based on LCD guidelines. Cancer Exome and Genome Sequencing criteria: Updated format of example test in Policy Reference Table; Updated access date for online reference. Tumor Specific PIK3CA Variant Analysis criteria: Removed uterine neoplasms from the references and the criteria to align with guidelines; Updated NCCN Breast Cancer Treatment Guidelines version to 4.2024 in references; updated NCCN guidelines on Breast Cancer from version 1.2024 to 2.2024; removed the following reference and information from the Background and Rationale: "The NCCN guidelines on Uterine Neoplasms (21.2024) state that PIK3CA mutations can be found in pleomorphic uterine rhabdomyosarcomas. (p. UTSARC-A 7 of 8)". Tumor Specific NPM1 Variant Analysis: Updated AML NCCN criteria to 3.2024 version; updates to Background and Rationale to reflect information in latest NCCN guidelines. Cutaneous Melanoma Focused Molecular Profiling Panels: Updated criteria to allow for coverage of stage III melanoma in addition to stage IV, in order to better align with NCCN guidelines; Updated NCCN guidelines for Cutaneous Melanoma from version 3.2023 to 2.2024. Tumor Specific JAK2 Variant Analysis: Updated Background and Rationale to reflect updated NCCN guidelines; Updated version dates to NCCN guidelines in Reference list. Tumor Specific BCR/ABL1 FISH, Qualitative, or Quantitative Tests: Updated NCCN guidelines on Pediatric Acute Lymphoblastic Leukemia from version 3.2024 to 5.2024; Updated NCCN guidelines on Acute Lymphoblastic Leukemia version from 3.2023 to 4.2023; Updated NCCN guidelines on B-cell Lymphomas from version 1.2024 and 2.2024; NCCN guidelines for Acute Myeloid Leukemia from version 6.2023 to 2.2024; Added the following statements to the Background and Rationale: 1. "Additionally, reverse transcriptase quantitative PCR assay of BCR::ABL1 is used to assess minimal residual disease (p. PEDALL-I, 1 of 2)."; 2. "Additionally, reverse transcriptase quantitative PCR (RT-qPCR) assays for BCR::ABL1 are used to monitor minimal residual disease (p. ALL-F)."; 3. "NCCN also recommends consideration of qualitative RT-PCR for the detection of atypical BCR::ABL1 transcripts. (p. CML-1)". Tumor Specific Microsatellite Instability (MSI) Analysis: Added cancer types to criteria set, based on updated NCCN guidelines (Metastatic chondrosarcoma, Metastatic chordoma, Widely metastatic Ewing sarcoma, Metastatic osteosarcoma, Recurrent or metastatic vaginal cancer) based on NCCN guidelines. Added recurrent ovarian cancer to list of criteria to reflect a change in the NCCN Guidelines; Added ovarian cancer discussion to Background and Rationale; Updated NCCN guidelines for Colon Cancer to version 4.2024; Updated NCCN guideline on Esophageal and Esophagogastric Junction Cancer to version 4.2024; Updated NCCN guidelines for Biliary Tract Cancers to version 3.2024; Updated NCCN guidelines for an Occult Primary to version 1.2025; Updated NCCN guidelines for Breast Cancer to version 4.2024; Streamlined portions of Background and Rationale section for brevity; Updated NCCN guidelines for Colon Cancer from version 1.2024 to 3.2024; Updated NCCN	1/25	3/31/25	5/1/25

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guidelines for Uterine Neoplasms from version 1.2024 to 2.2024; Updated NCCN guideline on Gastric Cancer from version 3.2023 to 2.2024; Updated NCCN guideline on Esophageal and Esophagogastric Junction Cancer from version 4.2023 to 3.2024; Updated NCCN guidelines for Cervical Cancer from version 1.2024 to 3.2024; Updated NCCN guideline for Testicular Cancer from version 1.2023 to 1.2024; Updated NCCN guidelines for Biliary Tract Cancers from version 3.2023 to 2.2024; Updated NCCN guidelines for Breast Cancer from version 1.2024 to 2.2024; Updated NCCN guidelines for Small Bowel Adenocarcinoma from 1.2024 to 3.2024; Updated NCCN guidelines for an Occult Primary from version 1.2024 to 2.2024; Updated NCCN guidelines for Pancreatic Adenocarcinoma from version 1.2024 to 2.2024; Updated NCCN guidelines for Vulvar Cancer from version 3.2024 to 4.2024; Added the following to the Background and Rationale: "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)". Myeloproliferative Neoplasms (MPNs) Panels: Minor expansion of criteria - removed "The panel includes genes JAK2, CALR, MPL and BCR/ABL1", and changed to "The panel includes, at a minimum, testing of the following genes: JAK2, CALR, and MPL; Updated NCCN guidelines on Myeloproliferative Neoplasms from version 3.2023 to 1.2024; Streamlined portions of Background and Rationale section for brevity. Tumor Specific TP53 Variant Analysis: Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. Tumor-Type Agnostic Solid Tumor Molecular Profiling Panel Tests: Added covered criteria: GIST tumor that is negative for KIT and PDGFRA mutations based on NCCN guidelines; Added FDA approval as a CDx to Background and Rationale; Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. Tumor Specific MPL Variant Analysis: Updated NCCN guideline version dates for myelodysplastic syndromes in Background and Rationale section; Updated NCCN guideline version dates for myelodysplastic syndromes in Reference list. Tumor Specific KRAS Variant Analysis: Added coverage criteria for unresectable or metastatic gallbladder cancer, and unresectable or metastatic intrahepatic or extrahepatic cholangiocarcinoma based on NCCN guidelines; Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. Broad RNA Fusion Panels: Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. Tumor Specific BRCA1/2 Variant Analysis: Updated NCCN guideline version dates in Background and Rationale section. Updated NCCN guideline version dates in Reference list. Hematologic Minimal Residual Disease (MRD) Testing: Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN			

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guideline version dates in Reference list. Tumor Specific CALR Variant Analysis: Added coverage criteria for members suspected of having a myelodysplastic syndromes based on NCCN guidelines; Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. Tumor Specific IDH1 and IDH2 Variant Analysis: Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. Tumor Specific NRAS Variant Analysis: Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. Acute Myeloid Leukemia (AML) Focused Molecular Profiling Panels: Updated content in the Background and Rationale section for clarity and brevity; Updated Reference to reflect current version date. Colorectal Cancer Focused Molecular Profiling Panels: Removed Praxis Extended RAS Panel (Illumina) 0111U from the Policy Reference Table given it does not meet the minimum gene list in the criteria; Updated NCCN guideline for Colon Cancer from version 1.2024 to 3.2024; Removed the following statement from the Background and Rationale; "as literature has shown that the KRAS, NRAS, and BRAF mutations are similar in both specimen types. (p. COL-B, 4 of 8); In addition, patients with documented metachronous metastases should have determination of tumor gene status for RAS and BRAF mutations. (p. COL-9). The testing can be performed on the primary colorectal cancers and/or the metastasis, as literature has shown that the KRAS, NRAS, and BRAF mutations are similar in both specimen types." Changed page number from COL-2 to COL-B, 4 of 10. Tumor Specific KIT Variant Analysis: Reworded criterion for systematic mastocytosis to be more streamlined (removed phrase "suspected to have"); Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. Tumor Specific IGHV Somatic Hypermutation Analysis: Added B-cell lymphoma to the criteria set based on NCCN guidelines; Removed Mantle cell lymphoma and post-transplant lymphoproliferative disorders as criteria to be more inclusive of all forms of B-cell lymphoma (see Expansions); Streamlined wording of criteria for readability; Updated NCCN guideline version dates in Background and Rationale Section; Updated NCCN guideline version dates in References list. Tumor Specific BRAF Variant Analysis: Added locally advanced, recurrent, or metastatic esophageal or esophagogastric junction cancer and locally advanced, recurrent, or metastatic gastric cancer based on NCCN guidelines; Streamlined wording of criteria for readability; Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. Tumor Specific EGFR Variant Analysis: Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. Tumor Specific BCR/ABL1 Kinase Domain Analysis: Updated clinical criteria to clarify that Ph-positive ALL is a covered indication (as opposed to Ph-like ALL); Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. Targeted RNA Fusion Panels: Updated NCCN guidelines for Acute Lymphoblastic			

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Leukemia from version 3.2023 to 4.2023; Updated NCCN guidelines for Pediatric Acute Lymphoblastic Leukemia from 3.2024 to 5.2024; Updated NCCN guidelines for Non-Small Cell Lung Cancer from version 2.2024 to 5.2024; Updated NCCN guidelines for Soft Tissue Sarcoma from version 3.2023 to 1.2024; Updated NCCN guidelines for Histiocytic Neoplasms from version 1.2023 to 1.2024; Updated NCCN guidelines for Gastrointestinal Stromal Tumors (from version 1.2023 to 1.2024; Removed the following statement from the Background and Rationale; "Targeted testing for these abnormalities at diagnosis may aid in risk stratification."; Added YAP1 gene to the NCCN guidelines for Central Nervous System Cancers section of the Background and Rationale; Streamlined portions of Background and Rationale section for brevity. Lung Cancer Focused Molecular Profiling Panel: Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. Tumor Specific CEBPA Variant Analysis: Expanded coverage to all patients undergoing evaluation for AML based on NCCN guidelines; Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. Red Blood Cell Genotyping in Multiple Myeloma: Expanded coverage to patients being considered for treatment with Isatuximab based on current literature; Streamlined portions of Background and Rationale section for brevity. Tumor Mutational Burden (TMB): Removed coverage criteria for specific tumor types and created coverage criteria for: any recurrent, refractory, metastatic, or advanced stage III or IV cancer (aside from a central nervous system tumor), with progression on prior treatment, for members with no satisfactory treatment options. Changes remain consistent with NCCN guidelines; Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. Tumor Specific ESR1 Variant Analysis: Expanded coverage to include pre-menopausal women with ovarian ablation or suppression, postmenopausal women, or adult men based on NCCN guidelines; Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. Tumor Specific FLT3 Variant Analysis: Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. Tumor Specific MLH1 Methylation Analysis: Restructured criteria and Background and Rationale section for clarity and readability. Broad Molecular Profiling Panels for Hematologic Malignancies and Myeloid Malignancy Panels: Updated NCCN guideline version dates in Background and Rationale section; Updated NCCN guideline version dates in Reference list. HPV-Related Solid Tumor Minimal Residual Disease (MRD) Testing: NEW Criteria for coverage based on LCD; Removed investigational criterion to be consistent with remainder of policy. Evidence-Based Solid Tumor Minimal Residual Disease (MRD) Testing: NEW Criteria for coverage based on LCD; Updated and rearranged criteria to reflect new (LCD) covered tumor types for Signatera immune checkpoint inhibitor testing; Clarified relevant surveillance types in criteria. Emerging Evidence Solid Tumor Minimal Residual Disease (MRD) Testing: NEW Criteria set created for solid			

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tumor minimal residual disease (MRD) tests for which clinical validity has not been established. HLA Typing for Transplantation: NEW Criteria set created to address testing indications for HLA typing for transplantation; Removed investigational criterion to be consistent with remainder of policy.			
Annual review. Policy title changed from Concert Genetic Testing Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies to Concert Genetic Testing Oncology: Hematologic Malignancy. Minor wording changes without clinical significance. Criteria name for Broad RNA Fusion Panels changed to Broad RNA Fusion Panels for Hematologic Malignancy. In criteria for Broad Molecular Profiling Panels For Hematologic Malignancies and Myeloid Malignancy Panels, added "after consolidation" to criterion point II.C.1. Myeloproliferative Neoplasms (MPNs) Panels: Criteria updated to remove list of example MPNs as MPN is already defined within the Definitions section. Hematologic Minimal Residual Disease (MRD) Testing: Added the following criterion to the Chronic Lymphocytic Leukemia (CLL) indication of this criteria to better align with existing NCCN Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma guidelines: "The member has completed treatment." Tumor Specific BCR-ABL1 FISH, Qualitative, and Quantitative Tests: Criterion updated to remove list of example MPNs from criteria set as MPN is defined within the Definitions section; removed "B-cell lymphoma" from criterion point C.1.4; added "Lymphoblastic lymphoma" to criterion point I.B. to align with current NCCN guidelines. Criteria for Tumor Specific CALR Variant Analysis, Tumor Specific JAK2 Variant Analysis and Tumor Specific MPL Variant Analysis: updated to remove list of example MPNs from criteria set as MPN is defined within the Definitions section. Tumor Specific NPM1 Variant Analysis: Removed criterion point I.A. "The member has cytogenetically normal acute myeloid leukemia (AML)" and replaced with "The member is undergoing evaluation for acute myeloid leukemia (AML)." Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) FISH Panel Analysis: Removed criterion I.A. "The panel includes analysis for +12, del(11q), del(13q), and del(17p)." Red Blood Cell Genotyping in Multiple Myeloma: Removed specific drugs from the criterion "Daratumumab (Darazalex) and Isatuximab (Sarclisa)" and replaced with "an anti-CD38 monoclonal antibody." Tumor Specific IDH1 and IDH2 Variant Analysis (Hematologic): prior criteria set was split is now solid-tumor specific (in policy Concert Genetic Testing Oncology: Solid Tumor Molecular Diagnostics) and hematologic-specific. Replaced "investigational" policy statements with "Current evidence does not support….." throughout policy. Policy reference table, rationale, background, coding table updated.	03/26	5/27/26	6/26/26

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2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Acute Lymphoblastic Leukemia. Version 3.2024. https://www.nccn.org/professionals/physician_gls/pdf/all.pdf
3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Myelodysplastic Syndromes. Version 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/mds.pdf
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10. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Primary Cutaneous Lymphomas. Version 3.2024. https://www.nccn.org/professionals/physician_gls/pdf/primary_cutaneous.pdf
11. Association for the Advancement of Blood and Biotherapies Association Bulletin #16-02: Mitigating the Anti-CD38 Interference with Serologic Testing. (2016, January 15) (Updated April 2024). https://www.aabb.org/docs/default-source/default-document-library/resources/association-bulletins/ab16-02.pdf

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government

agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

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

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

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

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