Medica Central Coverage Policy

Policy Name:	**Genetic Testing – Oncology Testing: Hematologic Malignancy Molecular Diagnostics MP9797**
Effective Date:	**07/01/2025**

Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica Central plans. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between this general information and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless these programs require different coverage.

Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions may call the Provider Service Center. Please use the Quick Reference Guide on the Provider Communications page for the appropriate phone number. https://mo-central.medica.com/Providers/SSM-employee-health-plan-for-IL-MO-OK-providers

Medica Central coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care, and treatment.

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.

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.

POLICY REFERENCE TABLE

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Molecular Profiling Panels for Hematologic Malignancies			

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
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

COVERAGE 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, C91.00 - C91.02, C92.0 - C92.12, D45, D47, D47.1, D47.3, D69.3	1, 2, 4, 5, 6
	BCR-ABL1 Transcript Detection for Chronic Myelogenous Leukemia (CML) and Acute Lymphocytic Leukemia (ALL), Quantitative (Labcorp)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
	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
Tumor Specific *IGHV* Somatic Hypermutation Analysis	IgVH Mutation Analysis (NeoGenomics)	81261, 81262, 81263, C83, C91, D47.Z1	7, 9, 10

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
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
	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)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
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 coverage criteria for hematologic malignancy molecular diagnostics. Please refer to:

- ***Oncology Testing: Solid Tumor Molecular Diagnostics*** for coverage 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 coverage criteria related to genetic testing for hereditary cancer predisposition syndromes.
- ***Oncology Testing: Cancer Screening and Surveillance*** for coverage criteria related to screening and biomarker cancer tests.
- ***Oncology Testing: Algorithmic Assays*** for coverage criteria related to gene expression profiling and tumor biomarker tests with algorithmic analyses.
- ***Specialty Testing: Multisystem Genetic Conditions*** for coverage 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 coverage 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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COVERAGE 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 is undergoing diagnostic workup for adult or pediatric acute lymphoblastic leukemia (ALL).

II. RNA fusion panel tests with 51 or more genes utilizing RNA analysis alone that are performed on hematologic malignancies are considered **investigational** 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 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**

      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**

      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 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 after consolidation or progression on treatment.

III. Broad molecular profiling panels for hematologic malignancies and myeloid malignancy panels in bone marrow or peripheral blood 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.

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

II. Acute myeloid leukemia focused molecular profiling panels 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.

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Myeloproliferative Neoplasms (MPNs) Panels

I. Myeloproliferative neoplasm (MPN) molecular profiling panels are considered **medically necessary** when:

A. The member 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. Myeloproliferative neoplasm (MPN) molecular profiling panels are considered **investigational** 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 has a diagnosis of:

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

a) The member 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 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.

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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 is suspected to have a myeloproliferative neoplasm (MPN), **OR**

B. The member 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 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 is suspected to have a myeloproliferative neoplasm (MPN), **OR**

B. The member 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 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 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 (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 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 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 is suspected to have a myeloproliferative neoplasm (MPN), **OR**

B. The member has acute lymphoblastic leukemia (ALL), **OR**

C. The member 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 is suspected to have a myeloproliferative neoplasm (MPN), **OR**

B. The member 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 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 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 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 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 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 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 has a diagnosis of multiple myeloma, **AND**

B. The member is currently being treated or will be treated with an anti-CD38 monoclonal antibody.

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PRIOR AUTHORIZATION

Prior authorization is not required. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.

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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Note: The Health Plan uses the genetic testing clinical criteria developed by Concert Genetics, an industry-leader in genetic testing technology assessment and policy development.

Original Effective Date:	07/01/2025
Re-Review Date(s):	June 18, 2025 - Concert Genetics Effective Date: July 01, 2025 (V.2.2025)
Administrative Update:	

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