Test Specific Guidelines

Somatic Mutation Testing-Hematological Malignancies

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Introduction

Somatic mutation testing for hematological malignancies is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

Procedures addressed by this guideline	Procedure codes
ASXL1 Full Gene Sequencing	81175
ASXL1 Mutation Analysis	81176
ABL1 Mutation Analysis	81170
ABL1 Targeted Mutation Analysis	81401
BCR-ABL1 detection, major breakpoint	81206
BCR-ABL1 detection, minor breakpoint	81207
BCR-ABL1 detection, other breakpoint	81208
BCR-ABL1 major and minor breakpoint fusion transcripts	0016U
CALR Exon 9 Mutation Analysis	81219
CCND1/IGH (t(11;14)) Translocation Analysis, Major Breakpoint	81168
CEBPA Full Gene Sequencing	81218
EZH2 Common Variant(s) (e.g. codon 646)	81237
EZH2 Full Gene Sequencing	81236
FISH Analysis for t(9;22) BCR-ABL1	88271
FLT3 internal tandem duplication MRD-Invivoscribe	0046U
FLT3 Mutation Analysis (internal tandem duplication variants)	81245
FLT3 Mutation Analysis (tyrosine kinase domain variants)	81246

Procedures addressed by this guideline	Procedure codes
IDH1 Mutation Analysis	81120
IDH2 Mutation Analysis	81121
IGH@/BCL2 (t(14;18)) Translocation Analysis, Major Breakpoint Region (MBR) and Minor Cluster Region (mcr) Breakpoints	81278
JAK2 Exons 12 to 15 Sequencing	0027U
JAK2 Mutation	0017U
JAK2 Targeted Mutation Analysis (e.g exons 12 and 13)	81279
JAK2 V617F Mutation Analysis	81270
KIT Targeted Mutation Analysis	81272
KIT Mutation Analysis (D816 variants)	81273
MPL Common Variants (e.g. W515A, W515K, W515L, W515R)	81338
MPL Mutation Analysis, Exon 10	81339
MRDx® BCR-ABL Test	0040U
MyAML NGS- Invivoscribe	0050U
NPM1 MRD- Invivoscribe	0049U
NPM1 Mutation Analysis	81310
NRAS Mutation Analysis	81311
RUNX1 Mutation Analysis	81334
TERT Targeted Sequence Analysis	81345
Hematolymphoid Neoplasm Molecular Profiling	81450
SF3B1 Common Variants (e.g. A672T, E622D, L833F, R625C, R625L)	81347
Solid Organ or Hematolymphoid Neoplasm Molecular Profiling - Expanded	81455
SRSF2 Common Variants (e.g. P95H, P95L)	81348
TP53 Sequencing	81351
TP53 Targeted Sequence Analysis	81352
U2AF1 Common Variants (e.g. S34F, S34Y, Q157R, Q157P)	81357
ZRSR2 Common Variants (e.g. E65fs, E122fs, R448fs)	81360
MyMRD NGS Panel	0171U

Procedures addressed by this guideline	Procedure codes
Molecular Tumor Marker Test	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Molecular Tumor Marker Test	88271

What Are Somatic Mutation Tests?

Definition

A somatic mutation test for hematologic malignancies is broadly defined here as any test that measures changes in DNA, RNA, or chromosomes and is used to make cancer management decisions.

Somatic mutation tests are increasingly useful for therapy selection. Many cancer therapies are targeted at particular gene functions (therapeutic targets) and some require information about the genetics of the malignancy to use the therapies effectively (companion diagnostics). In these cases, National Comprehensive Cancer Network (NCCN) as well as the U.S. Food and Drug Administration (FDA) have outlined tumor testing that is recommended for specific cancers and the associated treatment implications.[1-4]

Test Information

Somatic Mutation Testing

The specific methodology used to identify somatic mutations is dependent upon the type of mutation being investigated.

DNA mutations are generally detected through direct analysis of individual mutations, portions of a gene, a whole gene, panels of genes, or the entire exome.

Chromosome abnormalities, such as translocations or deletions, may be detected through direct visualization of the chromosomes (karyotyping), in situ hybridization of probes (e.g., FISH) to detect deletions or duplications that are too small to see directly, or by DNA-based methods (hybridization arrays or sequencing) that identify deletions or translocation breakpoints.

Gene expression profiling simultaneously measures the amount of RNA being made by many genes. Expression patterns may be used to predict the type of cancer present, the aggressiveness of the malignancy, and therapies that are likely to be effective.

The efficiency of next generation sequencing (NGS) has led to an increasing number of large, multi-gene somatic mutation panels. Given that malignancies can have multiple and unexpected genetic changes, these panels may provide physicians with information about therapeutic targets that would not otherwise be considered.

Guidelines and Evidence

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) provided the following guidance:

NCCN Guidelines for Treatment of Cancer by Site provided detailed guidelines on the use of individual markers for each cancer type addressed.[4]

NCCN also maintains a biomarker compendium and stated "the goal of the NCCN Biomarkers Compendium is to provide essential details for those tests which have been approved by NCCN Guideline Panels and are recommended by the NCCN Guidelines."[3] Biomarkers for specific cancer types that are listed in the NCCN Biomarker Compendium have a level of evidence associated with their clinical utility.

NCCN stated that for individuals with acute lymphoblastic leukemia (ALL), molecular characterization by comprehensive testing by next-generation sequencing (NGS) for gene fusions and pathogenic mutations is recommended for determining risk and planning treatment. Specific biomarkers can be found in the table contained within the policy.[5]

NCCN stated that for individuals with cytopenia when myelodysplasia is suspected, bone marrow or peripheral blood cells should be assayed for MDS-associated gene mutations using gene panels that include ASXL1, BCOR, CALR, CBL, DDX41, DNMT3A, ETV6, EZH2, FLT3, GATA2, IDH1, IDH2, JAK2, MPL, NF1, NPM1, NRAS, PHF6, PPM1D, RUNX1, SETBP1, SF3B1, SRSF2, STAG2, STAT3, TET2, TP53, U2AF1, WT1, and ZRSR2.[6]

NCCN stated that for individuals with acute myeloid leukemia (AML): "Several gene mutations are associated with specific prognoses in a subset of patients

(category 2A) and may guide treatment decisions (category 2B). Presently, c-KIT, FLT3-ITD, FLT3-TKD, NPM1, CEBPA (biallelic), IDH1/IDH2, RUNX1, ASXL1, TP53, BCR-ABL and PML-RAR alpha are included in this group. All patients should be tested for mutations in these genes, and multiplex gene panels and comprehensive next-generation sequencing (NGS) analysis are recommended for the ongoing management of AML and various phases of treatment."[7]

U.S. Food and Drug Administration

Some FDA labels require results from biomarker tests to effectively or safely use the therapy for a specific cancer type.[2] A list of all Pharmacogenomic Biomarkers included in FDA labeling and associated implications can be found here. While these tests generally consist of a single biomarker, some larger panels of biomarkers are also included in the FDA labeling.

Criteria

This guideline applies to all molecular somatic mutation testing intended for use in hematological malignancies.

Medical necessity criteria differ based on the type of testing being performed (i.e., tests for individual genes separately chosen based on the cancer type versus pre-defined panels of genes) and how that testing will be billed (one or more individual gene-specific procedure codes, specific panel procedure codes or unlisted procedure codes).

Individual Tumor Markers

When separate procedure codes will be billed for individual biomarkers (e.g., Tier 1 MoPath codes 81200-81355 or Tier 2 MoPath codes 81400-81408), each individually billed test will be evaluated separately. The following criteria will be applied:

The member has a malignancy type that will benefit from information provided by the requested test based on at least one of the following:

All criteria are met from a test-specific guideline, if available, or

An oncology therapy FDA label requires results from the test to effectively or safely use the therapy for the member's cancer type, or

NCCN guidelines include the test in the management algorithm for that particular cancer type and all other requirements are met (specific pathology findings, staging, etc.); however, the marker must be explicitly recommended in the guidelines and not simply included in a footnote as an intervention that may be considered (See *Common cancer types and associated tumor markers* table below for examples of currently recommended gene tests)

Note **If five or more individually billed biomarker tests are under review together (a "panel") and the member meets the below criteria for a multigene panel, the panel will be approved. However, the laboratory will be redirected to use an appropriate panel CPT code for billing purposes (e.g. 81450).**

Companion Diagnostic (CDx) Tumor Marker Panels

Hematological tumor marker companion diagnostic assay panels are considered medically necessary when the member meets ALL of the following criteria:

Member has a diagnosis of cancer, AND

Treatment with a medication for which there is an FDA-approved companion diagnostic assay is being considered, AND

FDA approval for the CDx being requested must include the member's specific cancer type as an approved indication, AND

FDA label for the drug and indication being considered states companion diagnostic testing is necessary for patient selection (See *Common cancer types and associated tumor markers* table below for examples of currently recognized companion diagnostics for available therapies), AND

Member has not had previous somatic and/or germline testing that would have identified the genetic change required to prescribe medication under consideration, AND

Family history:

Member does not have a close (1st or 2nd degree) biological relative with a known germline mutation in a gene that is a target of the requested companion diagnostic test (e.g. known familial mutation in BRCA1/2 and requested test is myChoice CDx), or

Member has a close (1st or 2nd degree) biological relative with a known germline mutation in a gene that is a target of the requested companion diagnostic test (e.g. known familial mutation in BRCA1/2 and requested test is myChoice CDx), and the member's germline test was negative, AND

Rendering laboratory is a qualified provider of service per the Health Plan policy.

Multigene Panel Testing

When a multigene panel is being requested and will be billed with a single panel CPT code (e.g. 81450), the panel will be considered medically necessary when the following criteria are met:

The member has a diagnosis of acute myeloid leukemia (AML), OR

The member has a diagnosis of one of the following cancers, when the panel includes at least five of the genes associated with that cancer type listed in the below table *Common cancer types and associated tumor markers*:

Acute Lymphoblastic Leukemia (ALL)

Hepatosplenic Gamma-Delta T-Cell Lymphoma

Myelodysplastic Syndrome (for cytopenia in which myelodysplasia is suspected), OR

All criteria for a multigene panel are met from a test-specific guideline, if available, OR

At least 5 markers included in the panel individually meet criteria for the member's cancer type based on one of the following:

All criteria are met from a test-specific guideline, if available, or

An oncology therapy FDA label requires results from the test to effectively or safely use the therapy for the member's cancer type, or

NCCN guidelines include the test in the management algorithm for that particular cancer type and all other requirements are met (specific pathology findings, staging, etc.); however, the marker must be explicitly included in the guidelines and not simply included in a footnote as an intervention that may be considered.

Note **If the member meets criteria for less than 5 of the individual biomarkers in the panel, the panel will not be reimbursed. The laboratory will be redirected to billing for individual tests for which the member meets criteria.**

Billing and Reimbursement Consideration

Panels over 50 genes, typically billed with CPT code 81455, are not considered medically necessary, as they are excessive for use in evaluating hematological malignancies and, therefore, are not eligible for reimbursement.

Multigene panels, when medically necessary, will only be considered for reimbursement when billed with an appropriate panel CPT code.

Only one tumor biomarker panel will be considered for reimbursement per occurrence of cancer.

If multiple CDx biomarker panels are ordered simultaneously based on FDA label requirements, only one panel will be considered for reimbursement. Additional unique biomarkers from the second panel may be considered for reimbursement if appropriate single marker or single gene procedure codes are billed.

If a biomarker panel was previously performed and an additional panel is being requested, only testing for the medically necessary, previously untested biomarkers will be reimbursable. Therefore, only the most appropriate procedure codes will be considered for reimbursement.

Other Considerations

For information on somatic mutation testing for solid tumors, please refer to the guideline *Somatic Mutation Testing - Solid Tumors*, as this testing is not addressed here.

For information on tumors markers assayed by liquid biopsy, please refer to the guideline *Liquid Biopsy Testing*, as this testing is not addressed here.

For information on testing for germline (inherited) mutations in genes related to hereditary cancer syndromes (e.g. Hereditary Breast and Ovarian Cancer, Lynch syndrome, etc), please refer to the appropriate test-specific guideline, as this testing is not addressed here. Although some of the same genes may be tested for inherited or acquired (somatic) mutations, this guideline addresses only testing for acquired mutations from hematological malignancies.

Table: Common Cancer Types and Associated Tumor Markers

This list is not all inclusive.

Cancer Type	Tumor Marker	CPT	Indication for Test	Associated Treatments
Acute Lymphoblastic Leukemia (ALL)	ABL1 Gene Fusion and Kinase Domain Mutation	81170, 81401, 81403	Classification, Diagnostic, Prognostic, Treatment	Bosutinib, Dasatinib, Nilotinib, Ponatinib
Acute Lymphoblastic Leukemia (ALL)	ABL2 Gene Fusion	81479	Classification, Diagnostic, Prognostic	N/A
Acute Lymphoblastic Leukemia (ALL)	CRLF2 Gene Fusion	81479	Classification, Diagnostic, Prognostic	N/A
Acute Lymphoblastic Leukemia (ALL)	CSF1R Gene Fusion	81479	Classification, Diagnostic, Prognostic	N/A
Acute Lymphoblastic Leukemia (ALL)	EPOR Gene Fusion	81479	Classification, Diagnostic, Prognostic	N/A
Acute Lymphoblastic Leukemia (ALL)	FLT3 Mutations	81245, 81246	Classification, Diagnostic, Prognostic	N/A

Cancer Type	Tumor Marker	CPT	Indication for Test	Associated Treatments
Acute Lymphoblastic Leukemia (ALL)	IL7R Mutations	81479	Classification, Diagnostic, Prognostic	N/A
Acute Lymphoblastic Leukemia (ALL)	JAK1 Mutations	81479	Classification, Diagnostic, Prognostic	N/A
Acute Lymphoblastic Leukemia (ALL)	JAK2 Gene Fusion and Mutations	81270	Classification, Diagnostic, Prognostic	N/A
Acute Lymphoblastic Leukemia (ALL)	JAK3 Mutations	81479	Classification, Diagnostic, Prognostic	N/A
Acute Lymphoblastic Leukemia (ALL)	PDGFRB Gene Fusion	81479	Classification, Diagnostic, Prognostic	N/A
Acute Lymphoblastic Leukemia (ALL)	SH2B3 Mutations	81479	Classification, Diagnostic, Prognostic	N/A
B-Cell Lymphoblastic Leukemia/Lymphoma	EVT6-RUNX1 Gene Fusion	81401	Classification, Diagnostic, Prognostic	N/A
B-Cell Lymphoblastic Leukemia/Lymphoma	IL3-IGH Gene Fusion	81479	Classification, Diagnostic, Prognostic	N/A
B-Cell Lymphoblastic Leukemia/Lymphoma	KMT2A Mutations	81479	Classification, Diagnostic, Prognostic	N/A
B-Cell Lymphoblastic Leukemia/Lymphoma	TCF3-PBX1 Gene Fusion	81479	Classification, Diagnostic, Prognostic	N/A
Hepatosplenic Gamma-Delta T-Cell Lymphoma	INO80 Mutations	81479	Diagnostic	N/A
Hepatosplenic Gamma-Delta T-Cell Lymphoma	PIK3CD Mutations	81479	Diagnostic	N/A

Cancer Type	Tumor Marker	CPT	Indication for Test	Associated Treatments
Hepatosplenic Gamma-Delta T-Cell Lymphoma	SETD2 Mutations	81479	Diagnostic	N/A
Hepatosplenic Gamma-Delta T-Cell Lymphoma	SMARCA2 Mutations	81479	Diagnostic	N/A
Hepatosplenic Gamma-Delta T-Cell Lymphoma	STAT3 Mutations	81405, 81479	Diagnostic	N/A
Hepatosplenic Gamma-Delta T-Cell Lymphoma	STAT5B Mutations	81479	Diagnostic	N/A
Hepatosplenic Gamma-Delta T-Cell Lymphoma	TET3 Mutations	81479	Diagnostic	N/A
Hepatosplenic Gamma-Delta T-Cell Lymphoma	TCR Mutations	81479	Diagnostic	N/A
Myelodysplastic Syndrome	ASXL1 Mutations	81175, 81176	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	BCOR Mutations	81479	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	CALR Mutations	81219, 81479	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	CBL Mutations	81479	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	DDX41 Mutations	81479	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	DNMT3A Mutations	81403	Prognostic (Initial Evaluation)	N/A

Cancer Type	Tumor Marker	CPT	Indication for Test	Associated Treatments
Myelodysplastic Syndrome	ETV6 Mutations	81479	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	EZH2 Mutations	81236, 81237	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	FLT3 Mutations	81245, 81246	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	GATA2 Mutations	81479	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	IDH1 Mutations	81120, 81403	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	IDH2 Mutations	81121, 81403, 81479	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	JAK2 Mutations	81270, 81279	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	MPL Mutations	81338, 81339	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	NF1 Mutations	81408	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	NPM1 Mutations	81310	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	NRAS Mutations	81311, 81404, 81479	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	PHF6 Mutations	81479	Prognostic (Initial Evaluation)	N/A

Cancer Type	Tumor Marker	CPT	Indication for Test	Associated Treatments
Myelodysplastic Syndrome	PPM1D Mutations	81479	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	RUNX1 Mutations	81334, 81479	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	SETBP1 Mutations	81479	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	SF3B1 Mutations	81347	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	SRSF2 Mutations	81348	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	STAG2 Mutations	81479	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	STAT3 Mutations	81405, 81479	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	TET2 Mutations	81479	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	TP53 Mutations	81351, 81352	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	U2AF1 Mutations	81357	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	WT1 Mutations	81405, 81479	Prognostic (Initial Evaluation)	N/A
Myelodysplastic Syndrome	ZRSR2 Mutations	81360	Prognostic (Initial Evaluation)	N/A

References

NCI. Tumor markers. Available at: http://www.cancer.gov/about-cancer/diagnosis-staging/diagnosis/tumor-markers-fact-sheet

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