Somatic Mutation Testing

MOL.TS.230.C
v1.0.2025

Introduction

Somatic mutation testing in solid tumors and hematological malignancies is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan's procedure code list for management requirements.

Procedures addressed by this guideline	Procedure codes
ABL1 mutation analysis	81170
ABL1 targeted mutation analysis	81401
APC sequencing	81201
ASXL1 full gene sequencing	81175
ASXL1 mutation analysis	81176
Aventa FusionPlus	0444U
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
BRAF V600 targeted mutation analysis	81210
BRCA1/2 sequencing	81163
BRCA1 sequencing	81165
BRCA2 sequencing	81216
BTK gene analysis	81233
CALR exon 9 mutation analysis	81219
CCND1/IGH (t(11;14)) translocation analysis, major breakpoint	81168
CEBPA full gene sequencing	81218
clonoSeq	0364U

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Procedures addressed by this guideline	Procedure codes
CRCdx RAS Mutation Detection Kit	0471U
EGFR targeted mutation analysis	81235
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
FoundationOne CDx	0037U
Guardant360 TissueNext	0334U
Hematolymphoid neoplasm molecular profiling	81450
IDH1 mutation analysis	81120
IDH2 mutation analysis	81121
IDH1, IDH2, and TERT Mutation Analysis, Next-Generation Sequencing, Tumor (IDTRT)	0481U
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 D816 targeted mutation analysis	81273
KIT targeted sequence analysis	81272
KRAS exon 2 targeted mutation analysis	81275
KRAS targeted mutation analysis, additional variants	81276
LeukoStrat CDx FLT3 Mutation Assay	0023U

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Procedures addressed by this guideline	Procedure codes
Lung HDPCR	0478U
MGMT promoter methylation analysis	81287
MI Cancer Seek - NGS Analysis	0211U
MLH1 sequencing	81292
Molecular tumor marker test	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
Molecular tumor marker test	88271
MPL common variants (e.g. W515A, W515K, W515L, W515R)	81338
MPL mutation analysis, exon 10	81339
MRDx® BCR-ABL Test	0040U
MSH2 sequencing	81295
MSH6 sequencing	81298
MSK-IMPACT	0048U
MyAML NGS- Invivoscribe	0050U
myChoice CDx	0172U
MYD88 mutation analysis	81305
MyMRD NGS Panel	0171U
NPM1 MRD- Invivoscribe	0049U
NPM1 mutation analysis	81310
NRAS exon 2 and exon 3 analysis	81311
NTRK1 translocation analysis	81191
NTRK2 translocation analysis	81192

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Procedures addressed by this guideline	Procedure codes
NTRK3 translocation analysis	81193
NTRK translocation analysis	81194
Oncomine Dx Target Test (NSCLC)	0022U
oncoReveal CDx	0523U
Oncotype MAP PanCancer Tissue Test	0244U
OptiSeq Dual Cancer Panel Kit	0499U
PALB2 sequencing	81307
PDGFRA targeted sequence analysis	81314
PGDx Elio Tissue Complete	0250U
PIK3CA targeted sequence analysis	81309
PLCG2 common variants (e.g. R665W, S707F, L845F)	81320
PMS2 sequencing	81317
Praxis Extended RAS Panel	0111U
PTEN sequencing	81321
RUNX1 mutation analysis	81334
SF3B1 common variants (e.g. A672T, E622D, L833F, R625C, R625L)	81347
Solid organ neoplasm, genomic sequence analysis panel, 5-50 genes, interrogation for sequence variants and copy number variants or rearrangements, if performed; DNA analysis or combined DNA and RNA analysis	81445
Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, microsatellite instability	81457
Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, copy number variants and microsatellite instability	81458

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Procedures addressed by this guideline	Procedure codes
Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements	81459
Solid organ or hematolymphoid neoplasm or disorder, 51 or greater genes, genomic sequence analysis panel, interrogation for sequence variants and copy number variants or rearrangements, or isoform expression or mRNA expression levels, if performed; DNA analysis or combined DNA and RNA analysis	81455
Solid Tumor Expanded Panel	0379U
SRSF2 common variants (e.g. P95H, P95L)	81348
TERT targeted sequence analysis	81345
therascreen FGFR RGQ RT-PCR Kit	0154U
therascreen PIK3CA RGQ PCR Kit	0155U
TP53 sequencing	81351
TP53 targeted sequence analysis	81352
U2AF1 common variants (e.g. S34F, S34Y, Q157R, Q157P)	81357
xT CDx (Tempus)	0473U
ZRSR2 common variants (e.g. E65fs, E122fs, R448fs)	81360

Criteria

Introduction

Requests for molecular somatic mutation testing in solid tumors and hematological malignancies are reviewed using these criteria.

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).

Note This guideline addresses molecular markers only. It is intended to address DNA and RNA markers that are present on tumor marker panels, including microsatellite instability (MSI) when requested as part of panel. It does not address immunohistochemistry (IHC) or other markers that may be detected through other methods such as FISH, chromosomal microarray, routine chromosome analysis, etc.

Individual Tumor Markers

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

- The member has a tumor type that will benefit from information provided by the requested tumor marker test based on at least one of the following:
  - All criteria are met from an eviCore test-specific guideline, if one is available, or
  - An oncology therapy FDA label requires results from the tumor marker test to effectively or safely use the therapy for the member's cancer type, or
  - NCCN guidelines include the tumor marker test in the management algorithm for that particular cancer type and all other requirements are met (specific pathology findings, staging, etc.); however, the tumor marker must be explicitly included in the guidelines and not simply included in a footnote as an intervention that may be considered

Note If five or more individually billed tumor marker tests are under review together (a "panel") and the member meets criteria for 5 or more individual tumor markers on an NGS panel, the panel will be approved. However, the laboratory will be redirected to use a panel CPT code for billing purposes.

Companion Diagnostic (CDx) Tumor Marker Panels

Somatic mutation 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, 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 Tumor Marker Panel Testing

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

- The member is a candidate for a targeted therapy associated with a specific tumor biomarker(s) or disease site and has a diagnosis of one of the following cancers:
    - Advanced, metastatic solid tumor
    - Recurrent cutaneous melanoma
    - Non-small cell lung cancer
    - Recurrent pancreatic cancer
    - Epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer
    - Recurrent or unresectable salivary gland tumors
    - Unresectable biliary tract cancer
    - Myeloproliferative disease
    - Multiple myeloma
    - Systemic mastocytosis, OR
- The member has a confirmed or suspected diagnosis of acute myeloid leukemia (AML), OR
- The member has a confirmed or suspected diagnosis of myelodysplastic syndrome (MDS), OR

- The member has a diagnosis of cancer with at least 5 tumor markers included in the panel that individually meet criteria for the member's tumor type based on the medical necessity criteria for individual tumor markers listed above, OR
- Tumor mutational burden (TMB) testing is recommended in the NCCN management algorithm for the member's particular cancer type and all other requirements are met (specific pathology findings, staging, etc.); however, TMB testing 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 tumor markers 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.

clonoSEQ

clonoSEQ testing is medically necessary for initial assessment of dominant clonal sequences and once for response assessment after primary treatment for members diagnosed with one of the following:

- Acute lymphoblastic leukemia (ALL), or
- Chronic lymphocytic leukemia (CLL), or
- Multiple myeloma (MM), AND

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

Other Considerations

- For hematological malignancies, panels over 50 genes are considered not medically necessary as they are excessive.
- For information on tumor markers assayed by liquid biopsy, please refer to the guideline *Liquid Biopsy Testing*, as this testing is not addressed here.
- For information on MSI performed outside of a somatic mutation panel, please refer to the guideline *Microsatellite Instability and Immunohistochemistry Testing in Cancer*, 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 eviCore 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.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

When otherwise reimbursable, the following limitations will apply:

- For hematological malignancies, panels over 50 genes, typically billed with CPT code 81455, are not reimbursable.
    - If the laboratory's testing platform consists of more than 50 genes, yet a panel of 5 to 50 genes is considered medically necessary based on the above criteria, the laboratory can choose to bill using a panel procedure code (e.g., 81450) that represents a smaller number of genes on the panel.
- TMB testing may be considered an eligible tumor marker only when testing is performed by NGS on a solid tumor with a panel size of >667 Kb (typically more than 50 genes and billed with an appropriate panel code).
- Multigene panels will only be considered for reimbursement when billed with an appropriate panel CPT code (e.g. 81445, 81450, 81455, a PLA code, etc.)*.
- Only one somatic mutation 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.

Note *The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

What are somatic mutation tests?

Definition

Somatic mutation tests are broadly defined here as any test that measures changes in DNA, RNA, or chromosomes found in malignant tissue that 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 tumor genetics to use the therapies effectively (companion diagnostics). In these cases, NCCN as well as the FDA have outlined somatic testing that is recommended for specific cancers and the associated treatment implications.[1-5]

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.

Tumor Mutation Burden (TMB) Testing

Tumor mutational burden (TMB) is a quantitative measure of the number of mutations in the genome of a solid tumor "sometimes defined as the total number of non-synonymous point mutations per coding area of a tumor genome".[5] High TMB, typically defined as ≥10 mut/Mb for formalin-fixed paraffin-embedded (FFPE) tumor tissue, is thought to be a useful marker in predicting tumor response to immune checkpoint

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inhibitor therapies and is often used as a type of biomarker.[5-8] "Panel sizes >667 Kb are necessary to maintain adequate PPA [positive percent agreement] and NPA [negative percent agreement] for calling TMB high versus TMB low across the range of cut-offs used in practice."[8]

While TMB testing can be completed by whole exome sequencing (WES), this method tends to be high cost and requires an extensive analysis and data management.[6] As a result, NGS testing through targeted panels has become a preferred method for measuring TMB; however, this allows for variation among panels, including "sample input, tumor content, panel size, gene content, quality control (QC), NGS platform, and bioinformatics pipeline, which may influence TMB estimates and lead to inconsistent TMB calculation and reporting."[8] This has resulted in the need to align variability between TMB assays, which led to the formation of the Friends of Cancer Research (Friends) TMB Harmonization Consortium, which is made up of "diagnostic manufacturers, academics, pharmaceutical companies, the National Cancer Institute (NCI), Frederick National Laboratory for Cancer Research, and the FDA.[8]

Guidelines and evidence

College of American Pathologists

The College of American Pathologists, in collaboration with the Association for Molecular Pathology, American Society of Clinical Oncology, and patient advocacy group Fight Colorectal Cancer (CAP/AMP/ASCO/FCC, 2022) examined the best methodology for testing for MSI and published the following recommendations:[9]

- "For patients with CRC being considered for immune checkpoint inhibitor therapy, pathologists should use MMR-IHC and/or MSI by PCR for the detection of DNA mismatch repair defects. Although MMR-IHC or MSI by PCR are preferred, pathologists may use a validated MSI by NGS assay for the detection of DNA mismatch repair defects. Note: MSI by NGS assay must be validated against MMR-IHC or MSI by PCR and must show equivalency." (Strong Recommendation)
- "For patients with gastroesophageal and small bowel cancer being considered for immune checkpoint inhibitor therapy, pathologists should use MMR-IHC and/or MSI by PCR over MSI by NGS for the detection of DNA mismatch repair defects. Note: This recommendation does not include esophageal squamous cell carcinoma." (Strong Recommendation)
- "For patients with endometrial cancer being considered for immune checkpoint inhibitor therapy, pathologists should use MMR-IHC over MSI by PCR or NGS for the detection of DNA mismatch repair defects." (Strong Recommendation)
- "For patients with cancer types other than CRC, GEA [gastroesophageal adenocarcinoma], small bowel, and endometrial being considered for immune checkpoint inhibitor therapy, pathologists should test for DNA mismatch repair, although the optimal approach for the detection of mismatch repair defects has not been established. Note: Assays must be adequately validated for the specific cancer type being tested with careful consideration of performance characteristics

of MMR-IHC and MSI by NGS or PCR for the detection of DNA mismatch repair defects." (Conditional Recommendation)

- "For all cancer patients being considered for immune checkpoint inhibitor therapy based on defective mismatch repair, pathologists should not use TMB as a surrogate for the detection of DNA mismatch repair defects. If a tumor is identified as TMB-High, pathologists may perform IHC and/or MSI by PCR to determine if high TMB is secondary to mismatch repair deficiency." (Strong Recommendation)

European Society of Medical Oncology

The European Hematology Association and European Society for Medical Oncology (EHA/ESMO, 2021) clinical guidelines for multiple myeloma (MM) stated:[10]

- The detection of clonal plasma cells is obligatory at diagnosis.
- The confirmation of minimal residual disease (MRD) negativity is obligatory at response.
- "The use of MRD to drive treatment decisions is under investigation, e.g. whether maintenance/continuous therapy in MRD-negative patients can be stopped or whether treatment needs to be changed in MRD-positive patients, especially in high-risk MM. The results of several phase III trials in the field will clarify the role of MRD in making decisions about therapy in MM."

The Friends TMB Harmonization Consortium

The Friends TMB Harmonization Consortium reported the following:[8]

- "At a TMB cutoff of 10[mut/Mb], the panels assayed have a theoretical NPA [negative percent agreement] of at least 95%, with a theoretical NPA falling <95% for panel sizes under 667 Kb," supporting the claim that "a sufficiently sized panel is required to maintain reasonable PPA [positive percent agreement] of panel TMB measurements"
- An observed "substantial acceleration of the decrease in PPA of panels at critical intersections of small panel sizes and low TMB cut-offs", supporting the claim that "small panels are insufficient to maintain adequate PPA and NPA for calling TMB high versus TMB low across the range of cut-offs for positivity likely to be used in practice"

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) provided the following guidance on somatic mutation testing.

Solid Tumors:

- NCCN Guidelines for Treatment of Cancer by Site provided detailed guidelines on the use of individual tumor markers for each cancer type addressed.[2,4,11-18]

- NCCN made the following recommendations specifically for using multi-gene panels in the evaluation of non-small cell lung cancer (NSCLC): “The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is defined as molecular testing that identifies all biomarkers identified in NSCL-20 [gene rearrangements in ALK, NTRK1/2/3, RET, and ROS1, BRAF V600E mutation, certain EGFR mutations, KRAS G12C mutation, ERBB2 mutations, and MET exon 14 skipping mutation], in either a single assay or a combination of a limited number of assays, and optimally identifies emerging biomarkers. Tiered approaches based on low prevalence of co-occurring biomarkers are acceptable. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC.” [2]
- NCCN made the following recommendations specifically for using multi-gene panels in the evaluation of metastatic colorectal cancer: “All patients with metastatic CRC [colorectal cancer] should have tumor genotyped for RAS (KRAS and NRAS) and BRAF mutations individually or as part of a next-generation sequencing (NGS) panel.”[11]
- NCCN made the following recommendation for cutaneous melanoma: “For initial presentation with stage IV disease or clinical recurrence, obtain tissue to ascertain alterations in BRAF, and in the appropriate clinical setting, KIT from either biopsy of the metastasis (preferred) or archival material if the patient is being considered for targeted therapy. Broader genomic profiling (eg, larger NGS panels, BRAF non-V600 mutations) is recommended if feasible, especially if the test results might guide future treatment decisions or eligibility for participation in a clinical trial. If BRAF single-gene testing was the initial test performed, and is negative, clinicians should strongly consider larger NGS panels to identify other potential genetic targets (eg, KIT, BRAF non-V600).”[12]
- NCCN made the following recommendation for locally advanced/metastatic pancreatic adenocarcinoma: "Tumor/somatic molecular profiling is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. Consider specifically testing for potentially actionable somatic findings including, but not limited to: fusions (ALK, NRG1, NTRK, ROS1, FGFR2, and RET), mutations (BRAF, BRCA1/2, KRAS, and PALB2), amplifications (HER2), microsatellite instability (MSI), mismatch repair deficiency (dMMR), or tumor mutational burden (TMB) via an FDA-approved and/or validated next-generation sequencing (NGS)-based assay. RNA sequencing assays are preferred for detecting RNA fusions because gene fusions are better detected by RNA-based NGS."[13]
- NCCN made the following recommendation for epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer, prior to selection of systemic therapy for refractory or recurrent disease: “Validated molecular testing should be performed in a CLIA-approved facility using the most recent available tumor tissue. Tumor molecular analysis is recommended to include, at a minimum, tests to identify potential benefit from targeted therapeutics that have tumor-specific or

tumor-agnostic benefit including, but not limited to, HER2 status (by IHC), BRCA1/2, HRD status, microsatellite instability (MSI), mismatch repair (MMR), tumor mutational burden (TMB), BRAF, FRα (FOLR1), RET, and NTRK if prior testing did not include these markers."[14]

- NCCN made the following recommendation for ampullary adenocarcinoma: "Tumor/somatic molecular profiling is recommended for patients with locally advanced/metastatic disease who are candidates for anti-cancer therapy to identify uncommon mutations. Consider specifically testing for potentially actionable somatic findings including, but not limited to: fusions (ALK, NRG1, NTRK, ROS1, FGFR2, and RET), mutations (BRAF, BRCA1/2, KRAS, and PALB2), amplifications (HER2), microsatellite instability (MSI), mismatch repair deficiency deficiency (dMMR), or tumor mutational burden (TMB) via an FDA-approved and/or validated next-generation sequencing (NGS)-based assay. RNA sequencing assays are preferred for detecting RNA fusions because gene fusions are better detected by RNA-based NGS. Testing on tumor tissue is preferred; however, cell-free DNA can be considered if tumor tissue testing is not feasible."[15]
- NCCN made the following recommendation for distantly metastatic salivary gland tumors: "Targeted systemic therapy is increasingly becoming an option for patients with distantly metastatic salivary gland tumors. NGS and other biomarker tests should be used to evaluate AR, NTRK, HRAS, PIK3CA, TMB, and HER2 status."[16]
- NCCN made the following recommendation for metastatic prostate cancer: "Multigene tumor testing for alterations in HRR genes, including but not limited to BRCA1, BRCA2, ATM, PALB2, FANCA, RAD51D, CHEK2, and CDK12, is recommended in patients with metastatic prostate cancer."[17]
- NCCN made the following recommendation for patients with unresectable or metastatic biliary tract cancer (BTC): "Comprehensive molecular profiling is recommended for patients with unresectable or metastatic BTC who are candidates for systemic therapy. ... If tissue is too scant or not available, consider repeat biopsy depending on tumor accessibility, safety, and clinical context. A cell-free DNA (cfDNA) test may also be considered for identifying gene mutations. This technique may not reliably identify gene fusions or rearrangements depending on the panel used and the specific partner gene."[18]

Hematological Malignancies:

- NCCN Guidelines for Treatment of Cancer by Site provided detailed guidelines on the use of individual markers for each cancer type addressed.[4,19-22]
- 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.[19]
- NCCN stated that for individuals with cytopenia when myelodysplasia is suspected, "genetic testing for somatic mutations (ie, acquired mutations) in genes associated with myelodysplastic syndromes (MDS)" was recommended.[20]

- NCCN stated that for individuals being evaluated for and with acute myeloid leukemia (AML): "The field of genomics in myeloid malignancies and related implications in AML are evolving rapidly. Mutations should be tested in all patients. Multiplex gene panels and targeted next-generation sequencing (NGS) analysis are recommended for the ongoing management of AML and various phases of treatment."[21] Multiplex gene panel testing is also recommended by NCCN during the evaluation and initial workup for blastic plasmacytoid dendritic cell neoplasm.[21]
- NCCN stated that for individuals with chronic lymphocytic leukemia (CLL): "Evidence from clinical trials suggests that undetectable MRD in the peripheral blood after the end of fixed duration treatment is an important predictor of efficacy. … MRD evaluation should be performed using an assay with a sensitivity of 10-4 according to the standardized European Research Initiative on CLL (ERIC) method or standardized NGS method."[22]

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.[3] A list of all Pharmacogenomic Biomarkers included in FDA labeling and associated implications can be found here. While these tumor marker tests generally consist of a single biomarker, some larger panels of biomarkers are also included in the FDA labeling.

Note This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for somatic mutation testing will ensure that testing will be available to those members most likely to benefit from the information provided by the assays. For those not meeting criteria, it ensures alternate diagnostic/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

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