



CLINICAL MEDICAL POLICY	
Policy Name:	Somatic Mutation Testing
Policy Number:	MP-109-MC-PA
Responsible Department(s):	Medical Management
Provider Notice/Issue Date:	08/31/2026
Effective Date:	11/01/2026
Next Annual Review:	11/2027
Implementation Date:	04/15/2026
Products:	Pennsylvania Medicare Assured
Application:	All participating and nonparticipating practitioners and facilities unless contractually precluded
Page Number(s):	1 of 10

Policy History

Date	Activity
11/01/2026	Provider Effective date
04/15/2026	QI/UM Committee review
04/15/2026	Policy initially developed

Disclaimer

Highmark WholecareSM medical policy is intended to serve only as a general reference resource regarding coverage for the services described. This policy does not constitute medical advice and is not intended to govern or otherwise influence medical decisions.

Policy Statement

Highmark WholecareSM may provide coverage under the laboratory benefits of the Company's Medicare products for medically necessary somatic mutation testing.

This policy is designed to address medical necessity guidelines that are appropriate for the majority of individuals with a particular disease, illness, or condition. Each person's unique clinical circumstances warrant individual consideration, based upon review of applicable medical records.

Definitions

Tumor marker - anything present in or produced by cancer cells or other cells of the body in response to cancer or certain benign (noncancerous) conditions that provides information about a cancer, such as how aggressive it is, what kind of treatment it may respond to, or whether it is responding to treatment.

Procedures

1. Requests for molecular somatic mutation testing in solid tumors and hematological malignancies are reviewed using the following 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.

2. **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:

- A. The individual has a tumor type that will benefit from information provided by the requested tumor marker test based on at least one of the following:
 - 1) All criteria are met from a Highmark Wholecare test-specific guideline, if one is available; OR
 - 2) An oncology therapy FDA label requires results from the tumor marker test to effectively or safely use the therapy for the individual's cancer type; OR
 - 3) 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 (5) or more individually billed tumor marker tests are under review together (a "panel") and the individual meets criteria for five (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.

3. **Companion Diagnostic (CDx) Tumor Marker Panels**

Somatic mutation companion diagnostic assay panels may be considered medically necessary when the individual meets ALL of the following criteria:

- A. Individual has a diagnosis of cancer; AND
- B. Treatment with a medication for which there is an FDA-approved companion diagnostic assay is being considered; AND
- C. FDA approval for the CDx being requested must include the individual's specific cancer type as an approved indication; AND

- D. FDA label for the drug and indication being considered states companion diagnostic testing is necessary for patient selection; AND
- E. Individual has not had previous somatic and/or germline testing that would have identified the genetic change required to prescribe medication under consideration; AND
- F. Family History:
 - 1) Individual 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
 - 2) Individual 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 individual's germline test was negative.

4. **Multigene Tumor Marker Panel Testing (Non-CDx)**

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

- A. The individual has a confirmed or suspected diagnosis of acute myeloid leukemia (AML); OR
- B. The individual has a confirmed or suspected diagnosis of myelodysplastic syndrome (MDS); OR
- C. The individual has a diagnosis of cancer with at least five (5) tumor markers included in the panel that individually meet criteria for the individual's tumor type based on the medical necessity criteria for individual tumor markers listed above, OR
- D. The individual has a diagnosis of one of the following cancers:
 - 1) Locally advanced or metastatic ampullary adenocarcinoma; OR
 - 2) Metastatic colorectal cancer; OR
 - 3) Stage IV or recurrent cutaneous melanoma; OR
 - 4) Non-small cell lung cancer; OR
 - 5) Locally advanced, metastatic, or recurrent pancreatic cancer; OR
 - 6) Epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer; OR
 - 7) Recurrent, unresectable, or metastatic salivary gland tumors; OR
 - 8) Metastatic prostate cancer; OR
 - 9) Unresectable or metastatic biliary tract cancer; OR
 - 10) Acute lymphoblastic leukemia (ALL).

Tumor mutational burden (TMB) testing is recommended in the NCCN management algorithm for the individual'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 individual meets criteria for less than five (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 individual meets criteria.

5. **Contraindications**

- For hematological malignancies, panels over 50 genes are considered not medically necessary as they are excessive.

6. **Post-payment Audit Statement**

The medical record must include documentation that reflects the medical necessity criteria and is subject to audit by Highmark WholecareSM at any time pursuant to the terms of your provider agreement.

7. Place of Service

The proper place of service for somatic mutation testing is outpatient.

Governing Bodies Approval

CLIA

Somatic mutation tests are offered as laboratory-developed tests under Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories. Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratories offering such tests as a clinical service must meet general regulatory standards of CLIA and must be licensed by CLIA for high complexity testing.

FDA

Some FDA labels require results from biomarker tests to effectively or safely use the therapy for a specific cancer type. While these tumor marker tests generally consist of a single biomarker, some larger panels of biomarkers are also included in the FDA labeling.

CMS

The Centers for Medicare & Medicaid Services (CMS) has no published guidance on this topic.

Summary of Literature

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.

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 nonsynonymous point mutations per coding area of a tumor genome". 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 inhibitor therapies and is often used as a type of biomarker. "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.

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. 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." 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.

Coding Requirements

- 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.
- Only one (1) 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.

Procedure Codes

CPT Code	Description
81170	ABL1 (ABL proto-oncogene 1, non-receptor tyrosine kinase) (eg, acquired imatinib tyrosine kinase inhibitor resistance), gene analysis, variants in the kinase domain
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81201	APC (adenomatous polyposis coli) (eg, familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
81175	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; full gene sequence
81176	ASXL1 (additional sex combs like 1, transcriptional regulator) (eg, myelodysplastic syndrome, myeloproliferative neoplasms, chronic myelomonocytic leukemia), gene analysis; targeted sequence analysis (eg, exon 12)
81206	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; major breakpoint, qualitative or quantitative
81207	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; minor breakpoint, qualitative or quantitative
81208	BCR/ABL1 (t(9;22)) (eg, chronic myelogenous leukemia) translocation analysis; other breakpoint, qualitative or quantitative
81210	BRAF (B-Raf proto-oncogene, serine/threonine kinase) (eg, colon cancer, melanoma), gene analysis, V600 variant(s)
81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81165	BRCA1 (BRCA1, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81216	BRCA2 (BRCA2, DNA repair associated) (eg, hereditary breast and ovarian cancer) gene analysis; full sequence analysis
81233	BTK (Bruton's tyrosine kinase) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, C481S, C481R, C481F)
81219	CALR (calreticulin) (eg, myeloproliferative disorders), gene analysis, common variants in exon 9
81168	CCND1/IGH (t(11;14)) (eg, mantle cell lymphoma) translocation analysis, major breakpoint, qualitative and quantitative, if performed
81218	CEBPA (CCAAT/enhancer binding protein [C/EBP], alpha) (eg, acute myeloid leukemia), gene analysis, full gene sequence
81235	EGFR (epidermal growth factor receptor) (eg, non-small cell lung cancer) gene analysis, common variants (eg, exon 19 LREA deletion, L858R, T790M, G719A, G719S, L861Q)
81237	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, diffuse large B-cell lymphoma) gene analysis, common variant(s) (eg, codon 646)
81236	EZH2 (enhancer of zeste 2 polycomb repressive complex 2 subunit) (eg, myelodysplastic syndrome, myeloproliferative neoplasms) gene analysis, full gene sequence
88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
81245	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; internal tandem duplication (ITD) variants (ie, exons 14, 15)
81246	FLT3 (fms-related tyrosine kinase 3) (eg, acute myeloid leukemia), gene analysis; tyrosine kinase domain (TKD) variants (eg, D835, I836)

81450	Hematolymphoid neoplasm or disorder, genomic sequence analysis panel, 5-50 genes, 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
81120	IDH1 (isocitrate dehydrogenase 1 [NADP+], soluble) (eg, glioma), common variants (eg, R132H, R132C)
81121	IDH2 (isocitrate dehydrogenase 2 [NADP+], mitochondrial) (eg, glioma), common variants (eg, R140W, R172M)
81278	IGH@/BCL2 (t(14;18)) (eg, follicular lymphoma) translocation analysis, major breakpoint region (MBR) and minor cluster region (mcr) breakpoints, qualitative or quantitative
81279	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) targeted sequence analysis (eg, exons 12 and 13)
81270	JAK2 (Janus kinase 2) (eg, myeloproliferative disorder) gene analysis, p.Val617Phe (V617F) variant
81273	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, mastocytosis), gene analysis, D816 variant(s)
81272	KIT (v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog) (eg, gastrointestinal stromal tumor [GIST], acute myeloid leukemia, melanoma), gene analysis, targeted sequence analysis (eg, exons 8, 11, 13, 17, 18)
81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; variants in exon 2 (eg, codons 12 and 13)
81276	KRAS (Kirsten rat sarcoma viral oncogene homolog) (eg, carcinoma) gene analysis; additional variant(s) (eg, codon 61, codon 146)
81287	MGMT (O-6-methylguanine-DNA methyltransferase) (eg, glioblastoma multiforme) promoter methylation analysis
81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81400	Molecular pathology procedure, Level 1 (eg, identification of single germline variant [eg, SNP] by techniques such as restriction enzyme digestion or melt curve analysis)
81401	Molecular pathology procedure, Level 2 (eg, 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
81402	Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)

81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81479	Unlisted molecular pathology procedure
88271	Molecular cytogenetics; DNA probe, each (eg, FISH)
81338	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; common variants (eg, W515A, W515K, W515L, W515R)
81339	MPL (MPL proto-oncogene, thrombopoietin receptor) (eg, myeloproliferative disorder) gene analysis; sequence analysis, exon 10
81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81298	MSH6 (mutS homolog 6 [E. coli]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81305	MYD88 (myeloid differentiation primary response 88) (eg, Waldenstrom's macroglobulinemia, lymphoplasmacytic leukemia) gene analysis, p.Leu265Pro (L265P) variant
81310	NPM1 (nucleophosmin) (eg, acute myeloid leukemia) gene analysis, exon 12 variants
81311	NRAS (neuroblastoma RAS viral [v-ras] oncogene homolog) (eg, colorectal carcinoma), gene analysis, variants in exon 2 (eg, codons 12 and 13) and exon 3 (eg, codon 61)
81191	NTRK1 (neurotrophic receptor tyrosine kinase 1) (eg, solid tumors) translocation analysis
81192	NTRK2 (neurotrophic receptor tyrosine kinase 2) (eg, solid tumors) translocation analysis
81193	NTRK3 (neurotrophic receptor tyrosine kinase 3) (eg, solid tumors) translocation analysis
81194	NTRK (neurotrophic receptor tyrosine kinase 1, 2, and 3) (eg, solid tumors) translocation analysis
81307	PALB2 (partner and localizer of BRCA2) (eg, breast and pancreatic cancer) gene analysis; full gene sequence
81314	PDGFRA (platelet-derived growth factor receptor, alpha polypeptide) (eg, gastrointestinal stromal tumor [GIST]), gene analysis, targeted sequence analysis (eg, exons 12, 18)
81309	PIK3CA (phosphatidylinositol-4, 5-bisphosphate 3-kinase, catalytic subunit alpha) (eg, colorectal and breast cancer) gene analysis, targeted sequence analysis (eg, exons 7, 9, 20)
81320	PLCG2 (phospholipase C gamma 2) (eg, chronic lymphocytic leukemia) gene analysis, common variants (eg, R665W, S707F, L845F)
81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (eg, hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
81321	PTEN (phosphatase and tensin homolog) (eg, Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
81334	RUNX1 (runt related transcription factor 1) (eg, acute myeloid leukemia, familial platelet disorder with associated myeloid malignancy), gene analysis, targeted sequence analysis (eg, exons 3-8)

81347	SF3B1 (splicing factor [3b] subunit B1) (eg, myelodysplastic syndrome/acute myeloid leukemia) gene analysis, common variants (eg, A672T, E622D, L833F, R625C, R625L)
81445	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
81457	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, microsatellite instability
81458	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis, copy number variants and microsatellite instability
81459	Solid organ neoplasm, genomic sequence analysis panel, interrogation for sequence variants; DNA analysis or combined DNA and RNA analysis, copy number variants, microsatellite instability, tumor mutation burden, and rearrangements
81455	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
81348	SRSF2 (serine and arginine-rich splicing factor 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, P95H, P95L)
81345	TERT (telomerase reverse transcriptase) (eg, thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (eg, promoter region)
81351	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; full gene sequence
81352	TP53 (tumor protein 53) (eg, Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (eg, 4 oncology)
81357	U2AF1 (U2 small nuclear RNA auxiliary factor 1) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variants (eg, S34F, S34Y, Q157R, Q157P)
81360	ZRSR2 (zinc finger CCCH-type, RNA binding motif and serine/arginine-rich 2) (eg, myelodysplastic syndrome, acute myeloid leukemia) gene analysis, common variant(s) (eg, E65fs, E122fs, R448fs)

Reimbursement

Participating facilities will be reimbursed per their Highmark WholecareSM contract.

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