MEDICAL POLICY

POLICY TITLE	**SOMATIC BIOMARKER TESTING FOR IMMUNE CHECKPOINT INHIBITOR THERAPY (BRAF, MSI/MMR, PD-L1, TMB)**
POLICY NUMBER	**MP 2.388**

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☐ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☒ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	**RETIRED 7/1/2026**

I. POLICY

BRAF V600 Variant Testing

BRAF V600 variant testing of tumor tissue to select individuals for immune checkpoint inhibitor therapy may be considered **medically necessary** in the following circumstances:

- Individuals with unresectable or metastatic melanoma
  AND
- The individual does not have any U.S. Food and Drug Administration (FDA)-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label.

Analysis of tumor tissue for the somatic *BRAF* V600 variant to select individuals for immune checkpoint inhibitor therapy is considered **investigational** in all other situations. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Mismatch Repair/Microsatellite Instability Testing

Mismatch repair/microsatellite instability (MMR/MSI) testing of tumor tissue to select individuals for immune checkpoint inhibitor therapy may be considered **medically necessary** in the following circumstances:

- Individuals with advanced or metastatic colorectal cancer; **OR**
- Individuals with advanced endometrial carcinoma who have disease progression following prior systemic therapy and are not candidates for curative surgery or radiation; **OR**

- Individuals with unresectable or metastatic solid tumors who have progressed following prior treatment and who have no satisfactory alternative treatment options.

  AND

- The individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label.

Mismatch repair/microsatellite instability testing to select individuals for immune checkpoint inhibitor therapy is considered **investigational** in all other situations. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure for these indications.

Programmed Cell Death Ligand-1 Testing

Programmed cell death ligand protein-1 (PD-L1) testing of tumor tissue to select individuals for immune checkpoint inhibitor therapy may be considered medically necessary in the following circumstances:

- Individuals with metastatic non-small cell lung cancer (NSCLC); **OR**
- Individuals with metastatic or unresectable, recurrent head and neck squamous cell carcinomas; **OR**
- Individuals with locally advanced or metastatic esophageal or gastroesophageal junction carcinoma that is not amenable to surgical resection or definitive chemoradiation after 1 or more prior lines of systemic therapy for patients with tumors of squamous cell histology; **OR**
- Individuals with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction adenocarcinoma; **OR**
- Individuals with persistent, recurrent, or metastatic cervical cancer; **OR**
- Individuals with locally recurrent unresectable or metastatic hormone receptor-negative/HER2-negative (triple negative) breast cancer.

  AND

- The individual does not have any FDA-labeled contraindications to the requested agent and the agent is intended to be used consistently with the FDA-approved label.

PD-L1 testing of tumor tissue to select individuals for immune checkpoint inhibitor therapy is considered investigational in all other situations. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure for these indications.

Tumor Mutational Burden Testing

Tumor mutational burden (TMB) testing of tumor tissue to select individuals for immune checkpoint inhibitor therapy is considered **investigational**. There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure for these indications.

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POLICY GUIDELINES

This policy does not address neurotrophic tyrosine receptor kinase (NTRK) testing. The use of tropomyosin receptor kinase (TRK) inhibitors for individuals with NTRK gene fusion-positive solid tumors is addressed separately in evidence review 5.01.31.

Testing for individual biomarkers (not panels) associated with U.S. Food and Drug Administration (FDA)-approved therapeutics (i.e., as companion diagnostic tests) for therapies with National Comprehensive Cancer Network (NCCN) recommendations of 2A or higher are not subject to extensive evidence review. Note that while the FDA approval of companion diagnostic tests for genes might include tests that are conducted as panels, the FDA approval is for specific genes (such as driver mutations) and not for all of the genes on the test panel.

For guidance on testing criteria between policy updates, refer to the FDA's List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools) (https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools) for an updated list of FDA-approved tumor markers and consult the most current version of NCCN management algorithms.

A number of cancer types have NCCN recommendations of 2A or higher for tumor mutational burden (TMB) testing to identify an FDA-approved therapeutic. No additional evidence outside of what is reviewed in this reference medical policy appears to have guided those recommendations.

Repeat Genomic Testing

There may be utility in repeated testing of gene variants for determining immunotherapy, as tumor molecular profiles may change with subsequent treatments and re-evaluation may be considered at time of cancer progression for treatment decision-making. The American Society of Clinical Oncology (ASCO) currently suggests repeat genomic testing for individuals on targeted therapy with suspected acquired resistance, especially if choice of next-line therapy would be guided. The ASCO guidance is not tumor specific, and it cautions to consider clinical utility (Chakravarty et al, 2022; PMID 35175857). Refer to NCCN cancer-specific guidelines for guidance.

Cross-References:

MP 2.241 Molecular Analysis Targeted for Non-Small Cell Lung Cancer
MP 2.259 Expanded Molecular Panel Testing of Cancers to Identify Targeted Therapies
MP 2.364 Somatic Genetic Testing to Select Individuals with Melanoma or Glioma for Targeted Therapy or Immunotherapy
MP 2.316 Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, MMR-MSI, HER2, and TMP)

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II. PRODUCT VARIATIONS

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This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies .

III. DESCRIPTION/BACKGROUND

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BRAF V600

Variants in the b-raf proto-oncogene, serine/threonine kinase (BRAF) kinase gene are common in tumors of individuals with advanced melanoma and result in constitutive activation of a key signaling pathway (RAF-mitogen-activated protein kinase kinase (MEK)-ERK pathway) that is associated with oncogenic proliferation. In general, 50% to 70% of melanoma tumors harbor a BRAF variant; of these, 80% are positive for the BRAF V600E variant, and 16% are positive for BRAF V600K.1, Thus, 45% to 60% of patients with advanced melanoma may respond to a BRAF inhibitor targeted to this mutated kinase. BRAF inhibitors may be used alone or in combination with immunotherapy in individuals with BRAF pathogenic variants. The immune checkpoint inhibitor atezolizumab (Tecentriq®) is FDA approved in combination with cobimetinib and vemurafenib in individuals with BRAF V600 mutation-positive unresectable or metastatic melanoma.

Mismatch Repair Deficiency/Microsatellite Instability

Mismatch repair deficiency (dMMR) and high levels of microsatellite instability (MSI-H) describe cells that have alterations in certain genes involved in correcting errors made when DNA is replicated. dMMR tumors are characterized by a high tumor mutational load and potential responsiveness to anti-programmed cell death ligand-1 (PD-L1)-immunotherapy. Mismatch repair (MMR) deficiency is most common in colorectal cancer, other types of gastrointestinal cancer, and endometrial cancer, but it may also be found in other cancers including breast cancer.

Testing for dMMR and MSI is used to identify individuals most likely to respond to anti-PD-L1 therapy. Either MMR testing or MSI testing can be used to screen for MMR functional defects. MMR testing is performed using IHC for 4 MMR proteins (MLH1, MSH2, PMS2, and MSH6). Microsatellite instability testing is generally performed using polymerase chain reaction (PCR) for 5 biomarkers (*MLH1*, *MSH2*, *MSH6*, *PMS1* and *PMS2*). High MSI is defined as 2 or more of the 5 biomarkers showing instability or more than 30% of the tested biomarkers showing instability depending on what panel is used.

Programmed Cell Death Ligand Protein-1

Programmed cell death ligand-1 is a transmembrane protein expressed on the surface of multiple tissue types, including many tumor cells. Blocking the PD-L1 protein may prevent cancer cells from inactivating T cells.

FDA-approved PD-L1 immune checkpoint inhibitors include atezolizumab, avelumab, durvalumab, nivolumab, and pembrolizumab.

Tumor Mutational Burden

Tumor mutational burden (TMB) is a measure of gene mutations within cancer cells. Initially, assessments of TMB involved whole exome sequencing (WES). More recently, targeted next generation sequencing (NGS) panels are being adapted to estimate TMB. Currently, FoundationOne CDx is the only U.S. Food and Drug Administration (FDA) approved panel for estimating TMB, but others are in development.

IV. RATIONALE

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For individuals with cancer who are being evaluated for immune checkpoint inhibitor therapy who receive somatic testing for BRAF V600 variants, the evidence includes a placebo-controlled phase 3 randomized controlled trial (RCT) of atezolizumab in individuals with unresectable advanced BRAF V600-positive melanoma. Relevant outcomes are overall survival (OS), disease-specific survival, change in disease status, and treatment-related morbidity. In the IMspire150 trial, participants who received atezolizumab with vemurafenib and cobimetinib (n=256) experienced a median progression-free survival (PFS) of 15.1 months compared to 10.6 months in the control group of placebo, vemurafenib, and cobimetinib (n=258) (hazard ratio, 0.78; 95% confidence interval [CI], 0.63 to 0 97; p=.025). Based on these clinical trial results, testing for the BRAF V600E variant in individuals with unresectable or metastatic melanoma for determining treatment with atezolizumab in combination with cobimetinib and vemurafenib has received U.S. Food and Drug Administration (FDA) approval and a National Comprehensive Cancer Network (NCCN) recommendation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with cancer who are being evaluated for immune checkpoint inhibitor therapy who receive mismatch repair/microsatellite instability (MMR/MSI) testing, the evidence includes RCTs and nonrandomized trials. Relevant outcomes are OS, disease-specific survival, change in disease status, and treatment-related morbidity. Based on clinical trial data, MSI/MMR testing has received FDA approval and NCCN recommendations to select immune checkpoint inhibitor therapy in individuals with advanced or metastatic colorectal cancer, individuals with advanced endometrial carcinoma, and individuals with unresectable or metastatic solid tumors who have progressed following prior treatment and who have no satisfactory alternative treatment options. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with cancer who are being evaluated for immune checkpoint inhibitor therapy who receive somatic testing for programmed cell death ligand protein-1 (PD-L1) variants, the evidence includes RCTs and nonrandomized trials. Relevant outcomes are OS, disease-specific survival,

change in disease status, and treatment-related morbidity. Based on clinical trial data, PD-L1 testing has received FDA approval and NCCN recommendations to select immune checkpoint inhibitor therapy in individuals with metastatic non-small cell lung cancer; individuals with metastatic or unresectable, recurrent head and neck squamous cell carcinomas; individuals with locally advanced or metastatic esophageal or gastroesophageal junction carcinoma; individuals with persistent, recurrent, or metastatic cervical cancer; and individuals with locally recurrent unresectable or metastatic triple negative breast cancer. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with cancer who receive tumor mutational burden (TMB) testing to select treatment with immune checkpoint inhibitors, the evidence includes prospective and retrospective subgroup analyses of nonrandomized trials. Relevant outcomes include OS, disease-specific survival, test validity, quality of life, and treatment-related morbidity. In a prespecified subgroup analysis of a nonrandomized trial of pembrolizumab in individuals with various solid tumors, objective responses were observed in 24 (35%; 95% CI, 24 to 48) of 68 participants who had both tissue TMB (tTMB)-high status and PD-L1-positive tumors and in 6 (21%; 95% CI, 8 to 40) of 29 participants who had tTMB-high status and PD-L1-negative tumors. High TMB status was associated with improved response irrespective of PD-L1 status. Median OS and PFS were not significantly different between TMB groups. In exploratory analyses, retrospective observational studies have reported an association between higher TMB and longer PFS and overall survival in patients receiving immunotherapy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

V. DEFINITIONS

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N/A

VI. DISCLAIMER

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Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These polices are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VII. CODING INFORMATION

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Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement. The codes need to be in numerical order.

Covered when medically necessary:

Procedure Codes							
81210	81301	88341	88342	88360	88361	81479	0037U
0473U							

ICD-10-CM Diagnosis Code	Description
C00-D49	Cancer Diagnosis Range

VIII. REFERENCES

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34. *National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Uterine Neoplasms. V.2.2024.*
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IX. POLICY HISTORY

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MP 2.388	**06/21/2023 Major Review**. **New policy**
	04/11/2024 Administrative Update. Added indications related to immunotherapy from MP 2.364 Somatic Genetic Testing to Select Individuals with Melanoma or Glioma for Targeted Therapy or Immunotherapy. CPT 81210 also added from MP 2.364. No change to policy statements. Effective 05/01/2024.
	06/10/2024 Administrative Update. Added 0473U. Effective 07/01/2024.
	03/03/2025 Major Review. Added policy statement to include MMR/MSI testing for individuals with advanced or metastatic colorectal cancer and PD-L1 testing for individuals with metastatic non-small cell lung cancer. Added policy guidelines. Background and Rationale updated. References updated. Coding reviewed and added 88360 and 88361.
	06/25/2025 Administrative Update. Removed Benefit Variations Section and updated Disclaimer.
	03/05/2026 Retirement Review. EviCore Delegation.

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