MEDICAL POLICY

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

Effective Date:	12/1/2023

I. POLICY

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 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 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 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.

The National Comprehensive Cancer Network (NCCN) is a nonprofit alliance of cancer centers throughout the United States. NCCN develops the Clinical Practice Guidelines in Oncology which are recommendations aimed to help healthcare professionals diagnose, treat and manage patients with cancer. Guidelines evolve continuously as new treatments and diagnostics emerge and may be used by Capital BlueCross when determining medical necessity according to this policy.

Cross-reference:

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)

II. PRODUCT VARIATIONS TOP

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

FEP PPO:

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at:

III. DESCRIPTION/BACKGROUND

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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 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. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and

providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VII. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VIII. 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							
81301	88341	88342	0037U				

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

IX. REFERENCES

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X. POLICY HISTORY

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MP X.XXX	6/21/2023 Major Review. New policy

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