Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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Title: GT-Somatic Biomarker Testing for Immune Checkpoint Inhibitor Therapy (BRAF, MSI/MMR, PD-L1, TMB)

Description/Background

Immune Checkpoint Inhibitors and Associated Biomarkers
Immune checkpoint inhibitors are a type of cancer immunotherapy used to treat a wide range of cancer types, often in individuals with advanced or metastatic disease for which other treatment options are unavailable.
Currently, there are 8 FDA-approved immune checkpoint inhibitors:

- Atezolizumab (Tecentriq®)
- Avelumab (Bavencio®)
- Cemiplimab (Libtayo®)
- Dostarlimab-gxly (Jemperli®)
- Durvalumab (Imfinzi®)
- Ipilimumab (Yervoy®)
- Nivolumab (Opdivo®)
- Pembrolizumab (Keytruda®)

Multiple biomarkers have been identified as predictive of response to immune checkpoint inhibitor therapy. Some biomarker tests are required as part of FDA labeled indications and are routinely used to select individuals for treatment. The following section provides a brief overview of these biomarkers. Refer to Table 1 for a complete list of currently available immune checkpoint inhibitors, their labeled indications, and associated companion diagnostic biomarker tests.

***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.[2,]

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.[3,]

Circulating Tumor DNA (Liquid Biopsy)
Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA. Cell-free DNA from nonmalignant cells is released by apoptosis. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or circulating tumor cells. Unlike apoptosis, necrosis is considered a pathologic process and generates larger DNA fragments due to incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. Circulating tumor DNA (ctDNA) can be used for genomic characterization of the tumor.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of these tests.

Table 1 summarizes currently available immune checkpoint inhibitors with FDA approval, and the FDA cleared or approved companion diagnostic tests associated with each. An up-to-date list of FDA cleared or approved companion diagnostics is available at https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools.

Table 1. FDA Companion Diagnostic Tests for Immune Checkpoint Inhibitor Therapy

Biomarker	Immune Checkpoint Inhibitor	Indication	Companion Test
BRAF V600	Atezolizumab (Tecentriq®) + cobimetinib (Cotellic®) + vemurafenib (Zelboraf®)	Patients with BRAF V600 mutation-positive unresectable or metastatic melanoma	FoundationOne CDx
dMMR/MSI-H	Nivolumab (Opdivo®) +/- Ipilimumab (Yervoy®)	Patients ≥12 years of age with dMMR or MSI-H metastatic colorectal cancer that has progressed following treatment, as a single agent or in combination with ipilimumab	None
dMMR/MSI-H	Pembrolizumab (Keytruda®)	Adult and pediatric patients with unresectable or metastatic dMMR or MSI-H solid tumors, as determined by an FDA-approved test, which have progressed following prior treatment and who have no satisfactory alternative treatment options* *Safety and effectiveness in pediatric patients with MSI-H central nervous system cancers have not been established*	Ventana MMR RxDx (dMMR) FoundationOne CDx (MSI-H)
dMMR/MSI-H	Pembrolizumab (Keytruda)	Patients with unresectable or metastatic MSI-H or dMMR CRC as determined by an FDA-approved test	None
pMMR/ MSI-H	Pembrolizumab (Keytruda) + Lenvatinib (Lenmiva®)	Patients with advanced endometrial carcinoma that is pMMR as determined by an FDA-approved test or not MSI-H, who have disease progression following prior systemic therapy in any setting and are not candidates for curative surgery or radiation	Ventana MMR RxDx
dMMR	Dostarlimab (Jemperli®)	Adult patients with dMMR recurrent or advanced solid tumors, as determined by an FDA-approved test, which have progressed on or following prior treatment and who have no satisfactory alternative treatment options*	Ventana MMR RxDx Panel

Biomarker	Immune Checkpoint Inhibitor	Indication	Companion Test
dMMR	Dostarlimab (Jemperli)	Adult patients with dMMR recurrent or advanced endometrial cancer, as determined by an FDA-approved test, which has progressed on or following prior treatment with a platinum-containing regimen*	Ventana MMR RxDx Panel
PD-L1	Pembrolizumab (Keytruda)	First-line treatment of patients with NSCLC expressing PD-L1 as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations, and is: • stage III where patients are not candidates for surgical resection or definitive chemoradiation, or • metastatic Patients with metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy	PD-L1 IHC 22C3 pharmDx
PD-L1	Pembrolizumab (Keytruda)	First-line treatment of patients with metastatic or with unresectable, recurrent HNSCC whose tumors express PD-L1 as determined by an FDA-approved test	PD-L1 IHC 22C3 pharmDx
PD-L1	Pembrolizumab (Keytruda)	Patients with locally advanced or metastatic esophageal or gastroesophageal junction carcinoma that is not amenable to surgical resection or definitive chemoradiation as a single agent after one or more prior lines of systemic therapy for patients with tumors of squamous cell histology that express PD-L1 as determined by an FDA-approved test	PD-L1 IHC 22C3 pharmDx
PD-L1	Pembrolizumab (Keytruda)	In combination with chemotherapy, with or without bevacizumab, patients with persistent, recurrent, or metastatic cervical cancer whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test As a single agent for the treatment of patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy whose tumors express PD-L1 (CPS ≥1) as determined by an FDA-approved test	PD-L1 IHC 22C3 pharmDx
PD-L1	Pembrolizumab (Keytruda)	In combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10) as determined by an FDA approved test	PD-L1 IHC 22C3 pharmDx
PD-L1	Cemiplimab (Libtayo®)	First-line treatment of adult patients with NSCLC whose tumors have high PD-L1 expression (TPS≥ 50%) as determined by an FDA-approved test, with no EGFR, ALK or ROS1 aberrations, and is: • locally advanced where patients are not candidates for surgical resection or definitive chemoradiation or • metastatic	PD-L1 IHC 22C3 pharmDx

Biomarker	Immune Checkpoint Inhibitor	Indication	Companion Test
PD-L1	Nivolumab (Opdivo) + Ipilimumab (Yervoy)	Patients with metastatic NSCLC expressing PD-L1 as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations	PD-L1 IHC 28-8 pharmDx
PD-L1	Atezolizumab (Tecentriq)	Adult patients with Stage II to IIIA NSCLC whose tumors have PD-L1 expression on ≥ 1% of tumor cells, as determined by an FDA-approved test	Ventana PD-L1 (SP263) Assay
TMB	Pembrolizumab (Keytruda)	Adult and pediatric patients with unresectable or metastatic TMB-high (≥10 mutations/megabase) solid tumors, as determined by an FDA-approved test that have progressed following prior treatment and who have no satisfactory alternative treatment options	FoundationOne CDx

Abbreviations: ALK, anaplastic lymphoma kinase; CPS, combined positive score; CRC, colorectal cancer; dMMR, mismatch repair-deficient; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HNSCC, head and neck squamous cell carcinoma; MSI-H, microsatellite instability-high; NSCLC, non-small cell lung cancer; pMMR, mismatch repair-proficient; ROS1, c-ros oncogene1; TNBC, triple-negative breast cancer; TMB, tumor mutational burden; TPS, tumor proportion score.
Source: U.S. Food & Drug Administration (2023).[4,;5,]
*This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Medical Policy Statement

The safety and effectiveness of somatic biomarker testing for immune checkpoint inhibitor therapy has been established. It may be considered a useful option when indicated.

Inclusionary and Exclusionary Guidelines

BRAF V600 Variant Testing

BRAF V600 variant testing of tumor tissue or circulating tumor DNA (liquid biopsy)* to select individuals for immune checkpoint inhibitor therapy may be considered **established** in the following circumstances:

- Individuals with unresectable or metastatic melanoma or
- Metastatic colorectal cancer

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 **experimental/investigational** in all other situations.

Mismatch Repair/Microsatellite Instability Testing
Mismatch repair/microsatellite instability (MMR/MSI) testing of tumor tissue or circulating tumor DNA (liquid biopsy)* to select individuals for immune checkpoint inhibitor therapy may be considered **established** 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 **experimental/investigational** in all other situations.

Programmed Cell Death Ligand-1 Testing
Programmed cell death ligand protein-1 (PD-L1) testing of tumor tissue or circulating tumor DNA (liquid biopsy)* to select individuals for immune checkpoint inhibitor therapy may be considered **established** 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 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 **experimental/investigational** in all other situations.

Circulating Tumor DNA (liquid biopsy)*
Variant analysis using circulating tumor DNA (liquid biopsy) is considered established for individuals with unresectable or metastatic melanoma or metastatic colorectal cancer to select treatment with FDA-approved targeted therapies when tissue-based analysis is not clinically feasible.

Tumor Mutational Burden Testing (TMB)
TMB testing may be established for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, which have progressed following prior treatment and who have no satisfactory alternative treatment options (example Keytruda).

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

81210	81301	81455	81462	81463	81464
81479	88341	88342	88360	88361	0037U
0239U	0242U	0326U	0334U		

Other codes (investigational, not medically necessary, etc.):

N/A

Note: Individual policy criteria determine the coverage status of the CPT/HCPCS code(s) on this policy. Codes listed in this policy may have different coverage positions (such as established or experimental/investigational) in other medical policies.

Rationale

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Somatic Testing for the *BRAF* V600E Variant to Guide Immune Checkpoint Inhibitor Therapy

Clinical Context and Test Purpose

The purpose of somatic testing for the *BRAF* V600 variant in individuals who have cancer is to inform a decision about immune checkpoint inhibitor therapy.

The following PICO was used to select literature to inform this review.

Population

The relevant population of interest is individuals with cancer who are being considered for immune checkpoint inhibitor therapy.

Intervention

The therapy being considered is somatic testing for the *BRAF* V600E variant.

Comparator
The comparator of interest is standard treatment without *BRAF* variant testing.

Outcomes
The primary outcomes of interest are overall survival (OS) and progression-free survival (PFS). False-positive *BRAF* test results could lead to inappropriate treatment with BRAF and/or mitogen-activated protein kinase kinase (MEK) inhibitors, which have not been shown to be effective in patients without *BRAF* V600 pathogenic variants, and also could lead to delay in treatment with immunotherapy.

Study Selection Criteria
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.

Review of Evidence

Melanoma
Gutzmer et al (2020) reported primary results from IMspire150, a phase 3, double-blind, randomized controlled trial (RCT) of atezolizumab, vemurafenib, and cobimetinib (n=256) compared to placebo, vemurafenib, and cobimetinib (n=258) as first-line treatment for unresectable advanced *BRAF* V600-positive melanoma.[6,] The primary endpoint was investigator-assessed PFS. The median follow-up in the overall study population was 18.9 months. At data cut-off, 327 patients had progressive disease by investigator assessment or had died, including 148 (58%) patients in the atezolizumab group and 179 (69%) in the control group. The atezolizumab with vemurafenib and cobimetinib group experienced a median PFS per investigator assessment of 15.1 months (95% confidence interval [CI], 0.63 to 0.97) compared to 10.6 months (95% CI, 9.3 to 12.7) in the control group (hazard ratio [HR], 0.78; 95% CI, 0.63 to 0 97; p=.025).

Section Summary: Somatic Testing for *BRAF* Variants to Guide Immune Checkpoint Inhibitor Therapy
Based on 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 FDA approval and an NCCN recommendation.

Microsatellite Instability High/Mismatch Repair Deficient Testing to Guide Immune Checkpoint Inhibitor Therapy
The purpose of microsatellite instability/mismatch repair (MSI/MMR) testing in individuals who have cancer is to inform a decision about immune checkpoint inhibitor therapy.

Review of Evidence

Colorectal Cancer

Evidence for the effectiveness of pembrolizumab in patients with MSI-high/MMR-deficient (MSI-H/dMMR) metastatic colorectal cancer (CRC) comes from the KEYNOTE-177 trial, reported by Andre et al (2020).[7,] The trial demonstrated a statistically significant improvement in PFS for patients randomized to pembrolizumab compared with chemotherapy (HR, 0.60; 95% CI, 0.45 to 0.80; p=.0002). Final results were reported by Diaz et al (2022).[8,] Median PFS was 16.5 months (95% CI, 5.4 to 38.1) with pembrolizumab versus 8.2 months (6.1 to 10.2) with chemotherapy (HR, 0.59; 95% CI 0.45 to 0.79). Treatment-related adverse events of grade 3 or worse occurred in 33 of 153 (22%) patients in the pembrolizumab group versus 95 of 143 (66%) patients in the chemotherapy group.

Endometrial Cancer

The FDA approval for pembrolizumab in advanced endometrial cancer that is MMR proficient was based on the KEYNOTE-775 phase 3 trial, reported by Makker et al (2022).[9,]

The FDA approval for dostarlimab for dMMR recurrent or advanced endometrial cancer was based on the nonrandomized, phase 1, GARNET trial (NCT02715284, N=104), reported by Oaknin et al (2020).[10,] At a median follow-up of 11.2 months, the confirmed objective response rate was 42%; 13% of patients had a confirmed complete response, and 30% of patients had a confirmed partial response.

Two additional phase 3 RCTs of immune checkpoint inhibitor therapy for endometrial cancer indications that do not yet have FDA approval were published in March 2023 and are discussed below.

Mirza et al (2023) reported on a trial of dostarlimab plus carboplatin-paclitaxel among patients with primary advanced or recurrent endometrial cancer.[11,] Of the 494 patients who underwent randomization, 118 (23.9%) had dMMR, MSI-H tumors. In the dMMR, MSI-H population, estimated PFS at 24 months was 61.4% (95% CI, 46.3 to 73.4) in the dostarlimab group and 15.7% (95% CI, 7.2 to 27.0) in the placebo group (HR for progression or death, 0.28; 95% CI, 0.16 to 0.50; p<.001). In the overall population, PFS at 24 months was 36.1% (95% CI, 29.3 to 42.9) in the dostarlimab group and 18.1% (95% CI, 13.0 to 23.9) in the placebo group (HR, 0.64; 95% CI, 0.51 to 0.80; p<.001). Overall survival at 24 months was 71.3% (95% CI, 64.5 to 77.1) with dostarlimab and 56.0% (95% CI, 48.9 to 62.5) with placebo (HR for death, 0.64; 95% CI, 0.46 to 0.87).

Eskander et al (2023) reported on a phase 3 RCT of the addition of pembrolizumab to standard chemotherapy in individuals with advanced or recurrent endometrial cancer.[12,] Participants were stratified into 2 cohorts according to whether they had dMMR or mismatch repair-proficient (pMMR) disease. In the 12-month analysis, PFS in the dMMR cohort was 74% in the pembrolizumab group and 38% in the placebo group (HR for progression or death, 0.30; 95% CI 0.19 to 0.48; p<.001). In the pMMR cohort, median progression-free survival was 13.1 months with pembrolizumab and 8.7 months with placebo (HR , 0.54; 95% CI, 0.41 to 0.71; p<.001).

Solid Tumors

The FDA approval of pembrolizumab in individuals with dMMR or MSI-H solid tumors was supported by the phase 2 KEYNOTE-158 study, reported by Marabelle et al (2020).[13,] The trial included a total of 233 previously treated participants with MSI-H solid tumors. The objective response rate (ORR) was 34.3% (95% CI, 28.3 to 40.8). Median PFS was 4.1 months (95% CI, 2.4 to 4.9 months) and median OS was 23.5 months (95% CI, 13.5 months to not reached). Treatment-related adverse events occurred in 151 patients (64.8%).

Section Summary: Microsatellite Instability High/Mismatch Repair Deficient Testing to Guide Immune Checkpoint Inhibitor Therapy
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 CRC, 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.

Programmed Cell Death Ligand Protein-1 Testing to Guide Immune Checkpoint Inhibitor Therapy
The purpose of programmed cell death ligand protein-1 (PD-L1) testing in individuals who have cancer is to inform a decision about immune checkpoint inhibitor therapy.

Review of Evidence

Non-Small Cell Lung Cancer
In RCTs, individuals with high PD-L1 expression had longer PFS and fewer adverse events when treated with anti-PD-L1 monoclonal antibodies than with platinum chemotherapy. In the KEYNOTE trial, first-line treatment with nivolumab plus ipilimumab resulted in a longer duration of OS than did chemotherapy in patients with non-small cell lung cancer (NSCLC), independent of the PD-L1 expression level.

The EMPOWER-Lung 1 trial (NCT03088540) was a multicenter, open-label trial that randomized 710 patients 1:1 to receive either cemiplimab-rwlc or platinum-based chemotherapy.[14,] Median OS was 22.1 months (95% CI, 17.7 to not estimable) in the cemiplimab-rwlc arm compared to 14.3 months (95% CI, 11.7 to 19.2) in the chemotherapy arm (HR, 0.68; 95% CI, 0.53 to 0.87; p=.0022). Median PFS was 6.2 months with cemiplimab-rwlc versus 5.6 months with chemotherapy (HR, 0.59; 95% CI, 0.49 to 0.72; p<.0001). Corresponding ORRs were 37% (95% CI, 32 to 42) versus 21% (95% CI, 17 to 25), respectively. The most common adverse events were musculoskeletal pain, rash, anemia, fatigue, decreased appetite, pneumonia, and cough.

Herbst et al (2020) published results of a phase 3, open label RCT of atezolizumab compared to platinum-based chemotherapy in 572 patients with NSCLC who had not previously received chemotherapy and who had PD-L1 expression on at least 1% of tumor cells or at least 1% of tumor-infiltrating immune cells (NCT02409342).[15,] In the subgroup of patients with tumors who had the highest expression of PD-L1 (205 patients), the median OS was longer by 7.1 months in the atezolizumab group than in the chemotherapy group (20.2 months vs. 13.1 months; HR for death, 0.59; p=.01). Atezolizumab treatment resulted in significantly longer OS than platinum-based chemotherapy among patients with NSCLC with high PD-L1 expression, regardless of histologic type. Grade 3 or 4 adverse events occurred in 30.1% and 52.5% of the patients in the atezolizumab group and the chemotherapy group, respectively.

Reck et al (2016) published results of the KEYNOTE-024 Trial (NCT02142738), which compared pembrolizumab to platinum-based chemotherapy in 305 patients with NSCLC and PD-L1 expression on at least 50% of tumor cells.[16,] At a median follow-up of 11.2 months, PFS was longer with pembrolizumab compared with chemotherapy (median PFS, 10.3 vs. 6 months; HR, 0.50; 95% CI, 0.37 to 0.68). The median duration of response was not reached in the pembrolizumab group and was 6.3 months in the chemotherapy group.

In the CHECKMATE-227 trial (NCT02477826) reported by Hellmann et al (2019), among the patients with a PD-L1 expression level of 1% or more, the median duration of OS was 17.1 months (95% CI, 15.0 to 20.1) with nivolumab plus ipilimumab and 14.9 months (95% CI, 12.7 to 16.7) with chemotherapy (p=.007), with 2-year OS rates of 40.0% and 32.8%, respectively.[17,] The median duration of response was 23.2 months with nivolumab plus ipilimumab and 6.2 months with chemotherapy. First-line treatment with nivolumab plus ipilimumab resulted in a longer duration of OS than did chemotherapy in patients with NSCLC, independent of the PD-L1 expression level.

Head and Neck Squamous Cell Carcinoma
The FDA approval of pembrolizumab for head and neck squamous cell carcinoma was based on the KEYNOTE-048 trial of pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy.[18,]

Esophageal Cancer
The FDA approval of pembrolizumab monotherapy for individuals with esophageal cancer of squamous cell etiology that express PD-L1 was based on the placebo-controlled, phase 3 KEYNOTE-590 trial.[19,]

Cervical Cancer
The FDA approval of pembrolizumab for individuals with persistent, recurrent, or metastatic cervical cancer was based on the phase 3 KEYNOTE-826 trial.[20,]

Triple Negative Breast Cancer
The efficacy of pembrolizumab plus chemotherapy compared to placebo plus chemotherapy for previously untreated, locally recurrent inoperable or metastatic triple-negative breast cancer (N=847) was evaluated in the KEYNOTE-355 study. Dual primary efficacy endpoints were PFS and overall survival in patients with PD-L1 combined positive score of at least 1. Interim study results were published in 2020,[21,] and final results were published in 2022.[22,] This study formed the basis of pembrolizumab accelerated approval in patients with unresectable or metastatic triple-negative breast cancer and PD-L1 combined positive score (CPS) of at least 10. Two nonrandomized trials of pembrolizumab for patients with PD-L1 positive triple negative breast cancer reported objective response rates of 21.4% (95% CI, 13.9 to 31.4) and 18.5% (95% CI, 6.3 to 38.1).[23,24,]

Urothelial Carcinoma
In December 2022, Genentech voluntarily withdrew its accelerated approval for atezolizumab for the treatment of urothelial carcinoma after its required follow-up trial did not demonstrate improved OS for atezolizumab plus chemotherapy compared with chemotherapy alone.[25,]

Section Summary: Programmed Cell Death Ligand Protein-1 Testing to Guide Immune Checkpoint Inhibitor Therapy
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 NSCLC; 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.

Tumor Mutational Burden Testing to Guide Immune Checkpoint Inhibitor Therapy
The purpose of somatic tumor mutational burden (TMB) testing in individuals who have cancer is to inform a decision about immune checkpoint inhibitor therapy.

Review of Evidence
Marabelle et al (2020) reported the association of high TMB to response to pembrolizumab in patients with solid tumors enrolled in a prespecified exploratory analysis of the KEYNOTE-158 study.[26,] High TMB was defined as more than 10 mutations per megabase according to the FoundationOne CDx panel. The proportion of patients with an objective response in the tissue TMB (tTMB)-high group was 29%. At a median follow-up of approximately 3 years, the median duration of response was not reached in the tTMB-high group and was 33.1 months in the non-tTMB-high group. Notably, TMB-high status was associated with improved response irrespective of PD-L1. Median PFS and OS did not differ between the high and non-high TMB groups. Objective responses were observed in 24 (35%; 95% CI, 24 to 48) of 68 participants who had both tTMB-high status and PD-L1-positive tumors (i.e., PD-L1 combined positive score of ≥1) and in 6 (21%; 95% CI, 8 to 40) of 29 participants who had tTMB-high status and PD-L1-negative tumors. The KEYNOTE-158 nonrandomized phase 2 trial examined pembrolizumab; objective responses were observed in 35% of participants who had both TMB-high status and PD-L1-positive tumors and in 21% of participants who had TMB-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.

Section Summary: Tumor Mutational Burden Testing to Guide Immune Checkpoint Inhibitor Therapy
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 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 progression-free survival were not significantly different between TMB groups. In exploratory analyses, retrospective observational studies have reported an association between higher TMB and longer PFS and OS in patients receiving immunotherapy.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American Society of Clinical Oncology
Solid Tumors

In 2022, the American Society of Clinical Oncology (ASCO) published a provisional clinical opinion (PCO) on the appropriate use of tumor genomic testing in patients with metastatic or advanced solid tumors.[27,] The opinion notes the following:

PCO 1.1. Genomic testing should be performed for patients with metastatic or advanced solid tumors with adequate performance status in the following 2 clinical scenarios:

- When there are genomic biomarker-linked therapies approved by regulatory agencies for their cancer.
- When considering a treatment for which there are specific genomic biomarker-based contraindications or exclusions (strength of recommendation: strong).

PCO 1.2.1. For patients with metastatic or advanced solid tumors, genomic testing using multigene genomic sequencing is preferred whenever patients are eligible for a genomic biomarker-linked therapy that a regulatory agency has approved (strength of recommendation: moderate).

PCO 1.2.2. Multigene panel-based genomic testing should be used whenever more than one genomic biomarker is linked to a regulatory agency-approved therapy (strength of recommendation: strong).

PCO 2.1. Mismatch repair deficiency (dMMR) status should be evaluated on patients with metastatic or advanced solid tumors who are candidates for immunotherapy. There are multiple approaches, including using large multigene panel-based testing to assess microsatellite instability (MSI). Consider the prevalence of dMMR and/or MSI-high (MSI-H) status in individual tumor types when making this decision (strength of recommendation: strong).

PCO 2.2. When tumor mutational burden (TMB) may influence the decision to use immunotherapy, testing should be performed with either large multigene panels with validated TMB testing or whole-exome analysis (strength of recommendation: strong).

PCO 4.1. Genomic testing should be considered to determine candidacy for tumor-agnostic therapies in patients with metastatic or advanced solid tumors without approved genomic biomarker–linked therapies (strength of recommendation: moderate).

Head and Neck Cancers

In 2023, the ASCO released a guideline on immunotherapy and biomarker testing in recurrent and metastatic head and neck cancers.[28,] The guideline included a recommendation for programmed cell death ligand protein-1 (PD-L1) testing for individuals with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), and a consideration for TMB testing for individuals with recurrent or metastatic disease when the PD-L1 combined positive score is not available or in individuals with rare tumors.

National Comprehensive Cancer Network

The National Comprehensive Cancer Network (NCCN) cancer-specific guidelines provide recommendations for biomarkers that should be tested to guide decisions about immune checkpoint inhibitor therapy, and recommend testing techniques. Guidelines are updated frequently; refer to the source documents for current recommendations. The following NCCN guidelines were used to inform this evidence opinion:

- Bladder Cancer (v.3.2023)[29],
- Breast Cancer (v.4.2023)[30],
- Cervical Cancer (v.1.2024)[31],
- Colon Cancer. (v.3.2023)[32],
- Esophageal and Esophagogastric Junction Cancers (v.3.2023)[33],
- Head and Neck Cancers. (v.1.2024)[34],
- Melanoma: Cutaneous. (v.3.2023)[35],
- Non-Small Cell Lung Cancer. (v..5.2023)[36],
- Uterine Neoplasms. (v.1.2024)[37],

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 2.

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT04949113	Multicenter Phase 3 Trial Comparing Neoadjuvant Ipilimumab Plus Nivolumab Versus Standard Adjuvant Nivolumab in Macroscopic Stage III Melanoma - NADINA	420	Jan 2027
NCT05727904	A Phase 3, Multicenter, Randomized, Open-label, Parallel Group, Treatment Study to Assess the Efficacy and Safety of the Lifileucel (LN-144, Autologous Tumor Infiltrating Lymphocytes [TIL]) Regimen in Combination With Pembrolizumab Compared With Pembrolizumab Monotherapy in Participants With Untreated, Unresectable or Metastatic Melanoma	670	Mar 2030
NCT05722886	DETERMINE (Determining Extended Therapeutic Indications for Existing Drugs in Rare Molecularly Defined Indications Using a National Evaluation Platform Trial): An Umbrella-Basket Platform Trial to Evaluate the Efficacy of Targeted Therapies in Rare Adult, Paediatric and Teenage/Young Adult (TYA) Cancers With Actionable Genomic Alterations, Including Common Cancers With Rare Actionable Alterations	825	Oct 2029
NCT04008030	A Phase 3 Randomized Clinical Trial of Nivolumab Alone, Nivolumab in Combination With Ipilimumab, or Investigator's Choice Chemotherapy in Participants With Microsatellite Instability High (MSI-H) or Mismatch Repair Deficient (dMMR) Metastatic Colorectal Cancer	831	Jun 2026
NCT05328908	A Phase 3, Randomized, Open-label Study of Relatlimab-nivolumab Fixed-dose Combination Versus Regorafenib or Trifluridine + Tipiracil (TAS-102) for Participants With Later-lines of Metastatic Colorectal Cancer	700	May 2028
NCT04674683	A Multicenter, Randomized, Double-Blind Phase 3 Study of HBI-8000 Combined With Nivolumab Versus Placebo With Nivolumab in Patients With Unresectable or Metastatic Melanoma Not Previously Treated With PD-1 or PD-L1Inhibitors	480	Oct 2025
NCT04334759	DREAM3R: DuRvalumab (MEDI4736) With chEmotherapy as First Line treAtment in Advanced Pleural Mesothelioma - A Phase 3 Randomised Trial	480	Dec 2025
NCT05328908	A Phase 3, Randomized, Open-label Study of Relatlimab-nivolumab Fixed-dose Combination Versus Regorafenib or Trifluridine + Tipiracil (TAS-102) for Participants With Later-lines of Metastatic Colorectal Cancer	700	May 2028

NCT03036098	A Phase 3, Open-label, Randomized Study of Nivolumab Combined With Ipilimumab, or With Standard of Care Chemotherapy, Versus Standard of Care Chemotherapy in Participants With Previously Untreated Unresectable or Metastatic Urothelial Cancer	1307	Jul 2025
NCT03811015	A Phase III Randomized Study of Maintenance Nivolumab Versus Observation in Patients With Locally Advanced, Intermediate Risk HPV Positive OPSCC	636	Jan 2027
NCT03366272	Improvement of Outcome in Elderly Patients or Patients Not Eligible for High-dose Chemotherapy With Aggressive NHL in First Relapse/Progression by Adding Nivolumab to Gemcitabine, Oxaliplatin Plus Rituximab in Case of B-cell Lymphoma	388	Nov 2024
NCT05677490	Randomized Phase III Trial of mFOLFIRINOX vs. FOLFOX With Nivolumab for First-Line Treatment of Metastatic HER2-Gastroesophageal Adenocarcinoma	382	Nov 2028

NCT: national clinical trial.

Government Regulations

National:

No NCD available

Local:

CMS Billing and Coding: MolDX: FDA-approved BRAF Tests, A55161, effective 07/27/2023

Two tests have met the FDA criteria for BRAF genetic testing:

1. Effective 09/07/2012.
   cobas® 4800 BRAF V600 to detect the presence of a mutation in the BRAF gene in melanoma cells and determine if a patient is eligible for Zelboraf ™(vemurafenib), a treatment indicated for a melanoma that cannot be surgically excised or has spread in the body.
2. Effective 5/29/2013.
   ThxID™ BRAF V600/K to detect the BRAF V600E and V600K mutations in selecting melanoma patients whose tumors carry the BRAF V600E mutation for treatment with dabrafenib [Tafinlar®] and as an aid in selecting melanoma patients whose tumors carry the BRAF V600E or V600K mutation for treatment with trametinib [Mekinist™].

Billing and Coding: MolDX: Microsatellite Instability-High ((MSI-H) and Mismatch Repair Deficient (dMMR) Biomarker for Patients with Unresectable or Metastatic Solid Tumors. A56501. Effective 10/28/21. Retired 1/26/23.

This contractor will allow one of the following:

- dMMR by immunohistochemistry (IHC), **or**
- MSI by PCR, **or**
- Multi-gene NGS panel inclusive of MSI microsatellite loci, and MLH1, MSH2, MSH6 and PMS2 genes

Testing by one of the above methodologies is reasonable and necessary if testing for dMMR or MSI has not previously been performed on the patient's tumor sample. A multi-gene NGS panel inclusive of MSI microsatellite loci and MLH1, MSH2, MSH6 and PMS2 gene is reasonable and necessary. A multi-gene NGS panel and separate MSI by PCR will be denied as not reasonable and necessary. If testing is performed by NGS, the test must be a properly

designed and appropriately validated assay demonstrating 95% concordance to the reference method ((MSI by PCR).
To report a dMMR service, please submit the following claim information:

- CPT code 88342 – One (1) unit of service
- CPT code 88341 – Three (3) units of service

To report a MSI service, please submit the following claim information:

- CPT code 81301 – One (1) unit of service

To report by NGS, please submit the following claim information:

- CPT code 81479 – One (1) unit of service

Billing and Coding: MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer. A58756. Effective date: 10/01/23.
The information in this article contains billing, coding or other guidelines that complement the Local Coverage Determination (LCD) for MolDX: Lab-Developed Tests for Inherited Cancer Syndromes in Patients with Cancer L39040.
To report a service, please submit the following claim information:

- Select appropriate CPT® code
- Enter 1 unit of service (UOS)
- Enter the appropriate DEX Z-Code® identifier adjacent to the CPT® code in the comment/narrative field for the following Part B claim field/types:
    - Loop 2400 or SV101-7 for the 5010A1 837P
    - Box 19 for paper claim
- Enter the appropriate DEX Z-Code® identifier adjacent to the CPT® code in the comment/narrative field for the following Part A claim field/types:
    - Line SV202-7 for 837I electronic claim
    - Block 80 for the UB04 claim form
- Select the appropriate ICD-10-CM code

Regarding single-gene and panel testing of genes-Refer to Billing and Coding: MolDX: Testing of Multiple Genes A57880.
Tier 1 and/or Tier 2 individual biomarker CPT® codes should not be used for a single gene or any combination of genes when testing is performed as part of a NGS or other multiplexing technology panel.

MolDX: Next-Generation Sequencing for Solid Tumors. L38158. Effective 06/08/23.
This policy describes and clarifies coverage for Lab-Developed Tests (LDTs), Food and Drug Administration (FDA)-cleared, and FDA-approved clinical laboratory tests utilizing Next-Generation Sequencing (NGS) in cancer as allowable under the National Coverage Determination (NCD) 90.2, under section D describing Medicare Administrative Contractor (MAC) discretion for coverage. This policy's scope is specific for solid tumor testing, and is exclusive of hematologic malignancies, circulating tumor DNA testing (ctDNA), and other cancer-related uses of NGS, such as germline testing in/for patients with cancer.
All the following must be present for coverage eligibility:

- As per NCD 90.2, this test is reasonable and necessary when:
    - the patient has either:
        - Recurrent cancer
        - Relapsed cancer
        - Refractory cancer
        - Metastatic cancer
        - Advanced cancer (stages III or IV)

    - AND has not been previously tested by the same test for the same genetic content
    - AND is seeking further treatment
- The test has satisfactorily completed a TA by MolDX for the stated indications of the test
- The assay performed includes at *least* the minimum genes and genomic positions required for the identification of clinically relevant FDA-approved therapies with a companion diagnostic biomarker as well as other biomarkers known to be necessary for clinical decision making for its intended use that can be reasonably detected by the test. Because these genes and variants will change as the literature and drug indications evolve, they are listed separately in associated documents such as the MolDX TA forms.

Situations in which Test should not be used or coverage is denied: The test in question will be non-covered if:

- It does not fulfill all the criteria set forth in the NCD 90.2 as stated above
- Another CGP test was performed on the same tumor specimen (specimen obtained on the same date of service)
- A TA is not completed satisfactorily by MolDX for new tests
- For tests that are currently covered but a TA submission has not been made, providers must submit completed TA materials by February 10th, 2020, or coverage will be denied

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Prostate Cancer (BRCA1/2, Homologous Recombination Repair Gene Alterations, Microsatellite Instability/Mismatch Repair, Tumor Mutational Burden
- Germline and Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Ovarian Cancer (BRACA1/2, HRD, TMB, MI/MMR)
- Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Non-Small-Cell Lung Cancer (KRAS, NRAS, BRAF, MMR/MSI, HER2 AND TMB)
- gT—BRAF Mutation in Selecting Melanoma Patients for Targeted Therapy Including Liquid Biopsy

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through November 2023, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/24	1/2/14		Joint policy established. Vendor managed: N/A (ds)

Next Review Date: 4th Qtr., 2024

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN:	Revised:
BCBSM:	Revised:

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: GT-SOMATIC BIOMARKER TESTING FOR IMMUNE CHECKPOINT INHIBITOR THERAPY (BRAF, MSI/MMR, PD-L1, TMB)

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered per policy
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.