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DESCRIPTION:

Serum tumor markers are molecules or substances shed by a tumor into the circulation where they can be detected and quantitated. Noncirculating tumor markers include those that can be detected histochemically or cytogenetically on a tissue sample.

Since serum tumor markers can also be detected in normal or benign lesions, significantly elevated circulating levels may occur with malignancy by one or more of the following mechanisms: overexpression of the antigen by malignant cells; a large tumor burden; or slower clearance of the marker. For example, since the liver clears most tumor markers, liver abnormalities (whether benign, malignant, or inflammatory) may elevate tumor marker concentrations due to impaired clearance. Because most tumor markers are not unique to malignancy, cut-off points must be established for normal versus abnormal marker levels.

The clinical applicability of tumor markers depends on how their measurements are used to influence the management of the patient and whether these management changes will result in an improvement in net health outcome.

Summary and Analysis of Evidence: Markers in fine needle aspiration (FNA) of the thyroid: The evidence for patients who receive FNA sample testing with these tests to rule out malignancy and to avoid surgical biopsy or resection, the evidence includes prospective clinical validity studies with the Afirma GSC, a systematic review of prospective and retrospective clinical validity studies, a meta-analysis of real-world post validation data for the Afirma GSC platform with comparison to the validation study, and a chain of evidence to support clinical utility. The meta-analysis of real-world Afirma GSC data indicated significantly higher NPV (as well as specificity and positive predictive value [PPV]) than in the validation study. In other multicenter and single-center studies, there is suggestive evidence that rates of malignancy are low in Afirma GSC or ThyroSeq v3 patients who are classified as benign or negative, with high NPVs in a prospective trial with 31.8 months of post-testing imaging surveillance. The available

evidence suggests that the decisions a physician makes regarding surgery are altered by Afirma GSC or ThyroSeq v3 results. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Evidence for testing to rule in malignancy and to guide surgical planning includes prospective and retrospective studies of clinical validity. Single-center studies have suggested that testing for a panel of genetic variants associated with thyroid cancer may allow for the appropriate selection of patients for surgical management for the initial resection. Prospective studies in additional populations are needed to validate these results. Although the presence of certain variants may predict more aggressive malignancies, the management changes that would occur as a result of identifying higher risk tumors, are not well-established. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Evidence for testing to rule out malignancy and avoid surgical biopsy or to rule in malignancy for surgical planning includes multiple retrospective and prospective clinical validation studies for the ThyroSeq test, a systematic review of retrospective and prospective studies, and 2 retrospective clinical validation studies that used a predicate test 17-variant panel (miRInform) test to the current ThyGenX and ThyraMIR. A prospective clinical validation study of ThyroSeq v3 reported an NPV of 97% and PPV of 68%. Similarly, a systematic review including 3 prospective and 3 retrospective clinical validity studies reported an NPV of 92% and PPV of 70%. No prospective studies were identified demonstrating evidence of direct outcome improvements. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Alzheimer disease (AD): Patients who have mild cognitive impairment (MCI) or mild dementia due to AD who are being considered for initial treatment with an approved amyloid beta plaque targeting therapy, the evidence includes randomized controlled trials, multisite longitudinal studies, and an analysis of a mixed cohort. Overall, the diagnostic accuracy of CSF biomarkers versus amyloid PET scans to identify MCI-AD was found to be similar. CSF biomarkers have been used as an alternative to PET amyloid scans to establish eligibility regarding the presence of amyloid beta pathology in randomized controlled trials that showed the efficacy of anti-amyloid therapies, which in turn demonstrates that the CSF biomarkers can identify patients who may benefit from therapy. The FDA-approved labels for lecanemab and donanemab state that the presence of amyloid beta pathology should be confirmed prior to initiating treatment. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. Patients who are being treated with an amyloid beta plaque targeting therapy and are being evaluated for therapy continuation, the evidence includes multisite longitudinal studies and an analysis of a mixed cohort. The diagnostic accuracy of CSF biomarkers versus amyloid beta PET scans to identify MCI-AD was found to be similar. Further research is required to determine whether the use of CSF biomarkers alone in conjunction with amyloid beta PET scans is useful for determining whether amyloid beta targeting therapy should be continued. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Patients with MCI or dementia who receive urinary biomarker testing for AD, the evidence includes a systematic review. Clinical validity studies have included normal healthy controls and defined optimal test cutoffs without validation; thus, clinical validity is uncertain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Gene expression profiling for cutaneous melanoma (CM): Suspicious pigmented lesions considered for biopsy tested who receive gene expression profiling (GEP) with the DermTech Pigmented Lesion Assay to determine which lesions should proceed to biopsy, the evidence includes observational studies. The Pigmented Lesion Assay has clinical validity studies with many methodologic and reporting limitations and thus, performance characteristics are not well-characterized. No direct evidence of clinical utility

was identified. Given that the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility through a chain of evidence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Melanocytic lesions with indeterminate histopathologic features who receive GEP with the myPath Melanoma test added to histopathology to aid in the diagnosis of melanoma, the evidence includes observational studies. The myPath test has clinical validity studies including long-term follow-up for metastasis as the reference standard. In one study, it is not clear whether the study population included lesions that were indeterminate following histopathology. Another study focused on indeterminate lesions but had limitations including a retrospective design and less than 5-year follow-up in 31% of cases. Therefore, performance characteristics are not well-characterized. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Patients who receive GEP with the DecisionDx-Melanoma test to inform management decisions regarding surveillance, adjuvant therapy, or to determine whether to perform sentinel lymph node (SLN) biopsy the evidence includes several retrospective and prospective observational studies. Greenhaw et al (2018) concluded "the GEP test proved to be a prognostic tool with high accuracy for low-risk patients and accuracy approximating SLNB accuracy for high-risk patients. The information it provides has the potential to help direct patient management. Long-term follow-up studies will be needed to further strengthen our findings". Grossman et al (2020) state "The MPWG [Melanoma Prevention Working Group] consensus is that there are insufficient data to support routine use of currently available prognostic GEP tests to inform management for patients with CM. The MPWG recommends further research to assess the validity and clinical applicability of existing and emerging GEP tests. Decisions on performing GEP testing and patient management based on these results should only be made in the context of discussion of testing limitations with the patient or within a multidisciplinary group". The authors noted "The limitations of our study include inability to review all relevant data, including proprietary industry data and other data published after the manuscript was submitted. Additionally, there was a relatively low combined response rate to both surveys." Hsueh et al (2021) concluded "This study confirms the clinical validity of the 31-GEP test in patients with stage I-IIA CM with class 2 GEP results who may benefit from more intense follow-up. Patients with a class 2 31-GEP, including patients with stage I-IIA CM, have 3-year survival rates similar to those for patients with stage IIB-III CM. Moreover, the combination of GEP testing with AJCC staging improves the accuracy of prognosis. These data provide a rationale for using the 31-GEP test in conjunction with AJCC staging to obtain an optimal prognosis for patients with CM". A 2023 ECRI Genetic Test Assessment, DecisionDx-Melanoma for Evaluating Prognosis and Guiding Management of Cutaneous Melanoma concluded "DecisionDx-Melanoma GEP stratifies patients with CM by high and low risk of recurrence and by survival likelihood, informs patient management decisions, and may improve patient outcomes (e.g., overall survival) by informing decisions to escalate surveillance when the test is added to best available care (i.e., tumor staging, SLNB). The available studies do not permit conclusions on whether DecisionDx-Melanoma enables patients to safely forgo SLNB, and longitudinal studies are needed that report on long-term health outcomes (e.g., recurrence) in patients who forgo biopsy". Podlipnik et al (2024) concluded "incorporating the 31-GEP into clinical practice may benefit patients by providing additional information that clinicians can use to make personalized, risk-aligned treatment and surveillance management plans". The authors reported the study had limitations. "Although using the SEER database allows for observations of a diverse, unselected population, the dataset limitations include underreported (chemotherapy and radiation) and incomplete information for some variables (e.g., Breslow thickness, and ulceration status for newer SEER registries). Additionally,

SEER data do not include information about patient outcomes other than survival and cause of death, and the treatment data are limited to the first course of treatment (surgery, radiation and chemotherapy). Therefore, staging cannot be assessed using SEER data for some patients." Durgham et al (2024) state "In conclusion, while further research is needed to fully define its optimal clinical use, in terms of clarifying which patients may benefit most from the prognostic insight provided by the 31-GEP assay as well as how best to integrate these findings into treatment and management algorithms, the 31-GEP assay represents a promising tool for enhancing risk stratification and potentially improving patient outcomes in the management of this challenging malignancy". Pazhava et al (2025) evaluated the clinical utility and performance of the 31-GEP test in a real-world setting. Results of the study: "The study included 65 CM patients. Dermatologists ordered more than 80% of 31-GEP tests. In 81.5% of cases, 31-GEP results did not alter standard clinical management. SLNB decisions were unaffected in 92% of patients with pre-SLNB 31-GEP results. Among patients with stage I-IIA melanoma, 25% of those with high-risk 31-GEP results were referred to medical oncology. Contrary to expectations, the rate of nodal metastasis was higher in low-risk than in high-risk 31-GEP cases. Survival analysis showed overlapping RFS and MSS curves between different 31-GEP classes, suggesting limited prognostic value." The authors concluded that "The 31-GEP test has a limited impact on clinical management decisions and shows limited prognostic value". The 2025 Society of Surgical Oncology Consensus Statement: Assessing the Evidence for and Utility of Gene Expression Profiling of Primary Cutaneous Melanoma (Bartlett et al) described the findings of a panel of melanoma experts from the Society of Surgical Oncology who convened to develop recommendations regarding the use of GEP to guide management of patients with melanoma. Results were that "current evidence often fails to account for known clinicopathologic risk factors and lacks high-level data. The panel recognizes that the study of GEP tests is still evolving. The integration of GEP into routine clinical practice for predicting sentinel lymph node status and patient prognosis in melanoma is therefore not currently recommended". The authors concluded, "At present, GEP should be considered primarily an investigational tool, ideally used in the context of clinical trials or specialized research settings." The current evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Multicancer early detection testing (Galleri®): Patients screened for cancer who receive multicancer early detection (MCED) testing, the relevant published evidence includes systematic reviews, and a US-based prospective study. A systematic review of 36 studies on MCED tests highlighted variability in diagnostic accuracy. Evidence was limited, with no completed RCTs. Insufficient follow-up for negative results led to high risk of bias across studies. One prospective study of the Galleri test reported a positive predictive value of 38% and specificity and negative predictive value of approximately 99%. The specifics regarding the practical application of the test, including the appropriate at-risk target populations, frequency of testing, and follow-up for positive and negative results, have not been fully described. No clinical utility studies have been published to date, and estimates of changes in cancer-specific mortality, quality of life, functional outcomes, and rates of overdiagnosis and overtreatment remain unknown. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Urinary markers (e.g. Cxbladder™): The evidence for the use of urinary tumor marker tests (e.g. Cxbladder™) for patients who have signs or symptoms of bladder cancer, the evidence includes a number of diagnostic accuracy studies and meta-analyses of these studies. A meta-analysis of diagnostic accuracy studies determined that urinary tumor marker tests have a sensitivity ranging from 47% to 82% and specificity ranging from 53% to 95%. This analysis found that combining urinary tumor markers with cytology improves diagnostic accuracy, but about 10% of cancers would still be missed. The evidence is

insufficient to determine that the technology results in an improvement in the net health outcome. Circulating tumor cells (e.g. CellSearch tests): The evidence for testing circulating tumor cells in patients who have cancer to select treatment or monitor treatment response includes observational studies and randomized controlled trial. Published studies reporting clinical outcomes and/or clinical utility are lacking. The uncertainties concerning clinical validity and clinical utility preclude conclusions about whether the use of circulating tumor cells can replace variant analysis of tissue. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Multimarker testing for ovarian cancer: Evidence for the use of multimarker serum testing for patients who have adnexal masses undergoing surgery for possible ovarian cancer includes studies assessing technical performance and diagnostic accuracy. OVA1 and Overa are intended for use in patients for whom clinical assessment does not clearly indicate cancer. When used in this manner, sensitivity for ovarian malignancy was 92% and specificity was 42% with OVA1; with Overa, sensitivity was 94% and specificity was 65%. ROMA is intended for use with clinical assessment, but no specific method has been defined. One study, which used clinical assessment and ROMA results, showed a sensitivity of 90% and specificity of 67%. However, the National Comprehensive Cancer Network guidelines recommend (category 2A) that all patients with suspected ovarian cancer should be evaluated by an experienced gynecologic oncologist. Given the National Comprehensive Cancer Network recommendation, direct evidence will be required to demonstrate that the use of the testing to inform decisions regarding referral to a gynecologic oncology specialist for surgery has clinical usefulness. Direct evidence of clinical usefulness is provided by studies that have compared health outcomes for patients managed with and without the FDA cleared multimarker serum testing. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Human epididymis protein 4 (HE4) biomarker: The evidence for the use of biomarker HE4 for patients who have ovarian cancer includes 7 nonrandomized prospective and retrospective studies comparing the diagnostic accuracy of HE4 with CA 125 for predicting disease progression and/or recurrence. The superiority of HE4 to CA 125 (alone or in combination), the key question in the evidence review, was not demonstrated in the available literature. In addition, there is no established cutoff in HE4 levels for monitoring disease progression, and cutoffs in studies varied. For patient who adnexal masses the evidence includes diagnostic accuracy studies and meta-analyses. The number of studies evaluating the combined test is relatively low, and publication bias in studies of HE4 has been identified. In addition, studies have not found that HE4 improves diagnostic accuracy beyond that of subjective assessment of transvaginal ultrasound. There is no direct evidence from prospective controlled studies on the impact of HE4 testing on health outcomes, and no clear chain of evidence that changes in management based on HE4 would lead to an improved health outcome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Pulmonary nodules (e.g. REVEAL, Nodify XL2): Evidence for the use of plasma based proteomic screening for patients with undiagnosed pulmonary includes prospective cohorts, retrospective studies, and prospective retrospective studies. The Nodify XL2 classifier has undergone substantial evolution, from a 13-protein assay to a 2-protein assay integrated with clinical factors. The classifier has been designed to have high specificity for malignant pulmonary nodules, and the validation study showed a specificity of 97% for patients with a low-to-moderate pretest probability (≤50%) of a malignant pulmonary nodule. The primary limitation of this study is that a high number of patients were excluded from the study due to incomplete clinical data or because they were subsequently determined to be outside of the intended use population. Validation

in an independent sample in the intended use population is needed. The REVEAL validation study was a retrospective study that demonstrated use as a rule-out test in conjunction with the Veteran's Affairs (VA) Clinical Factors Model when the samples were considered inconclusive or intermediate risk by the VA model. The REVEAL model subsequently correctly identified 65% of intermediate-risk samples as either low or high risk. The negative predictive value and sensitivity were both 94%. Limitations included a small sample size and use in conjunction with just 1 type of testing model. Validation in an independent sample in the intended use population with additional probability models is needed. Indirect evidence suggests that a proteomic classifier with a high negative predictive value has the potential to reduce the number of unnecessary invasive procedures to definitively diagnose benign disease versus malignancy. However, long-term follow-up data would be required to determine the survival outcomes in patients with a missed diagnosis of lung cancer at earlier, more treatable stages. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Cancers of unknown primary (e.g. Tissue of Origin): Patients who have cancers of unknown primary who receive gene expression profiling, the evidence includes studies of clinical validity and randomized controlled trials. The clinical validity is the ability of a test to determine the site of origin. Using different reference standards (known tumor type, reference diagnosis, a primary tumor identified during follow-up, immunohistochemical analysis) for the tissue of origin, the tests have reported sensitivities or concordances generally high (e.g., 80% to 90% or more). However, the reference standard is imperfect, and evidence for clinical validity does not support potential benefit. Direct evidence of clinical utility is provided by studies that compare health outcomes for patients managed with and without the test. The benefit would be most convincingly demonstrated through a trial randomizing patients with cancers of unknown primary to receive treatment based on gene expression profiling results or usual care. One published RCT and 1 conference presentation with this design were identified. These trials did not find a survival benefit for patients with cancers of unknown primary who received treatment based on the site of origin as determined by molecular testing. A limitation in interpretation of the published trial results is that there were few treatments that were site specific, so there was minimal difference in the actual treatments given to the 2 groups. In the second RCT, most cancers responded to the control treatments. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Proteomic testing (VeriStrat®): The evidence for the use of VeriStrat test for patients with advanced non-small cell lung cancer (NSCLC) includes retrospective studies and randomized control trials. The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer includes, “Recommend proteomic testing for patients with NSCLC and wild-type EGFR or with unknown EGFR status. A patient with a “poor” classification should not be offered erlotinib in the second-line setting. Proteomic testing can be used to determine whether erlotinib should be used in patients with unknown EGFR status. Erlotinib is superior to best supportive care with significantly improved survival and delayed time in symptom deterioration in patients with non-squamous NSCLC.” The evidence is sufficient for the use of the testing for wild-type tumor (no mutation detected) EGFR OR with unknown EGFR status, failed first-line systemic chemotherapy, and results of the testing to be used to determine whether to proceed with erlotinib therapy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome for all other indications.
Systemic lupus erythematosus (SLE) and other connective tissue diseases: Patients with signs or symptoms of SLE who receive serum biomarker panel testing, the evidence includes several diagnostic accuracy studies and prospective evaluation of clinical utility that compared the impact of the test

results on physicians' evaluation of individuals with a clinical suspicion for SLE. Observational studies have been primarily retrospective in design, not performed in the intended-use population and lacking concurrent, appropriate comparator. Additionally, a randomized controlled trial (RCT) evaluated the influence of test results from Avise and standard diagnosis laboratory testing on rheumatologists' change in physician global assessment for the likelihood of SLE, which is not a health outcome. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Patients with signs or symptoms of other connective tissue diseases who receive serum biomarker panel testing, more studies are needed. Relevant outcomes are test accuracy, symptoms, and quality of life. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.
Squamous cell carcinoma (e.g. DecisionDx®-SCC): A 2024 article titled, Limitations of the Commercially Available Gene Expression Test in Predicting Cutaneous Squamous Cell Carcinoma Metastasis and Clinical Outcomes (Sax et al) concludes, "Analysis of DecisionDx-SCC indicates potential biases and ambiguities, exacerbated by differences between FDA and CLIA standards. This highlights the need for systematic validation and a unified regulatory approach, stressing the necessity for precise and dependable genetic testing in patient care". The current data are inadequate to permit scientific conclusions regarding the impact on management decisions and net health outcomes. Guardant360 TissueNext™: A 2023 article titled, Brief Report: Discordance Between Liquid and Tissue Biopsy-Based Next-Generation Sequencing in Lung Adenocarcinoma at Disease Progression (Tran et al) states, "There are limitations to this study. It is a retrospective study at a single, urban academic medical center. Prospective validation in a more heterogeneous patient population or meta-analysis with aggregate datasets may be useful. Paired tests occurred within 24 weeks of each other and without an intervening change in therapy. While this time window was based on prior literature, we acknowledge this is a wide window and ideally this testing would have occurred simultaneously. Only a single platform (Guardant360) was included, and it is unclear if these results are generalizable to all ctDNA testing. Additionally, liquid biopsy tests have historically performed poorly in detecting fusions, which may have limited liquid biopsy sensitivity. Additionally, our analysis centered on variants that are clinically actionable now, at the present time. Both the threshold variant allele frequencies and variants themselves can change over time, thus becoming more (or less) actionable. Therefore, an update to this study will be needed in the future." No published data was found that assessed the clinical utility and clinical validity of the Guardant360 TissueNext test. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. There is insufficient evidence to support the use of the following tests for all indications: HelioLiver™, Multiple Sclerosis Disease Activity Test (MSDA), Praxis Extended RAS Panel, PreDx Diabetes Risk Score™; Darwin OncoTreat™; Decipher® Bladder TURBT; MSK-Impact; LC-MS/MS Targeted Proteomic assay; NavDx®. Although there may be ongoing clinical studies, the current data are inadequate to permit conclusions regarding the impact on management decisions and net health outcomes.

POSITION STATEMENT:

Note: Coverage may be governed by state or federal mandates.

Evaluation of Biomarkers for Alzheimer Disease	Cerebrospinal fluid biomarker testing of amyloid beta peptides and tau protein as part of an evaluation for the initiation of amyloid beta targeting therapy in members

Note: Genetic testing for Alzheimer disease (see MCG 05-82000-28) may be offered along with analysis of cerebral spinal fluid levels of the tau protein and amyloid-b peptide 1-42. This group of tests may be collectively referred to as the Admark™ Profile, offered by Athena Diagnostics.	with mild cognitive impairment or mild dementia due to Alzheimer disease **meets the definition of medical necessity**. Cerebrospinal fluid biomarker testing of neural thread proteins as part of an evaluation for the initiation of amyloid beta targeting therapy in members with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **experimental or investigational**. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome. Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as an adjunct to clinical diagnosis in members with mild cognitive impairment or members with mild dementia due to Alzheimer disease is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. Cerebrospinal fluid biomarker testing, including but not limited to amyloid beta peptides, tau protein, or neural thread proteins, as part of an evaluation for the continuation of amyloid beta targeting therapy in members with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. Measurement of urinary and blood biomarkers as an adjunct to clinical diagnosis in members with mild cognitive impairment or mild dementia due to Alzheimer disease is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.
Breast Tumor Markers	CA 15-3 (CA 27.29 or Truquant RIA) **meets the definition of medical necessity** for the following indications: • As an aid in the management of Stage II and Stage III breast cancer members. Serial testing for CA 15-3 assay values should be used in conjunction with other clinical methods for monitoring breast cancer

	• As an aid to predict recurrent breast cancer in members with previously treated Stage II or Stage III disease • As an aid in monitoring response to therapy in members with Stage IV breast cancer. A partial or complete response to treatment will be confirmed by declining levels. A persistent rise of CA 27-29 levels despite therapy strongly suggests progressive disease. CA 15-3 (CA 27.29 or Truquant RIA) is considered **experimental or investigational**, as there is insufficient clinical evidence to support the use of CA 15-3 (CA 27.29 or Truquant RIA) as a screening test for breast cancer. There is a lack of clinical data to permit conclusions on efficacy and net health outcomes.
Cancer Antigen 125 (CA-125)	CA-125 testing **meets the definition of medical necessity** in individuals with symptoms suggestive of ovarian cancer; symptoms may include: • Swelling of the abdomen (ascites) • Gastrointestinal symptoms (e.g., gas, bloating, long-term stomach pain, indigestion) • Bleeding between periods or after menopause • Pelvic pain • Feeling of pressure in the pelvis • Leg pain. CA-125 testing **meets the definition of medical necessity** in individuals with other gynecologic malignancies, such as endometrial cancer, in whom baseline levels of CA-125 have been shown to be elevated. CA-125 testing in asymptomatic individuals is considered **experimental or investigational.** There is insufficient clinical evidence to support the use of CA-125 testing as a screening technique for ovarian cancer.
Cardiovascular Disease Risk Panels (Cardiovascular risk panels may include: Applied Genetics	Cardiovascular disease risk panels, consisting of multiple individual biomarkers intended to assess cardiac risk (other than simple lipid panels*****), are considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.

Cardiac Panel; Boston Heart Advanced Risk Markers Panel; Cleveland HeartLab CVD Inflammatory Profile; Genetiks Genetic Diagnosis and Research Center Cardiovascular Risk Panel; Genova Diagnostics CV Health Plus Genomics™ Panel; Health Diagnostics Cardiac Risk Panel; Metametrix Cardiovascular Health Profile; MI-HEART Ceramides; Spectracell LPP™.)	*****A simple lipid panel is generally composed of the following lipid measures:Total cholesterol; LDL cholesterol; HDL cholesterol; Triglycerides. Certain calculated ratios, such as the total/HDL cholesterol may also be reported as part of a simple lipid panel. Other types of lipid testing, i.e., apolipoproteins, lipid particle number or particle size, lipoprotein (a), etc., are not considered to be components of a simple lipid profile.
Gene Expression Profiling for Colorectal Cancer	Gene expression profiling (e.g., ColonSentry®, BeScreened™-CRC) is considered **experimental or investigational** for colorectal cancer screening. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.
Tumor-Informed Circulating Tumor DNA	Tumor-informed circulating tumor DNA testing (e.g., Signatera™) is considered **experimental or investigational** for all indications. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.
Cutaneous Melanoma (DecisionDx DiffDx- Melanoma)	Gene expression testing, including but not limited to the Pigmented Lesion Assay (PLA), in the evaluation of members with suspicious pigmented lesions is considered **experimental or investigational**. Gene expression testing, including but not limited to the myPath Melanoma test, in the evaluation of members with melanocytic lesions with indeterminate histopathologic features is considered **experimental or investigational**. Gene expression testing, including but not limited to DecisionDx-Melanoma, in the evaluation of members with cutaneous melanoma is considered **experimental or investigational** for all indications. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Microarray-Based Gene Expression Profile Testing for Multiple Myeloma Risk Stratification (MyPRS™/MyPRS Plus™)	Microarray-based gene expression profile testing for multiple myeloma is considered **experimental or investigational** for all indications. The evidence is insufficient to determine the effects of the technology on health outcomes.
FDA Cleared or Approved Companion Diagnostic Devices	Biomarker identification **meets the definition of medical necessity** when confirmation is required per the "Indications and Usage" of the FDA-approved prescribing label prior to initiating therapy. List of Cleared or Approved Companion Diagnostic Devices can be found at: https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools
Molecular Markers in Fine Needle Aspirates of the Thyroid	For members who have thyroid nodules without strong clinical or radiologic findings suggestive of malignancy in whom surgical decision making would be affected by test results, the use of either of the following types of molecular marker testing or gene variant analysis in fine needle aspirates of thyroid nodules with indeterminate cytologic findings (i.e., Bethesda diagnostic category III [atypia/follicular lesion of undetermined significance] or Bethesda diagnostic category IV [follicular neoplasm/suspicion for a follicular neoplasm]) **meets the definition of medical necessity**: • Afirma® Genomic Sequencing Classifier; or • ThyroSeq®. The use of any of the following types of molecular marker testing or gene variant analysis in fine needle aspirates of thyroid nodules with indeterminate findings (Bethesda diagnostic category III [atypia/follicular lesion of undetermined significance] or Bethesda diagnostic category IV [follicular neoplasm/suspicion for a follicular neoplasm]) or suspicious findings (Bethesda diagnostic category V [suspicious for malignancy]) to rule in malignancy to guide surgical planning for initial resection rather than a 2-stage surgical biopsy followed by definitive surgery **meets the definition of medical necessity**: • ThyroSeq;

	• ThyraMIR® microRNA/ThyGenX®; • Afirma BRAF after Afirma Genomic Sequencing Classifier; or • Afirma MTC after Afirma Genomic Sequencing Classifier. Gene expression classifiers, genetic variant analysis, and molecular marker testing in fine needle aspirates of the thyroid not meeting criteria outlined above, including but not limited to use of RosettaGX Reveal and single-gene TERT testing, are considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.
Holo-Transcobalamin	Measurement of holo-transcobalamin, including but not limited to its use in the diagnosis and management of vitamin B12 deficiency, is considered **experimental or investigational.** There is insufficient clinical evidence to support the use of the measurement of holo-transcobalamin to identify early states of vitamin B12 deficiency. There are inadequate data to establish holo-TC testing as an alternative to either serum cobalamin or levels of MMA or homocysteine.
Long-Chain Omega-3 Fatty Acids in Red Blood Cell Membranes	Measurement of long chain omega-3 fatty acids in red blood cell membranes is considered **experimental or investigational**, as there is insufficient clinical evidence to support the use of the measurement of long chain omega-3 fatty acids as a cardiac risk factor. There is a lack of scientific evidence in the published literature regarding how measurements of red blood cell omega-3 fatty acid would affect management of individuals at risk for or members with coronary artery disease (CAD).
Management of Pulmonary Nodules (Nodify CDT®, REVEAL Lung Nodule Characterization)	Plasma-based proteomic screening, including but not limited to BDX-XL2 (Nodify XL2®), in members with undiagnosed pulmonary nodules detected by computed tomography is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes. Gene expression profiling on bronchial brushings, including but not limited to Percepta® Genomic Sequencing Classifier, in members with indeterminate bronchoscopy results from undiagnosed pulmonary

	nodules is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.
Measurement of Serum Antibodies to Selected Biologic Agents (e.g. infliximab, adalimumab, vedolizumab, or ustekinumab) (LabCorp® Adalimumab Concentration & Anti-Adolimumab Antibody; Prometheus® Anser™ IFX; Prometheus® Anser™ ADA; Prometheus® Anser UST; Prometheus® Anser™ VDZ)	Measurement of antidrug antibodies in a member receiving treatment with a biologic agent, either alone or as a combination test, which includes the measurement of serum TNF blocking agent levels, is considered **experimental or investigational**. There is insufficient evidence in medical literature regarding the clinical utility and impact on clinical outcomes to permit conclusions on net health outcomes.
Gene Expression-Based Assays for Cancers of Unknown Primary (CancerTYPE ID®, MiRview® tests, Tissue of Origin®, ProOnc TumorSource DX™, RosettaGX Cancer Origin™ (formerly miRview® met^2).	Gene expression profiling is considered **experimental or investigational** to evaluate the site of origin of a tumor of unknown primary, or to distinguish a primary from a metastatic tumor. The evidence is insufficient to determine the effects of the technology on health outcomes.
Multianalyte Assays for Chronic Liver Disease	A single FibroSURE® multianalyte assay **meets the definition of medical necessity** for the evaluation of members with chronic liver disease. FibroSURE® multianalyte assays are considered **experimental or investigational** for monitoring members with chronic liver disease. The evidence is insufficient to determine the effects of the technology on health outcomes. The use of other multianalyte assays with algorithmic analyses (e.g. FIBROSpect® II) is considered **experimental or investigational** for the evaluation or monitoring of members with chronic liver disease. The evidence is insufficient to determine the effects of the technology on health outcomes.

Multibiomarker Disease Activity Score for Rheumatoid Arthritis (Prism™ RA)	The use of a multibiomarker disease activity score for rheumatoid arthritis (e.g., Vectra® score) is considered **experimental or investigational** in all situations. The evidence is insufficient to determine the effects of the technology on health outcomes.
Multicancer Early Detection Testing	The use of multicancer early detection (MCED) tests (e.g. Galleri®) is considered **experimental or investigational** for cancer screening. The evidence is insufficient to determine the effects of the technology on health outcomes.
Multimarker Serum Testing Related to Ovarian Cancer	All uses of the Ova1®, Ova1Plus®, Overa™, OvaWatch℠, and ROMA™ tests are considered **experimental or investigational**, including but not limited to: • preoperative evaluation of adnexal masses to triage for malignancy • screening for ovarian cancer • selecting members for surgery for an adnexal mass • evaluation of members with clinical or radiologic evidence of malignancy • evaluation of members with nonspecific signs or symptoms suggesting possible malignancy, or • postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.
Pharmacogenomic and Metabolite Markers for Members Treated with Thiopurines	One-time genotypic or phenotypic analysis of thiopurine methyltransferase (TPMT) and nudix hydrolase (NUDT15) **meets the definition of medical necessity** in members beginning therapy with azathioprine (AZA), mercaptopurine (6-MP), thioguanine, or in members on thiopurine therapy with abnormal complete blood count (CBC) results that do not respond to dose reduction. Genotypic and/or phenotypic analysis of TPMT and NUDT15 is considered **experimental or investigational** for all other indications. The evidence is insufficient to determine the effects of technology on net health outcomes.

	Analysis of the metabolite markers of azathioprine (AZA) and mercaptopurine (6-MP), including 6-methyl-mercaptopurine ribonucleotides (6-MMRP) and 6-thioguanine nucleotides (6-TGN), is considered **experimental or investigational.** The evidence is insufficient to determine the effects of technology on net health outcomes.
Proteogenomic Testing for Members With Cancer	Proteogenomic testing of members with cancer (including but not limited to GPS Cancer™ test) is considered **experimental or investigational** for all indications. The evidence is insufficient to determine the effect of the technology on health outcomes.
Proteomic Testing for Advanced Non-Small Cell Lung Cancer (NSCLC)	Proteomic testing (VeriStrat®) **meets the definition of medical necessity** for members with advanced non-small cell lung cancer (NSCLC) meeting **ALL** of the following criteria: • tumor is wild-type (no mutation detected) EGFR **OR** with unknown EGFR status; • failed first-line systemic chemotherapy; **AND** • test results will determine whether to proceed with erlotinib (Tarceva®) therapy. Proteomic testing (VeriStrat) is considered **experimental or investigational** for all other indications. There is insufficient evidence to permit conclusions on clinical utility or net health outcomes.
Serum Biomarker Human Epididymis Protein 4 (Architect HE4 assay, Elecsys HE4, HE4 EIA Kit, HE4 immunoassay, Lumipulse G HE4 Immunoreaction)	Measurement of human epididymis protein 4 (HE4) is considered **experimental or investigational** for all indications. The evidence is insufficient to determine the effects of the technology on health outcomes.
Serum Biomarker Panel Testing for Systemic Lupus Erythematosus and Other Connective Tissue Diseases (Avise® CTD, Avise® Lupus, Avise® Monitor, Avise® MCV, Avise® MTX, Avise® PG, Avise®	Serum biomarker panel testing with proprietary algorithms and/or index scores for the diagnosis of systemic lupus erythematosus and other connective tissue diseases is considered **experimental or investigational.** The evidence is insufficient to determine the effects of the technology on health outcomes.

Prognostic, Avise® SLE, Avise® SLE+, Avise® SLE Monitor)	
Serum Biomarker Tests for Multiple Sclerosis	Serum biomarker tests (e.g. gMS® Dx, gMS® Pro EDSS) for multiple sclerosis are considered **experimental or investigational** for all indications. There is insufficient evidence from prospective studies demonstrating improved health outcomes in individuals who may have multiple sclerosis and who are treated according to test results.
Uveal Melanoma	Gene expression profiling for uveal melanoma with DecisionDx-UM **meets the definition of medical necessity** for members with primary, localized uveal melanoma. Gene expression profiling for uveal melanoma that do not meet the above criteria is considered **experimental or investigational**. The evidence is insufficient to determine the effects of the technology on health outcomes.

The following tumor markers are considered **experimental or investigational** for all indications, as there is insufficient evidence in the peer reviewed medical literature to support the use of these markers for screening, diagnosing, staging, surveillance or monitoring response to treatment:

Table 1

a2-PAG	pregnancy-associated alpha-2-glycoprotein
BCM	breast cancer mucin
CA50	cancer antigen 50
CA72-4	cancer antigen 72-4
CA195	cancer antigen 195
CA242	cancer antigen 242
CA549	carbohydrate antigen/cancer antigen 594
CA-SCC	squamous cell carcinoma antigen
CAM17-1	monocolonal antimucin antibody 17-1
CAM26	monocolonal antimucin antibody 26
CAM29	monocolonal antimucin antibody 29
CAR-3	antigenic determinant recognized by monoclonal antibody AR-3
DU-PAN-2	sialylated carbohydrate antigen DU-PAN-2
MCA	mucin-like carcinoma-associated antigen
NSE	neuron-specific enolase
PLAP	placental alkaline phosphatase
PNA/ELLA	peanut lectin bonding assay
SLEX	sialylated Lewis X-I antigen
SLX	sialylated SSEA-1 antigen

SPAN-1	sialylated carbohydrate antigen SPAN-1
ST-439	sialylated carbohydrate antigen ST-439
TAG12	tumor-associated glycoprotein 12
TAG72	tumor-associated glycoprotein 72
TAG72.3	tumor-associated glycoprotein 72.3
TATI	tumor-associated trypsin inhibitor
TNF-a	tumor necrosis factor alpha
TPA	tissue polypeptic antigen

Home testing (including self-testing home kits) is considered **experimental or investigational** for all indications. The clinical validity of the tests have not been established and the evidence is insufficient to determine the effects of the technology on health outcomes.

The following tests are considered experimental or investigational, as there is insufficient evidence to support the use of these tests for all indications. Although there are ongoing clinical studies the current data are inadequate to permit scientific conclusions regarding the impact on management decisions and net health outcomes.

- Academic Profile
- CellSearch® Circulating Multiple Myeloma Cell
- CellSearch® HER2 Circulating Tumor Cell
- Cxbladder™/Cxbladder Detect
- Darwin OncoTreat™ (formerly OncoTreat)
- Decipher® Bladder TURBT
- DecisionDx®-SCC
- DetermaRx™ mRNA
- FiT IQ™
- GeneSearch™ BLNHeproDx-TM
- Guardant360 TissueNext™ (Guardant360 Tissue™)
- HelioLiver™
- HERmark®
- InflammaDry®
- KidneyIntelX™
- LC-MS/MS Targeted
- Multiple Sclerosis Disease Activity (MSDA)
- MSK-Impact™
- NavDx®
- NETest
- OncoExTra™ (formerly Oncomap ExTra and GEM ExTra)
- Oncomap™ (formerly Oncotype MAP)
- Ova Check™
- OvaSure™
- PathwayFit®
- PGDx elio™ Tissue Complete
- PharmaRisk™

- Post-Op Px™ (previously known as ProstatePX)
- Praxis Extended RAS Panel
- PreDx Diabetes Risk Score™
- Prostate Px+
- ResponseDX: Lung™
- ResponseDX: Colon™
- Thyroid Cancer Mutation Panel.

BILLING/CODING INFORMATION:

Note: Code list may not be all-inclusive.

CPT Coding:

80145	Adalimumab **(Investigational)**
80230	Infliximab **(Investigational)**
80280	Vedolilzumab **(Investigational)**
81335	TPMT (thiopurine S-methyltransferase) (e.g., drug metabolism), gene analysis, common variants (e.g., *2, *3)
81345	TERT (telomerase reverse transcriptase) (e.g., thyroid carcinoma, glioblastoma multiforme) gene analysis, targeted sequence analysis (e.g., promoter region) **(Investigational)**
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score **(Investigational)**
81500	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score (**Investigational**)
81503	Oncology (ovarian), biochemical assays of five proteins (CA-125, apoliproprotein A1, beta-2 microglobulin, transferrin and pre-albumin), utilizing serum, algorithm reported as a risk score **(Investigational)**
81504	Oncology (tissue of origin), microarray gene expression profiling of > 2000 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as tissue similarity scores **(Investigational)**
81506	Endocrinology (type 2 diabetes), biochemical assays of seven analytes (glucose, HbA1c, insulin, hs-CRP, adiponectin, ferritin, interleukin 2-receptor alpha), utilizing serum or plasma, algorithm reporting a risk score **(Investigational)**
81517	Liver disease, analysis of 3 biomarkers (hyaluronic acid [HA], procollagen III amino terminal peptide [PIIINP], tissue inhibitor of metalloproteinase 1 [TIMP-1]), using immunoassays, utilizing serum, prognostic algorithm reported as a risk score and risk of liver fibrosis and liver-related clinical events within 5 years **(Investigational)**
81529	Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis **(Investigational)**

81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival
81540	Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a probability of a predicted main cancer type and subtype **(Investigational)**
81546	Oncology (thyroid), mRNA, gene expression analysis of 10,196 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (e.g., benign or suspicious)
81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis
81554	Pulmonary disease (idiopathic pulmonary fibrosis [IPF]), mRNA, gene expression analysis of 190 genes, utilizing transbronchial biopsies, diagnostic algorithm reported as categorical result (e.g., positive or negative for high probability of usual interstitial pneumonia [UIP]) **(Investigational)**
81596	Infectious disease, chronic hepatitis C virus (HCV) infection, six biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, and haptoglobin) utilizing serum, prognostic algorithm reported as scores for fibrosis and necroinflammatory activity in liver
82233	Beta-amyloid; 1-40 (Abeta 40)
82234	Beta-amyloid; 1-42 (Abeta 42)
84393	Tau, phosphorylated (eg, pTau 181, pTau 217), each
84394	Tau, total (tTau)
84433	Thiopurine S-methyltransferase (TPMT)
86152	Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood) **(Investigational)**
86153	Cell enumeration using immunologic selection and identification in fluid specimen (e.g., circulating tumor cells in blood); physician interpretation and report, when required **(Investigational)**
86300	Immunoassay for tumor antigen, Quantitative; CA 15-3 (27.29)
86304	Immunoassay for tumor antigen, CA-125
86305	Human epididymis protein 4 (HE4) **(Investigational)**
86316**	Immunoassay for tumor antigen; other antigen, quantitative (e.g., CA 50, 72-4, 549), each **(Investigational)**
0002M	Liver disease, ten biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol and triglycerides) utilizing serum, prognostic algorithm reported as quantitative scores for fibrosis, steatosis and alcoholic steatohepatitis (ASH)
0003M	Liver disease, ten biochemical assays (ALT, A2-macroglobulin, apolipoprotein A-1, total bilirubin, GGT, haptoglobin, AST, glucose, total cholesterol and triglycerides) utilizing serum, prognostic algorithm reported as quantitative scores for fibrosis, steatosis and nonalcoholic steatohepatitis (NASH)

0006M	Oncology (hepatic), mRNA expression levels of 161 genes, utilizing fresh hepatocellular carcinoma tumor tissue, with alpha-fetoprotein level, algorithm reported as a risk classifier **(Investigational)**
0007M	Oncology (gastrointestinal neuroendocrine tumors), real-time PCR expression analysis of 51 genes, utilizing whole peripheral blood, algorithm reported as a nomogram of tumor disease index **(Investigational)**
0012M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and XCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma **(Investigational)**
0013M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma **(Investigational)**
0016M	Oncology (bladder), mRNA, microarray gene expression profiling of 219 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like) (**Investigational**)
0009U	Oncology (breast cancer), ERBB2 (HER2) copy number by FISH, tumor cells from formalin fixed paraffin embedded tissue isolated using image-based dielectrophoresis (DEP) sorting, reported as ERBB2 gene amplified or non-amplified **(Investigational)**
0003U	Oncology (ovarian) biochemical assays of five proteins (apolipoprotein A-1, CA 125 II, follicle stimulating hormone, human epididymis protein 4, transferrin), utilizing serum, algorithm reported as a likelihood score **(Investigational)**
0018U	Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy
0019U	Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as potential targets for therapeutic agents **(Investigational)**
0026U	Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result ("Positive, high probability of malignancy" or "Negative, low probability of malignancy")
0034U	TPMT (thiopurine S-methyltransferase), NUDT15 (nudix hydroxylase 15)(e.g., thiopurine metabolism) gene analysis, common variants (i.e., TPMT *2, *3A, *3B, *3C, *4, *5, *6, *8, *12; NUDT15 *3, *4, *5)
0048U	Oncology (solid organ neoplasia), DNA, targeted sequencing of protein-coding exons of 468 cancer-associated genes, including interrogation for somatic mutations and microsatellite instability, matched with normal specimens, utilizing formalin-fixed paraffin-embedded tumor tissue, report of clinically significant mutation(s) **(Investigational)**
0062U	Autoimmune (systemic lupus erythematosus), IgG and IgM analysis of 80 biomarkers, utilizing serum, algorithm reported with a risk score **(Investigational)**

0080U	Oncology (lung), mass spectrometric analysis of galectin-3-binding protein and scavenger receptor cysteine-rich type 1 protein M130, with five clinical risk factors (age, smoking status, nodule diameter, nodule-spiculation status and nodule location), utilizing plasma, algorithm reported as a categorical probability of malignancy **(Investigational)**
0089U	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es) **(Investigational)**
0090U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (i.e., benign, indeterminate, malignant) **(Investigational)**
0091U	Oncology (colorectal) screening, cell enumeration of circulating tumor cells, utilizing whole blood, algorithm, for the presence of adenoma or cancer, reported as a positive or negative result **(Investigational)**
0092U	Oncology (lung), three protein biomarkers, immunoassay using magnetic nanosensor technology, plasma, algorithm reported as risk score for likelihood of malignancy **(Investigational)**
0105U	Nephrology (chronic kidney disease), multiplex electrochemiluminescent immunoassay (ECLIA) of tumor necrosis factor receptor 1A, receptor superfamily 2 (TNFR1, TNFR2), and kidney injury molecule-1 (KIM-1) combined with longitudinal clinical data, including APOL1 genotype if available, and plasma (isolated fresh or frozen), algorithm reported as probability score for rapid kidney function decline (RKFD) **(Investigational)**
0111U	Oncology (colon cancer), targeted KRAS (codons 12, 13, and 61) and NRAS (codons 12, 13, and 61) gene analysis utilizing formalin-fixed paraffin-embedded tissue **(Investigational)**
0119U	Cardiology, ceramides by liquid chromatography-tandem mass spectrometry, plasma, quantitative report with risk score for major cardiovascular events **(Investigational)**
0163U	Oncology (colorectal) screening, biochemical enzyme-linked immunosorbent assay (ELISA) of 3 plasma or serum proteins (teratocarcinoma derived growth factor-1 [TDGF-1, Cripto-1], carcinoembryonic antigen [CEA], extracellular matrix protein [ECM]), with demographic data (age, gender, CRC-screening compliance) using a proprietary algorithm and reported as likelihood of CRC or advanced adenomas **(Investigational)**
0166U	Liver disease, 10 biochemical assays (α2-macroglobulin, haptoglobin, apolipoprotein A1, bilirubin, GGT, ALT, AST, triglycerides, cholesterol, fasting glucose) and biometric and demographic data, utilizing serum,algorithm reported as scores for fibrosis, necroinflammatory activity, and steatosis with a summary interpretation **(Investigational)**
0169U	NUDT15 (nudix hydrolase 15) and TPMT (thiopurine S-methyltransferase) (e.g., drug metabolism) gene analysis, common variants
0174U	Oncology (solid tumor), mass spectrometric 30 protein targets, formalin-fixed paraffin-embedded tissue, prognostic and predictive algorithm reported as likely, unlikely, or uncertain benefit of 39 chemotherapy and targeted therapeutic oncology agents **(Investigational)**

0179U	Oncology (non-small cell lung cancer), cell free DNA, targeted sequence analysis of 23 genes [single nucleotide variations, insertions and deletions, fusions without prior knowledge of partner/breakpoint, copy number variations], with report of significant mutation(s) **(Investigational)**
0206U	Neurology (Alzheimer disease); cell aggregation using morphometric imaging and protein kinase C-epsilon (PKCe) concentration in response to amylospheroid treatment by ELISA, cultured skin fibroblasts, each reported as positive or negative for Alzheimer disease **(Investigational)**
0207U	Neurology (Alzheimer disease); cell aggregation using morphometric imaging and protein kinase C-epsilon (PKCe) concentration in response to amylospheroid treatment by ELISA, quantitative imaging of phosphorylated ERK1 and ERK2 in response to bradykinin treatment by in situ immunofluorescence, using cultured skin fibroblasts, reported as a probability index for Alzheimer disease (List separately in addition to code for primary procedure) **(Investigational)**
0244U	Oncology (solid organ), DNA, comprehensive genomic profiling, 257 genes, interrogation for single-nucleotide variants, insertions/deletions, copy number alterations, gene rearrangements, tumor-mutational burden and microsatellite instability, utilizing formalin-fixed paraffin-embedded tumor tissue **(Investigational)**
0245U	Oncology (thyroid), mutation analysis of 10 genes and 37 RNA fusions and expression of 4 mRNA markers using next generation sequencing, fine needle aspirate, report includes associated risk of malignancy expressed as a percentage
0250U	Oncology (solid organ neoplasm), targeted genomic sequence DNA analysis of 505 genes, interrogation for somatic alterations (SNVs [single nucleotide variant], small insertions and deletions, one amplification, and four translocations), microsatellite instability and tumor-mutation burden **(Investigational)**
0287U	Oncology (thyroid), DNA and mRNA, next generation sequencing analysis of 112 genes, fine needle aspirate or formalinfixed paraffin-embedded (FFPE) tissue, algorithmic prediction of cancer recurrence, reported as a categorical risk result (low, intermediate, high) **(Investigational)**
0288U	Oncology (lung), mRNA, quantitative PCR analysis of 11 genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A) and 3 reference genes (ESD, TBP, YAP1), formalin-fixed paraffin-embedded (FFPE) tumor tissue, algorithmic interpretation reported as a recurrence risk score **(Investigational)**
0312U	Autoimmune diseases (e.g., systemic lupus erythematosus [SLE]), analysis of 8 IgG autoantibodies and 2 cell-bound complement activation products using enzyme-linked immunosorbent immunoassay (ELISA), flow cytometry and indirect immunofluorescence, serum, or plasma and whole blood, individual components reported along with an algorithmic SLE-likelihood assessment **(Investigational)**
0314U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 35 genes (32 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (i.e., benign, intermediate, malignant) **(Investigational)**

0315U	Oncology (cutaneous squamous cell carcinoma), mRNA gene expression profiling by RT-PCR of 40 genes (34 content and 6 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical risk result (i.e., Class 1, Class 2A, Class 2B) (**Investigational**)
0329U	Oncology (neoplasia), exome and transcriptome sequence analysis for sequence variants, gene copy number amplifications and deletions, gene rearrangements, microsatellite instability and tumor mutational burden utilizing DNA and RNA from tumor with DNA from normal blood or saliva for subtraction, report of clinically significant mutation(s) with therapy associations **(Investigational)**
0333U	Oncology (liver), surveillance for hepatocellular carcinoma (HCC) in high-risk patients, analysis of methylation patterns on circulating cell-free DNA (cfDNA) plus measurement of serum of AFP/AFP-L3 and oncoprotein des-gamma-carboxy-prothrombin (DCP), algorithm reported as normal or abnormal result (**Investigational**)
0334U	Oncology (solid organ), targeted genomic sequence analysis, formalin-fixed paraffin-embedded (FFPE) tumor tissue, DNA analysis, 84 or more genes, interrogation for sequence variants, gene copy number amplifications, gene rearrangements, microsatellite instability and tumor mutational burden **(Investigational)**
0337U	Oncology (plasma cell disorders and myeloma), circulating plasma cell immunologic selection, identification, morphological characterization, and enumeration of plasma cells based on differential CD138, CD38, CD19, and CD45 protein biomarker expression, peripheral blood (**Investigational**)
0338U	Oncology (solid tumor), circulating tumor cell selection, identification, morphological characterization, detection and enumeration based on differential EpCAM, cytokeratins 8, 18, and 19, and CD45 protein biomarkers, and quantification of HER2 protein biomarker–expressing cells, peripheral blood **(Investigational)**
0340U	Oncology (pan-cancer), analysis of minimal residual disease (MRD) from plasma, with assays personalized to each patient based on prior next-generation sequencing of the patient's tumor and germline DNA, reported as absence or presence of MRD, with disease-burden correlation, if appropriate **(Investigational)**
0356U	Oncology (oropharyngeal or anal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence **(Investigational)**
0358U	Neurology (mild cognitive impairment), analysis of B-amyloid 1-42 and 1-40, chemiluminescence enzyme immunoassay, cerebral spinal fluid, reported as positive, likely positive, or negative
0360U	Oncology (lung), enzyme-linked immunosorbent assay (ELISA) of 7 autoantibodies (p53, NY-ESO-1, CAGE, GBU4-5, SOX2, MAGE A4, and HuD), plasma, algorithm reported as a categorical result for risk of malignancy **(Investigational)**
0363U	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of 5 genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm incorporates age, sex, smoking history, and macrohematuria frequency, reported as a risk score for having urothelial carcinoma **(Investigational)**

0375U	Oncology (ovarian), biochemical assays of 7 proteins (follicle stimulating hormone, human epididymis protein 4, apolipoprotein A-1, transferrin, beta-2 macroglobulin, prealbumin [i.e., transthyretin], and cancer antigen 125), algorithm reported as ovarian cancer risk score **(Investigational)**
0412U	Beta amyloid, Aβ42/40 ratio, immunoprecipitation with quantitation by liquid chromatography with tandem mass spectrometry (LC-MS/MS) and qualitative ApoE isoformspecific proteotyping, plasma combined with age, algorithm reported as presence or absence of brain amyloid pathology **(Investigational)**
0420U	Oncology (urothelial), mRNA expression profiling by real-time quantitative PCR of MDK, HOXA13, CDC2, IGFBP5, and CXCR2 in combination with droplet digital PCR (ddPCR) analysis of 6 single-nucleotide polymorphisms (SNPs) genes TERT and FGFR3, urine, algorithm reported as a risk score for urothelial carcinoma **(Investigational)**
0445U	β-amyloid (Abeta42) and phosphor tau (181P) (pTau181), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology
0459U	B-amyloid (Abeta42) and total tau (tTau), electrochemiluminescent immunoassay (ECLIA), cerebral spinal fluid, ratio reported as positive or negative for amyloid pathology
0490U	Oncology (cutaneous or uveal melanoma), circulating tumor cell selection, morphological characterization and enumeration based on differential CD146, high molecular–weight melanoma associated antigen, CD34 and CD45 protein biomarkers, peripheral blood (**Investigational**)
0491U	Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of estrogen receptor (ER) protein biomarker–expressing cells, peripheral blood (**Investigational**)
0492U	Oncology (solid tumor), circulating tumor cell selection, morphological characterization and enumeration based on differential epithelial cell adhesion molecule (EpCAM), cytokeratins 8, 18, and 19, CD45 protein biomarkers, and quantification of PD-L1 protein biomarker– expressing cells, peripheral blood (**Investigational**)

**May be covered when used to report the Chromogranin A (CgA) test for neuroendocrine tumors (i.e. carcinoid tumors).

ICD-10 Diagnosis Codes That Support Medical Necessity for 81335, 0034U, 0169U

K50.00-K50.019	Crohn's disease of small intestine
K51.00-K51.319	Ulcerative colitis

ICD-10 Diagnosis Codes That Support Medical Necessity for 81538

C34.00 – C34.92	Malignant neoplasm of bronchus and lung

ICD-10 Diagnosis Codes That Support Medical Necessity for 81546

C73	Malignant neoplasm of thyroid gland
D44.0	Neoplasm of uncertain behavior of thyroid gland

ICD-10 Diagnosis Codes That Support Medical Necessity for 81552

C69.00-C69.92	Malignant neoplasm of eye and adnexa

ICD-10 Diagnosis Codes That Support Medical Necessity for 86300

C50.011 – C50.929	Malignant neoplasm of breast
C79.2	Secondary malignant neoplasm of skin
C79.81	Secondary malignant neoplasm of breast
G89.3	Neoplasm related pain (acute) (chronic)
R97.8	Other abnormal tumor markers
Z85.3	Personal history of malignant neoplasm of breast

ICD-10 Diagnosis Codes That Support Medical Necessity for 86304

C45.1	Mesothelioma of peritoneum
C48.1	Malignant neoplasm of specified parts of peritoneum
C48.2	Malignant neoplasm of peritoneum, unspecified
C48.8	Malignant neoplasm of overlapping sites of retroperitoneum and peritoneum
C53.0	Malignant neoplasm of endocervix
C53.1	Malignant neoplasm of exocervix
C54.1 – C54.9	Malignant neoplasm of corpus uteri
C56.1 – C56.9	Malignant neoplasm of ovary
C57.00 – C57.9	Malignant neoplasm of other and unspecified female genital organs
C79.60	Secondary malignant neoplasm of ovary, unspecified side
C79.61	Secondary malignant neoplasm of right ovary
C79.62	Secondary malignant neoplasm of left ovary
C79.82	Secondary malignant neoplasm of genital organs
C79.89	Secondary malignant neoplasm of other specified sites
D39.0, D39.10 – D39.12 D39.7 – D39.9	Neoplasm of uncertain behavior of female genital organs
G89.3	Neoplasm related pain (acute) (chronic)
R19.00	Intra-abdominal and pelvic swelling, mass and lump, unspecified site
R19.01	Right upper quadrant abdominal swelling, mass and lump
R19.02	Left upper quadrant abdominal swelling, mass and lump
R19.03	Right lower quadrant abdominal swelling, mass and lump
R19.04	Left lower quadrant abdominal swelling, mass and lump
R19.05	Periumbilical swelling, mass or lump
R19.06	Epigastric swelling, mass or lump
R19.07	Generalized intra-abdominal and pelvic swelling, mass and lump
R19.09	Other intra-abdominal and pelvic swelling, mass and lump
R97.1	Elevated cancer antigen 125 [CA 125]
R97.8	Other abnormal tumor markers
Z85.40	Personal history of malignant neoplasm of unspecified female genital organ
Z85.41	Personal history of malignant neoplasm of cervix uteri

Z85.42	Personal history of malignant neoplasm of other parts of uterus
Z85.43	Personal history of malignant neoplasm of ovary
Z85.44	Personal history of malignant neoplasm of other female genital organs

ICD-10 Diagnosis Codes That Support Medical Necessity for 0018U

C73	Malignant neoplasm of thyroid gland
D44.0	Neoplasm of uncertain behavior of thyroid gland

ICD-10 Diagnosis Codes That Support Medical Necessity for 0026U

C73	Malignant neoplasm of thyroid gland
D44.0	Neoplasm of uncertain behavior of thyroid gland

REIMBURSEMENT INFORMATION:

The following information is required documentation to support medical necessity: physician history and physical, physician progress notes, laboratory studies, treatment plan, and physician operative report (if applicable).

LOINC Codes

Documentation Table	LOINC Codes	LOINC Time Frame Modifier Code	LOINC Time Frame Modifier Codes Narrative
Physician history and physical	28626-0	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim
Attending physician progress note	18741-9	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.
Plan of treatment	18776-5	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim.
Laboratory studies	26436-6	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim
Physician operative report	28573-4	18805-2	Include all data of the selected type that represents observations made six months or fewer before starting date of service for the claim

PROGRAM EXCEPTIONS:

Federal Employee Program (FEP): Follow FEP guidelines.

State Account Organization (SAO): Follow SAO guidelines.

Medicare Advantage Products:

The following National Coverage Determinations (NCD) were reviewed on the last guideline reviewed date and located at cms.gov: Tumor Antigen by Immunoassay-CA 125 (190.28); Tumor Antigen by Immunoassay-CA 15-3/CA 27.29 (190.29); Tumor Antigen by Immunoassay-CA19-9 (190.30); Next Generation Sequencing (NGS) (90.2).

The following Local Coverage Determinations (LCDs) are located at fcso.com: Molecular Pathology Procedures (L34519); Pharmacogenomics Testing (L39073).

The following Billing and Coding Articles are located at fcso.com: Molecular Pathology and Genetic Testing (A58918); Molecular Pathology Procedures (A57451).

The following are located at cms.gov: Molecular Diagnostic Services (MolDX) coverage determinations.

If this Medical Coverage Guideline contains a step therapy requirement, in compliance with Florida law 627.42393, members or providers may request a step therapy protocol exemption to this requirement if based on medical necessity. The process for requesting a protocol exemption can be found at Coverage Protocol Exemption Request.

DEFINITIONS:

A2-PAG: pregnancy-associated alpha-2 glycoprotein (a chemical made by some cancers, consisting of a combination of protein and sugars).

BCM: breast cancer mucin; a marker made by some breast cancers.

CAM17-1, CAM26, CAM29: also known as monoclonal anti-mucin antibody markers, are markers noted in certain cancers.

CAR-3: a marker that reacts with a special test using a specific protein testing substance called “monoclonal antibody AR-3”.

Carbohydrate cancer antigens: CA 19-9, CA-125, CA 15-3/CA27-23, CA 242, CA 50, CA 72-4, CA 195, CA 549, M26, M29: these and other markers are a way to test for special markers on tumors, that are made of carbohydrates (a chemical that resembles a type of sugar).

CgA: a major protein of the granin family that has been described as a potential marker for neuroendrocrine tumors.

CellSearch®: a serum-based test that measures circulating tumor cells.

DU-PAN-2: a chemical (sialylated carbohydrate antigen) that may be found with some cancers.

FibroSpect II: serum marker panels for the diagnosis or clinical management of liver disease.

FibroSure: serum marker panels for the diagnosis or clinical management of liver disease.

GeneSearch BLN: an assay for the detection of greater than 0.2mm metastases in nodal tissue removed from sentinel lymph node biopsies of breast cancer patients.

HE4: an enzyme immunoassay for the quantitative determination of Human Epididymis Protein 4 (HE4) antigen in ovarian cancer.

LPA: lysophosphatidic acid; a chemical that has bee suggested as a possible test for ovarian cancer, body levels may be high in other cancers as well.

MCA: a chemical (Mucin-like Carcinoma-associated Antigen) that may be found in breast cancers.

MSA: a chemical (Mammary Serum Antigen) that may be found in breast cancers.

NSE: Neuron-Specific Enolase, a chemical made in the presence of some cancers.

Ova Check™: a serum-based test for the early detection of epithelial ovarian cancer.

OvaSure™: ovarian cancer-screening test that may be able to assess the presence of early stage ovarian cancer in high-risk woman.

Pathwork Tissue of Origin: a diagnostic test that may aid in the diagnosis of tumors with uncertain origins.

P-LAP: placental alkaline phosphatase, a chemical made in the presence of some cancers.

PNA/ELLA: peanut lectin bonding assay, a test for a certain tumor marker.

Proteogenomic Testing: involves the integration of proteomic, transcriptomic, and genomic information.

Proteomic Testing: the measurement of protein products *alone*, without integration of genomic and transcriptomic information.

SLEX, SLX: sialylated Lewis X-I antigen and sialylated SSEA-1 antigen.

SPAN-1: a sialylated carbohydrate antigen.

ST-439: a sialylated carbohydrate antigen.

TAG12, TAG 72, TAG 72.3: tumor associated glycoproteins; chemicals made by some cancers, consisting of a combination of protein and sugars.

TATI: tumor-associated trypsin inhibitor, a chemical made by the body, in the presence of some cancers.

TNF-a: tumor necrosis factor alpha, a chemical made by the immune system in the presence of some cancers.

TPA: tissue polypeptide antigen is a marker that may be present on some cancers.

RELATED GUIDELINES:

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer, 05-86000-26

Genetic Testing, 05-82000-28

Molecular Testing for the Management of Pancreatic Cysts and Solid Pancreaticobiliary Lesions, 05-86000-27

Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment in Metastatic Colorectal Cancer (KRAS, NRAS, BRAF, NTRK, and HER2), 05-86000-28

OTHER:

None applicable.

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20. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.14, Evaluation of Biomarkers for Alzheimer Disease, 06/25.
21. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.19 Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines, 12/24.
22. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.41 Noninvasive Techniques for the Evaluation and Monitoring of Patients with Chronic Liver Disease, 12/24.
23. Blue Cross Blue Shield Association Evidence Positioning System®, 2.04.54 Molecular Genomic Profiling for Cancers of Unknown, 05/25.
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COMMITTEE APPROVAL:

This Medical Coverage Guideline (MCG) was approved by the Florida Blue Medical Policy and Coverage Committee on 07/24/25.

GUIDELINE UPDATE INFORMATION:

02/15/04	Developed separate guideline for non-covered tumor markers from the Tumor Markers guideline. Added program exception and added diagnoses [155.1, 156.1, 156.8, 156.9, 157.0 – 157.9, 197.8, 235.3, 235.5, V10.09] for 86301 for Medicare & More.
02/15/05	Deleted CA 19-9 from the investigational statement. Deleted Medicare program exception. Deleted the following from the when services are covered section of the MCG (per MPCC recommendation): Non-covered/investigational serum tumor markers may be covered if the individual subscriber has a benefit to cover non-covered/investigational services (refer to contract benefits). Updated related guidelines section.
08/15/07	Review, investigational status maintained, guideline reformatted, references updated.
09/15/08	Annual review: Position statements maintained. Description section and references updated.
08/15/09	Annual review: Guideline title changed, position statements updated, position statements from other tumor marker guidelines incorporated, description section, coding and references updated.
12/15/09	Updated the list of experimental/investigational tests.
01/01/10	Annual HCPCS coding update: added code 86305.
04/15/10	Updated the list of experimental/investigational tests and the Medicare Advantage program exception.
11/15/10	Revision; updated the list of experimental/investigational tests and added related ICD-10 codes.
08/15/11	Revision; Medicare Advantage and references updated; formatting changes.
01/01/12	Annual HCPCS update. Added CPT codes 0279T, 0280T.
04/01/12	Quarterly HCPCS update. Deleted HCPCS code S3711.
08/24/12	Reimbursement section updated.
10/15/12	Serum Antibodies for the Diagnosis of Inflammatory Bowel Disease position statement removed and added to the Genetic Testing guideline; reimbursement section updated.
11/15/12	List of experimental/investigational tests updated.
01/01/13	Annual HCPCS update. Added codes 81500, 81503, 81506, 86152, 86153, 0001M-0003M; deleted codes 0279T & 0280T.Updated position statement section and references.
02/15/13	Revision; position statement section and references updated.

03/15/13	Revision; position statement section including the list of investigational tests and references updated; title change.
05/15/13	Revision; position statement, billing/coding, program exception, and reference sections updated.
09/15/13	Revision; position statement section and references updated.
01/01/14	Annual HCPCS update. Added code 81504.
02/15/14	Revision; position statement section, Medicare program exception, and references updated.
06/15/14	Revision; position statement section, Coding, Medicare program exception, and references updated.
07/01/14	Quarterly HCPCS update. Added code 0007M.
10/15/14	Revision; Update the position statement and coding sections, program exception, and references.
01/01/15	Annual HCPCS/CPT update. Added codes 87505-87507.
06/15/15	Revision; position statement section, billing/coding, and references updated.
11/01/15	Revision: ICD-9 Codes deleted.
11/15/15	Revision; program exception and references updated.
01/01/16	Annual HCPCS/CPT update; codes 81490, 81538, 81540, 81545 added, code 0103T deleted.
03/15/16	Revision; position statement section, codeing and references updated.
09/15/16	Revision; position statement section, program exception, and references updated.
11/15/16	Revision; position statement section and references updated.
12/15/16	Revision; position statement, coding, and references updated.
02/01/17	Coding Update; new code 0003U added; investigational test list updated.
02/15/17	Revision; position statements, coding, and references updated.
03/15/17	Revision; Multianalyte assays for chronic liver disease position statements revised; coding and references updated.
04/15/17	Revision; Uveal Melanoma position statement added and references updated.
06/15/17	Revision; test names added to Biochemical Markers of Alzheimer's Disease & Circulating Tumor DNA position statements section; investigational test list updated.
07/15/17	Revision; Investigational test list updated.
08/01/17	Coding update; Added code 0009U.
12/15/17	Revision; Position statement section updated including the addition of ROS1 coverage statement; program exception and references updated.
01/01/18	Annual CPT/HCPCS update. Added code 0026U.
02/15/18	Revision; Circulating tumor DNA position statement added; OVA1, Overa, and ROMA tests position statement added and references updated.
04/01/18	Quarterly HCPCS/CPT update. Added codes 0012M and 0013M.
05/15/18	Revision; position statements, coding, and references updated.
09/15/18	Revision; position statements and references updated.
10/01/18	Quarterly HCPCS/CPT update. Added code 0062U.
12/15/18	Revision; Guardant360 test and OncoBEAM test added to the circulating tumor DNA for management of NSCLC position statement; investigational statement for microarray-

	based gene expression profile testing for multiple myeloma added; molecular analysis for targeted therapy of NSCLC position statements updated; coding, and references updated.
01/01/19	Annual CPT/HCPCS coding update. Added codes 81345, 81596; deleted code 0001M.
02/15/18	Revision; Fecal calprotectin testing position revised; coding and references updated.
05/15/19	Revision; Serum Biomarker Human Epididymis Protein 4 position statement added; references updated.
06/15/19	Revision; Xpresys test deleted (test no longer on the market).
07/01/19	Quarterly CPT/HCPCS update; Added codes 0089U-0092U. Revision; Gene expression profiling for cutaneous melanoma & molecular testing in the management of pulmonary nodules position statements added; OVA1 status maintained; coding and references updated.
08/15/19	Revision; Afirma test name updated.
01/01/20	Review; Analysis for targeted therapy of NSCLC & circulating tumor DNA for management of NSCLC statements updated; coding and references updated.Annual CPT/HCPCS coding update. Added codes 80145, 80230, 80280, 81552;deleted code 0081U.
04/01/20	Quarterly CPT/HCPCS update. Added code 0166U.
05/15/20	Coding and references updated.
07/01/20	Gene expression profiling for cutaneous melanoma reviewed and position statements maintained; references updated. Quarterly CPT/HCPCS update. Added codes 0174U & 0179U.
09/15/20	Revision; References updated.
09/18/20	Revision; Liquid biopsy test names updated.
10/01/20	Quarterly CPT/HCPCS update. Added codes 0016M, 0204U-0208U, and 0211U.
11/15/20	Revision; coding and references updated.
01/01/21	Annual CPT/HCPCS update. Codes 81191-81194,81529,81546,81554 added; codes 81545, 0111T deleted.
02/15/21	Review; Circulating tumor DNA management of NSCLC, molecular analysis for targeted therapy for NSCLC, measurement of serum antibodies to selected biologic agents, and pharmacogenomics markers for members treated with thiopurines position statements updated; coding and references updated.
04/01/21	Quarterly CPT/HCPCS update. Codes 0242U, 0244U, 0245U added.
04/16/21	Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) statement added.
05/15/21	Revision; Homocysteine position statement deleted; investigational test list, coding and references updated.
06/15/21	Reimbursement section updated.
07/01/21	Quarterly CPT/HCPCS update. Codes 0249U and 0250U added.
08/15/21	Review; DecisionDx-Melanoma position statement maintained, references updated.
09/03/21	Revision: Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy) section updated.
10/15/21	Review; OVA1 position statement maintained, references updated.
11/15/21	Revision; Fecal Calprotectin position statement removed; coding and references updated.

01/01/22	Annual CPT/HCPCS coding update. Codes 0287U, 0288U added; 0090U revised; 0208U deleted.
02/15/22	Revision: Liquid biopsy for management of NSCLC position statements moved to the molecular analysis for targeted therapy or immunotherapy of NSCLC section; statements for KRAS testing for treatment with sotorasib added; coding and references updated.
04/01/22	Quarterly CPT/HCPCS update. Code 0314U added.
04/29/22	Codes 81445-81455 removed.
06/15/22	Expanded test panel list updated.
07/01/22	Review: Gene expression profiling for cutaneous melanoma position statements maintained; references updated. Quarterly CPT/HCPCS update: code 0016M revised.
08/15/22	Review: OVA1 position statement maintained; references updated.
09/15/22	Review: Comprehensive genomic profiling statement removed; investigational test list, coding section, and references updated.
10/01/22	Revision: Tumor-informed circulating tumor DNA testing for cancer management investigational statement added; references updated. Quarterly CPT/HCPCS update. Codes 0337U, 0338U, 0340U added; codes 0013U, 0014U, 0056U deleted.
11/15/22	Revision: Gene expression profiling for colorectal cancer statement added; coding and references updated.
01/01/23	Annual CPT/HCPCS coding update. Codes 84433 and 0363U added.
06/15/23	Revision: Note added to the position statement section. References and coding updated.
07/15/23	Revision: Gene expression profiling for cutaneous melanoma position statements maintained; investigational test list, coding, and references updated.
08/15/23	Revision: Multicancer early detection testing investigational position statement added; references updated.
10/01/23	Revision: Position statements, coding, and references updated. Quarterly CPT/HCPCS coding update: Code 0412U added.
11/15/23	Revision: Multimarker serum testing related to ovarian cancer statement updated; investigational test list, coding, and references updated.
01/01/24	Position statements maintained. Annual CPT/HCPCS coding update. Codes 81517, 0420U added. Program exception and references updated.
03/15/24	Coding and references updated.
04/01/24	Quarterly CPT/HCPCS coding update: Code 0445U added.
04/15/24	Investigational test list, coding, and references updated.
07/01/24	Quarterly CPT/HCPCS coding update. Code 0204U deleted.
08/15/24	Review: Position statements and investigational test list reviewed and updated; description, coding and references updated.
10/01/24	Quarterly CPT/HCPCS coding update. Codes 0490U-0492U added.
12/15/24	Revision: Alzheimer disease CSF biomarker testing statement updated; multianalyte assays for chronic liver disease statements maintained; investigational test list, coding, and references updated.
01/01/25	Annual CPT/HCPCS coding update. Codes 82233, 82234, 84393, 84394 added.

02/15/25	Revision: Multimarker serum testing related to ovarian cancer position statements maintained; references and coding updated.
08/15/25	Annual review: Investigational test list updated; all other statements maintained; description, coding, and references updated.
11/15/25	Investigational test list updated.