Anthem

Medical Policy

Subject: Selected Protein Biomarker Algorithmic Assays
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Description/Scope

This document addresses the use of selected protein biomarker algorithmic assays, which involve the qualitative and/or quantitative analysis of protein constituents in a biological sample that are reported as a predictive, diagnostic or prognostic algorithmic result. Protein biomarker algorithmic assays are under investigation in certain tumors and for other applications such as predicting the likelihood of preterm delivery in pregnancy.

Please see the following related documents for additional information on protein biomarker tests for specific indications:

- LAB.00033 Protein Biomarkers for the Screening, Detection and Management of Prostate Cancer
- LAB.00035 Multi-biomarker Disease Activity Blood Tests for Rheumatoid Arthritis
- LAB.00037 Serologic Testing for Biomarkers of Irritable Bowel Syndrome (IBS)
- LAB.00040 Serum Biomarker Tests for Risk of Preeclampsia
- LAB.00048 Analysis of Urine Biomarkers for Chronic Pain Management

Position Statement

Investigational and Not Medically Necessary:

The following protein biomarker algorithmic assays are considered **investigational and not medically necessary** for all indications:

A. BDX-XL2 (Nodify XL2®)
B. EarlyCDT®-Lung test (Nodify CDT®)
C. IMMray® PanCan-d
D. LC-MS/MS Targeted Proteomic Assay
E. PreTRM
F. REVEAL Lung Nodule Characterization
G. Theralink® Reverse Phase Protein Array
H. VeriStrat®.

Rationale

Ovarian Cancer

Petricoin and colleagues reported on the technical feasibility of protein biomarker screening in a test series of serum from 50 women with and 50 women without ovarian cancer (Petricoin, 2002). The spectra of proteins were analyzed by an iterative searching algorithm that identified a cluster pattern that segregated those with ovarian cancer from those without ovarian cancer. This discovered pattern was then used to classify an independent set of 116 masked serum samples, 50 from women with ovarian cancer, and 66 from unaffected women or those with non-malignant conditions. Individuals without cancer were considered at high risk, due either to familial breast or cancer syndrome or the presence of BRCA1 or BRCA2 mutations. All 50 with ovarian cancer were correctly identified, including the 18 with stage I cancer. Of the 66 benign cases, 63 were identified as not cancer, yielding a sensitivity of 100% and a positive predictive value of 94%. The authors note that while a positive predictive value of 94% may be acceptable for those high-risk women, in the larger population of average-risk women the positive predictive value must be close to 100% to avoid a high number of false positives, which in turn would generate additional work-up. One of the key outcomes of an ovarian cancer screening test is

the ability to identify Stage I ovarian cancer that is potentially curable with surgery. The above study only included 18 women with Stage I ovarian cancer. The authors state that an important future goal is the confirmation of the diagnostic performance of proteomic screening for the prospective detection of Stage I ovarian cancer in trials of both high- and low-risk women. Such trials are currently underway at the National Cancer Institute. It should be noted that other comments and correspondence in the literature question the statistical analysis and other technical issues in the Petricoin study (Diamandis, 2002, 2004).

Lung Cancer

VeriStrat® Test

A number of studies have been published addressing the use of the VeriStrat (Biodesix, Inc., Boulder, CO), a mass spectrometry-based protein biomarker profiling test, to predict outcomes in individuals with non-small cell lung cancer (NSCLC) for whom treatment with erlotinib is being considered. This test provides data that stratifies individuals into either “Good” responders to treatment (VS-G) or “Poor” responders to treatment (VS-P) based on pre-treatment sample evaluation.

Carbone describes the prognostic value of the VeriStrat test in a subpopulation of participants enrolled in the National Cancer Institute of Canada (NCIC) Clinical Trials Group BR.21 phase II trial, a randomized, placebo-controlled study (Carbone, 2012). Banked baseline pre-treatment samples from 441 participants were tested using the VeriStrat test. Individuals classified as VS-G survived significantly longer than those classified as Poor. For VS-G responders, the median survival was 10.5 months on erlotinib versus 6.6 months for placebo (p=0.002). For VS-P responders, there was not a significant difference in the median survival between erlotinib and placebo (4 months vs. 3.1 months, p=0.11). In the 252 erlotinib-treated participants, VS-G responders had a significantly higher response rate than VS-P responders (11.5% vs. 1.1%, p=0.002).

Amann (2010) reported the use of the VeriStrat test on a cohort of 102 participants from the Eastern Cooperative Oncology Group (ECOG) 3503 study with advanced NSCLC with wild-type Epidermal Growth Factor Receptor (EGFR) status and treated with erlotinib. The authors reported that 9 of 41 (22%) participants had KRAS mutations and 3 of 41 (7%) had EGFR mutations. The VeriStrat test identified 64 of 88 (73%) participants as predicted to have Good outcomes and 24 of 88 (27%) to have Poor outcomes. A statistically significant correlation of VeriStrat status (p<0.001) was found with survival. Also, EGFR mutations, but not KRAS mutations, were correlated with survival. The authors concluded that the VeriStrat test was a highly clinically significant predictor of survival after first-line treatment with erlotinib in individuals with wild-type EGFR and independent of mutations in KRAS.

In another study, Kuiper and colleagues used the VeriStrat test as a pre-treatment stratification tool in 50 participants receiving a combination of erlotinib and sorafenib for advanced stage NSCLC (2012). The authors reported that the test was successful in identifying those individuals with significantly better overall survival (OS), with VS-G responders having a median OS of 13.7 months and VS-P responders having 5.6-month median OS (p<0.009). Progression-free survival (PFS) was 5.5 months for VS-G responders and 2.7 months for VS-P responders (p<0.035). Another study looked at OS using samples pooled from two separate phase II studies (Gautschi, 2013). This study evaluated frozen pre-treatment samples from 117 individuals tested with the VeriStrat test. The results demonstrated that individuals in the VS-G group had a significantly better OS rate than the VS-P group (13.4 months vs. 6.2 months; p=0.0027). Data for PFS demonstrated no significant difference between the VS-G and VS-P groups. Akerley and others (2013) conducted an observational pre-post study of physician treating preferences in 2822 individuals who underwent treatment for NSCLC. In this study, the investigators collected pre-test treatment recommendations from physicians along with pre-treatment blood samples of the participants. All samples were evaluated with VeriStrat and the results were shared with the treating physicians. With the VeriStrat results known, the physicians were asked to provide their treatment recommendations again. Full pre- and post-test recommendations data were available for 403 individuals (403/2822, 14.3%). The results indicated that knowing the test outcome resulted in changes in treatment plan in 19.1% of individuals. However, there was no data to demonstrate any short- or long-term health outcomes related to these changes in treatment decisions. Randomized, prospective studies of the VeriStrat test demonstrating a health outcome benefit are lacking. Further study is warranted.

In 2014, Gregorc and colleagues reported on the results of a double-blind randomized controlled trial (RCT) designed to classify individuals according to whether they are likely to have a Good or Poor outcome after treatment with erlotinib using the VeriStrat test. The study involved 285 participants with histologically or cytologically confirmed second-line, stage IIIB or IV NSCLC. Participants were randomized in a 1:1 ratio to receive erlotinib (n=143) or chemotherapy (n=142). In the per-protocol analysis, 134 (94%) experimental group participants and 129 (91%) control participants were included. Median OS was 9 months in the chemotherapy group and 7.7 months in the erlotinib group. A significant Interaction was noted

between treatment and proteomic classification ($p_{interaction}$=0.017, when adjusted for stratification factors; $p_{interaction}$=0.031, when unadjusted for stratification factors). Participants with a proteomic test classification of VS-P had worse survival on erlotinib than on chemotherapy (hazard ratio [HR] 1.72, p=0.022). There was no significant difference in OS between treatments for participants with a proteomic test classification of VS-G (adjusted HR 1.06, p=0.714). The authors concluded that findings indicate that serum protein test status is predictive of differential benefit in OS for erlotinib versus chemotherapy in the second-line setting. However, it should be noted that this study is insufficiently powered and fails to demonstrate improved survival in the VS-G group. Additionally, this study indicated that VeriStrat testing identified poor prognosis individuals with wild-type EFGR status who would not benefit from the use of erlotinib. Unfortunately, this information is not clinically useful, as that population would not usually receive erlotinib therapy. Furthermore, the FDA recently released additional label changes indicating that erlotinib should only be used in individuals with NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations (FDA, 2016).

Grossi and others (2017) described the results of a blinded prospective cohort study involving 76 participants with non-squamous NSCLC treated with either a combination of carboplatin and pemetrexed (n=43) or cisplatin and pemetrexed (n=33). The authors stated that 66% (n=55) of participants were classified as VS-G and 34% (n=26) as VS-P. PFS and OS were significantly better in the VS-G group vs. the VS-P group (median PFS=6.5 vs. 1.6 months, respectively [p<0.0001]; median OS=10.8 vs. 3.4 months [p<0.0001]). In a multivariate analysis, the VeriStrat test was found to be prognostic for both PFS (p=0.0002) and OS (p<0.0001). This remained valid when controlling for treatment method and maintenance treatment (p=0.0019 and p<0.0001, respectively). Overall response rate was 31% in the VS-G group vs. 0% in the VS-P group (p=0.0032). The authors concluded that, “The trial demonstrated clinical utility of VeriStrat as a prognostic test for standard first-line chemotherapy of non-squamous advanced NSCLC.” However, it is not clear based on this data how the VeriStrat test may impact treatment outcomes when used prospectively to guide treatment. Additional studies are warranted to investigate this question.

Gadgeel (2017) reported a retrospective analysis of 691 samples from participants enrolled in the LUX-Lung 8 study. The LUX-Lung 8 study was a phase III RCT that enrolled 795 individuals with Stage IIIB/IV NSCLC of squamous (including mixed) histology, with progressive disease after at least 4 cycles of first-line platinum-based chemotherapy, who were randomized (1:1) to receive either afatinib or erlotinib. The primary objective of this Gadgeel study was to evaluate whether pretreatment VeriStrat classification was predictive of OS benefit with afatinib versus erlotinib and associated with improved OS, irrespective of treatment, both in all VeriStrat-classified responders, and in afatinib-treated responders. A secondary objective was to evaluate whether pretreatment VeriStrat classification was predictive of PFS, objective response rate (ORR), disease control rate (DCR) or tumor shrinkage benefit with afatinib versus erlotinib; associated with improved PFS, ORR, DCR or tumor shrinkage, irrespective of treatment, in all VeriStrat-classified participants, and in afatinib-treated participants. The authors reported no significant interaction between VeriStrat classification and treatment group (afatinib vs. erlotinib) for OS (p=0.5303). The VeriStrat test had a strong stratification effect on OS; VS-G status was associated with significantly improved OS compared with VS-P status, both in the overall VeriStrat-classified population (median 9.8 vs 4.8 months; HR, 0.41; p<0.0001) and in afatinib-treated participants (median 11.5 vs 4.7 months; HR, 0.40; p<0.0001). Although HRs for OS and PFS were lower in VS-G than VS-P responders, notably, the confidence intervals overlapped. A multivariate analysis showed that VeriStrat was an independent predictor of OS in afatinib-treated individuals, regardless of ECOG performance score, best response to first-line chemotherapy, age or race. PFS was reported to be significantly improved with afatinib vs. erlotinib in the VS-G population (median 3.3 vs 2.0 months; HR, 0.73). VeriStrat status had a strong stratification effect on PFS, with VS-G responders having significantly improved PFS vs. VS-P responders, both in the overall VeriStrat-classified population (median 2.6 vs 1.9 months; HR, 0.65, p<0.0001), and in afatinib-treated participants (median 3.3 vs 1.9 months; HR, 0.56; p<0.0001). There were significant improvements with afatinib vs. erlotinib in VS-G responders in ORR (6.8% vs. 2.4%; OR, 2.90) and DCR (57.5% vs. 43.9%; OR, 1.73). VeriStrat status was found to be non-predictive of ORR or DCR advantage of afatinib over erlotinib, with the interaction p-values non-significant for ORR ($p_{interaction}$=0.1590) and DCR ($p_{interaction}$=0.5547). In all VeriStrat-classified participants, VeriStrat status had a strong stratification effect on DCR, with significant improvement in VS-G vs. VS-P responders (50.7% vs 36.9%; OR, 1.77; p=0.0002). The result of this retrospective study is promising. However, whether the VeriStrat test has significant clinical benefit when used prospectively is yet to be established.

Akerley (2017) published the results of a survey study of 989 physicians who reported on 2494 VeriStrat tests in individuals being considered for treatment with EGFR tyrosine kinase inhibotors(TKIs). The VeriStrat test classified 1950 individuals as VS-G and 544 individuals as VS-P. Overall, the authors reported that treatment recommendations were consistent with VeriStrat test results in 98% of cases, and that the availability of VeriStrat test results decreased use of ineffective treatment recommendations by 89% for VS-P responders. No data were presented on clinical outcomes for any of the individuals treated based on VeriStrat results. It is not clear if any clinically significant changes resulted in treatment

plans guided by the VeriStrat test. This study is limited by the small proportion of VS-P responders (22%), which calls into question the validity of the conclusion and the actual clinical utility of the test.

Lee and others (2019) published the results of a retrospective analysis derived from participants originally enrolled in a clinical trial evaluating untreated NSCLC considered unfit for platinum chemotherapy, treated with usual care plus erlotinib or placebo. From this study 527 participants had plasma samples available for VeriStrat classification. The authors reported that among participants managed with usual care plus placebo only, the adjusted HR was 0.54 ($p<0.001$) for VS-G vs. VS-P. The conclusion was that VeriStrat was not a *predictive* marker for survival for individuals with NSCLC and poor performance status receiving first-line erlotinib due to inability to undergo platinum-based treatment. However, they did note that VeriStrat was an independent *prognostic* marker of survival. They concluded that it "represents an objective measurement that could be considered alongside other patient factors to provide a more refined assessment of prognosis for this particular patient group". The retrospective nature of this study and lack of data demonstrating outcomes based on the use of the VeriStrat test limits the utility of these results.

In 2021, Rich and colleagues published interim findings from the INSIGHT registry study, which enrolled individuals 18 years of age or older with all stages of NSCLC who had tumors identified as EGFR wild type or unknown type. This analysis included 877 individuals who had advanced disease and no prior therapy, and were tested with the VeriStrat test at the time of study enrollment. A total of 622 individuals (70.9%) were classified by the VeriStrat test as "Good" responders and 255 (29.1%) were classified as "Poor" responders. Individuals classified as "Good" responders had significantly longer OS than individuals classified as "Poor" responders. The median OS for the individuals classified as "Good" responders who were treated with platinum-based chemotherapy was 14.8 months compared with 7.0 months for individuals classified as "Poor" responders (HR=0.56, 95% confidence interval [CI], 0.42 to 0.75). For individuals treated with immune checkpoint inhibitors, median OS had not been reached for individuals classified as "Good" responders and was 5.0 months for individuals classified as "Poor" responders (HR, 0.38, 95% CI, 0.27 to 0.53). In this study, findings of the VeriStrat test were not used prospectively to guide treatment decisions.

EarlyCDT®-Lung test

Several observational studies have been published describing the sensitivity of the EarlyCDT-Lung test (Biodesix, Inc., Boulder, CO), which evaluated samples for tumor-associated autoantibodies found in individuals with lung cancer. The first study involved 574 participants from four separate cohorts (Lam, 2011). Group 1 (n=122) included individuals with only small cell lung cancer (SCLC); Group 2 (n=249) was composed of 97% of participants with non-small cell lung cancer (NSCLC); Group 3 (n=122) included only individuals with NSCLC; and Group 4 (n=81), was made up of 62% of participants with NSCLC. For Group 1, the results indicated a sensitivity of 57% for SCLC (specificity data not calculated). The sensitivity and specificity for Group 2 was 34% and 87% for NSCLC. For Group 3, sensitivity and specificity was 31% and 84% for NSCLC. Finally, in Group 4, sensitivity and specificity was 35% and 89% for NSCLC and 43% and 89% for SCLC. No significant difference in positivity was reported for the EarlyCDT-Lung test with regard to different lung cancer stages.

Chapman (2012) published the results of a case-control study involving 235 individuals with newly diagnosed lung cancer with 235 healthy controls used to evaluate both 6- and 7-antigen versions of the test. In addition, two prospective consecutive series of 776 and 836 individuals at an increased risk of developing lung cancer were also evaluated with both versions of the EarlyCDT-Lung test. The 6-antigen panel gave a sensitivity of 39% and a specificity of 89%, while the 7-antigen panel resulted in a sensitivity of 41% and a specificity of 91%. Once adjusted for occult cancers in the population, this resulted in a specificity of 93%.

González Maldonado (2021) examined the diagnostic accuracy of the EarlyCDT test in 46 individuals with lung cancer detected by low-dose computed tomography (CT). The EarlyCDT lung test produced positive ("high level") results in 6 of the 46 individuals, for a sensitivity of 13.0% (95% CI, 4.9 to 26.3%). In the individuals with lung nodules < 10 mm in diameter, "high level" results were obtained in 1 out of 11 cases (sensitivity: 9.1%; 95% CI, 0.23 to 41.3%). For the remaining individuals with lung nodules ≥ 10 mm, the estimated sensitivity was 14.7% (95% CI, 4.9 to 31.3%) (number of 'high level' results were not reported for the latter group). The investigators also tested 90 individuals randomly selected from all cancer-free individuals (baseline controls) and 90 individuals randomly selected from among cancer-free individuals with suspicious nodules on CT scans (suspicious nodule controls). They found that the EarlyCDT test had a specificity of 88.9% (95% CI, 80.5 to 94.5%) in the baseline control group and 91.1% (95% CI, 83.2 to 96.1%) in the suspicious nodule control group.

An observational study evaluating the EarlyCDT lung test in 246 individuals with suspected lung cancer was published by Borg and colleagues in 2021. After completing a diagnostic work-up, 75 of 246 individuals (30%) were found to have lung cancer, 12 of 246 individuals (5%) had lung metastases originating from primary tumors in other locations and 159 of 246

(65%) had cancer ruled out. The sensitivity of the EarlyCDT lung test for detecting lung cancer was 33% (25 of 75 individuals were identified by the test). The sensitivity for detecting any lung malignancy (including lung metastases from tumors in other locations) was 31% (27 of 87 individuals were identified by the test). Test sensitivity was higher in older individuals; sensitivities were 11%, 31% and 55% in those age 60 or younger, 61-75 years and over 75 years, respectively. The test also had a higher sensitivity in heavier smokers. Sensitivity was 33% in individuals with at least 10 tobacco pack years and 44% in those with at least 50 pack years. The authors concluded, "the current study finds insufficient sensitivity of the EarlyCDT Lung test to be used as part of inclusion criteria in a low-dose CT program for detection of lung cancer."

A study by Wu and colleagues (Wu, 2023) evaluated the EarlyCDT test in ever-smokers. The design was a case-control study nested within two cohort studies. The cases were 154 individuals who were diagnosed with lung cancer within 3 years of providing the blood sample for analysis and there were 154 matched controls without lung cancer. The results of the case-control analysis were that there was not a statistically significant association between lung cancer diagnosis and a moderate risk EarlyCDT test result (OR [odds ratio], 0.89; 95% CI, 0.34 to 2.30). The authors concluded that their findings did not support a role for the EarlyCDT test in identifying high-risk individuals with a history of smoking in the cohorts that were studied.

Nodify XL2™ Test

The Nodify XL2 proteomic classifier test (Biodesix, Inc., Boulder, CO) is a test involving the assessment of two proteins (LG3BP and C163A) combined with five clinical risk factors (age, smoking status, nodule diameter, edge characteristics, and location) to assist in identifying the risk of cancer in individuals with benign lung nodules. Use of the Nodify XL2 test has been studied in the PANOPTIC trial reported by Silvestri et al in 2018. This blinded prospective observational study involved retrospective evaluation of the performance of the Nodify XL2 test, and the test results were not used in treatment decisions. A total of 392 participants 40 years of age or older with lung nodules between 8 and 30 mm detected by CT were included in the study, but the report focused on 178 participants who had a pre-test probability of the nodule being cancerous of ≤ 50%. The authors reported sensitivity of 97% and a specificity of 44%. The posttest probability of distinguishing benign from cancerous nodules was 98%. In a subset of participants who were determined to be "likely benign" according to the Nodify XL2 test, 44% were identified correctly as being likely benign and 3% with cancerous nodes were incorrectly identified as being benign. The authors concluded that when used for lung nodules with a ≤ 50% probability of a node being cancerous, the Nodify XL2 test accurately identifies benign lung nodules with good performance characteristics and that invasive procedures could be reduced by diverting benign nodules to surveillance. However, the findings of this study must be considered to be preliminary before the test is used in clinical practice. Additional study is needed to fully understand the true health outcome benefits of this test.

In 2023, Pritchett and colleagues published findings of an observational study evaluating the impact of Nodify XL2 test use on physician decision-making. The study included individuals with a pre-test probability of cancer risk according to Nodify XL2 test results of less than 50%, at last 40 years of age, a pulmonary nodule 8 to 30 mm in diameter and no history of lung cancer or non-melanoma skin cancer in the past 5 years. The investigators established a comparison group of individuals identified by retrospective chart review who met the above inclusion criteria, other than Nodify XL2 testing, and were treated prior to use of the Nodify XL2 test. Propensity-score matching was used in an effort to control for confounding variables. Prior to propensity-matching, the study population included 588 individuals, 280 underwent Nodify XL2 testing and 278 were untested. After matching, there were 197 individuals in each group. The investigators found that individuals with a benign nodule in the Nodify XL2 group underwent fewer invasive procedures (n=8, 5%) than those in the comparison group (n=30, 19%) a statistically significant difference between groups, p<0.001. No individuals in the Nodify XL2 group who had a benign nodule underwent an invasive procedure, whereas 4 individuals (2%) of individuals in the comparison group who had a benign diagnosis had an invasive procedure. In the intervention group, 161 individuals were routed to CT surveillance and 12 (7.5%) were eventually diagnosed with a malignancy. In the comparison group, 113 individuals were routed to CT surveillance and 4 (3.5%) were diagnosed with a malignancy; the difference between groups was not statistically significant. The study was limited in that it was not randomized and control participants were retrospectively selected. Ideally the Nodify XL2 would be studied prospectively in a blinded RCT to confirm that use of the test results in less invasive biopsies vs. standard care and that a positive net health outcome has been demonstrated.

The National Comprehensive Cancer Network's (NCCN) guideline for NSCLC (V5.2024) did not mention the use of proteomic or protein biomarker algorithmic testing.

Pancreatic Cancer

IMMray® PanCan-d test

The IMMray PanCan-d test (Immunovia) is designed to detect pancreatic ductal adenocarcinoma (PDAC) by a serum-based test measuring 9 biomarkers, including CA 19-9. The values for each biomarker are entered into proprietary computer software and an algorithm calculates whether the sample has a high-risk signature present, is negative for a high-risk signature or is a borderline result.

In 2022, Brand and colleagues published a study evaluating the IMMray test for detection of PDAC. The study included three sample cohorts: healthy individuals (n=216), individuals at high genetic risk of PDAC (n=203), and individuals with PDAC (n=167). The authors found that in the individuals with PDAC and excluding cases with borderline results, the IMMray test had an 85% sensitivity for detecting early stage (stages I and II) PDAC and an 87% sensitivity for detecting all-stage PDAC. The specificity was 98% against the high-risk cohort and 99% against the healthy cohort. CA 19-9 alone had a 73.8% sensitivity and 97.6% specificity. A total of 6% of the healthy cohort (n=13), 10% of the high-risk cohort (n=20) and 14% of the PDAC cohort (n=23) had borderline results. The study does not evaluate the clinical utility of IMMray testing compared with CA 19-9 testing for specific clinical scenarios.

A 2023 study by Katona and colleagues performed the IMMray test in a clinical practice setting. The study included 96 high-risk individuals undergoing surveillance for PDAC and 6 individuals with a known diagnosis of PDAC. A total of 93% of the high-risk individuals had undergone surveillance imaging within the 2 months before testing. Only 1 (1%) of high-risk individuals had a positive IMMray test, 7 (7%) had a borderline result, 73 (78%) had a negative result and 13 (14%) did not have viable test results. Four (67%) of the individuals with PDAC had a positive result and 2 (33%) had a negative result. Test performance characteristics were assessed in several ways e.g., with borderline results included as positive or negative results. In all of the analyses, the NPV of the IMMray test was above 99%. The PPV was 35.3% to 52.4% when borderline results were not considered positive, and 12.1% or less when borderline results were considered positive. Like the Brand study, discussed above, this study did not evaluate the clinical utility of IMMray test.

The NCCN guideline for pancreatic cancer (V2.2024) states that it is important to identify biomarkers for early detection of pancreatic cancer and that the best-validated biomarker for early detection is CA 19-9. The guideline recommends “measurement of serum CA 19-9 levels after neoadjuvant treatment, prior to surgery, following surgery immediately prior to administration of adjuvant therapy, and for surveillance (category 2B)”. The guideline noted that CA 19-9 has a low positive predictive value which “makes it a poor biomarker for screening”. The guideline does not recommend testing for other biomarkers or using protein biomarker panels.

Preterm delivery

Saade and colleagues (2016) published findings of the Proteomic Assessment of Preterm Risk (PAPR) study on the development and validation of a spontaneous pre-term delivery (sPTD) prediction tool (known as PreTRM®, Sera Prognostics, Inc.). The study enrolled 5501 pregnant women between 17 weeks, 0 days and 28 weeks, 6 days gestational age, 217 of whom experienced sPTD. Using blood samples from study participants, the investigators determined that 2 proteins, IBP4 and SHBG, used as a ratio (IBP4/SHBG), was the best predictor of sPTD. For the primary analysis of sPTD (< 37 weeks) versus term birth (at least 37 weeks), the sensitivity and specificity of the predictive tool was 75% and 74%, respectively, with an area under the curve (AUC) of 75% (95% CI, 0.56 to 0.91). This study did not address whether prospective use of an sPTD prediction tool improves clinical care or health outcomes.

A secondary analysis of data from the PAPR study was published by Burchard and colleagues in 2022. The analysis compared the performance of the predictive tool in women included in the validation cohort of the PAPR study whose pregnancies were dated by any method (all participants), compared with women whose pregnancies were dated with “more certainty”, defined as a first- or second-trimester ultrasound and not by last menstrual period (LMP) only. The AUC of the risk predictor tool was 75% in the total population, and 80% in the population that excluded pregnancies dated by LMP. The correlation between the risk predictor tool and gestational age at birth was statistically significant in both populations.

In 2020, Markenson and colleagues reported on individuals enrolled in the first of two phases of the prospective observational study, the Multicenter Assessment of a Spontaneous Preterm Birth Risk Predictor (TREETOP) study evaluating PreTRM prediction tool. The study enrolled 5011 individuals with singleton pregnancy between 17 weeks, 0 days and 21 weeks, 6 days gestational age with no symptoms of preterm labor or rupture of membranes who were deemed at low risk for preterm birth. In a subgroup analysis, which included 847 individuals, the investigators reported on the ability of the IBP4/SHBG ratio to predict early preterm birth, both spontaneous and medically indicated. There was a total of 9 very preterm deliveries in the analysis, defined as delivery before 32 weeks, 0 days. Eight of the 9 cases were due to medically indicated deliveries. The investigators found that the mean IBP4/SHBG score was significantly higher in preterm birth cases (mean, -1.22) vs. non-cases (mean, -1.48), p=0.16, with an AUC of 0.71, 95% CI, 0.55 to 0.87. Nonetheless, the range of IBP4/SHBG scores ranged widely for both non-cases and preterm birth cases, with substantial

overlap in predictor scores between both groups. Given this, the authors also stratified mean IBP4/SHBG predictor scores by neonatal composite outcome score (NMI), finding that higher NMI scores were associated with a higher mean IBP4/SHBG score. Nonetheless, many cases with an NMI of 0 had IBP4/SHBG scores overlapping with infants with an NMI of 4. A total of 21 of the 847 infants had high (at least 3 of 4) scores on the NMI, an index of neonatal morbidity and mortality. Seven of 9 cases of preterm birth before 32 weeks' gestation had NMI scores of 3 and neonatal death occurred in the other 2 cases (NMI=4). The second phase of the study will be a validation of clinically relevant threshold to use for IBP4/SHBG risk stratification and will assess sensitivity, specificity and positive and negative predictive values.

Burchard and colleagues (2021) published a sub-analysis of data from the verification and validation cohorts of the PAPR and TREETOP studies, focusing on the threshold of the protein biomarker algorithmic test. The investigators found that a -1.37 threshold was significantly associated with spontaneous pre-term birth (sPTB) in both the PAPR and TREETOP studies (p=0.041 in each study). Participants at or above the threshold had earlier delivery than those below the threshold. When data from the two studies were combined, preterm birth was significantly more likely in participants at or above the threshold.

In 2021, Branch and colleagues published findings of an RCT evaluating the impact of PreTRM testing on birth outcomes in singleton pregnancies. The study included 1191 women with a mid-trimester ultrasound finding of a cervical length at least 2.5 cm who were at low risk for sPTB. Participants were randomized to PreTRM testing (n=595) or to no PreTRM testing (n=596). The PreTRM test was used to stratify participants as having an increased risk of sPTB (screen-positive, risk ≥ 14%) or lower risk of sPTB (screen-negative, risk < 14%). Screen-positive women were offered a risk reduction protocol including progesterone supplementation, cervical length surveillance, daily low-dose aspirin, and weekly review of symptoms. The primary outcome of interest was the proportion of participants experiencing sPTB < 37 weeks due to preterm labor or to premature rupture of membranes in the absence of other indications for preterm delivery. Data were not available for 10 participants; 1181 were included in the analysis. sPTB < 37 weeks occurred in 16 (2.7%) of screened and 21 (3.5%) of unscreened women; the difference in the rate of sPTB did not differ significantly between groups (p=0.413). There were also no differences between groups in neonatal secondary outcomes such as gestational age at delivery, rate of admission to the neonatal intensive care unit (NICU) or NICU length of stay. In this study, randomization to preTRM testing and subsequent management based on preTRM results, did not improve birth outcomes.

No national physician specialty societies and associations, including the American College of Obstetricians and Gynecologists (ACOG), have published recommendations on use of the PreTRM test for assessment or management of preterm labor. The ACOG 2016 Practice Bulletin on Management of Preterm Labor addressed fetal fibronectin status and cervical length to stratify risk for preterm delivery in individuals with preterm contractions. The Bulletin stated, "positive predictive value of a positive fetal fibronectin test result or a short cervix alone is poor and should not be used exclusively to direct management in the setting of acute symptoms."

The ACOG 2021 Practice Bulletin on Prediction and Prevention of Spontaneous Preterm Birth states:

> A number of multifactorial risk-scoring systems have been developed and tested to identify patients at risk for preterm birth based on history, physical findings, and social and economic risk factors. In general, these have performed poorly in clinical use. Ongoing studies are evaluating the use of serum biomarkers, genital tract microbiome, salivary hormone and protein concentrations, cervical texture, and genetic profiling for preterm birth risk assessment.

At present, there are insufficient data to support the clinical utility of protein biomarker algorithmic assays for management of sPTD.

Other tests

Published studies have described the development of protein biomarker algorithmic tests for other applications such as breast cancer (Bohm, 2011; Costa, 2011), thyroid cancer (Cheng, 2011), coronary artery disease (Ganz, 2016) and malignant pleural mesothelioma (Ostroff, 2012). Theralink® Reverse Phase Protein Array (RPPA) markets a panel for breast cancer but no published studies of clinical use of this panel are currently available. Additional studies are necessary to establish standards for these clinical applications of protein biomarker algorithmic analysis, as well as the clinical utility of such testing.

Other Relevant Information

No FDA labeled indications have been identified for the selected protein biomarker algorithmic assays addressed in this document. The Centers for Medicare & Medicaid Services (CMS) Local Coverage Determinations (LCD) L35396 Biomarkers for Oncology includes the code for the Veristrat test in the group of covered services; other tests in this

document are not mentioned in the LCD. Nationally recognized clinical practice guidelines do not recommend the tests included in this document.

Conclusion

At this time, there is insufficient evidence of an impact of the selected protein biomarker algorithmic tests addressed in this document on health outcomes in clinical practice. Further investigation into the possible impact of testing, such as decreased cancer-related deaths and other positive outcomes, is needed.

Background/Overview

Proteins are the functional units of cells and represent the end product of the interactions among the underlying genes. A number of tests have been developed to provide a qualitative and/or quantitative analysis of protein constituents in a biological sample that are reported as a predictive, diagnostic or prognostic algorithmic result. Protein biomarkers represent objectively measured indicators of normal or disease processes or measures of response to therapy. Protein biomarker algorithmic assays may include demographic factors, including age, gender, or race, as biologically relevant, and can include a range of protein constituents.

While protein biomarker algorithmic assays have the potential to offer powerful predictive and diagnostic capabilities, many are not supported by high-quality evidence. In some cases, algorithms may effectively predict disease risk, but the result of testing does not ultimately alter care in a manner that improves net healthcare outcomes (sometimes because an effective treatment does not exist). Faulty algorithm-based laboratory tests may lead to individuals being over- or undertreated or incorrectly diagnosed, which can result in exposure to unnecessary, harmful treatments and/or inappropriate therapies or not getting effective therapies. Algorithm-based tests are laboratory-developed tests (LDT) – tests that are designed, manufactured and used within a single laboratory – and are generally not reviewed by the Food and Drug Administration (FDA). Development of an algorithm may be heavily dependent on the dataset used as part of test development/validation, and some clinical, racial, and/or sociodemographic characteristics found in the test dataset may influence the algorithm test results, leading to findings that are biased and/or not generalizable to all populations. In some cases, algorithms have the potential to systematically under- or over-represent risk associated with individuals who differ from those assessed in the original dataset, thereby leading to disparate treatment and healthcare outcomes. Finally, the formulas used to develop the algorithm are often proprietary, meaning that values assigned to each individual biomarker, or calculations necessary to produce the final test result may not be publicly available or independently reproducible by other researchers.

Definitions

Algorithm: A set of mathematical rules for solving complex problems with the aid of computer technology.

Biomarker: A biological characteristics that can objectively measured and evaluated as an indicator or a normal or abnormal biological process or a response to a pharmacologic or therapeutic intervention.

Proteomics: The study of the structure and function of proteins.

Screening: Checking or testing for disease when there are no symptoms.

Serum: The clear portion of clotted blood.

Coding

The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

When Services are Investigational and Not Medically Necessary:
When the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival

	VeriStrat, Biodesix, Inc
81599	Unlisted multianalyte assay with algorithmic analysis
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 BDX-XL2, Biodesix®, Inc, Biodesix®, Inc
0092U	Oncology (lung), three protein biomarkers, immunoassay using magnetic nanosensor technology, plasma, algorithm reported as risk score for likelihood of malignancy REVEAL Lung Nodule Characterization, MagArray, Inc
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 LC-MS/MS Targeted Proteomic Assay, OncoOmicDx Laboratory, LDT
0247U	Obstetrics (preterm birth), insulin-like growth factor–binding protein 4 (IBP4), sex hormone–binding globulin (SHBG), quantitative measurement by LC-MS/MS, utilizing maternal serum, combined with clinical data, reported as predictive-risk stratification for spontaneous preterm birth PreTRM®, Sera Prognostics, Sera Prognostics, Inc®
0249U	Oncology (breast), semiquantitative analysis of 32 phosphoproteins and protein analytes, includes laser capture microdissection, with algorithmic analysis and interpretative report Theralink® Reverse Phase Protein Array (RPPA), Theralink® Technologies, Inc, Theralink® Technologies, Inc
0342U	Oncology (pancreatic cancer), multiplex immunoassay of C5, C4, cystatin C, factor B, osteoprotegerin (OPG), gelsolin, IGFBP3, CA125 and multiplex electrochemiluminescent immunoassay (ECLIA) for CA19-9, serum, diagnostic algorithm reported qualitatively as positive, negative, or borderline IMMray® PanCan-d, Immunovia, Inc, Immunovia, Inc
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 Nodify CDT®, Biodesix, Inc, Biodesix, Inc

ICD-10 Diagnosis

All diagnoses

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Nodify XL2
Paraneoplastic Autoantibody Evaluation
PreTRM
Serum-Based Diagnostic Test for Ovarian Cancer
Theralink
VeriStrat

The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.

Document History

Status	Date	Action
Reviewed	08/08/2024	Medical Policy & Technology Assessment Committee (MPTAC) review. Updated Rationale and References sections.
Revised	08/10/2023	MPTAC review. Added IMMray® PanCan-d test to the INV/NMN statement. Reformatted bullet points to letters. Updated Description/Scope, Rationale, References and Index sections. Updated Coding section, added 0342U.
	12/28/2022	Updated Coding section with 01/01/2023 CPT changes; added 0360U (81599 no longer applicable for Nodify CDT test).
Revised	08/11/2022	MPTAC review. Title and position statement changed to Selected Protein Biomarker Algorithmic Assays. Specific tests addressed in document added to position statement. Updated Description, Rationale, Background/Overview, Definitions and References sections. Updated Coding section to remove codes 83519, 83520, 84999, 86255, 86256 no longer applicable; added 81599 NOC.
Reviewed	08/12/2021	MPTAC review. Updated Rationale, References and Index sections.
	07/01/2021	Updated Coding section with 07/01/2021 CPT changes; added 0249U.
Reviewed	02/11/2021	MPTAC review. Updated Rationale, References, and Index sections. Updated Coding section with 04/01/2021 CPT changes to add 0247U; removed 0012M, 0013M no longer applicable.
Revised	08/13/2020	MPTAC review. Updated INV and NMN statement to address all indications. Updated Scope, Rationale, References, and Index sections.
	07/01/2020	Updated Coding section with 07/01/2020 CPT changes; added 0174U.
Revised	02/20/2020	MPTAC review. Added disease management to INV and NMN statement. Updatec Rationale, References and Index sections.
	10/01/2019	Updated Coding section with 10/01/2019 CPT changes; revised descriptor for 008
	06/27/2019	Updated Coding section with 07/01/2019 CPT changes; added 0092U.
Reviewed	03/21/2019	MPTAC review.
Reviewed	03/20/2019	Hematology/Oncology Subcommittee review. Updated Rationale, References, anc Index sections.
	12/27/2018	Updated Coding section with 01/01/2019 CPT changes; added 0080U.
Reviewed	05/03/2018	MPTAC review.
Reviewed	05/02/2018	Hematology/Oncology Subcommittee review. Updated Rationale, References, and Index sections.
	03/29/2018	Updated Coding section with 04/01/2018 CPT changes; added 0012M, 0013M.
Reviewed	11/02/2017	MPTAC review.
Reviewed	11/01/2017	Hematology/Oncology Subcommittee review. The document header wording updated from “Current Effective Date” to “Publish Date.” Updated Rationale and References sections.
Reviewed	11/03/2016	MPTAC review.
Reviewed	11/02/2016	Hematology/Oncology Subcommittee review. Updated Rationale, Coding, Reference, and Index sections.
Reviewed	11/05/2015	MPTAC review.
Reviewed	11/04/2015	Hematology/Oncology Subcommittee review. Updated Rationale, Reference, and Index sections. Updated Coding section with 01/01/2016 CPT changes; removed ICD-9 codes.
Reviewed	08/06/2015	MPTAC review. Updated Rationale, References and Index sections.
Reviewed	08/14/2014	MPTAC review. Updated Coding, Rationale, References, and Index sections.

Reviewed	08/08/2013	MPTAC review. Rationale and References updated.
Reviewed	08/09/2012	MPTAC review. Rationale and References updated.
Reviewed	08/18/2011	MPTAC review. Updated Rationale and Reference sections.
Reviewed	08/19/2010	MPTAC review. References updated.
Reviewed	08/27/2009	MPTAC review. Rationale and references updated.
Revised	08/28/2008	MPTAC review. Position statement revised to address proteomic analysis for any indications as investigational and not medically necessary. Rationale, background and references updated.
Reviewed	05/15/2008	MPTAC review.
Reviewed	05/14/2008	Hematology/Oncology Subcommittee review. Rationale, background and references updated.
	02/21/2008	The phrase "investigational/not medically necessary" was clarified to read "investigational and not medically necessary." This change was approved at the November 29, 2007 MPTAC meeting.
Reviewed	05/17/2007	MPTAC review. Background and references updated.
Reviewed	05/16/2007	Hematology/Oncology Subcommittee review. References updated.
Reviewed	06/08/2006	MPTAC review. Updated rationale and reference sections.
Revised	07/14/2005	MPTAC review. Revision based on Pre-merger Anthem and Pre-merger WellPoint Harmonization.

Pre-Merger Organizations	Last Review Date	Document Number	Title
Anthem, Inc.	10/28/2004	LAB.00011	Analysis of Proteomic Patterns in Serum to Identify Ovarian Cancer
WellPoint Health Networks, Inc.	06/24/2004	2.11.21	Analysis of Proteomic Patterns in the Serum as a Screening Technique for Ovarian Cancer

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Applicable to Commercial HMO members in California: When a medical policy states a procedure or treatment is investigational, PMGs should not approve or deny the request. Instead, please fax the request to Anthem Blue Cross Grievance and Appeals at fax # 818-234-2767 or 818-234-3824. For questions, call G&A at 1-800-365-0609 and ask to speak with the Investigational Review Nurse.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member’s contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.