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Medical Policy

Subject:	Analysis of Proteomic Patterns		
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Description/Scope

~~T~~This document addresses the use of proteomics, which is the qualitative and quantitative analysis of the collection of protein constituents in a biological sample. Proteomics is typically performed using a modification of polyacrylamide gel electrophoresis (PAGE) or matrix-assisted laser desorption/ionization (MALDI) approaches to provide measures of the types and abundance of proteins in a biological sample. Proteomics assays are under investigation in certain tumors.

Position Statement

Investigational and Not Medically Necessary:

Analysis of proteomic patterns to screen for, diagnose, or manage~~for screening or diagnosis of~~ disease is considered **investigational and not medically necessary.**

Rationale

Ovarian Cancer

There has been considerable interest regarding the potential role for proteomics for the screening and detection of various cancers (Conrads, 2003; Wu, 2002; Zhu, 2003). Petricoin and colleagues studied proteomics for ovarian cancer detection in women considered at high risk of ovarian cancer. They reported on the technical feasibility of proteomic 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

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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

Several studies have been published addressing the use of the VeriStrat (Biodesix, Inc., Boulder, CO), a mass spectrometry-based proteomic 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 subjects 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 subjects 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 subjects were tested using the VeriStrat test. Subjects classified as VS-G survived significantly longer than those classified as Poor. For VS-G subjects, the median survival was 10.5 months on erlotinib versus 6.6 months for placebo (p=0.002). For VS-P subjects, 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 subjects, VS-G subjects had a significantly higher response rate than VS-P subjects (11.5% vs. 1.1%, p=0.002).

Amann (2010) reported the use of the VeriStrat test on a cohort of 102 subjects from the Easter 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%) subjects had KRAS mutations

and 3 of 41 (7%) had EGFR mutations. The VeriStrat test identified 64 of 88 (73%) subjects as predicted to have Good outcomes and 24 of 88 (27%) subjects 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 subjects receiving a combination of erlotinib and sorafenib for advanced stage NSCLC (2012). The authors reported that the test was successful in identifying those subjects with significantly better overall survival (OS) with VS-G subjects having a median OS of 13.7 months and VS-P subjects having 5.6 month median OS ($p<0.009$). Progression-free survival (PFS) was 5.5 months for VS-G subjects and 2.7 months for VS-P subjects ($p<0.035$). 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 subjects tested with the VeriStrat test. The results demonstrated that subjects 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 subjects 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 subjects. 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 subjects (403/2822, 14.3%). The results indicated that knowing the test outcome resulted in changes in treatment plan in 19.1% of subjects. 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 subjects 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 subjects 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 subjects and 129 (91%) control subjects were included. Median overall survival 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). Subjects 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 overall survival between treatments for subjects 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 overall survival 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 subjects 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 subjects 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.

A meta-analysis conducted by Sun et al. in 2014 evaluated the existing evidence addressing the VeriStrat test. The study included 11 cohorts involving 706 subjects from seven studies. The authors reported that VS-G status predicted a better clinical outcome with a pooled HR of 0.40 (p<0.001) for overall survival, and 0.49 (p<0.001) for progression-free survival. There was no significant heterogeneity, but a slight publication bias was reported. They concluded that their study demonstrated that the VeriStrat test has a predictive value for individuals with NSCLC treated with Epidermal Growth Factor Receptor (EGFR) tyrosine kinase inhibitors (TKI), but that additional studies are needed to validate and update their results.

Gadgeel (2017) reported a retrospective analysis of 691 samples from subjects enrolled in the LUX-Lung 8 study. The LUX-Lung 8 study was a phase III RCT enrolled 795 subjects with Stage IIIB/IV NSCLC of squamous (including mixed) histology, with progressive disease after at least 4 cycles of first-line platinum-based chemotherapy, 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 subjects, and in afatinib-treated subjects. 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 subjects, and in afatinib-treated subjects. 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; p<0.0001) and in afatinib-treated patients (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 patients, notably, the confidence intervals overlapped. A multivariate analysis showed that VeriStrat was an independent predictor of OS in afatinib-treated subjects, regardless of ECOG PS, 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 subjects having significantly improved PFS vs. VS-P subjects, both in the overall VeriStrat-classified population (median 2.6 vs 1.9 months; HR, 0.65, p<0.0001), and in afatinib-treated subjects (median 3.3 vs 1.9 months; HR, 0.56; <0.0001). There were significant improvements with afatinib vs. erlotinib in VS-G subjects 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 with afatinib over erlotinib, with the interaction p-values were non-significant for ORR ($p_{interaction}$=0.1590) and DCR ($p_{interaction}$=0.5547). In all VeriStrat-classified subjects, VeriStrat status had a strong stratification effect on DCR, with significantly improvement in VS-G vs. VS-P subjects (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-TKIs. The VeriStrat test classified 1950 subjects as VS-G and 544 subjects 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 subjects. No data were presented on clinical outcomes

for any of the subjects 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 subjects (22%), which calls into question the validity of the conclusion and the actual clinical utility of the test.

In October of 2016, the FDA modified its clinical indications for erlotinib in maintenance therapy or second (or greater) line treatment of NSCLC, limiting erlotinib use in tumor cells expressing EGFR mutations only, based on the findings of a randomized, double-blind, controlled trial (IUNO Trial), which demonstrated that survival following treatment with erlotinib was not better than placebo administered as maintenance in individuals with metastatic NSCLC tumors not harboring EGFR-activating mutations (ClincalTrials.gov, 2016).

EarlyCDT®-Lung test

Two case-control studies have been published describing the sensitivity of the EarlyCDT-Lung test, which evaluated samples for tumor-associated autoantibodies found in individuals with lung cancer. The first study involved 574 subjects from four separate cohorts (Lam, 2011). Group 1 (n=122) included subjects with only small cell lung cancer (SCLC); Group 2 (n=249) was composed of 97% of subjects with non-small cell lung cancer (NSCLC); Group 3 (n=122) included only subjects with NSCLC; and Group 4 (n=81), was made up of 62% of subjects 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 another case-control study involving 235 subjects 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%.

~~*Xpresys™ Lung test*~~

~~In 2013, Li and others described the result of the first study addressing the Xpresys Lung test, a 13-protein classifier test proposed for the differentiation of benign and malignant pulmonary lung nodules. This case-control study involved 143 serum samples from subjects with either benign or stage 1A lung cancer matched for nodule~~

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~~size, age, gender, and clinical site. The authors reported that the test was validated in a 104 subject group, resulting in a negative predictive value (NPV) of 90%. This result was independent of age, nodule size, or smoking history. No data were presented to address the results of clinical outcomes in subjects who have had treatment guided by this test.~~

~~Another validation study addressing the use of an 11-protein classifier for individuals with pulmonary lung nodules was also reported by Vachani in 2015. This blinded, retrospective case-control study involved 141 lung nodule plasma samples and demonstrated an NPV of 90%, positive predictive values (PPV) of 26%, sensitivity of 92% and specificity of 20%. Results were independent of age, tobacco use, nodule size and diagnosis of chronic obstructive pulmonary disease (COPD). As with the Li study mentioned above, no data were presented to address the results of clinical outcomes in subjects who have had treatment guided by this test.~~

Authoritative Organization Recommendations for Proteomic Pattern Testing for Lung Cancer

The current version of the National Comprehensive Cancer Network's (NCCN) guideline for NSCLC (~~V8~~V3.20~~17~~02) does not recommend or mention the use of proteomic testing.

Urinary Biomarker Tests

Riaz and colleagues (2010) investigated the use of proteomics to identify urinary biomarkers in individuals with type 2 diabetes. This study involved 100 subjects with type 2 diabetes and 50 age- and gender-matched healthy controls. Urinary protein samples from all participants were analyzed by first phase chromatofocusing chromatography and then reverse phase chromatography for the second phase. This was followed by mass spectrometric analysis. Proteins that were found to vary in subjects versus controls were then determined by enzyme-linked immunosorbent assay. The authors reported significant decreases in transthyretin and haptoglobin precursor, and significant increases in the levels of albumin, zinc a2 glycoprotein, retinol binding protein 4, and E-cadherin in subjects with diabetes. No data were presented addressing the use of this information in the clinical setting and, at this time, no such evidence has been published.

Roesser (2013) described a case-control study of 102 subjects with known urothelial carcinoma and 206 controls evaluating the novel proteomic model when compared to standard cytologic testing and the UroVysion assay. The UroVysion assay assesses the concentration of 8 biomarkers (IL-8, MMP-9 and 10, PAI-1, VEGF, ANG, CA9 and APOE) using an enzyme-linked immunosorbent assay (ELISA). The authors reported that 7 of the 8 urine biomarkers were increased in subjects with bladder cancer relative to those without bladder cancer.

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Excluding CA9, the 7 remaining biomarkers were assessed in a new model, 74% sensitivity, 90% specificity, 79% positive predictive value, and 87% negative predictive value were calculated. In a multivariate analysis, it was found that IL-8, PAI-1, and MMP-9 were most frequently ranked as the top factors for risk of cancer detection. Using a model with these markers only, the results indicated 79% sensitivity, 84% specificity, 70% positive predictive value, and 89% negative predictive value. In contrast, the sensitivity of voided urine cytology (VUC) and the UroVysion cytogenetic test in this cohort was 39% and 54%, respectively. The 7- and 3-biomarker signatures achieved significantly higher sensitivity than VUC (each $p<0.001$) and the cytogenetic assay ($p<0.005$ and <0.001, respectively). The authors indicate that the limitations of this study include analysis performed on banked urine samples and the lack of voided urine cytology and cytogenetic test data on controls.

Other tests

Other published studies describe the identification and development of other tests such as CXbladder and PAVAL (Bohm, 2011; Boyle, 2010; Chapman, 2007; Cheng, 2011; Costa, 2011; Ganz, 2016; Murray, 2010; Ostroff, 2012; Riley, 2011) and the application of proteomic analysis for medical management of disease (Chacko, 2011). Additional randomized controlled studies are necessary to establish standards for the clinical applications of proteomic analysis.

Conclusion

While these studies are interesting and show some promise for proteomic testing, at this time no study has demonstrated any real impact of such testing on health outcomes in clinical practice. Further investigation into the possible impact of proteomic testing, such as decreased cancer-related deaths and other positive outcomes, is needed.

Background/Overview

Genetic mutations do not reflect the complicated interactions between individual cells, tissue and organs. Proteins are the functional units of cells and represent the end product of the interactions among the underlying genes. Therefore, recent research interest has increased in the pattern of proteins associated with disease. This field may be referred to as proteomics (to distinguish it from genomics) and is defined as the study of all protein forms expressed within an organism as a function of time, age, state, and external factors.

Proteomics is the study of the structure and function of proteins. Proteins are vital parts of living organisms, as they are the main components of the physiological metabolic pathways of cells. The term "proteomics" was coined to make an analogy with genomics, the study of the genes. Proteomics differs from genomics mostly because an organism's genome is rather constant, while a proteome differs from cell to cell and constantly changes through its biochemical interactions with the genome and the environment. One organism has radically different protein expression in different parts of its body, different stages of its life cycle and different environmental conditions.

One research application of proteomics has been the association of protein patterns in serum or other body fluids with malignancy. The identification of patterns of proteins in the serum could function as a serum tumor marker, similar in concept to the more familiar prostate specific antigen (PSA) or CA-125, which are used in the detection and monitoring of prostate and ovarian cancer. This type of proteomic profiling has also been referred to as a "protein fingerprint."

Use of proteomic patterns in serum to identify ovarian cancer is one of the first clinical applications of proteomics and is the result of a joint project initiated between the National Cancer Institute and the U.S. Food and Drug Administration (FDA) to develop proteomics for cancer screening and diagnosis.

Proteomics are also being used to study neurological diseases such as brain injury, stroke, dementia, depression and Parkinson's disease. Other areas of interest are:

- Cardiac ischemia and cardiomyopathy;
- Diabetes and obesity;
- Cancer screening: lung, colon, prostate and breast cancers;
- Solid organ transplant rejection.

Definitions

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

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

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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
84999	Unlisted chemistry procedure [when specified as proteomic testing]
0012M	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 urothelial carcinoma Cxbladder™ Detect, Pacific Edge Diagnostics USA, Ltd
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 Cxbladder™ Monitor, Pacific Edge Diagnostics USA, Ltd
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

ICD-10 Diagnosis

All diagnoses

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When Services are also Investigational and Not Medically Necessary:
For the procedure and diagnosis codes listed below or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.

CPT	
83519	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, by radioimmunoassay (eg, RIA) [when specified as a component of paraneoplastic autoantibody evaluation (PAVAL)]
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified [when specified as EarlyCDT lung cancer assessment or as a component of paraneoplastic autoantibody evaluation (PAVAL)]
86255	Fluorescent noninfectious agent antibody; screen, each antibody [when specified as a component of paraneoplastic autoantibody evaluation (PAVAL)]
86256	Fluorescent noninfectious agent antibody; titer, each antibody [when specified as a component of paraneoplastic autoantibody evaluation (PAVAL)]

ICD-10 Diagnosis	
C00.0-C96.9	Malignant neoplasms
Z12.2	Encounter for screening for malignant neoplasm of respiratory organs
Z72.0	Tobacco use
Z77.22	Contact with and (suspected) exposure to environmental tobacco smoke
Z80.0-Z80.9	Family history of primary malignant neoplasm
Z85.00-Z85.9	Personal history of malignant neoplasm

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   - Bladder Cancer (V13.201920). Revised December 20, 2018January 17, 2020.
   - Non-Small Cell Lung Cancer (V.32.201920). Revised January 18, 2018February 11, 2020.
   - Ovarian Cancer V2V3.20189. Revised March 9, 2018November 26, 2019.
   - Prostate Cancer (V4.20189). Revised August 159, 20182019.

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

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Index

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
Revised	02/20/2020	Medical Policy & Technology Assessment Committee (MPTAC) review. Added disease management to INV and NMN statement. Updated Rationale, References and Index sections.
	10/01/2019	Updated Coding section with 10/01/2019 CPT changes; revised descriptor for 0080U.
	06/27/2019	Updated Coding section with 07/01/2019 CPT changes; added 0092U.
Reviewed	03/21/2019	~~Medical Policy & Technology Assessment Committee (~~MPTAC~~)~~ review.
Reviewed	03/20/2019	Hematology/Oncology Subcommittee review. Updated Rationale, References, and 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.

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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.

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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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