

Policy: MP265

Section: Medical Benefit Policy

Subject: Proteomic Serum Analysis

Applicable Lines of Business

Commercial	X	CHIP	X
Medicare	X	ACA	X
Medicaid	X		

I. Policy: Proteomic Serum Analysis

II. Purpose/Objective:

To provide a policy of coverage regarding Proteomic Serum Analysis

III. Responsibility:

- A. Medical Directors
- B. Medical Management

IV. Required Definitions

1. Attachment – a supporting document that is developed and maintained by the policy writer or department requiring/authoring the policy.
2. Exhibit – a supporting document developed and maintained in a department other than the department requiring/authoring the policy.
3. Devised – the date the policy was implemented.
4. Revised – the date of every revision to the policy, including typographical and grammatical changes.
5. Reviewed – the date documenting the annual review if the policy has no revisions necessary.

V. Additional Definitions

Medical Necessity or Medically Necessary means Covered Services rendered by a Health Care Provider that the Plan determines are:

- a. appropriate for the symptoms and diagnosis or treatment of the Member's condition, illness, disease or injury;
- b. provided for the diagnosis, and the direct care and treatment of the Member's condition, illness disease or injury;
- c. in accordance with current standards of good medical treatment practiced by the general medical community.
- d. not primarily for the convenience of the Member, or the Member's Health Care Provider; and
- e. the most appropriate source or level of service that can safely be provided to the Member. When applied to hospitalization, this further means that the Member requires acute care as an inpatient due to the nature of the services rendered or the Member's condition, and the Member cannot receive safe or adequate care as an outpatient.

Medicaid Business Segment

Medically Necessary — A service, item, procedure, or level of care that is necessary for the proper treatment or management of an illness, injury, or disability is one that:

- Will, or is reasonably expected to, prevent the onset of an illness, condition, injury or disability.

- Will, or is reasonably expected to, reduce or ameliorate the physical, mental or developmental effects of an illness, condition, injury or disability.
- Will assist the Member to achieve or maintain maximum functional capacity in performing daily activities, taking into account both the functional capacity of the Member and those functional capacities that are appropriate for Members of the same age

DESCRIPTION:

OvaCheck®, developed by Correlogic Systems Inc, is a serum-based test that uses proteomics for the early detection of ovarian cancer. The test is based on proteomic patterns detected in the serum, which are then further analyzed with the use of a mass spectrometer to profile a population of proteins based on their size and electrical charge. This type of analysis contains thousands of data points, which undergo further computer analysis using artificial intelligence-based algorithms to identify a pattern that is consistent with ovarian cancer.

OVA1® (Vermillion, Inc) is a blood test to help assess the likelihood an ovarian mass is malignant prior to a planned surgery. In conjunction with clinical evaluation of members age 18 and older who have an ovarian mass and planned surgery, OVA1 may help triage according to probability of malignancy. OVA1® measures the levels of five proteins found in the blood and then uses a proprietary software to calculate a single score. Risk is measured using a 0-10 scale versus predetermined cut-off points. Members who are pre-menopausal have a cut off of 5.0 whereas postmenopausal members have a 4.4 cutoff.

VeriStrat (Biodesix Inc) test uses mass spectrometry and a proprietary algorithm to analyze pretreatment plasma or serum to predict the benefit of single-agent chemotherapy or EGFR Tyrosine Kinase Inhibitor treatment in patients with non-small cell lung cancer with an unknown or wild-type variant of EGFR, or to identify patients with particularly aggressive disease. The NCCN recommends that proteomic testing be conducted in patients with NSCLC and wild-type or unknown EGFR status, and that a “poor” assignment indicates that the patient should not be treated with erlotinib in the second-line setting

Xpresys Lung and BDX-XL2 (Xpresys Lung 2) are plasma-based proteomic screening tests that measures the relative amount of proteins associated with lung cancer using multiple reaction monitoring mass spectroscopy. The testing is proposed to aid in differentiating likely benign from likely malignant nodules.

REVEAL Lung Nodule Characterization is a plasma protein biomarker test proposed to aid in characterizing indeterminate pulmonary nodules (4-30 mm) in current smokers aged 25 years and older. Using immunoassay, microarray, and magnetic nanoparticle detection techniques, the REVEAL Lung Nodule Characterization score is presented on a scale from 0 to 100 with a single cut point at 50. The score is based on an algorithm using factors from the patient’s history (smoking history, age, and nodule size), and the presence of three blood proteins associated with lung cancer (epidermal growth factor receptor [EGFR], prosurfactant protein B (ProSB), and tissue inhibitor of metalloproteinases 1 (TIMP1).

The IMMray PanCan-d test combines an 8-plex biomarker signature with CA19-9 in a proprietary algorithm to detect pancreatic ductal adenocarcinoma (PDAC) in serum samples. The biomarkers are a combination of immunoregulatory and tumor biomarkers.

INDICATIONS:

Commercial and Medicaid Business Segment:

SEE ALSO MP355 Plasma-based Proteomic Testing in the Management of Pulmonary Nodules

VeriStrat®

Proteomic testing (VeriStrat®) is considered medically necessary for members with advanced non-small cell lung cancer (NSCLC) when ALL of the following criteria are met:

- The test results will assist in informing whether to proceed with erlotinib (Tarceva®) therapy.
- The test results will assist in informing overall prognosis and treatment strategy

Medicare Business Segment:

In compliance with Novitas LCD L35396 the **OVA1** proteomic assay will be covered according to the FDA label. OVA1 is intended only for members, 18 years and older, who are already selected for surgery because of their pelvic mass. It is not intended for ovarian cancer screening or for a definitive diagnosis of ovarian cancer.

In compliance with Novitas LCD L35396 the **Risk of Ovarian Malignancy Algorithm (ROMA™)** serum test will be covered to aid in assessing whether a premenopausal or postmenopausal woman who presents with an ovarian adnexal mass is at high or low likelihood of finding malignancy at surgery. ROMA™ will be considered reasonable and necessary for women who meet the following FDA labeling criteria:

- Over age 18;
- Ovarian adnexal mass present for which surgery is planned; and,
- Not yet referred to an oncologist.

In compliance with Novitas LCD L35396 the **VeriStrat** proteomic assay will be covered to predict the benefit of single-agent chemotherapy or EGFR Tyrosine Kinase Inhibitor treatment in patients with non-small cell lung cancer with an unknown or wild-type variant of EGFR, or to identify patients with particularly aggressive disease.

MolDx has determined that **BDX-XL2** test will be covered for the management of a lung nodule, between 8 and 30mm in diameter, in patients 40 years or older and with a pre-test cancer risk (as assessed by the Mayo Clinic Model for Solitary Pulmonary Nodules) of 50% or less.

EXCLUSIONS: All Business Segments Except as Annotated

PA Dept. of Human Services has determined OVA1 assay may be considered on a per-case basis through the Program Exception process

Unless otherwise mandated (eg, Medicare), the Plan does **NOT** provide coverage for Proteomic Serum analysis to Identify Ovarian Cancer because it is considered **experimental, investigational or unproven**. There is insufficient evidence in the peer-reviewed published medical literature to establish the effectiveness of this test on health outcomes when compared to established tests or technologies.

Any use of VeriStrat® serum proteomic testing except as noted above is considered experimental/investigational or unproven and **NOT COVERED**.

Unless otherwise mandated (eg, Medicare), the Plan does **NOT** provide coverage for Proteomic Serum analysis to Identify Lung Cancer (Xpresys Lung, BDX-XL2, REVEAL Lung Nodule Characterization) because it is considered **experimental, investigational or unproven**. There is insufficient evidence in the peer-reviewed published medical literature to establish the effectiveness of this test on health outcomes when compared to established tests or technologies.

The Plan does **NOT** provide coverage for Proteomic Serum analysis to bladder cancer (Cxbladder™ Detect, Cxbladder™ Monitor) because it is considered **unproven**. There is insufficient evidence in the peer-reviewed published medical literature to establish the effectiveness of this test on health outcomes when compared to established tests or technologies.

The Plan does **NOT** provide coverage for IMMray PanCan-d test because it is considered **experimental, investigational or unproven**. There is insufficient evidence in the peer-reviewed published medical literature to establish the effectiveness of this test on health outcomes when compared to established tests or technologies.

Medicaid Business Segment:

Any requests for services, that do not meet criteria set in the PARP, may be evaluated on a case by case basis.

Note: A complete description of the process by which a given technology or service is evaluated and determined to be experimental, investigational or unproven is outlined in **MP 15 - Experimental Investigational or Unproven Services or Treatment**.

CODING ASSOCIATED WITH: Proteomic Serum Analysis

The following codes are included below for informational purposes and may not be all inclusive. Inclusion of a procedure or device code(s) does not constitute or imply coverage nor does it imply or guarantee provider reimbursement. Coverage is determined by the member specific benefit plan document and any applicable laws regarding coverage of specific services. Please note that per Medicare coverage rules, only specific CPT/HCPCS Codes may be covered for the Medicare Business Segment. Please consult the CMS website at www.cms.gov or the local Medicare Administrative Carrier (MAC) for more information on Medicare coverage and coding requirements.

- 81500 Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score (This code is for reporting the ROMA™ test)
- 81503 Oncology (ovarian) biochemical assays of five proteins (CA-125, apolipoprotein A1, beta-2 microglobulin, transferrin, and pre-albumin) utilizing serum, algorithm reported as a risk score.
- 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)
- 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 (This code is for reporting Cxbladder™ Detect)
- 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 (This code is for reporting Cxbladder™ Monitor),
- 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 (This code is for reporting BDX-XL2, Biodesix®)
- 0092U Oncology (lung), three protein biomarkers, immunoassay using magnetic nanosensor technology, plasma, algorithm reported as risk score for likelihood of malignancy (This code is for reporting REVEAL Lung Nodule Characterization)
- 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}

Current Procedural Terminology (CPT®) © American Medical Association: Chicago, IL

LINE OF BUSINESS:

Eligibility and contract specific benefit limitations and/or exclusions will apply. Coverage statements found in the line of business specific benefit document will supersede this policy. For Medicare, applicable LCD's and NCD's will supercede this policy For PA Medicaid Business segment, this policy applies as written.

REFERENCES:

Geisinger Technology Assessment Committee Triage Group. January 2012.

American Cancer Society. Ovarian Cancer Overview. 2017

Society of Gynecologic Oncologists. Chicago, Illinois. Statement regarding OvaCheck™ February 7, 2004. Accessed on 9/19/11 at www.sgo.org/WorkArea/linkit.aspx?LinkIdentifier=id&ItemID=954

National Cancer Institution. Department of Health and Human Services. Questions and Answers: OvaCheck™ and NCI/FDA Ovarian Cancer Clinical Trials Using Proteomics Technology. Bethesda, MD. Accessed on 9/27/2011 <http://home.ccr.cancer.gov/ncifdaproteomics/pdf/OvaCheckQandA.pdf>

National Cancer Institution. Proteomics and Cancer. Revised on 8/7/09. Accessed on 9/21/11 at <http://www.cancer.gov/cancertopics/factsheet/detection/proteomics>

Zhang Z, et al. Three Biomarkers Identified from Serum Proteomic Analysis for the Detection of Early Stage Ovarian Cancer. *Cancer Res* August 15, 2004 64; 5882

Boylan KLM, et al. Quantitative proteomic analysis by iTRAQ® for the identification of candidate biomarkers in ovarian cancer serum *Proteome Science* 2010, 8:31

Petricoin EF, Use of proteomic patterns in serum to identify ovarian cancer. *Lancet* 2002 Feb 16;359(9306):572-7

Amon LM, Law W, Fitzgibbon MP, Gross JA, O'Briant K, et al. Integrative Proteomic Analysis of Serum and Peritoneal Fluids Helps Identify Proteins that Are Up-Regulated in Serum of Women with Ovarian Cancer. 2010 PLoS ONE 5(6): e11137. doi:10.1371/journal.pone.0011137

Anderson GL, et al. Assessing lead time of selected ovarian cancer biomarkers: a nested case-control study. 2010 Jan 6;102(1):26-38.

Novitas Solutions Inc. A52986 Biomarkers in Oncology <https://www.cms.gov/medicare-coverage-database/details/article-details.aspx?articleId=52986&ver=52&Date=06%2f09%2f2016&DocID=A52986&bc=hAAAAAgAAAAAA%3d%3d&>

Akerley WL, Nelson RE, Cowie RH, Spinella DG, Hornberger J. The impact of a serum based proteomic mass spectrometry test on treatment recommendations in advanced non-small-cell lung cancer. *Curr Med Res Opin.* 2013b;29(5):517-525.

Carbone DP, Ding K, Roder H, et al. Prognostic and predictive role of the VeriStrat plasma test in patients with advanced non-small-cell lung cancer treated with erlotinib or placebo in the NCIC Clinical Trials Group BR.21 trial. *J Thorac Oncol.* 2012;7(11):1653-1660.

Gautschi O, Dingemans AM, Crowe S, et al. VeriStrat has a prognostic value for patients with advanced non-small cell lung cancer treated with erlotinib and bevacizumab in the first line: pooled analysis of SAKK19/05 and NTR528. *Lung Cancer.* 2013;79(1):59-64.

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 1.2020

Sun W, Hu G, Long G, et al. Predictive value of a serum-based proteomic test in non-small-cell lung cancer patients treated with epidermal growth factor receptor tyrosine kinase inhibitors: a meta-analysis. *Curr Med Res Opin.* 2014 Oct;30(10):2033-9.

Hayes GTE Report. VeriStrat (Biodesix Inc.) May 5, 2016

Gregorc V, Novello S, Lazzari C, et al. Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker-stratified, randomised phase 3 trial. *Lancet Oncol.* 2014;15(7):713-721

Kuiper JL, Lind JS, Groen, et al. VeriStrat® has prognostic value in advanced stage NSCLC patients treated with erlotinib and sorafenib. *Br J Cancer.* 2012;107(11):1820-1825.

Stinchcombe TE, Roder J, Peterman AH, et al. A Retrospective analysis of VeriStrat status on outcome of a randomized phase II trial of first-line therapy with gemcitabine, erlotinib, or the combination in elderly patients (Age 70 or Older) with stage IIIB/IV non-small-cell lung cancer. *J Thorac Oncol.* 2013;8:443-451.

Polychronidou G, Papakotoulas P. Long-term treatment with erlotinib for EGFR wild-type non-small lung Cancer: A case report. *Karger.* 2013;(6)1:189-196

College of American Pathologists, International Association for the Study of Lung Cancer, Association for Molecular Pathology. Molecular testing guidelines for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors. 2013

Hornberger J, Hirsch FR, Li Q, et al. Outcome and economic implications of proteomic test-guided second- or third-line treatment for advanced non-small cell lung cancer: extended analysis of the PROSE trial. *Lung Cancer.* May 2015;88(2):223-230.

Lee CK, Brown C, Gralla RJ, et al. Impact of EGFR inhibitor in non-small cell lung cancer on progression-free and overall survival: a meta-analysis. *J Natl Cancer Inst.* May 1 2013;105(9):595-605.

Keshtgarpour M, Tan WS, Zwanziger J, et al. Prognostic Value of Serum Proteomic Test and Comorbidity Index in Diversified Population with Lung Cancer. *Anticancer Res.* Apr 2016;36(4):1759-1765.

Masters GA, Temin S, Azzoli CG, et al. Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* Oct 20 2015;33(30):3488-3515.

Nelson RE, Stenehjem D, Akerley W. A comparison of individualized treatment guided by VeriStrat with standard of care treatment strategies in patients receiving second-line treatment for advanced non-small cell lung cancer: A cost-utility analysis. *Lung Cancer.* Dec 2013;82(3):461-468.

Grossi F, Rijavec E, Genova C, et al. Serum proteomic test in advanced non-squamous non-small cell lung cancer treated in first line with standard chemotherapy. *Br J Cancer.* 2016 Nov 29.

Simmons AR, Clarke CH, Badgwell DB, et al. Validation of a biomarker panel and longitudinal biomarker performance for early detection of ovarian cancer. *Int J Gynecol Cancer.* July 2016;26(6):1070-1077

Dayyani F, Uhlig S, Colson B, et al. Diagnostic performance of risk of ovarian malignancy algorithm against CA125 and HE4 in connection with ovarian cancer: a meta analysis. *Int J Gynecol Cancer.* Nov 2016;26(9):1586-1593.

Longoria TC, Ueland FR, Zhang Z, et al. Clinical performance of a multivariate index assay for detecting early-stage ovarian cancer. *Am J Obstet Gynecol.* 2014;210(1):78.e71-78.e79.

Grenache DG, Heichman KA, Werner TL, Vucetic Z. Clinical performance of two multi-marker blood tests for predicting malignancy in women with an adnexal mass. *Clin Chim Acta*. 2015;438:358-363.

Forde GK, Hornberger J, Michalopoulos S, Bristow RE. Cost-effectiveness analysis of a multivariate index assay compared to modified American College of Obstetricians and Gynecologists criteria and CA-125 in the triage of women with adnexal masses. *Curr Med Res Opin*. 2016;32(2):321-329

Eskander RN, Carpenter BA, Wu HG, Wolf JK. The clinical utility of an elevated-risk multivariate index assay score in ovarian cancer patients. *Curr Med Res Opin*. 2016;32(6):1161-1165

Coleman RL, Herzog TJ, Chan DW, et al. Validation of a second-generation multivariate index assay for malignancy risk of adnexal masses. *Am J Obstet Gynecol*. 2016;215(1):82.e81-82.e11.

American College of Obstetricians and Gynecologists (ACOG). Committee on Practice Bulletins—Gynecology. Practice Bulletin No. 174: Evaluation and Management of Adnexal Masses. *Obstet Gynecol*. 2016;128(5):e210-e226

Gadgeel S, Goss G, Soria JC, et al. Evaluation of the VeriStrat® serum protein test in patients with advanced squamous cell carcinoma of the lung treated with second-line afatinib or erlotinib in the phase III LUX-Lung 8 study. *Lung Cancer*. 2017; 109:101-108.

Grossi F, Rijavec E, Genova C, et al. Serum proteomic test in advanced non-squamous non-small cell lung cancer treated in first line with standard chemotherapy. *Br J Cancer*. 2017; 116(1):36-43.

Peters, S., Stahel, R.A., Dafni, U., Ponce, A., Massuti, B., Gautschi, O, et al. Randomized phase III trial of erlotinib versus docetaxel in patients with advanced squamous cell non-small cell lung cancer failing first-line platinum-based doublet chemotherapy stratified by VeriStrat good versus VeriStrat poor. The European thoracic oncology platform (ETOP) EMPHASIS-lung trial. *Journal of Thoracic Oncology* 2017; 12 (4), 752-762.

Fish A, Vachani A, Massion P et. al. Novel multiplexed plasma biomarkers and clinical factors augment risk assessment for indeterminate pulmonary nodules in former smokers. *American Journal of Respiratory and Critical Care Medicine* 2019;199:A7452

Trivedi N, Arjomandi M, Brown J, et.al Risk assessment for indeterminate pulmonary nodules using a novel, plasma protein based biomarker assay. *Biomedical Research and Clinical Practice* 2018 Volume 3(4):1-8

Smester G, Median JG, Brown C, et. al. Overcoming the pitfalls of current lung cancer risk assessment: improved lung nodule characterization by a novel plasma protein biomarker test. *Biomedical Research and Reviews* 2019 Volume 3: 1-4

Trivedi N, Brown J, Rubenstein T, et. al. Analytical validation of a novel multi-analyte plasma test for lung nodule characterization. *Biomedical Research and Reviews* 2018 Volume 2(9):1-10

Konety B, Shore N, Kader A, et al. Evaluation of Cxbladder and Adjudication of Atypical Cytology and Equivocal Cystoscopy. *Eur Urol*. 2019 Aug;76(2):238-243.

Davidson P, McGeoch G, Shand B. Inclusion of a molecular marker of bladder cancer in a clinical pathway for investigation of haematuria may reduce the need for cystoscopy. *N Z Med J*. 2019 Jun 21;132(1497):55-64.

National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology. Bladder cancer Version 4.2019
MoDx Local Coverage Determination (LCD): BDX-XL2 (L37031)

Managed Care Operations Memorandum Technology Assessment Group MCOPS Memo # 01/2021-001 Jan 5, 2021

Brand RE, Persson J, et al. Detection of Early-Stage Pancreatic Ductal Adenocarcinoma From Blood Samples: Results of a Multiplex Biomarker Signature Validation Study. *Clin Transl Gastroenterol* 2022 Feb 14;13(3):e00468

PA Dept. of Human Services. Office of Medical Assistance Programs. Technology Assessment Group Ops # 01/2023-001

Novitas Local Coverage Determination L35396 Biomarkers for Oncology

This policy will be revised as necessary and reviewed no less than annually.

Devised: 3/27/2012

Revised: 8/13 (add Medicare coverage), 7/16 (Gender Language); 10/16 (added VeriStrat) 3/18 (added ROMA); 3/20 (added Xpresys Lung, BDX-XL2, REVEAL Lung Nodule Characterization, Cxbladder™ Detect, Cxbladder™ Monitor); 2/21 (add Medicaid OVA1 exclusion); 11/21 (add CxBladder coverage for Medicare) ; 2/23 (add IMMray PanCan-d exclusion, revise Medicaid OVA-1 status); 2/24 (reverse CXBladder coverage for Medicare)

Reviewed: 4/13, 10/14; 10/15, 9/17, 3/19,

CMS UM Oversight Committee Approval: 12/23

Geisinger Health Plan may refer collectively to health care coverage sponsors Geisinger Health Plan, Geisinger Quality Options, Inc., and Geisinger Indemnity Insurance Company, unless otherwise noted. Geisinger Health Plan is part of Geisinger, an integrated health care delivery and coverage organization.

Coverage for experimental or investigational treatments, services and procedures is specifically excluded under the member's certificate with Geisinger Health Plan. Unproven services outside of an approved clinical trial are also specifically excluded under the member's certificate with Geisinger Health Plan. This policy does not expand coverage to services or items specifically excluded from coverage in the member's certificate with Geisinger Health Plan. Additional information can be found in MP015 Experimental, Investigational or Unproven Services.

Prior authorization and/or pre-certification requirements for services or items may apply. Pre-certification lists may be found in the member's contract specific benefit document. Prior authorization requirements can be found at <https://www.geisinger.org/health-plan/providers/ghp-clinical-policies>

Please be advised that the use of the logos, service marks or names of Geisinger Health Plan, Geisinger Quality Options, Inc. and Geisinger Indemnity Insurance Company on a marketing, press releases or any communication piece regarding the contents of this medical policy is strictly prohibited without the prior written consent of Geisinger Health Plan. Additionally, the above medical policy does not confer any endorsement by Geisinger Health Plan, Geisinger Quality Options, Inc. and Geisinger Indemnity Insurance Company regarding the medical service, medical device or medical lab test described under this medical policy.