Proteogenomic Testing for Patients With Cancer

Policy # 00512
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers proteogenomic testing of patients with cancer (including, but not limited to the GPS Cancer™‡ test) for all indications to be **investigational.***

Note: Proteogenomic testing involves the integration of proteomic, transcriptomic, and genomic information. Proteogenomic testing can be differentiated from proteomic testing, in that proteomic testing can refer to the measurement of protein products alone, without integration of genomic and transcriptomic information. When protein products alone are tested, this is not considered proteogenomic testing.

Background/Overview

This evidence review provides an overview of the emerging field of proteogenomics, with an emphasis on the currently available proteogenomic test, GPS Cancer test. In addition to focusing on the GPS Cancer test, this review describes and outlines types of proteogenomic research currently reported in the literature and that have potential clinical applications.

PROTEOGENOMICS

The term *proteome* refers to the entire complement of proteins produced by an organism or cellular system, and *proteomics* refers to the large-scale comprehensive study of a specific proteome. Similarly, the term *transcriptome* refers to the entire complement of transcription products (messenger RNAs [mRNAs]), and *transcriptomics* refers to the study of a specific transcriptome. *Proteogenomics* refers to the integration of genomic information with proteomic and transcriptomic information to provide a more complete picture of the function of the genome.

A system's proteome is related to its genome and genomic alterations. However, while the genome is relatively static over time, the proteome is more dynamic and may vary over time and/or in response to selected stressors. Proteins undergo a number of modifications as part of normal physiologic processes. Following protein translation, modifications occur by splicing events, alternative folding mechanisms, and incorporation into larger complexes and signaling networks. These modifications are linked to protein function and result in functional differences that occur by location and over time.

Some of the main potential applications of proteogenomics in medicine include:

- Identifying biomarkers for diagnostic, prognostic, and predictive purposes
- Detecting cancer by proteomic profiles or "signatures"

- Quantitating levels of proteins and monitoring levels over time for:
  - Cancer activity
  - Early identification of resistance to targeted tumor therapy
- Correlating protein profiles with disease states

Proteogenomics is an extremely complex field due to the intricacies of protein architecture and function, the many potential proteomic targets that can be measured, and the numerous testing methods used. Types of targets currently being investigated and the testing methods used and under development next are discussed briefly herein.

Proteomic Targets
A proteomic target can be any altered protein that results from a genetic variant. Protein alterations can result from both germline and somatic genetic variants. Altered protein products include mutated proteins, fusion proteins, alternative splice variants, noncoding mRNAs, and posttranslational modifications (PTMs).

Mutated Protein (Sequence Alterations)
A mutated protein has an altered amino acid sequence that arises from a genetic variant. A single amino acid may be replaced in a protein or multiple amino acids in sequence may be affected. Mutated proteins can arise from either germline or somatic genetic variants. Somatic variants can be differentiated from germline variants by comparison with normal and diseased tissue.

Fusion Proteins
Fusion proteins are the product of one or more genes that fuse together. Most fusion genes discovered to date have been oncogenic, and fusion genes have been shown to have clinical relevance in a variety of cancers.

Alternative Splice Events
Posttranslational enzymatic splicing of proteins results in numerous protein isoforms. Alternative splicing events can lead to abnormal protein isoforms with altered function. Some alternative splicing events have been associated with tumor-specific variants.

Noncoding RNAs
Noncoding portions of the genome serve as the template for noncoding RNA (ncRNA), which plays various roles in the regulation of gene expression. There are 2 classes of ncRNA: shorter ncRNAs, which include microRNAs and related transcript products, and longer ncRNAs, which are thought to be involved in cancer progression.

Posttranslational Modifications
PTMs of histone proteins occur in normal cells and are genetically regulated. Histone proteins are found in the nuclei and play a role in gene regulation by structuring the DNA into nucleosomes. A nucleosome is

composed of a histone protein core surrounded by DNA. Nucleosomes are assembled into chromatin fibers composed of multiple nucleosomes assembled in a specific pattern. PTMs of histone proteins include a variety of mechanisms, including methylation, acetylation, phosphorylation, glycosylation, and related modifications.

Proteogenomic Testing Methods
Proteogenomic testing involves isolating, separating, and characterizing proteins from biologic samples, followed by correlation with genomic and transcriptomic data. Isolation of proteins is accomplished by trypsin digestion and solubilization. The soluble mix of protein isolates is then separated into individual proteins. This is generally done in multiple stages using high-performance liquid chromatography ion-exchange chromatography, 2-dimensional gel electrophoresis, and related methods. Once individual proteins are obtained, they may be characterized using various methods and parameters, some of which we describe below. There is literature addressing the analytic validity of these testing techniques.

Immunohistochemistry/Fluorescence in situ Hybridization
Immunohistochemistry (IHC) and fluorescence in situ hybridization are standard techniques for isolating and characterizing proteins. IHC identifies proteins by using specific antibodies that bind to the protein. Therefore, this technique can only be used for known proteins and protein variants because it relies on the availability of a specific antibody. This technique also can only test a relatively small number of samples at once.

There are a number of reasons why IHC and fluorescence in situ hybridization are not well-suited for large-scale proteomic research. They are semiquantitative techniques and involve subjective interpretation. They are considered low-throughput assays that are time-consuming and expensive and require a relatively large tissue sample. Some advances in IHC and fluorescence in situ hybridization have addressed these limitations, including tissue microarray and reverse phase protein array.

- Tissue microarrays can be constructed that enable simultaneous analysis of up to 1000 tissue samples.
- Reverse phase protein array, a variation on tissue microarrays, allows for a large number of proteins to be quantitated simultaneously.

Mass Spectrometry
Mass spectrometry (MS) separates molecules by their mass to charge ratio and has been used as a research tool for studying proteins for many years. Development of technology that led to the application of MS to biologic samples has advanced the field of proteogenomics rapidly. However, the application of MS to clinical medicine is in its formative stages. There are currently several types of mass spectrometers and a lack of standardization in the testing methods. Additionally, MS equipment is expensive and currently largely restricted to tertiary research centers.

The potential utility of MS lies in its ability to provide a wide range of proteomic information in an efficient manner, including:

- Identification of altered proteins;
- Delineation of protein or peptide profiles for a given tissue sample;
- Amino acid sequencing of proteins or peptides;
- Quantitation of protein levels;
- 3-dimensional protein structure and architecture; and
- Identification of PTMs.

MS Sampling Applications
"Top-down" MS refers to identification and characterization of all proteins in a sample without prior knowledge of which proteins are present. This method provides a profile of all proteins in a system, including documentation of PMTs and other protein isoforms. This method, therefore, provides a protein "profile" or "map" of a specific system. Following initial analysis, intact proteins can be isolated and further analyzed to determine amino acid sequences and related information.

"Bottom-up" MS refers to the identification of known proteins in a sample. This method identifies peptide fragments that indicate the presence of a specific protein. This method depends on having peptide fragments that can reliably identify a specific protein. Selective reaction monitoring-MS is a bottom-up modification of MS that allows for direct quantification and specific identification of low-abundance proteins without the need for specific antibodies. This method requires the selection of a peptide fragment or "signature" that is used to target the specific protein. Multiplex assays have also been developed to quantitate the epidermal growth factor receptor, human epidermal growth factor receptors 2 and 3, and insulin-like growth factor-1 receptor.

Bioinformatics
Due to the complexity of proteomic information, the multiple tests used, and the need to integrate this information with other genomic data, a bioinformatics approach is necessary to interpret proteogenomic data. Software programs are available that integrate and assist in the interpretation of the vast amounts of data generated by proteogenomics research. One software platform that integrates genomic and proteomic information is PARADIGM, which is used by The Cancer Genome Atlas (TCGA) project for data analysis. Other software tools currently available include:

- The Genome Peptide Finder matches the amino acid sequence of peptides predicted de novo with the genome sequence.
- The Proteogenomic Mapping Tool is an academic software for mapping peptides to the genome.
- Peppy is an automated search tool that generates proteogenomic data from translated databases and integrates this information for analysis.
- VESPA is a software tool that integrates data from various platforms and provides a visual display of integrated data.

Ongoing Proteogenomic Database Projects

Table 1 lists some of the ongoing databases being constructed for proteogenomic research

There are also networks of researchers coordinating their activities in this field. The Clinical Proteomic Tumor Analysis Consortium is a coordinated project among 8 analysis sites sponsored by the National Cancer Institute. This project seeks to characterize the genomic and transcriptomic profiles of common cancers systematically. As of 2014, this consortium had cataloged proteomic information for breast, colon, and ovarian cancers. All data from this project are freely available.

Many existing genomic databases have begun to incorporate proteomic information. TCGA intends to profile changes in the genomes of 20 different cancers. As part of its analysis, mRNA expression is used to help define signaling pathways that are either upregulated or deregulated in conjunction with genetic variations. Currently, TCGA has published comprehensive molecular characterizations of breast, colorectal, lung, gliomas, renal, and endometrial cancers.

Table 1. Proteogenomic Databases

Name	Description
Human Protein Reference Database	Centralized platform integrating information related to protein structure alterations, posttranslational modifications, interaction networks, and disease association. The intent is to catalog this information for each protein in the human proteome. Data are compiled from published literature and publicly available databases.
Human Cancer Proteome Variation Database (CanProVar)	Protein sequence database that integrates information from various publicly available datasets into 1 platform. Contains germline and somatic variants with an emphasis on cancer-related variants.
Cancer Mutant Proteome Database (CMPD)	Protein sequence database compiled from the exome sequencing results of the NCI-60 cell lines, CCLE, and 5600 cases from TCGA network genomics studies. Contains germline and somatic variants with an emphasis on cancer-related variants.
The Synthetic Alternative Splicing Database (SASD)	A comprehensive database of alternative splicing peptides and transcript products constructed from the Integrated Pathway Analysis Database
lncRNAtor	Database of long noncoding RNA integrating data from multiple datasets including TCGA and ENCODE
CPTAC Data Portal	Centralized data repository for proteomic data collected by Proteome Characterization Centers in the CPTAC. The portal hosts >6.3 TB of data and includes proteomics, transcriptomics, and genomics data of breast, colorectal, and ovarian tumor tissues from TCGA.

CCLE: Cancer Cell Line Encyclopedia; CPTAC: Clinical Proteomic Tumor Analysis Consortium; TCGA: The Cancer Genome Atlas.

GPS CANCER TEST

The GPS Cancer test is a commercially available proteogenomic test intended for patients with cancer. The test includes whole-genome sequencing (20,000 genes, 3 billion base pairs), whole transcriptome (RNA) sequencing, and quantitative proteomics by mass spectrometry. The test is intended to inform personalized treatment decisions for cancer, and treatment options are listed when available, although treatment recommendations are not made. Treatment options may include U.S. Food and Drug Administration

(FDA)–approved targeted drugs with potential for clinical benefit, active clinical trials of drugs with potential for clinical benefit, and/or available drugs to which the cancer may be resistant.

FDA or Other Governmental Regulatory Approval

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The GPS Cancer test (NantHealth, Culver City, CA) is available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

Centers for Medicare and Medicaid Services (CMS)
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

Rationale/Source

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

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

PROTEOGENOMIC TESTING

Clinical Context and Test Purpose

The purpose of proteogenomic testing in patients who have cancer is to detect cancer, improve evaluation of prognosis, select treatments, and monitor for treatment response or resistance.

The question addressed in this evidence review is: Does proteogenomic testing using the GPS Cancer test improve the net health outcome in individuals with cancer?

The following PICOTS were used to select literature to inform this review.

Patients

The relevant population of interest is patients with cancer who have indications for genetic testing.

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Interventions
The test being considered is the GPS Cancer, a commercially available proteogenomic test for patients with cancer.

Comparators
The following tests and practices are currently being used: standard clinical workup and genetic testing for cancer diagnosis and prognosis, and for monitoring response. Genetic testing using companion diagnostic tests for targeted therapies are generally used to select cancer treatments when targeted therapies are available.

Outcomes
The general outcomes of interest are overall survival and disease-specific survival. The harmful outcomes from a false-negative test result include delayed diagnosis or treatment; the harms from a false-positive test include incorrect or unnecessary additional treatment.

Timing
The relevant duration of follow-up for survival outcomes varies by cancer type.

Setting
Decisions about cancer treatment are usually made in the oncology setting.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review, and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

No published literature was identified on the clinical validity of the GPS Cancer test. Also, searches of selected websites did not identify any data on clinical validity of the test.

The general published literature on the clinical validity of proteogenomics includes the following types of studies: proteomic biomarkers as prognostic markers, molecular characterization, and monitoring quantitative protein levels.

Proteomic Biomarkers as Prognostic Markers

Some researchers have compared proteogenomic results with clinical outcomes and assessed the strength of association between genomic and proteomic data. Yau et al (2015) published a report comparing whether proteogenomic and genomic data can predict metastatic outcomes in breast cancer. This study measured FOXM transcript messenger RNA (mRNA) levels and compared the prognostic ability with *FOXM1* target genes and a gene proliferation score. Table 2 shows the results obtained for each test.

Table 2. Association of mRNA Expression With Breast Cancer Metastases

Test	ER Positive		ER Negative	
	Hazard Ratio (95% CI)	**p**	**Hazard Ratio (95% CI)**	**p**
FOXM mRNA expression	2.8 (2.0 to 3.8)	8.1×10^{-10}	1.6 (0.9 to 2.9)	0.09
FOXM1 gene	2.4 (1.7 to 3.4)	4.2×10^{-7}	1.2 (0.5 to 1.2)	0.32
28-gene expression profile	2.6 (1.9 to 3.6)	1.1×10^{-8}	1.3 (0.8 to 2.2)	0.30

Adapted from Yau et al (2015)
CI: confidence interval; ER: estrogen receptor; mRNA: messenger RNA.

Zhang et al (2016) combined mass spectrometry–based proteomic measurements with genomic data of 174 ovarian tumors previously analyzed by The Cancer Genome Atlas. Copy number variants having high correlation with protein abundance or mRNA were found on chromosomes 2, 7, 20, and 22. A lasso-based Cox proportional hazards model was used to model the association between these copy number variants and overall survival on a training set of 82 tumors and then used to predict survival in 87 nonoverlapping tumors. A consensus of the 4 signatures was created, using a voting method, as a binary indicator for signature, relative level up vs down. The consensus indicator was highly associated with survival (hazard ratio not provided; $p<0.001$). Comparison to genomic stratification was not reported.

Defining Molecular Subtypes of Cancer

Comprehensive molecular characterization has been performed for various cancers, and in some cases, these investigations have defined subtypes that differ from standard histologic classification. Clinical validity can be demonstrated in this situation if the molecular subtypes are more homogeneous than the histologic class and correlate more closely with clinical outcomes.

An example of molecular subtyping of cancer by proteogenomics was published by The Cancer Genome Atlas network in 2015. This study integrated data from multiple platforms, including exome sequencing, DNA copy-number profiling, DNA methylation, and protein profiling by mass spectrometry. For each platform, clusters of similar cases were identified. Three distinct molecular subtypes were identified using second-level cluster analysis. They were most concordant with isocitrate dehydrogenase enzyme, 1p/19q, and *TP53* genetic variant status. The molecular subtypes showed differences in clinical characteristics, recurrence, and survival that could not be explained by histologic class.

Monitoring Quantitative Protein Levels Over Time

Quantification of protein levels over time may have applications for determining resistance to targeted therapy. Levels of protein markers may correlate with the presence of resistant tumor cells and may be an

early marker of resistance that occurs before tumor progression. Clinical validity can be demonstrated if quantitative protein levels identify resistance more accurately or earlier than other surveillance methods.

Currently, few studies have reported on monitoring protein levels over time. A case report, published in 2016, demonstrated that repeat quantitation of human epidermal growth factor receptors 2 and 3, as well as epidermal growth factor receptor proteins, was feasible and that protein levels changed in response to different therapies and over time.

More recently, Latonen et al (2018) generated distinct profiles from patient tissue samples of benign prostate hyperplasia (n=10), untreated prostate cancer (n=17), and locally recurrent castration-resistant prostate cancer (n=11), demonstrating changes in protein levels that may be associated with tumor progression.

Section Summary: Clinically Valid
There is no published evidence on the clinical validity of the GPS Cancer test and, therefore, the clinical validity of this test is undefined. For proteomic research in general, a few types of studies provided information on clinical validity. A small number of studies use proteogenomic biomarkers for diagnosis or prognosis and compare these biomarkers with traditional genomic testing. One study assessed whether proteomic data had potential to detect drug sensitivity. Other studies have performed comprehensive molecular characterization of different tumors and, in some cases, have shown that molecular characterization correlates more strongly with clinical outcomes than with histologic classification. The third type of study in the literature quantitates and monitors protein markers over time for surveillance purposes, particularly for the emergence of resistance to targeted cancer therapies. This available research on clinical validity outlines some types of research that will be needed to establish clinical validity for a variety of clinical situations. However, the research is currently in its early stages, and no conclusions on test validity can be drawn at present from the evidence.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No direct evidence on clinical utility was identified. Therefore, the clinical utility of the GPS Cancer test is uncertain. For proteogenomic testing in general, there is no published literature on clinical utility.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Absent additional evidence establishing the clinical validity of proteogenomic testing; it will not be possible to determine whether clinical utility is present.

Section Summary: Clinically Useful
No direct evidence on clinical utility was identified. Therefore, no inferences can be made about clinical utility.

SUMMARY OF EVIDENCE
For individuals who have cancer and indications for genetic testing who receive proteogenomic testing (eg, GPS Cancer test), the evidence includes cross-sectional studies that correlate results with standard testing and that report comprehensive molecular characterization of various cancers, and cohort studies that use proteogenomic markers to predict outcomes and that follow quantitative levels over time. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, and treatment-related mortality and morbidity. There is no published evidence on the clinical validity or utility of the GPS Cancer test. For proteogenomic testing in general, the research is at an early stage. Very few studies have used proteogenomic tumor markers for diagnosis or prognosis, and at least 1 study has reported following quantitative protein levels for surveillance purposes. Further research is needed to standardize and validate proteogenomic testing methods. Once standardized and validated testing methods are available, the clinical validity and utility of proteogenomic testing can be adequately evaluated. The evidence is insufficient to determine the effect of the technology on health outcomes.

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08/17/2016	Medical Policy Implementation Committee approval. New Policy
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
08/03/2017	Medical Policy Committee review
08/23/2017	Medical Policy Implementation Committee approval. Added "for all other indications" to coverage statement.
08/09/2018	Medical Policy Committee review
08/15/2018	Medical Policy Implementation Committee approval. Policy revised with updated genetics nomenclature. Policy statement unchanged. Title shortened to "Proteogenomic Testing for Patients With Cancer."

Next Scheduled Review Date: 08/2019

Coding

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Code Type	Code
CPT	81479 Code added eff 7/1/18: 0053U
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the FDA and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or

B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
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    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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