Proteogenomic Testing for Patients With Cancer

**Policy #** 00512  
**Original Effective Date:** 08/17/2016  
**Current Effective Date:** 10/10/2022

**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.*

**Policy Guidelines**  
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.

**Genetics Nomenclature Update**  
The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society’s nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard
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terminology - “pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign” - to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutation</td>
<td>Disease-associated variant</td>
<td>Disease-associated change in the DNA sequence</td>
</tr>
<tr>
<td>Variant</td>
<td>Change in the DNA sequence</td>
<td></td>
</tr>
<tr>
<td>Familial variant</td>
<td>Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathogenic</td>
<td>Disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Likely pathogenic</td>
<td>Likely disease-causing change in the DNA sequence</td>
</tr>
<tr>
<td>Variant of uncertain significance</td>
<td>Change in DNA sequence with uncertain effects on disease</td>
</tr>
<tr>
<td>Likely benign</td>
<td>Likely benign change in the DNA sequence</td>
</tr>
<tr>
<td>Benign</td>
<td>Benign change in the DNA sequence</td>
</tr>
</tbody>
</table>

ACMG: American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology.

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic
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testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Background/Overview

This evidence review provides an overview of the emerging field of proteogenomics, with an emphasis on the currently available proteogenomic test, the 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), 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.
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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 germline and somatic genetic variants. Altered protein products include mutated proteins, fusion proteins, alternative splice variants, noncoding messenger RNAs, and posttranslational modifications.

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 the sequence may be affected. Mutated proteins can arise from 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 1 or more genes that fuse together. Most fusion genes discovered 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
Posttranslational modifications 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. Posttranslational modifications 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 and Fluorescence in situ Hybridization
Immunohistochemistry (IHC) and fluorescence in situ hybridization are standard techniques for isolating and characterizing proteins. Immunohistochemistry 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.
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- 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. The development of technology that led to the application of MS to biological 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 efficiently, 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 Posttranslational modifications.

Mass Spectrometry Sampling Applications
"Top-down" MS refers to the 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 posttranslational modifications and other protein isoforms. This method, therefore, provides a protein "profile" or "map" of a specific system. Following the 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 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 sites sponsored by the National Cancer Institute. This project seeks to characterize the genomic and transcriptomic profiles of common cancers systematically. This consortium has cataloged proteomic information for several types of cancers including breast, colon, and ovarian cancers. All project data are freely available.

Many existing genomic databases have begun to incorporate proteomic information. TCGA intends to profile changes in the genomes of 33 different cancers. As part of its analysis, messenger RNA 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 multiple cancers, including breast, colorectal, lung, gliomas, renal, and endometrial cancers.
Table 1. Proteogenomic Databases

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Protein Reference Database</td>
<td>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.</td>
</tr>
<tr>
<td>Human Cancer Proteome Variation Database (CanProVar)</td>
<td>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.</td>
</tr>
<tr>
<td>Cancer Mutant Proteome Database (CMPD)</td>
<td>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.</td>
</tr>
<tr>
<td>CPTAC Data Portal</td>
<td>Centralized data repository for proteomic data collected by Proteome Characterization Centers in the CPTAC. The portal hosts &gt;6.3 TB of data and includes proteomics, transcriptomics, and genomics data of breast, colorectal, and ovarian tumor tissues from TCGA.</td>
</tr>
</tbody>
</table>


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 MS. The test is intended to inform personalized treatment decisions for cancer; treatment options are provided when available, although treatment recommendations are not. Treatment options may include U.S. Food and Drug Administration (FDA)-approved targeted drugs with potential for clinical benefit, active clinical
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trials of drugs with potential for clinical benefit, and/or available drugs to which cancer may be resistant.

FDA or Other Governmental Regulatory Approval

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

Rationale/Source
This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Proteogenomics refers to the integration of genomic information with proteomic and transcriptomic information to provide a more complete picture of genome function. The current focus of proteogenomics is primarily on the diagnostic, prognostic, and predictive potential of proteogenomics in various cancers. One commercial proteogenomic test is available, the GPS Cancer test.

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
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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 that the technology results in an improvement in the net health outcome.

**Supplemental Information**
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

**Practice Guidelines and Position Statements**
Guidelines or position statements will be considered for inclusion in ‘Supplemental Information’ if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

No guidelines or statements were identified.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Medicare National Coverage**
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

**Ongoing and Unpublished Clinical Trials**
Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.
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Table 2. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT04887545</td>
<td>Immune- and Microenvironment- Proteogenomics Profiling for Classifying Lung Cancer Patients</td>
<td>200</td>
<td>Dec 2022</td>
</tr>
<tr>
<td>NCT04445532</td>
<td>Acquisition of Blood and Tumor Tissue Samples From Patients With Hepatobiliary Tumors</td>
<td>450</td>
<td>Jun 2025</td>
</tr>
<tr>
<td>NCT03336931</td>
<td>A Multicenter Prospective Study of the Feasibility and Clinical Value of a Diagnostic Service for Identifying Therapeutic Targets and Recommending Personalized Treatment for Children and Adolescents With High-risk Cancer</td>
<td>400</td>
<td>Sep 2029</td>
</tr>
<tr>
<td>NCT01840293</td>
<td>Breast Cancer Proteomics and Molecular Heterogeneity</td>
<td>1780</td>
<td>Dec 2029</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

References
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Policy History
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08/04/2016    Medical Policy Committee review
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.”
08/01/2019    Medical Policy Committee review
08/14/2019    Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/06/2020    Medical Policy Committee review

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08/12/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
09/02/2021 Medical Policy Committee review
09/08/2021 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
03/09/2022 Coding update
09/01/2022 Medical Policy Committee review
09/14/2022 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 09/2023

Coding
The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®), copyright 2021 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

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<thead>
<tr>
<th>Code Type</th>
<th>Code</th>
</tr>
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<tbody>
<tr>
<td>CPT</td>
<td>81479</td>
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<td></td>
<td>Delete code effective 04/01/2022: 0053U</td>
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<tr>
<td>HCPCS</td>
<td>No codes</td>
</tr>
<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
</tr>
</tbody>
</table>

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (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:

1. Consultation with technology evaluation center(s);
2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
3. Reference to federal regulations.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient’s health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.
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