Corporate Medical Policy

Proteogenomic Testing for Patients with Cancer (GPS Cancer™ Test)

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Description of Procedure or Service

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 to 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 the following:

- 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. The types of targets currently being investigated and the testing methods used and under development are discussed next.

Proteomic Targets

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

Sequence Alterations (Mutated Protein)

A mutated protein has an altered amino acid sequence that arises due to 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 mutations. Somatic mutations can be differentiated from germline mutations by comparison with normal and diseased tissue.

Fusion Proteins
Fusion proteins are the product of 1 or more mutated 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.

Non-coding RNAs
Non-coding portions of the genome serve as the template for non-coding RNA, which plays various roles in the regulation of gene expression. There are 2 classes of non-coding RNA (ncRNA): shorter ncRNAs that include microRNAs and related transcript products, and longer ncRNAs 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 that are 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 the individual proteins are obtained, they may be characterized using various methods and parameters, some of which are described below.

Immunohistochemistry/Fluorescence in situ Hybridization
Immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) 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 FISH 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 FISH have addressed these limitations, including tissue microarray and reverse phase protein array.

- Tissue microarrays can be constructed that enable simultaneous analysis of up to 1,000 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. In addition, 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
- Identification of PTMs.

"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 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 mass spectrometry (SRM-MS) is a bottom-up approach 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 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 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 following:

- The Genome Peptide Finder (http://specht.github.lo.gpf/) matches the amino acid sequence of peptides predicted de novo with the genome sequence.
- The Proteogenomic Mapping Tool (http://www.agbase.msstate.edu/tools/pgm/) is an academic software for mapping peptides to the genome.
- Peppy (http://www.geneffects.com/peppy/) is an automated search tool that generates proteogenomic data from translated databases and integrates this information for analysis.
- VESPA (http://cbb.pnnl.gov/portal/software/vespa.html/) is a software tool that integrates data from various platforms and provides visual display of integrated data.

Ongoing Proteogenomic Database Projects

Numerous ongoing databases are being constructed for proteogenomic research. See Table 1.

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 systematically characterize the genomic and transcriptomic profiles of common cancers. This consortium has catalogued proteomic information for several types of cancers including 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 33 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 mutations. Currently, TCGA has published comprehensive molecular characterizations of multiple cancers including breast, colorectal, lung, gliomas, renal, and endometrial cancers.

Table 1. Proteogenomic Databases

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. Compiles data 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 mutations with an emphasis on cancer-related mutations.
Cancer Mutant Proteome Database (CMPD)	Protein sequence database sequencing results compiled from the exome sequencing results of the NCI-60 cell lines, The Cancer CellLine Encyclopedia (CCLE) and 5600 casses from the Cancer Genome Atlas (TCGA) network genomics studies. Contains germline and somatic mutations with an emphasis on cancer-related mutations.
The Synthetic Alternative Splicing Database (SASD)	A comprehensive database of alternative splicing peptides and transcript products constructed from the Integrated Pathway Analysis Database (IPAD).
IncRNAtor	Database of long non-coding RNA (InRNA) integrating data from multiple datasets including TCGA and ENCODE.

CCLE: Cancer Cell Line Encyclopedia; TCGA: The Cancer Genome Atlas.

GPS™ 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 Food and Drug Administration–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.

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

Proteogenomic testing for Patients with Cancer (GPS Cancer™ Test) is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Proteogenomic testing for patients with cancer is covered

Not applicable.

When Proteogenomic testing for patients with cancer is not covered

Proteogenomic testing of patients with cancer (including but not limited to GPS Cancer™ Test) is considered **investigational**. BCBSNC does not provide coverage for investigational services.

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. 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 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.

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

For individuals who have cancer and indications for genetic testing who receive proteogenomic testing, 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. When 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.

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) 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. HGVS nomenclature is recommended by HGVS, the Variome Project, and the Human Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Recommended standard terminology: "pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign," to describe variants identified that cause Mendelian disorders.

Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: *No specific code for this service*

The test would likely be reported with the unlisted molecular pathology procedure code 81479.

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.140, 6/16/2016

Medical Director review 6/2016

Specialty Matched Consultant Advisory Panel 3/2017

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.140, 6/8/2017

Specialty Matched Consultant Advisory Panel 3/2018

Medical Director review 4/2018

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.140, 6/14/2018

Policy Implementation/Update Information

7/26/16 New policy developed. Proteogenomic testing of patients with cancer (including but not limited to GPS Cancer™ Test) is considered investigational. Medical Director review 6/2016. (lpr)

4/28/17 Specialty Matched Consultant Advisory Panel review 3/29/2017. No change to policy statement. (lpr)

7/28/17 Updated Policy Guidelines with Genetics Nomenclature update. Reference added. No change to policy statement. (lpr)

4/27/18 Specialty Matched Consultant Advisory Panel review 3/28/2018. No change to policy statement. Medical Director review. (lpr)

7/27/18 Reference added. (lpr)