BlueCross BlueShield of Alabama

Name of Blue Advantage Policy:

Proteogenomic Testing for Patients with Cancer

Policy #: 630
Category: Laboratory
Latest Review Date: July 2020
Policy Grade: D

BACKGROUND:

Blue Advantage *medical policy does not conflict with Local Coverage Determinations (LCDs), Local Medical Review Policies (LMRPs) or National Coverage Determinations (NCDs) or with coverage provisions in Medicare manuals, instructions or operational policy letters. In order to be covered by Blue Advantage the service shall be reasonable and necessary under Title XVIII of the Social Security Act, Section 1862(a)(1)(A). The service is considered reasonable and necessary if it is determined that the service is:*

1. *Safe and effective;*
2. *Not experimental or investigational*;*
3. *Appropriate, including duration and frequency that is considered appropriate for the service, in terms of whether it is:*
   - *Furnished in accordance with accepted standards of medical practice for the diagnosis or treatment of the patient's condition or to improve the function of a malformed body member;*
   - *Furnished in a setting appropriate to the patient's medical needs and condition;*
   - *Ordered and furnished by qualified personnel;*
   - *One that meets, but does not exceed, the patient's medical need; and*
   - *At least as beneficial as an existing and available medically appropriate alternative.*

Routine costs of qualifying clinical trial services with dates of service on or after September 19, 2000 which meet the requirements of the Clinical Trials NCD are considered reasonable and necessary by Medicare. Providers should bill* ***Original Medicare* *for covered services that are related to* ***clinical trials*** *that meet Medicare requirements (Refer to Medicare National Coverage Determinations Manual, Chapter 1, Section 310 and Medicare Claims Processing Manual Chapter 32, Sections 69.0-69.11).*

POLICY:

Effective for dates of service on and after August 28, 2016:

Blue Advantage will treat **proteogenomics testing of patients with cancer** (including but not limited to GPS Cancer™ test) as a **non-covered benefit** and as **investigational** for all indications.

Blue Advantage does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Advantage administers benefits based on the members' contract and medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

DESCRIPTION OF PROCEDURE OR SERVICE:

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.

This evidence review will provide 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, the review will describe and outline some 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 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 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 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 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 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.

Noncoding RNAs
Noncoding portions of the genome serve as the template for noncoding RNA, which plays various roles in the regulation of gene expression. There are two classes of noncoding 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, two-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. There is literature addressing the analytic validity of these testing techniques.

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 semi quantitative 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 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. 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;
- three-dimensional protein structure and architecture;
- 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 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 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 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 eight analysis sites

sponsored by the National Cancer Institute. This project seeks to systematically characterize the genomic and transcriptomic profiles of common cancers. This consortium had 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 variations. Currently, TCGA has published comprehensive molecular characterizations of multiple cancers, including 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. 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 one 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
IncRNAtor	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 (PCCs) in the CPTAC. The portal currently hosts >6.3 TB of data and includes proteomics, transcriptomics, and genomics data of breast, colorectal, and ovarian tumor tissues from The Cancer Genome Atlas (TCGA).

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

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, three 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.

KEY POINTS:
The most recent literature review was updated through April 9, 2019.

Summary of Evidence
For individuals who have cancer and indications for genetic testing who receive proteogenomic testing (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 one 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.

Practice Guidelines and Position Statements
No guidelines or statements were identified.

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

KEY WORDS:
GPS Cancer Test, Mass Spectrometry, Proteogenomics, Proteome, Transcriptome, Bioinformatics, NantHealth

APPROVED BY GOVERNING BODIES:
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 U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

BENEFIT APPLICATION:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.

CURRENT CODING:

There is no specific CPT code for this test. It would likely be reported with the unlisted molecular pathology procedure code **81479.**

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POLICY HISTORY:

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Medical Policy Group, July 2017
Medical Policy Group, August 2018 **(2):** 2018 Updates to Description, Key Points, References & Policy Title; no change to policy statement.
Medical Policy Group, June 2019
Medical Policy Group, July 2020