Medical Coverage Policy | Proteogenomic Testing for Patients with Cancer

EFFECTIVE DATE: 12|01|2017
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OVERVIEW

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.

MEDICAL CRITERIA

BlueCHiP for Medicare and Commercial Products
Not applicable

PRIOR AUTHORIZATION

BlueCHiP for Medicare and Commercial Products
There is no specific CPT code for this service and an Unlisted CPT code should be used (See Coding Section for details). All Unlisted genetic testing CPT codes require prior authorization to determine what service is being rendered and if the service is covered or not medically necessary. See the Related Policies section.

Prior authorization is required for BlueCHiP for Medicare and recommended for Commercial Products and is obtained via the online tool for participating providers. See the Related Policies section.

POLICY STATEMENT

BlueCHiP for Medicare
Proteogenomic testing of patients with cancer (including, but not limited to the GPS Cancer test) is not covered for all indications as the evidence is insufficient to determine the effects of the technology on health outcomes.

Commercial Products
Proteogenomic testing of patients with cancer (including, but not limited to the GPS Cancer test) is considered not medically necessary for all indications as the evidence is insufficient to determine the effects of the technology on health outcomes.

COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable not medically necessary/not covered benefits/coverage.

BACKGROUND

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.

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.

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 (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 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 one 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

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.1 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 ionexchange 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. 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 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 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 PTMs 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 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.

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.28 The test is intended to inform personalized treatment decisions for cancer, and treatment options are provided when available, although treatment recommendations are not. Treatment options may include U.S. 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 cancer may be resistant.

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. The GPS Cancer™ test (NantHealth) is available under the auspices of Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

CODING

BlueCHiP for Medicare and Commercial Products

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

RELATED POLICIES

Genetic Testing Services

PUBLISHED

Provider Update, January 2019
Provider Update, October 2017

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