FEP Medical Policy Manual

FEP 2.04.140 Proteogenomic Testing for Patients With Cancer

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Related Policies:

None

Proteogenomic Testing for Patients With Cancer

Description

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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.

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.[1,2,] 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.[2,]

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.[3,] 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.[3,] 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.[3,]

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.[3,]

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.[4,]

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 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.[5,6,]

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.[4,]
- 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.[1,]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.[4,] 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.[2,] 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.[4,] 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.[7,]

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 following[3,]:

- The Genome Peptide Finder matches the amino acid sequence of peptides predicted de novo with the genome sequence.[8,]
- The Proteogenomic Mapping Tool is an academic software for mapping peptides to the genome.[9,]

- Peppy is an automated search tool that generates proteogenomic data from translated databases and integrates this information for analysis.[10,]
- VESPA is a software tool that integrates data from various platforms and provides a visual display of integrated data.[11,]

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.[12,] 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,[13,] colorectal,[14,] lung,[15,] gliomas,[5,] renal,[16,] and endometrial[17,] cancers.

Table 1. Proteogenomic Databases

Name	Description
Human Protein Reference Database[18,19,]	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)[20,]	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)][21,]	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.
CPTAC Data Portal[12,22,23,]	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.

OBJECTIVE

The objective of this evidence review is to determine whether proteogenomic testing using the GPS Cancer test improves the net health outcome in individuals with cancer.

POLICY STATEMENT

Proteogenomic testing (see Policy Guidelines section) of individuals with cancer (including, but not limited to the GPS Cancer test) is considered **investigational** for all indications.

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.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

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

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

SUPPLEMENTAL INFORMATION

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.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
September 2016	New policy	The GPS Cancer test is investigational for all indications
September 2018	Revised policy	Policy updated with literature review through April 26, 2018; reference 35 added. Policy revised with updated genetics nomenclature. Policy statement unchanged. Title shortened to "Proteogenomic Testing for Patients With Cancer.,
September 2019	Revised policy	Policy updated with literature review through April 9, 2019, no references added. Policy statement unchanged.
September 2020	Revised policy	Policy updated with literature review through April 1, 2020, no references added. Policy statement unchanged.
September 2021	Replace policy	Policy updated with literature review through April 29, 2021; no references added. Policy statement unchanged.
September 2022	Replace policy	Policy updated with literature review through April 20, 2022; no references added. Minor editorial refinements to policy statement; intent unchanged.
September 2023	Replace policy	Policy updated with literature review through April 13, 2023; no references added. Policy statement unchanged.