MEDICAL POLICY – 12.04.140
Proteogenomic Testing for Patients with Cancer

BCBSA Ref. Policy: 2.04.140

Effective Date: Sept. 1, 2018
Last Revised: Aug. 23, 2018
Replaces: N/A

RELATED MEDICAL POLICIES:
None

Introduction

Proteogenomic testing is a term describing a new type of testing. In this test, blood or tissue is examined to look at a person’s genome (their unique genetic material) as well as a detailed study of their proteins (proteomics). The genetic material that is looked at includes the DNA, the RNA translated from DNA used to make proteins, as well as the final protein products. Currently this type of testing is done in research settings. There is very little published scientific data that shows how this type of testing can help manage or treat different diseases or cancer. The plan considers this testing investigational or unproven and does not pay for it.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.

Policy Coverage Criteria

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Investigational</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proteogenomic Testing</td>
<td>Proteogenomic testing of patients with cancer (including but</td>
</tr>
</tbody>
</table>
Procedure | Investigational
---|---
| not limited to the GPS Cancer™ test) is considered investigational for all indications.

**Note:** 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.

**Coding**

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td></td>
</tr>
<tr>
<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
</tr>
<tr>
<td>81599</td>
<td>Unlisted multianalyte assay with algorithmic analysis</td>
</tr>
</tbody>
</table>

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**Related Information**

**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 (see Table 1). 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 2 shows the recommended standard terminology—“pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign”—to describe variants identified that cause Mendelian disorders.

Table 1. 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</td>
<td>Disease-associated variant identified in a proband for use in subsequent</td>
</tr>
</tbody>
</table>

Table 2. 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

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.
Evidence Review

Description

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 commercially proteogenomic test is available, the GPS Cancer test.

Background

This policy provides 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, 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.\(^1\) 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 below.

**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 (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.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 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.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**

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.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.\textsuperscript{5,6}

**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.\textsuperscript{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.\textsuperscript{1} 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.\textsuperscript{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 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.

**Ongoing Proteogenomic Database Projects**

Table 3 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 3. Proteogenomic Databases

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Protein Reference Database^{19,20}</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. Compiles data from published literature and publicly available databases.</td>
</tr>
<tr>
<td>Human Cancer Proteome Variation Database (CanProVar)^21</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)^22,23</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>The Synthetic Alternative Splicing Database (SASD)^4</td>
<td>A comprehensive database of alternative splicing peptides and transcript products constructed from the Integrated Pathway Analysis Database</td>
</tr>
<tr>
<td>IncRNAitor^{25}</td>
<td>Database of long noncoding RNA integrating data from multiple datasets including TCGA and ENCODE</td>
</tr>
<tr>
<td>CPTAC Data Portal^{11,26,27}</td>
<td>Centralized data repository for proteomic data collected by Proteome Characterization Centers 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 TCGA.</td>
</tr>
</tbody>
</table>

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

### 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.
Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 4.

Table 4. 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>NCT03073473</td>
<td>Quantitative Targeted Proteomics Detected by Mass Spectrometry With Whole Genome (DNA) and Whole Transcriptome (RNA) Sequencing in Advanced Cancers</td>
<td>640</td>
<td>Feb 2019</td>
</tr>
<tr>
<td>NCT01840293</td>
<td>Breast Cancer Proteomics and Molecular Heterogeneity</td>
<td>1780</td>
<td>Feb 2023</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

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 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 the effect of the technology on health outcomes.
Practice Guidelines and Position Statements

No guidelines or statements were identified.

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.

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. 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.

References


### History

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/01/16</td>
<td>New policy approved September 13, 2016. Add to Genetic Testing section. The GPS Cancer™ test is investigational for all indications.</td>
</tr>
<tr>
<td>03/28/17</td>
<td>Corrected the “Replaces” section; this policy does not replace any other policy. Minor formatting update.</td>
</tr>
</tbody>
</table>

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