MEDICAL POLICY – 12.04.140
Proteogenomic Testing in Patients with Cancer (GPS Cancer™ Test)

BCBSA Ref. Policy: 2.04.140

Effective Date: Aug. 1, 2017
Last Revised: July 25, 2017
Replaces: N/A

RELATED MEDICAL POLICIES:
N/A

Select a hyperlink below to be redirected to that section.

POLICY CRITERIA | CODING | RELATED INFORMATION
EVIDENCE REVIEW | REFERENCES | HISTORY

∞ Clicking this icon returns you to the hyperlinks menu above.

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
Proteogenomic Testing

The use of proteogenomic testing of patients with cancer (including but not limited to GPS Cancer™ test) is considered investigational for all indications.

Note: Proteogenomic testing involves the integration of proteomic, transcriptomic, and genomic information.

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

Genetic Counseling

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.
Description

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 (regarding the genome) with proteomic and transcriptomic information 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.

Background

This policy will provide an overview of the emerging field of proteogenomics, with an emphasis on the currently available proteogenomic test (GPS Cancer test).

Proteogenomics

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:
  o Cancer activity
  o 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.

Table 1. Proteogenomic Databases

<table>
<thead>
<tr>
<th>Name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human Protein Reference Database(^{17,18})</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)(^{19,20})</td>
<td>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.</td>
</tr>
<tr>
<td>Cancer Mutant Proteome Database (CMPD)(^{21,22})</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 mutations with an emphasis on cancer-related mutations.</td>
</tr>
<tr>
<td>ChimerDB 2.0(^{23})</td>
<td>A comprehensive database of fusion proteins including transcript products, compiled from various publicly available datasets</td>
</tr>
<tr>
<td>The Synthetic Alternative Splicing Database (SASD)(^{24})</td>
<td>A comprehensive database of alternative splicing peptides and transcript products constructed from the Integrated Pathway Analysis Database</td>
</tr>
<tr>
<td>NONCODE(^{25})</td>
<td>Database of noncoding RNAs integrating data from literature mining, specialized databases, and GenBank</td>
</tr>
<tr>
<td>IncRNaTor(^{26})</td>
<td>Database of long noncoding RNA integrating data from multiple</td>
</tr>
</tbody>
</table>
datasets including TCGA and ENCODE

CPTAC Data Portal

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.

CCLE: Cancer Cell Line Encyclopedia; CPTAC: Clinical Proteomic Tumor Analysis Consortium; 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.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this review are listed in Table 2.

**Table 2. 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>NCT03073473a</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>
</tbody>
</table>
Summary of Evidence

For individuals who have cancer and undergo 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 validity or utility of the GPS Cancer test. For proteogenomic testing in general, the research is at an early stage. There is a lack of standardization of testing methods, and uncertain accuracy for most proteogenomic technologies. A few studies have described assay development and validation for proteogenomic targets, and correlation of proteogenomic testing results with standard testing methods. Other studies have used proteogenomic testing in conjunction with genomic testing to provide a more comprehensive molecular characterization of various cancers. 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.

Practice Guidelines and Position Statements

No guidelines or statements were identified.

Medicare National Coverage

There is no national coverage determination (NCD). In the absence of an NCD, 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 (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.

References

<table>
<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
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<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 &quot;Replaces&quot; section; this policy does not replace any other policy. Minor formatting update.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2017 Premera All Rights Reserved.

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  - Information written in other languages

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Email AppealsDepartmentInquiries@Premera.com

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U.S. Department of Health and Human Services
200 Independence Avenue SW, Room 509F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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Italiano (Italian):


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