Policy Statement

I. 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.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

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.

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. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). 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 PG2 shows the recommended standard terminology - “pathogenic,” “likely pathogenic,” “uncertain significance,” “likely benign,” and “benign” - to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

<table>
<thead>
<tr>
<th>Previous</th>
<th>Updated</th>
<th>Definition</th>
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<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 identified in a proband for use in subsequent targeted genetic testing in first-degree relatives</td>
<td></td>
</tr>
</tbody>
</table>

Table PG2. ACMG-AMP Standards and Guidelines for Variant Classification

<table>
<thead>
<tr>
<th>Variant Classification</th>
<th>Definition</th>
</tr>
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<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
Genetic counseling is primarily aimed at individuals 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
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.

Related Policies
- N/A

Benefit Application
Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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
Background
This evidence review provides an overview of the emerging field of proteogenomics, with an emphasis on the currently available proteogenomic test, the 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 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. 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.

**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 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.

**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.5.

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. 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. 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 quantify 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 following:

• 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 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. 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>
<thead>
<tr>
<th>Table 1. Proteogenomic Databases</th>
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<tbody>
<tr>
<td><strong>Name</strong></td>
</tr>
<tr>
<td>Human Protein Reference Database</td>
</tr>
<tr>
<td>Name</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Human Cancer Proteome Variation Database (CanProVar)(^{20})</td>
</tr>
<tr>
<td>Cancer Mutant Proteome Database (CMPD) (^{21})</td>
</tr>
<tr>
<td>CPTAC Data Portal(^{12,22,23})</td>
</tr>
</tbody>
</table>


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 MS.\(^{24}\) The test is intended to inform personalized treatment decisions for cancer; treatment options are provided when available, although treatment recommendations are not. Treatment options may include U.S. Food and Drug Administration (FDA)-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.

Literature Review
Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Proteogenomic Testing
Clinical Context and Test Purpose
The purpose of proteogenomic testing in individuals who have cancer is to detect cancer, improve evaluation of prognosis, select treatments, and monitor for treatment response or resistance.
The following PICO was used to select literature to inform this review.

**Populations**
The relevant population of interest is individuals with cancer who have indications for genetic testing.

**Interventions**
The test being considered is the GPS Cancer™ test, a commercially available proteogenomic test for patients with cancer.

**Comparators**
The following tests and practices are currently being used: standard clinical workup and genetic testing for cancer diagnosis, prognosis, and monitoring response. Genetic testing using companion diagnostic tests for targeted therapies are generally used to select cancer treatments when targeted therapies are available.

**Outcomes**
The general outcomes of interest are overall survival and disease-specific survival. The harmful outcomes from a false-negative test result include delayed diagnosis or treatment; the harms from a false-positive test include incorrect or unnecessary additional treatment. The relevant duration of follow-up for survival outcomes varies by cancer type.

**Study Selection Criteria**
For the evaluation of clinical validity of the GPS Cancer test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

**Clinically Valid**
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

**Review of Evidence**
No published literature was identified on the clinical validity of the GPS Cancer test. Also, searches of selected websites did not identify any data on clinical validity of the test.

The general published literature on the clinical validity of proteogenomics includes the following types of studies: proteomic biomarkers as prognostic markers, molecular characterization, and monitoring quantitative protein levels.

**Proteomic Biomarkers as Prognostic Markers**
Some researchers have compared proteogenomic results with clinical outcomes and assessed the strength of association between genomic and proteomic data. Yau et al (2015) published a report comparing whether proteogenomic and genomic data can predict metastatic outcomes in breast cancer. This study measured FOXM transcript messenger RNA (mRNA) levels and compared the prognostic ability with FOXM1 target genes and a gene proliferation score. Table 2 shows the results obtained for each test.

<table>
<thead>
<tr>
<th>Test</th>
<th>ER Positive</th>
<th>ER Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td>FOXM mRNA expression</td>
<td>2.8 (2.0 to 3.8)</td>
<td>8.1×10⁻¹₀</td>
</tr>
</tbody>
</table>
Zhang et al (2016) combined mass spectrometry (MS)-based proteomic measurements with genomic data of 174 ovarian tumors previously analyzed by The Cancer Genome Atlas (TCGA). Copy number variants having a high correlation with protein abundance or mRNA were found on chromosomes 2, 7, 20, and 22. A lasso-based Cox proportional hazards model was used to model the association between these copy number variants and overall survival on a training set of 82 tumors and then used to predict survival in 87 nonoverlapping tumors. A consensus of the 4 signatures was created, using a voting method, as a binary indicator for signature, relative level up versus down. The consensus indicator was highly associated with survival (hazard ratio not provided; p<.001). Comparison to genomic stratification was not reported.

Defining Molecular Subtypes of Cancer

Comprehensive molecular characterization has been performed for various cancers, and in some cases, these investigations have defined subtypes that differ from standard histologic classification. Clinical validity can be demonstrated in this situation if the molecular subtypes are more homogeneous than the histologic class and correlate more closely with clinical outcomes.

An example of molecular subtyping of cancer by proteogenomics was published by TCGA network in 2015. This study integrated data from multiple platforms, including exome sequencing, DNA copy-number profiling, DNA methylation, and protein profiling by MS. For each platform, clusters of similar cases were identified. Three distinct molecular subtypes were identified using second-level cluster analysis. They were most concordant with isocitrate dehydrogenase enzyme, 1p/19q, and TP53 genetic variant status. The molecular subtypes showed differences in clinical characteristics, recurrence, and survival that could not be explained by histologic class.

Monitoring Quantitative Protein Levels Over Time

Quantification of protein levels over time may have applications for determining resistance to targeted therapy. Levels of protein markers may correlate with the presence of resistant tumor cells and may be an early marker of resistance that occurs before tumor progression. Clinical validity can be demonstrated if quantitative protein levels identify resistance more accurately or earlier than other surveillance methods.

Currently, few studies have reported on monitoring protein levels over time. A case report, published in 2016, demonstrated that repeat quantitation of human epidermal growth factor receptors 2 and 3, as well as epidermal growth factor receptor proteins, was feasible and that protein levels changed in response to different therapies and over time.

More recently, Latonen et al (2018) generated distinct profiles from patient tissue samples of benign prostate hyperplasia (n=10), untreated prostate cancer (n=17), and locally recurrent castration-resistant prostate cancer (n=11), demonstrating changes in protein levels that may be associated with tumor progression.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.
Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

No direct evidence on clinical utility was identified. Therefore, the clinical utility of the GPS Cancer test is uncertain. For proteogenomic testing in general, there is no published literature on clinical utility.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Since there is an absence of evidence establishing the clinical validity of proteogenomic testing; it will not be possible to determine whether clinical utility is present.

Section Summary: Proteogenomic Testing
There is no published evidence on the clinical validity of the GPS Cancer test and, therefore, the clinical validity of this test is undefined. For proteomic research in general, a few types of studies provided information on clinical validity. A small number of studies use proteogenomic biomarkers for diagnosis or prognosis and compare these biomarkers with traditional genomic testing. One study assessed whether proteomic data had the potential to detect drug sensitivity. Other studies have performed comprehensive molecular characterization of different tumors and, in some cases, have shown that molecular characterization correlates more strongly with clinical outcomes than with histologic classification. The third type of study in the literature quantitates and monitors protein markers over time for surveillance purposes, particularly for the emergence of resistance to targeted cancer therapies. This available research on clinical validity outlines some types of research that will be needed to establish clinical validity for a variety of clinical situations. However, the research is currently in its early stages, and no conclusions on test validity can be drawn at present from the evidence.

No direct evidence on clinical utility was identified. Therefore, no inferences can be made about clinical utility.

References


Documentation for Clinical Review

- No records required
Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

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<thead>
<tr>
<th>Type</th>
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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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<tr>
<th>Effective Date</th>
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<tbody>
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<td>09/01/2016</td>
<td>New policy.</td>
</tr>
<tr>
<td>08/01/2017</td>
<td>Annual review. Policy statement, guidelines and literature updated.</td>
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<tr>
<td>08/01/2018</td>
<td>Annual review. Policy statement, guidelines and literature updated. Policy title change from Proteogenomic Testing for Patients with Cancer (GPS Cancer™ Test).</td>
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<tr>
<td>09/01/2019</td>
<td>Annual review. Policy statement, guidelines and literature updated.</td>
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<tr>
<td>01/01/2020</td>
<td>Administrative update. Coding update.</td>
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<tr>
<td>09/01/2023</td>
<td>Policy reactivated. Previously archived from 07/01/2020 to 07/31/2023.</td>
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Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member’s illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and
effective for other indications or conditions, and therefore potentially medically necessary in those instances.

**Prior Authorization Requirements and Feedback (as applicable to your plan)**

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.
### Appendix A

<table>
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<th>POLICY STATEMENT</th>
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