I. Policy Description

Proteogenomic testing (encompassing analysis of both the genome and the proteome) is emerging as a new discipline in clinical settings. Until recently, genomic and proteomic analyses have remained in relative isolation. However, as techniques continue to improve, integrated analysis of both large-scale items has become more and more feasible. With precise and personalized medicine continuing to be a point of emphasis in clinical evaluation, proteogenomic analysis has received significant attention in treating cancer (Ang et al., 2019).

II. Related Policies

<table>
<thead>
<tr>
<th>Policy Number</th>
<th>Policy Title</th>
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<tbody>
<tr>
<td></td>
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III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual’s benefit coverage at the time of the request

*The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient’s illness.*

1. Proteogenomic testing, including transcriptome testing, **DOES NOT MEET COVERAGE CRITERIA**. This includes, but is not limited to, tests such as DarwinOncoTarget™/DarwinOncoTreat™ and Caris Molecular Intelligence Cancer Seek.

2. Tumor gene expression profiling with algorithmic analysis providing gene pathway activity scores **DOES NOT MEET COVERAGE CRITERIA**.

3. Optical genome mapping with or without whole genome sequencing and transcriptome analysis **DOES NOT MEET COVERAGE CRITERIA**.
IV. Scientific Background

As newer and faster technology makes evaluating enormous amounts of molecular information possible, proteogenomic testing is on the rise. Techniques such as whole genome sequencing, transcriptome sequencing, and proteomic analysis, previously not clinically viable, are now within the clinical laboratory landscape. Information yielded from these tests may be used for a variety of purposes, including prognosis, diagnosis, identifying targeted treatments, and more (Raby, 2020). Proteogenomic testing typically revolves around three different sets of analytes: DNA, RNA, and proteins.

DNA is the first stage in the genetic flow of information, represented by genes, including both exons and introns. All the protein-coding genes are represented in the exome, where at least 85% of pathogenic mutations are found. The exome represents a mere 1.5%-2% of the genome, thereby typically making it more cost-effective to sequence than the whole genome (Hulick, 2019). The entire exome includes approximately 30 megabases compared to the 3.3 gigabases of the genome. However, a pathogenic mutation may be in a noncoding region of the genome, such as mutations that result in dysfunction of gene regulation, resulting in situations where sequencing of the entire genome may be useful (Hulick, 2020).

RNA is the second stage in the genetic flow of information, as DNA is transcribed into RNA. Transcriptome sequencing refers to “digital counts” of each RNA molecule, or direct sequencing and quantification of RNA. The RNA transcript being quantified is not a perfect complement of the original DNA sequence; certain regulatory processes and post-transcriptional modifications, such as splicing, polyadenylation, and capping, alter the pre-mRNA sequence. Furthermore, additional regulatory RNA classes are not translated into a protein product, including but not limited to, ribosomal RNAs (rRNAs facilitate the translation of mRNA to protein) or short-interfering RNAs (siRNAs, capable of downregulating the translation of mRNA to protein). Transcriptome sequencing identifies these regulatory RNA sequences that are not otherwise identified at the DNA or protein level (Raby, 2018; Steiling, 2019).

Proteins are the third stage in the genetic flow of information, as most RNA is translated into protein products. Proteomics is a qualitative and quantitative assessment of the protein constituents in each biological sample. Mass spectrometry is typically used to identify peptide sequences and these sequences are used to infer protein identity and quantity. “Shotgun” proteomics is the most common method of identifying and labeling large amounts of proteins, analyzing both the “parent” ions eluting from the liquid chromatographer and the “daughter” ions, which are comprised of fragments of the parent ion. The apparatus then attempts to match the ions using several features, such as signal intensity and mass to charge ratio. From here, the peptide sequences (and therefore proteins) are inferred (Ang et al., 2019).

Integration of all three disciplines may be termed “proteogenomic” testing. The drive for “precision” and “personalized” medicine has encouraged more in-depth research on the genetic landscape, particularly for heterogenous conditions such as cancer. Proteogenomic testing has been proposed to fill clinical gaps that exist with disciplines in isolation, including finding the connections from genotype to phenotype. Identifying targeted therapies, drug resistance mechanisms, and other potentially crucial clinical factors are all questions that may be
answered with proteogenomic testing. Although the individual methodologies used to perform proteogenomic testing are well-validated in research settings (next generation sequencing [NGS], mass spectrometry), numerous challenges and limitations exist in translating them to the clinical realm. For example, there is currently no amplification technique available for proteins that would allow for smaller samples to be used. Additionally, reproducibility issues presented by the current techniques used in proteomic research can occur. Overall, validation of the enormous database of proteomics, as well as development of the bioinformatic infrastructure required to connect proteogenomics to the clinic, is still in progress (Ang et al., 2019).

In 2016, the Clinical Proteomic Tumor Analysis Consortium (CPTAC) created the Applied Proteogenomics Organizational Learning and Outcomes (APOLLO) network was launched to incorporate proteogenomics into patient care. The APOLLO network is a collaborative effort between the Department of Defense (DoD) and the Department of Veterans Affairs (VA). APOLLO is currently analyzing proteonomic data from 8,000 human tissue samples; this data will be publicly available once curated (NIH, 2016). As of 2021, the CPTAC has begun to release some individual genomic, proteomic, and imaging data sets from this ongoing research but combined proteogenomic analysis from this data is just beginning to emerge (Krug et al., 2020; L. B. Wang et al., 2021).

Several proteogenomic testing platforms are commercially available.

**DarwinOncoTarget™ and DarwinOncoTreat**

DarwinOncoTarget™ and DarwinOncoTreat™ are synergistic proteogenomic tests offered by Columbia University. DarwinOncoTarget™ identifies 193 potentially targetable proteins while DarwinOncoTreat™ assesses the regulatory activity of 6293 proteins ("tumor-checkpoints"). DarwinOncoTreat™ then “prioritizes” drugs based on their ability to revert the activity of these checkpoints. DarwinOncoTarget™ is available for all malignancies whereas DarwinOncoTreat™ is only available for certain cancer subtypes (Columbia, 2019).

**Caris Molecular Intelligence**

Other proprietary proteogenomic platforms are offered by Caris Molecular Intelligence. The MI Cancer Seek utilizes an NGS technique to identify “Whole exome sequencing for DNA mutations, copy number alterations, insertions/deletions, genomic signatures MSI [microsatellite instability] and TMB [tumor mutational burden], and whole transcriptome sequencing for RNA fusions and variant transcripts” (Caris, 2020b).

**Praxis Genomics Optical Genome Mapping, Whole Genome Sequencing, and Transcriptome Analysis**

Praxis Genomics offers a proteogenomics approach via combined testing with their Optical Genome Mapping, Whole Genome Sequencing, and Transcriptome Analysis. Optimal Genome Mapping (OGM), developed by Bionano Genomics LLC, evaluates DNA samples for large-scale changes such as chromosomal transfer of DNA fragments, chromosomal inversion.
or complex rearrangement, measurement of repetitive regions that control adjacent gene expression, and measurement of tandem repeat expansions. Whole Genome Sequencing (WGS) obtains sequence from the entire genome (roughly 3 billion units). Praxis uses the Dragen alignment and variant calling pipeline to identify genomic changes. Highly repetitive DNA content and genomic rearrangements cannot be detected with whole genome sequencing. Transcriptome Analysis allows for the evaluation of the functional consequences of DNA mutations found in Optical Genome Mapping or Whole Genome Sequencing. “Only by building on the diverse strength of OGM and ISR [Illumina Short Read] WGS and transcriptome sequencing can we increase the sensitivity and specificity of genetic diagnosis until novel technologies even more precise and faster come along” (Praxis, 2021)

**OncoSignal™**

Protean Biodiagnostics developed OncoSignal™ as an “innovative and unique test to expand the information that can be obtained from cancer tissue analysis.” OncoSignal™ uses advanced molecular and bioinformatic systems to measure mRNA expression patterns, calculating the specific activity of seven key oncogenic drive signal pathways (Estrogen Receptor, Androgen Receptor, Phosphoinositide 3-Kinase, Hedgehog Pathway, NOTCH Signal, Transforming Growth Factor Receptor Beta, and Mitogen Activated Protein Kinase). These pathways “measure key oncogenic drivers of numerous distinct cancer types including but not limited to breast cancer, prostate cancer, ovarian cancer, colon cancer, lymphoma and more.” Each pathway is given a score based on molecular and bioinformatic findings and pathway activity is interpreted as low, normal, or high in comparison to the normal physiological range. The report then provides targeted treatment recommendations based on these changes (Protean, 2021).

**Clinical Validity and Utility**

North et al. (2018) used NantHealth’s profile to characterize 32 cases of sebaceous carcinomas (SeC). The authors identified ultraviolet (UV) damage in 10 samples and microsatellite instability in 9 samples. UV cases of SeC were shown to have more severe histopathologic features, including poorer differentiation and an “infiltrative” growth pattern. The authors also noted that the transcriptomes of the UV SeC cases were similar to cutaneous squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs). Overall, three distinct classes of sebaceous carcinoma were identified based on mutation pattern and cell of origin (North et al., 2018).

Liao et al. (2015) used two genetic datasets (TCGA and METABRIC) to characterize over 2500 cases of breast cancer in pre-menopausal (preM) and post-menopausal women (postM) (defined as ≤45 years and ≥55 years respectively, women of ages 45-55 were not included). The following molecular features were examined: gene expression, somatic mutation, copy number, methylation, and protein expression. In preM tumors, the authors identified unique methylation patterns, copy numbers, and somatic mutations in estrogen receptor-positive (ER+) tumors. Further investigation of this subset revealed “elevated integrin/laminin and EGFR signaling, with enrichment for upstream TGFβ-regulation.” The authors concluded that preM ER+ tumors have “distinct molecular characteristics” compared to postM ER+ tumors (Liao et al., 2015).
Rabizadeh et al. (2018) compared tumor-only DNA sequencing to tumor-normal DNA (containing controls for germline mutations) plus RNA sequencing. A total of 621 patients with 30 different cancer types were studied using a 35-gene sequencer and the precision of somatic variant calling was evaluated. Without the germline controls, 94% of the variants were single nucleotide polymorphisms (SNPs) and considered false-positives. Removing these SNPs resulted in a 48% false-positive rate. Tumor-only sequencing ultimately led to a 29% false-positive rate in “at least one of twelve genes with directly targetable drugs” and RNA analysis revealed that 18% of variants were not expressed (Rabizadeh et al., 2018).

Sjostrom et al. (2019) evaluated the utility of transcriptomic profiling in breast cancer and whether these results could safely allow patients to decline systemic therapy. A 141-gene signature was derived from a node-negative cohort previously untreated with chemotherapy. This signature was used to evaluate 454 node-negative, ER+, and systemically untreated cancer patients. The authors noted that this was a low-risk subgroup but did find that of the patients in the lowest 25th percentile of signature scores, 95% of patients were metastasis-free after 15 years despite lack of endocrine therapy. The authors concluded that “transcriptomic profiling identifies patients with an excellent outcome without any systemic adjuvant therapy in clinically low-risk patients of…two separate cohorts” (Sjostrom et al., 2019).

Feng, Tung, Su, Tsao, and Wu (2019) evaluated the proteomic profile of sorafenib resistance in hepatocellular carcinoma patients. Tumor samples from 60 patients were examined. The authors identified three proteins that were overexpressed in sorafenib-resistant cells; 78 kDa glucose related protein (GRP78), 14-3-3ε, and heat shock protein 90β (HSP90β). Approximately 73% of cells had high GRP78 expression, 18% had high 14-3-3ε expression, and 85% had high HSP90β expression. The authors also noted that elevated GRP78 was associated with the shortest progression-free survival of patients treated with sorafenib. The authors concluded that “GRP78 can be a predictive biomarker in HCC patients treated with sorafenib” (Feng et al., 2019).

Shiba et al. (2019) evaluated the genetic landscape of pediatric acute myeloid leukemia. The authors performed a transcriptome analysis in 139 patients (of 369 in the total cohort). Fifty-four in-frame gene mutations and one RUNX1 out-of-frame fusion were found in 53 of the 139 patients. Moreover, 258 gene fusions were found in the 369 total patients. Five novel gene fusions were found, and several less common gene rearrangements were identified. Out of the 111 remaining patients, “KMT2A-PTD, biallelic CEBPA, and NPM1 gene mutations were found in 11, 23, and 17 patients, respectively.” The authors noted these mutations were mutually exclusive compared with other gene fusions. The authors remark that risk stratification should be reconsidered (Shiba et al., 2019).

Yang et al. (2019) evaluated the genomic landscape of rectal cancer patients who did not respond to chemotherapy. The authors performed whole exome sequencing on 28 paired tumors collected before and after chemotherapy. Several mutations were identified (CTDSP2, APC, KRAS, TP53 and NFKBIZ) that appeared to confer selective advantages to cancer cells and the authors noted that chemotherapy altered the genomic landscape of these tumors and that high intratumoral heterogeneity in any stage of cancer contributed to poor survival in patients (Yang et al., 2019).
Tredan et al. (2019) evaluated the impact of broad molecular profiling on identifying targeted therapies. A “molecular tumor board,” consisting of molecular biologists, medical oncologists, and pathologists, selected the genes to be included in the profile and a total of 69 genes were included on the final panel. A total of 1980 molecular profiles were constructed. Of these profiles, 948 had no actionable mutations (leaving 1032 with at least one actionable mutation) and a targeted therapy was recommended for 699 of these patients. A total of 182 targeted therapies were initiated, with only 23 patients experiencing an objective response (13% of patients receiving therapy, 0.9% of the total cohort of 2579 patients). The authors concluded that “molecular screening should not be used at present to guide decision-making in routine clinical practice outside of clinical trials” (Tredan et al., 2019).

Kwon et al. (2019) identified and analyzed mutant peptides in prostate cancer cell lines. The authors obtained four cell lines of varying aggression (LNCaP, LNCaP-LN3, PC-3, and PC-3M) and profiled the resulting mutant peptides. A total of 70 mutant peptides were identified. Expression of seven mutant peptides were found to be altered in tumors, with “CAPN2 D22E” as the most significantly up-regulated peptide. Increased levels of the \textit{INTS7} gene and decreased levels of the \textit{SH3BGRL} gene were found to be correlated with aggressiveness of prostate cancer (Kwon et al., 2019).

D. Wang et al. (2019) constructed a “quantitative proteome and transcriptome abundance atlas” of 29 paired healthy human tissues. A total of 18,072 transcripts and 13,640 proteins (including 37 without “prior protein-level evidence”) were represented. However, the authors concluded that proteogenomics remains challenging. The authors noted that out of 9848 amino acid variants found by exome sequencing, only 238 could be confidently detected at the protein level. The authors also remarked that many proteins could not be detected despite highly expressed mRNA, that very few proteins showed tissue-specific expression, and that strong differences existed between mRNA and protein quantities. Overall, the writers determined that proteogenomics “needs better computational methods and requires rigorous validation” (D. Wang et al., 2019).

Treue et al. (2019) performed analysis on a model of a drug-resistant \textit{EGFR}-mutated non-small cell lung cancer case. The authors integrated several proteogenomic techniques, including whole exome sequencing and “global time-course discovery phosphoproteomics” to identify molecular alterations. The writers remarked that this allowed them to reduce the complexity of the model down to 44 “predicted” phosphoproteins and 35 “topologically close” genetic alterations. From here, the authors found that targeting of HSPB1, DBNL, and AKT1 showed “potent antiproliferative effects overcoming resistance against EGFR-inhibitory therapy” (Treue et al., 2019).

Salem et al. (2018) evaluated the correlation of tumor mutational load (TML; “high” defined as greater than or equal to 17 mutations/MB), PD-L1 expression, and mismatch repair deficiency (dMMR) status with response to immune checkpoint inhibitors (ICIs). A total of 4125 tumors from 14 different gastrointestinal sites were examined. A 592 gene panel was used to calculate the TML. Microsatellite instability (MSI), PD-L1 expression, and dMMR status were all evaluated. The authors found that high TML was “strongly associated” with high MSI. Right-sided colon and small-bowel adenocarcinomas had the highest rates of high-TML tumors (14.6% and 10.2% respectively) whereas pancreatic neuroendocrine and...
gastrointestinal stromal tumors had the lowest (1.3%, 0%). The authors noted that high-TML rate varied “widely” among gastrointestinal cancers (Salem et al., 2018).

Gillette et al. (2020) utilized proteogenomics to reveal therapeutic vulnerabilities in lung adenocarcinoma. Comprehensive proteogenomic characterization was performed on 110 tumors. “Multi-omics clustering revealed four subgroups defined by key driver mutations, country, and gender” (Gillette et al., 2020). Therapeutic vulnerabilities were identified in the \textit{KRAS}, \textit{EGFR}, and \textit{ALK} genes and the authors note that “this proteogenomics dataset represents a unique public resource for researchers and clinicians seeking to better understand and treat lung adenocarcinomas” (Gillette et al., 2020).

Krug et al. (2020) integrated mass spectrometry-based proteomics and next-generation DNA and RNA sequencing to create a proteogenomic profile of 122 treatment-naïve primary breast cancer tumors. They found that “proteogenomics challenged standard breast cancer diagnoses, provided detailed analysis of the ERBB2 amplicon, defined tumor subsets that could benefit from immune checkpoint therapy, and allowed more accurate assessment of Rb status for prediction of CDK4/6 inhibitor responsiveness.” The authors note that their results “underscore the potential of proteogenomics for clinical investigation of breast cancer through more accurate annotation of targetable pathways and biological features of this remarkably heterogeneous malignancy” (Krug et al., 2020).

L. B. Wang et al. (2021) integrated genomic, proteomic, post-translational modification, and metabolomic data to examine 99 treatment-naïve glioblastomas (GBMs), where they identified key phosphorylation events as potential mediators of oncogenic pathway activation and potential targets for \textit{EGFR}-, \textit{TP53}-, and \textit{RB1}-altered tumors. The identified “immune subtypes with distinct immune cell types are discovered using bulk omics methodologies” and note that “histone H2B acetylation in classical-like and immune-low GBM is driven largely by BRDs, CREBBP, and EP300.” Their work highlights the importance of an integrated proteogenomic approach in GBM and also “highlights biological relationships that could contribute to stratification of GBM patients for more effective treatment” (L. B. Wang et al., 2021).

Joshi et al. (2021) examined the stepwise evolution of gilteritinib resistance in \textit{FLT3}-mutated acute myeloid leukemia (AML). To mechanistically define both early and late resistance in AML, they integrated whole-exome sequencing, CRISPR-CAS9, metabolomics, proteomics, and pharmacologic approaches. They found that “early resistant cells undergo metabolic reprogramming, grow more slowly, and are dependent upon Aurora kinase B (AURKB). Late resistant cells are characterized by expansion of pre-existing NRAS mutant subclones and continued metabolic reprogramming,” creating a model that closely mirrors the timing and mutations of AML patients treated with gilteritinib. They also note that “pharmacological inhibition of AURKB resensitizes both early resistant cell cultures and primary leukemia cells from gilteritinib-treated AML patients.” Their findings support a “combinatorial strategy to target early resistant AML cells with AURKB inhibitors and gilteritinib before the expansion of pre-existing resistance mutations occurs” (Joshi et al., 2021).
V. Guidelines and Recommendations

Since this is an emerging field, there is limited guidance from applicable professional societies. As of publication date, no specific guidance was found from professional medical societies, including NCCN, ASCO, ACMG, NICE, AMP, CAP, and NGSC.

National Comprehensive Cancer Network (NCCN, 2021)

Currently, the NCCN does not list proteogenomic testing as a recommended technique for any type of cancer. Furthermore, proprietary comprehensive genomic profiles have been submitted for inclusion in guidelines for several types of cancer, but they have never been included as a recommended technique as of August 4, 2021 (NCCN, 2021).

American Society of Clinical Oncology (ASCO, 2021a, 2021b; Domchek, Mardis, Carlisle, & Owonikoko, 2020)

One guideline regarding genomic profiling is in development from ASCO. The proposed title is “Somatic Genomic Panel Testing for Metastatic Disease.” No other guidelines regarding proteogenomic profiling were identified (ASCO, 2021a).

In 2020, the ASCO published a clinical oncology educational book which included an article on integrating genetic and genomic testing into oncology practice. Transcriptome and proteomic sequencing were not mentioned in the article. However, the authors note that “Examples of the integration of genomic information into the care of patients with cancer include germline testing for BRCA1/2 in breast, ovarian, pancreatic, and prostate cancer; evaluation of mismatch repair in endometrial cancer; and somatic sequencing in lung cancer” (Domchek et al., 2020). In 2021, they published a guideline on “Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer,” where it was noted that “although tumor histology, grade, stage, and estrogen, progesterone, and human epidermal growth factor receptor 2 (HER2) expression should routinely be used to guide clinical decisions, there is insufficient evidence to support the use of other markers or genomic profiles” (ASCO, 2021b).

VI. State and Federal Regulations, as applicable

A search for “proteogenomic” on the FDA website on 08/05/2021, yielded zero results. Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA ’88). As an LDT, the U. S. Food and Drug Administration has not approved or cleared this test; however, FDA clearance or approval is not currently required for clinical use.

VII. Applicable CPT/HCPCS Procedure Codes

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<th>CPT</th>
<th>Code Description</th>
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<td>0019U</td>
<td>Oncology, RNA, gene expression by whole transcriptome sequencing, formalin-fixed paraffin embedded tissue or fresh frozen tissue, predictive algorithm reported as</td>
</tr>
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<td>Code</td>
<td>Test Description</td>
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<td>0260U</td>
<td>Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping</td>
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<td>0262U</td>
<td>Oncology (solid tumor), gene expression profiling by real-time RT-PCR of 7 gene pathways (ER, AR, PI3K, MAPK, HH, TGFB, Notch), formalin-fixed paraffin-embedded (FFPE), algorithm reported as gene pathway activity score</td>
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<td>0264U</td>
<td>Rare diseases (constitutional/heritable disorders), identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping</td>
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<td>0266U</td>
<td>Unexplained constitutional or other heritable disorders or syndromes, tissue-specific gene expression by whole-transcriptome and next-generation sequencing, blood, formalin-fixed paraffin-embedded (FFPE) tissue or fresh frozen tissue, reported as presence or absence of splicing or expression changes</td>
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<tr>
<td>0267U</td>
<td>Rare constitutional and other heritable disorders, identification of copy number variations, inversions, insertions, translocations, and other structural variants by optical genome mapping and whole genome sequencing</td>
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*Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.*

**VIII. Evidence-based Scientific References**


Blue Cross and Blue Shield of Louisiana is an independent licensee of the Blue Cross Blue Shield.

Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.


sebaceous carcinoma. *Nature Communications, 9*(1), 1894. doi:10.1038/s41467-018-04008-y


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M2168 Proteogenomic Testing of Individuals with Cancer
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Avalon is an independent company that serves as a laboratory insights advisor for Blue Cross and Blue Shield of Louisiana and HMO Louisiana, Inc.

### IX. Review/Revision History

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