

## Corporate Medical Policy

### Proteogenomic Testing of Individuals with Cancer AHS-M2168

**File Name:** proteogenomic\_testing\_of\_individuals\_with\_cancer  
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#### Description of Procedure or Service

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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, but as techniques continue to improve, integrated analysis of both large-scale items has become more and more feasible. Proteogenomic analysis has received significant attention in treating cancer, as precise and personalized medicine continues to be a point of emphasis in clinical evaluation (Ang et al., 2019).

**Related Policies:**

AHS-G2054 Liquid Biopsy

AHS-M2030 Testing for Targeted Therapy of Non-Small-Cell Lung Cancer

AHS-M2178 Microsatellite Instability and Tumor Mutational Burden Testing

*\*\*\*Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.*

#### Policy

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**BCBSNC will provide coverage for proteogenomic testing of individuals with cancer when it is determined to be medically necessary because the medical criteria and guidelines shown below are met.**

#### Benefits Application

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This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

#### When Proteogenomic Testing of Individuals with Cancer is covered

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For individuals with cancer, integrated comprehensive tumor profiling to calculate a tumor mutational burden score using genomic and/or transcriptomic data in conjunction with immunohistochemistry analysis (e.g., OncoExTra™, Caris MI Tumor Seek™, Caris MI Profile™ Comprehensive Testing) is considered medically necessary as defined within AHS-M2178-Microsatellite Instability and Tumor Mutational Burden Testing.

#### When Proteogenomic Testing of Individuals with Cancer is not covered

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1. For individuals with cancer, integrated analysis of proteomic, genomic, **and/or** transcriptomic testing with or without algorithmic analysis (e.g., GPS Cancer®, DarwinOncoTarget™/DarwinOncoTreat™).

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2. Tumor gene expression profiling with algorithmic analysis providing gene pathway activity scores is considered investigational.
3. Optical genome mapping with or without whole genome sequencing and transcriptome analysis is considered investigational.

## Policy Guidelines

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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 that previously were 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, 2022). 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. The exome represents all the protein-encoding genes, and at least 85% of pathogenic mutations are found in the exome. The exome only represents approximately 1.5%-2% of the genome, thereby typically making it more cost-effective than whole genome sequencing. The entire exome includes approximately 30 megabases as compared to the 3.3 gigabases of the genome (Hulick, 2022). However, a pathogenic mutation may be in a noncoding region of the genome, such as gene regulation dysfunction of gene regulation, resulting in situations where sequencing of the entire genome may be useful (Hulick, 2022).

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 ultimate RNA transcript 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, including but not limited to, ribosomal RNAs (that facilitate translation to protein) or short-interfering RNAs (siRNAs, capable of downregulating translation of mRNA to protein) are not translated into a protein product. Transcriptome sequencing identifies these regulatory RNA sequences that are otherwise not identified at the DNA or protein level (Raby, 2022; Steiling, 2023).

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 within a given biological sample. Mass spectrometry is typically used to identify peptide sequences, which are then used to infer proteins. “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 is comprised of fragments of the parent ion. The apparatus then attempts to match the ions using several features (such as signal intensity, mass to charge ratio, et al). 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 existed with disciplines in isolation (such as 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

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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. The APOLLO network was launched to incorporate proteogenomics into patient care and is a collaborative effort between the Department of Defense (DoD) and the Department of Veterans Affairs (VA). APOLLO is currently analyzing proteogenomic data from 8,000 human tissue samples; this data will be publicly available once curated (NIH, 2016). As of 2022, 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 (Dong et al., 2022; Krug et al., 2020; Wang et al., 2021).

## ***Proprietary Testing***

Several proteogenomic testing platforms are commercially available.

### *GPS Cancer®*

The GPS Cancer® test from NantOmics, a member of the NantWorks family, utilizes quantitative proteomics through mass spectrometry, whole genome sequencing (over 20,000 genes across three billion base pairs), and whole transcriptome sequencing technologies (over 200,000 RNA transcripts). These three factors combined provide oncologists with a comprehensive molecular profile of a patient's cancer. The test is intended to provide information about targeted therapies, such as which therapies a patient may benefit from or which therapies a patient may resist (NantOmics, 2023). Finally, the third component of GPS Cancer® is the tumor “normal” sequencing. This component provides a comparison of a patient's healthy, unaffected genome to the genome affected by the tumor. It is intended to provide “pharmacogenomic analysis for potential drug toxicity and/or interactions” and to separate mutations caused by cancer from those that were present prior to cancer (NantOmics, 2023).

### *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, 2023).

### *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, 2023b). The Caris Molecular Intelligence Comprehensive Tumor Profiling test uses precision medicine to assess DNA, RNA, and proteins to aid individualized treatment regimens (Caris, 2023a).

### *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.

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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, 2022).

## *OncoSignal™*

Philips’ OncoSignal™ technology is used by Protean Biodiagnostics as an “innovative and unique test to expand the information that can be obtained from cancer tissue analysis,” as part of their proprietary Oncology MAPS™ solution. 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 protean 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 clinically-used Oncology MAPS™ report then provides targeted treatment recommendations (AccessWire, 2022; Protean, 2023).

## *MosaicNeedle™*

Nanomosaic Inc. developed MosaicNeedle™ technology for proteomic and multi-omic investigation and application (PRNewswire, 2022). The commercial launch of their Tessie™ platform for proteomics and multi-omics is slated to occur in 2022. According to Nanomosaic, their proteomics technology “bridges the gaps of functional information lost due to post-transcriptional and post-translational modifications in a genomic approach.” Because the traditional proteogenomic approach typically requires multiple diverse assays and workflows, this novel technology simplifies by using “densely integrated nanoneedle sensors on a planar substrate that integrates proteogenomic analysis in one platform.” Each nanoneedle binds a single molecule and detects both nucleic acids and proteins in a single assay process. The result is a full proteogenomic quantification in one single reaction, on one platform, with high sensitivity and lower cost (Quan et al., 2022).

## ***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 such as 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 pre-menopausal (preM) and post-menopausal individuals (postM) with breast cancer (defined as  $\leq 45$  years and  $\geq 55$  years respectively, individuals of ages 45-55 were not included). The following molecular features were examined: “gene expression, copy number, methylation, somatic mutation”, and protein expression. The authors identified unique methylation patterns, copy numbers, and somatic mutations in estrogen receptor-positive (ER+) tumors in preM tumors. Further investigation of this subset revealed “elevated integrin/laminin and EGFR signaling, with enrichment for upstream TGF $\beta$ -regulation”. The authors concluded that ER+ preM tumors have “distinct molecular characteristics” compared to ER+ postM 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. 621 patients with 30 different cancer types were studied

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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. (2020) evaluated the utility of transcriptomic profiling in breast cancer and whether their results could safely allow patients to decline systemic therapy. A 141-gene signature was derived from a node-negative cohort previously untreated with chemotherapy, and 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 found that of patients in the lowest 25<sup>th</sup> 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., 2020).

Feng et al., (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), 14-3-3 $\epsilon$ , and heat shock protein 90 $\beta$  (HSP90 $\beta$ ). 73% of cells had high GRP78 expression, 18% had high 14-3-3 $\epsilon$  expression, and 85% had high HSP90 $\beta$  expression. The authors also noted that GRP78 was associated with 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). 54 in-frame gene mutations and 1 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 fewer 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 to be mutually exclusive 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 in whom did not respond to chemotherapy. The authors performed whole exome sequencing on 28 paired tumors collected before and after chemotherapy. The authors found several mutations (*CTDSP2*, *APC*, *KRAS*, *TP53* and *NFKB1Z*) that appeared to confer “selective advantages” to cancer cells. The authors also noted that chemotherapy altered 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 of these profiles 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, and only 23 patients experienced 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 total 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 INTS7 and decreased levels of SH3BGRL were also found to be correlated with aggressiveness of prostate cancer (Kwon et al., 2019).

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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 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” (Wang et al., 2019).

Treue et al. (2019) performed analysis of a model of a drug-resistant 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 *KRAS*, *EGFR*, and *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).

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 *EGFR*-, *TP53*-, and *RBI*-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 important of an integrated proteogenomic approach in GBM and “highlights biological relationships that could contribute to stratification of GBM patients for more effective treatment” (Wang et al., 2021).

Joshi et al. (2021) examined the stepwise evolution of gilteritinib resistance in *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.

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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 re-sensitizes 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).

Akcakanat et al. (2021) integrated DNA, RNA, and functional proteogenomics from tumor samples of 52 patients with metastatic breast cancer (inclusive of 10 patients with both primary and metastatic tumors to chart the evolution of the tumor’s profile). The aim was to determine potentially actionable alterations in metastatic breast cancer and analyze the molecular evolution of the tumors. Regarding proteomic profiling, needle biopsy samples were evaluated via reverse phase protein arrays. The panel was composed of 295 antibodies and the PI3K pathway activity score was “defined as the sum of the normalized values of the 7phosphor-protein levels of Akt, 4E-BP1, S6K, and S6.” Samples were considered PI3K activated if their PI3K scores were in the top quartile. In discussion, the authors noted: “Neither genomic alterations predicted gene or protein expression nor was there a strong correlation between proteomic and transcriptomic data. [However] we cannot exclude the possibility that the lack of concordance between DNA alterations and RNA and protein and protein phosphorylation are not merely the result of tumor heterogeneity and the tumor cellularity of the samples” (Akcakanat et al., 2021).

## 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, ACMG, NICE, AMP, and CAP.

## National Comprehensive Cancer Network

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, and they have never been included as a recommended technique as of June 23, 2022 (NCCN, 2023).

## American Society of Clinical Oncology

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 2022, 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, 2022).

In 2022, ASCO published a provisional clinical opinion titled, “Somatic Genomic Testing in Patients with Metastatic or Advanced Cancer.” They note an increasing number of therapies have been approved to treat cancers harboring specific genomic biomarkers. The following represents their recommendations:

- “Patients with metastatic or advanced cancer should undergo genomic sequencing in a certified laboratory if the presence of one or more specific genomic alterations has regulatory approval as biomarkers to guide the use of or exclusion from certain treatments for their disease.”
- “Multigene panel-based assays should be used if more than one biomarker-linked therapy is approved for the patient's disease.”

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- “Site-agnostic approvals for any cancer with a high tumor mutation burden, mismatch repair deficiency, or neurotrophic tyrosine receptor kinase (NTRK) fusions provide a rationale for genomic testing for all solid tumors.”
- “Multigene testing may also assist in treatment selection by identifying additional targets when there are few or no genotype-based therapy approvals for the patient's disease.”
- “For treatment planning, the clinician should consider the functional impact of the targeted alteration and expected efficacy of genomic biomarker–linked options relative to other approved or investigational treatments.”

Regarding proteogenomic or protein profiling, ASCO recommended:

- “Several hundred genes and their mutant protein products have been linked to increased cell signaling, proliferation, and survival in cell lines or mouse models and thus proposed to be cancer drivers. However, at this time, few genomic alterations have been clinically proven as therapeutic targets. Therefore, in addition to the functional effects of mutations on protein chemistry and signaling, evidence of clinical relevance should be considered.”
- “Clinical decision making should incorporate (1) the known or predicted impact of a specific genomic alteration on protein expression or function and (2) clinical data on the efficacy of targeting that genomic alteration with a particular agent (strength of recommendation: strong)” (ASCO, 2021; Chakravarty et al., 2022).

## Applicable State and Federal Regulations

### Food and Drug Administration

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). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

## Billing/Coding/Physician Documentation Information

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This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at [www.bcbsnc.com](http://www.bcbsnc.com). They are listed in the Category Search on the Medical Policy search page.

*Applicable service codes: 81479, 81599, 0019U, 0260U, 0262U, 0264U, 0266U, 0267U, 0298U, 0299U, 0300U, 0329U, 0362U, 0413U, 0436U*

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

## Scientific Background and Reference Sources

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Medical Director review 10/2020

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Medical Director review 11/2022

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Medical Director review 10/2023

Medical Director review 1/2024

## **Policy Implementation/Update Information**

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- 2/11/20 New policy developed. Proteogenomic testing, including but not limited to GPS Cancer®, DarwinOncoTarget™/DarwinOncoTreat™, and Caris Molecular Intelligence® Comprehensive Tumor Profiling are considered investigational. Medical Director review 2/2020. (lpr)
- 3/31/20 Specialty Matched Consultant Advisory Panel review 3/18/2020. No change to policy statement. (lpr)
- 11/10/20 Reviewed by Avalon 3<sup>rd</sup> Quarter 2020 CAB. Added PLA code 0211U to Billing/Coding section. Added Caris Molecular Intelligence Cancer Seek to non-covered statement. Medical Director review 10/2020. (lpr)
- 4/6/21 Specialty Matched Consultant Advisory Panel review 3/17/2021. No change to policy statement. (lpr)
- 11/16/21 Reviewed by Avalon 3<sup>rd</sup> Quarter 2021 CAB. Added PLA codes 0260U, 0262U, 0264U, 0266U, 0267U to Billing/Coding section. Added two investigational statements to When “Not Covered” section: 2)Tumor gene expression profiling with algorithmic analysis providing gene pathway activity scores is considered investigational and 3)Optical genome mapping with or without whole genome sequencing and transcriptome analysis is considered investigational. Updated policy guidelines and references. Medical Director review 10/2021. (lpr)
- 2/8/22 Reviewed by Avalon Q4 2021 CAB. Removed PLA code 0211U from Billing/Coding section. Medical Director review 1/2022. No change to policy statement. (lpr)
- 12/13/22 Reviewed by Avalon 3<sup>rd</sup> Quarter 2022 CAB. Medical Director review 11/2022. Deleted related policy AHS-M2109. Updated policy guidelines and references. Removed Caris MI Cancer seek from “When Not Covered” section as this test is used for TMB/MSI detection and is addressed under AHS-M2178. No changes to policy statement. Added CPT codes: 0298U, 0299U, 0300U to Billing/Coding section. (lpr)
- 12/30/22 Added PLA code 0362U to Billing/Coding section for effective date 1/1/2023. (lpr)
- 9/29/23 Added PLA code 0413U to Billing/Coding section for 10/1/23 code update. (lpr)
- 12/5/23 Reviewed by Avalon 3<sup>rd</sup> Quarter 2023 CAB. Medical Director review 10/2023. Edited “when not covered” section for clarity. Updated policy guidelines and references. (lpr)
- 12/29/23 Added PLA code 0436U to Billing/Coding section for 1/1/2024 code update. (lpr)
- 2/21/24 Reviewed by Avalon Q4 2023 CAB--off cycle review. Medical Director review 1/2024. Under “when covered” section, added medical necessity coverage criteria for OncoExTra, Caris MI Tumor Seek, and Caris MI Profile comprehensive testing. Added AHS-M2178 Microsatellite Instability and Tumor Mutational Burden Testing to related policies section. Under Billing/Coding section, added PLA codes 0329U and 0019U. (lpr)

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