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Corporate Medical Policy

Proteogenomic Testing of Individuals with Cancer AHS-M2168

File Name:	proteogenomic_testing_of_individuals_with_cancer
Origination:	2/2020
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Last Review:	10/2021

Description of Procedure or Service

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:
Detection of Circulating Tumor Cells and Cell Free DNA in Cancer Management (Liquid Biopsy) AHS-G2054
Testing for Targeted Therapy of Non-Small-Cell Lung Cancer AHS-M2030
Molecular Panel Testing of Cancers for Diagnosis, Prognosis and Identification of Targeted Therapy AHS-M2109

******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

Proteogenomic testing of individuals with cancer is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

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

Not applicable.

When Proteogenomic Testing of Individuals with Cancer is not covered

1. Proteogenomic testing, including but not limited to GPS Cancer®, DarwinOncoTarget ™/DarwinOncoTreat™, Caris Molecular Intelligence®, Comprehensive Tumor Profiling and Caris Molecular Intelligence Cancer Seek are considered investigational.

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

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, 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. 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, 2019). 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, 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 ultimate RNA transcript is not a perfect complement of the original DNA sequence; certain regulatory processes and post-transciptional 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, 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 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

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 proteogenomic 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.

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 3 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, 2021). 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, 2021).

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 transciptome sequencing for RNA fusions and variant transcripts" (Caris, 2020b). The Caris Molecular Intelligence Comprehensive Tumor Profiling test uses precision medicine to assess DNA, RNA, and proteins to aid individualized treatment regimens (Caris, 2020a).

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 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 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 hisopathologic 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 women (postM) with breast cancer (defined as ≤45 years and ≥55 years respectively, women 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 TGFβ-regulation". The authors concluded that ER+ preM tumors have "distinct molecular characteristics" compared to ER+ postM tumors (Liao et al., 2015).

Rabizadeh et al 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 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. (2018) 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 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)". 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 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 "rare" 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 *NFKBIZ*) 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. 1980 molecular profiles were constructed. 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. 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. 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).

D.Wang et al. (2019) constructed a "quantitative proteome and transcriptome abundance atlas" of 29 paired healthy human tissues. 18072 transcripts, 13640 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 an 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). 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).

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 *EGFR*-, *TP53*-, and *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 important of an integrated proteogenomic approach in GBM and "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 *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).

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, and 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).

Billing/Coding/Physician Documentation Information

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. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 0019U, 0211U, 0260U, 0262U, 0264U, 0266U, 0267U, 81479, 81599

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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Specialty Matched Consultant Advisory Panel 3/2020

Medical Director review 3/2020

Medical Director review 10/2020

Specialty Matched Consultant Advisory Panel 3/2021

Medical Director review 3/2021

Medical Director review 10/2021

Policy Implementation/Update Information

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 3rd 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 3rd 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)