

Investigational Gene Expression, Biomarker, and Multianalyte Testing

Effective: January 1, 2023

Next Review: November 2023

Last Review: December 2022

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Gene expression, biomarker, and multianalyte tests have been proposed to aid in the risk-assessment, diagnosis, and prognosis of many disorders.

MEDICAL POLICY CRITERIA

Notes: See Cross References section for policies related to gene expression and multianalyte testing for specific indications.

The following tests are considered **investigational**, because the current scientific evidence is not yet sufficient to establish the impact of these tests on health outcomes:

Test Name	Laboratory
Awise [®] Lupus	Exagen, Inc.
Borrelia burgdorferi, OspA protein evaluation	Galaxy Diagnostics, Inc.
Dawn [™] IO Melanoma	Intervenn
DecisionDx [®] -SCC	Castle Biosciences, Inc.
DetermaRx [™]	Oncocyte [™] Corporation

EpiSwitch® Checkpoint-inhibitor Response Test (CiRT)	Next Bio Research Services
HART CADhs®	Prevencio, Inc.
HART CVE®	Prevencio, Inc.
HART KD®	Prevencio, Inc.
HeproDx™	GoPath Laboratories
IMMray® PanCan-d	Immunovia
MeMed BV®	MeMed Diagnostics
Mind.Px™	Mindera Health™
MindX Blood Test™ - Longevity	MindX Sciences™ Laboratory
MindX Blood Test™ - Memory/Alzheimer's	MindX Sciences™ Laboratory
MindX Blood Test™ - Mood	MindX Sciences™ Laboratory
MindX Blood Test™ - Pain	MindX Sciences™ Laboratory
MindX Blood Test™ - Stress	MindX Sciences™ Laboratory
MindX Blood Test™ - Suicidality	MindX Sciences™ Laboratory
mRNA CancerDetect™	Viome® Life Sciences, Inc.
NETest™	Wren Laboratories
Neurofilament Light Chain	Mayo Clinic
NPDX ASD Test Panel I, II, and III	NeuroPointDX
OWLiver®	CIMA Sciences
PancreaSeq® Genomic Classifier	University of Pittsburgh Medical Center
Thyroid GuidePx®	Protean Biodiagnostics
TissueCypher® Barrett's Esophagus Assay	Castle Biosciences, Inc.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. [Gene Expression-Based Assays for Cancers of Unknown Primary](#), Genetic Testing, Policy No. 15
2. [Gene-Based Tests for Screening, Detection, and Management of Prostate or Bladder Cancer](#), Genetic Testing, Policy No. 17
3. [Genetic and Molecular Diagnostic Testing](#), Genetic Testing, Policy No. 20
4. [Gene Expression Profiling for Melanoma](#), Genetic Testing, Policy No. 29
5. [Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer](#), Genetic Testing, Policy No. 42
6. [Genetic Testing for Diagnosis and Management of Behavioral Health Conditions](#), Genetic Testing, Policy No. 53
7. [Microarray-Based Gene Expression Profile Testing for Multiple Myeloma Risk Stratification](#), Genetic Testing, Policy No. 70
8. [Analysis of Proteomic and Metabolomic Patterns for Cancer Detection, Risk, Prognosis, or Treatment Selection](#), Laboratory, Policy No. 41
9. [Multianalyte Assays with Algorithmic Analysis for the Evaluation and Monitoring of Patients with Chronic Liver Disease](#), Laboratory, Policy No. 47

10. [Multimarker and Proteomics-based Serum Testing Related Ovarian Cancer](#), Laboratory, Policy No. 60
11. [Protein Biomarkers for Screening, Detection, and/or Management of Prostate Cancer](#), Laboratory, Policy No. 69
12. [Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance](#), Laboratory, Policy No. 72
13. [Molecular Testing in the Management of Pulmonary Nodules](#), Laboratory, Policy No. 73
14. [Multianalyte and Gene Expression Assays for Predicting Recurrence in Colon Cancer](#), Laboratory, Policy No. 76

BACKGROUND

GENE EXPRESSION TESTING

Gene expression tests are used to measure the relative levels of gene transcription for select genes. This provides information on how much a gene is expressed, or active, in a particular tissue. Because changes in gene expression may be associated with the presence or prognosis of many disorders, such tests have been developed and studied for various purposes: primarily cancer diagnosis and prognosis, but also for other disorders, including behavioral health conditions.

Gene expression testing can be performed with a variety of methods, including polymerase chain reaction (PCR), microarray, immunohistochemistry, and RNA sequencing. Results are usually expressed as a score, risk percentage, and/or a classification (e.g., “positive” or “high-risk”).

MULTIANALYTE ASSAYS

Similar to gene expression tests, multi-analyte assays measure a pattern of biomarkers that may differentiate between healthy tissue and disease. These tests measure multiple biochemical and molecular analytes, and may include metabolites, peptides, proteins, and/or genetic biomarkers. These biomarkers are often measured by mass spectrometry or immunoassays.

Multianalyte assays with algorithmic analyses (MAAAs) are tests that include the processing of the analyte measurements with an algorithm to generate a classification or score result. Often, such algorithms incorporate clinical or demographic information, such as age, sex, or cancer stage in addition to the analyte measures. MAAA algorithms may be proprietary or nonproprietary. MAAAs have been developed for many indications, including cancers, sepsis, acute kidney injury, and preeclampsia.^[1]

REGULATORY STATUS

Many of the tests listed above have not been submitted to the U.S. Food and Drug Administration (FDA) for marketing clearance but, if available, are offered as laboratory-developed tests by Clinical Laboratory Improvement Amendments (CLIA) licensed laboratories.

EVIDENCE SUMMARY

Gene expression tests and multianalyte tests have been developed for many indications, including cancer detection and prognosis, behavioral health disorders, dermatologic conditions, and neurodegenerative diseases. While studies using these tests may generate information that may help elucidate the biologic mechanisms of disease and eventually help

design treatments, the tests listed in this policy are currently in a developmental phase, with limited evidence of clinical utility for diagnosis, prognosis, or risk assessment.

SUMMARY

There is not enough research to show that the tests listed in this policy can improve health outcomes for patients. Therefore, these tests are considered investigational.

REFERENCES

1. KA Turner, Algeciras-Schimmich A. Multianalyte Assays With Algorithmic Analysis in Women's Health. [cited 8/23/2022]. 'Available from:' <https://www.aacc.org/cln/articles/2018/july/multianalyte-assays-with-algorithmic-analysis-in-womens-health>.

CODES

Codes	Number	Description
CPT	0006M	Oncology (hepatic), mRNA expression levels of 161 genes, utilizing fresh hepatocellular carcinoma tumor tissue, with alpha-fetoprotein level, algorithm reported as a risk classifier
	0007M	Oncology (gastrointestinal neuroendocrine tumors), real-time PCR expression analysis of 51 genes, utilizing whole peripheral blood, algorithm reported as a nomogram of tumor disease index
	0063U	Neurology (autism), 32 amines by LCMS/MS, using plasma, algorithm reported as metabolic signature associated with autism spectrum disorder
	0108U	Gastroenterology (Barrett's esophagus), whole slide-digital imaging, including morphometric analysis, computer-assisted quantitative immunolabeling of 9 protein biomarkers (p16, AMACR, p53, CD68, COX-2, CD45RO, HIF1a, HER-2, K20) and morphology, formalin-fixed paraffin-embedded tissue, algorithm reported as risk of progression to high-grade dysplasia or cancer
	0258U	Autoimmune (psoriasis), mRNA, next generation sequencing, gene expression profiling of 50-100 genes, skin-surface collection using adhesive patch, algorithm reported as likelihood of response to psoriasis biologics
	0263U	Neurology (autism spectrum disorder [ASD]), quantitative measurements of 16 central carbon metabolites (ie, αketoglutarate, alanine, lactate, phenylalanine, pyruvate, succinate, carnitine, citrate, fumarate, hypoxanthine, inosine, malate, S-sulfocysteine, taurine, urate, and xanthine), liquid chromatography tandem mass spectrometry (LC-MS/MS), plasma, algorithmic analysis with result reported as negative or positive (with metabolic subtypes of ASD)
	0288U	Oncology (lung), mRNA, quantitative PCR analysis of 11 genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A) and 3 reference genes (ESD, TBP, YAP1), formalin-fixed paraffin-embedded (FFPE) tumor tissue, algorithmic interpretation reported as a recurrence risk score
	0289U	Neurology (Alzheimer disease), mRNA, gene expression profiling by RNA sequencing of 24 genes, whole blood, algorithm reported as predictive risk score

Codes	Number	Description
	0290U	Pain management, mRNA, gene expression profiling by RNA sequencing of 36 genes, whole blood, algorithm reported as predictive risk score
	0291U	Psychiatry (mood disorders), mRNA, gene expression profiling by RNA sequencing of 144 genes, whole blood, algorithm reported as predictive risk score
	0292U	Psychiatry (stress disorders), mRNA, gene expression profiling by RNA sequencing of 72 genes, whole blood, algorithm reported as predictive risk score
	0293U	Psychiatry (suicidal ideation), mRNA, gene expression profiling by RNA sequencing of 54 genes, whole blood, algorithm reported as predictive risk score
	0294U	Longevity and mortality risk, mRNA, gene expression profiling by RNA sequencing of 18 genes, whole blood, algorithm reported as predictive risk score
	0296U	Oncology (oral and/or oropharyngeal cancer), gene expression profiling by RNA sequencing at least 20 molecular features (eg, human and/or microbial mRNA), saliva, algorithm reported as positive or negative for signature associated with malignancy
	0308U	Cardiology (coronary artery disease [CAD]), analysis of 3 proteins (high sensitivity [hs] troponin, adiponectin, and kidney injury molecule-1 [KIM-1]), plasma, algorithm reported as a risk score for obstructive CAD
	0309U	Cardiology (cardiovascular disease), analysis of 4 proteins (NT-proBNP, osteopontin, tissue inhibitor of metalloproteinase-1 [TIMP-1], and kidney injury molecule-1 [KIM-1]), plasma, algorithm reported as a risk score for major adverse cardiac event
	0310U	Pediatrics (vasculitis, Kawasaki disease [KD]), analysis of 3 biomarkers (NTproBNP, C-reactive protein, and T-uptake), plasma, algorithm reported as a risk score for KD
	0312U	Autoimmune diseases (eg, systemic lupus erythematosus [SLE]), analysis of 8 IgG autoantibodies and 2 cell-bound complement activation products using enzyme-linked immunosorbent immunoassay (ELISA), flow cytometry and indirect immunofluorescence, serum, or plasma and whole blood, individual components reported along with an algorithmic SLE-likelihood assessment
	0313U	Oncology (pancreas), DNA and mRNA next-generation sequencing analysis of 74 genes and analysis of CEA (CEACAM5) gene expression, pancreatic cyst fluid, algorithm reported as a categorical result (ie, negative, low probability of neoplasia or positive, high probability of neoplasia)
	0315U	Oncology (cutaneous squamous cell carcinoma), mRNA gene expression profiling by RT-PCR of 40 genes (34 content and 6 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical risk result (ie, Class 1, Class 2A, Class 2B)
	0316U	<i>Borrelia burgdorferi</i> (Lyme disease), OspA protein evaluation, urine
	0322U	Neurology (autism spectrum disorder [ASD]), quantitative measurements of 14 acyl carnitines and microbiome-derived metabolites, liquid chromatography with tandem mass spectrometry (LC-MS/MS), plasma, results reported as negative or positive for risk of metabolic subtypes associated with ASD
	0332U	Oncology (pan-tumor), genetic profiling of 8 DNA-regulatory (epigenetic) markers by quantitative polymerase chain reaction (qPCR), whole blood, reported as a high or low probability of responding to immune checkpoint–inhibitor therapy
	0342U	Oncology (pancreatic cancer), multiplex immunoassay of C5, C4, cystatin C, factor B, osteoprotegerin (OPG), gelsolin, IGFBP3, CA125 and multiplex

Codes	Number	Description
		electrochemiluminescent immunoassay (ECLIA) for CA19-9, serum, diagnostic algorithm reported qualitatively as positive, negative, or borderline
	0344U	Hepatology (nonalcoholic fatty liver disease [NAFLD]), semiquantitative evaluation of 28 lipid markers by liquid chromatography with tandem mass spectrometry (LC-MS/MS), serum, reported as at-risk for nonalcoholic steatohepatitis (NASH) or not NASH
	0351U	Infectious disease (bacterial or viral), biochemical assays, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), interferon gamma-induced protein-10 (IP10), and C-reactive protein, serum, algorithm reported as likelihood of bacterial infection
	0357U	Oncology (melanoma), artificial intelligence (AI)-enabled quantitative mass spectrometry analysis of 142 unique pairs of glycopeptide and product fragments, plasma, prognostic, and predictive algorithm reported as likely, unlikely, or uncertain benefit from immunotherapy agents
	0361U	Neurofilament light chain, digital immunoassay, plasma, quantitative
	0362U	Oncology (papillary thyroid cancer), gene-expression profiling via targeted hybrid capture–enrichment RNA sequencing of 82 content genes and 10 housekeeping genes, formalin-fixed paraffin embedded (FFPE) tissue, algorithm reported as one of three molecular subtypes
	81479	Unlisted molecular pathology procedure
	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	None	

Date of Origin: November 2021