Regence

Medical Policy Manual Laboratory, Policy No. 77

Investigational Gene Expression, Biomarker, and Multianalyte Testing

Effective: September 1, 2026

Next Review: November 2026
Last Review: July 2026

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
AdvanceAD-Tx	Castle Biosciences, Inc.
aiSLE™ DX Disease Activity Index and aiSLE™ DX Flare Risk Index	Progentec Diagnostics
Auria®	Namida Lab
Avise® Lupus	Exagen, Inc.

Clarifi™ (ASD)	Quadrant Biosciences
DecisionDx®-SCC	Castle Biosciences, Inc.
DiviTum® TKa	Biovica, Inc.
EndoSign® Barrett's Esophagus Test	Cyted Health
EpiSwitch® Checkpoint-inhibitor Response Test (CiRT)	Next Bio Research Services
ESOPREDICT® Barrett's Esophagus Risk Classifier Assay	Previse
FebriDx®	Lumos Diagnostics
FRAT® (Folate Receptor Antibody Test)	Religen, Inc.
HART CADhs®	Prevencio, Inc.
HART CVE®	Prevencio, Inc.
HART KD®	Prevencio, Inc.
HeproDx™	GoPath Laboratories
IGoCheck™	Milagen, Inc.
IMMray® PanCan-d	Immunovia
IntelliSep	Cytovale
KawasakiDx™	mProbe
KidneyIntelX.dkd™	Renalytix Inc.
Liposcale®	CIMA Sciences
LungOI	Imagene AI
MammoCheck™	Milagen, Inc.
MeMed BV®	MeMed Diagnostics
Mind.Px™	Mindera Health™
MindX™ Blood Tests: Anxiety Longevity Memory/Alzheimer's Mood Pain Stress Suicidality	MindX Sciences™ Laboratory
M-inSight®	Corgenix/Sebia
mRNA CancerDetect™	Viome® Life Sciences, Inc.
myOLARIS™-KTdx	Olaris, Inc.
NaviDKD™	Journey Biosciences
NETest™	Wren Laboratories

NPDX ASD Test Panel I, II, and III	NeuroPointDX
PancreaSeq® Genomic Classifier	University of Pittsburgh Medical Center
PancreaSure®	Immunovia
PreciseDx Breast Biopsy Test	PreciseDx
PrismRA®	Scipher Medicine®
Promarker®D	Proteomics International/Sonic Reference Laboratory
PurIST℠	Tempus AI
RiskReveal™ (previously DetermaRx™)	Razor Genomics
Salimetrics® Salivary Melatonin Profile	Salimetrics® Clinical Laboratory
SmartVascular DX	SmartHealth DX
SOMAmer®	SomaLogic
SAAmplify™-aSYN	Amprion Clinical Laboratory
Tempus p-MSI	Tempus AI
Tempus p-Prostate	Tempus AI
Thyroid GuidePx®	Protean Biodiagnostics
TissueCypher® Barrett's Esophagus Assay	Castle Biosciences, Inc.
TruD MDS Tests: Alzheimer's & MCI ASCVD Bipolar COPD Hepatocellular Carcinoma Lyme Disease Major Depressive Disorder Multiple Sclerosis NASH Osteoporosis Parkinson's Schizophrenia	TruDiagnostic™

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
15. Lyme Disease Testing, Laboratory, Policy No. 83

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.

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.

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
	0019M	Cardiovascular disease, plasma, analysis of protein biomarkers by aptamer-based microarray and algorithm reported as 4-year likelihood of coronary event in high-risk populations
	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
	0170U	Neurology (autism spectrum disorder [ASD]), RNA, next-generation sequencing, saliva, algorithmic analysis, and results reported as predictive probability of ASD diagnosis
	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
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]) with 3 clinical parameters (age, sex, history of cardiac intervention), 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)
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 electrochemiluminescent immunoassay (ECLIA) for CA19-9, serum, diagnostic algorithm reported qualitatively as positive, negative, or borderline
0351U	Infectious disease (bacterial or viral), biochemical assays, tumor necrosis factor-related apoptosis inducing ligand (TRAIL), interferon gamma-inducedprotein-10 (IP-10), and C-reactive protein, serum, or venous whole blood, algorithm reported as likelihood of bacterial infection
0362U	Oncology (papillary thyroid cancer), gene-expression profiling via targeted hybrid capture–enrichment RNA sequencing of 82 content genes and 10 housekeeping genes, fine needle aspirate or formalin-fixed paraffin embedded (FFPE) tissue, algorithm reported as one of three molecular subtypes
0377U	Cardiovascular disease, quantification of advanced serum or plasma lipoprotein profile, by nuclear magnetic resonance (NMR) spectrometry with report of a lipoprotein profile (including 23 variables)
0384U	Nephrology (chronic kidney disease), carboxymethyllysine, methylglyoxal hydroimidazolone, and carboxyethyl lysine by liquid chromatography with tandem mass spectrometry (LCMS/MS) and HbA1c and estimated glomerular filtration rate (GFR), with risk score reported for predictive progression to high-stage kidney disease
0385U	Nephrology (chronic kidney disease), apolipoprotein A4 (ApoA4), CD5 antigen-like (CD5L), and insulin-like growth factor binding protein 3 (IGFBP3) by enzyme-linked immunoassay (ELISA), plasma, algorithm combining results with HDL, estimated glomerular filtration rate (GFR) and clinical data reported as a risk score for developing diabetic kidney disease
0389U	Pediatric febrile illness (Kawasaki disease [KD]), interferon alphainducible protein 27 (IFI27) and mast cell-expressed membrane protein 1 (MCEMP1), RNA, using reverse transcription polymerase chain reaction (RT-qPCR), blood, reported as a risk score for KD
0393U	Neurology (eg, Parkinson disease, dementia with Lewy bodies), cerebrospinal fluid (CSF), detection of misfolded α-synuclein protein by seed amplification assay, qualitative
0398U	Gastroenterology (Barrett esophagus), P16, RUNX3, HPP1, and FBN1 DNA methylation analysis using PCR, formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as risk score for progression to high-grade dysplasia or cancer
0399U	Neurology (cerebral folate deficiency), serum, detection of anti-human folate receptor IgG binding antibody and blocking autoantibodies by enzyme-linked immunoassay (ELISA), qualitative, and blocking autoantibodies, using a functional blocking assay for IgG or IgM, quantitative, reported as positive or not detected
0404U	Oncology (breast), semiquantitative measurement of thymidine kinase activity by immunoassay, serum, results reported as risk of disease progression
0407U	Nephrology (diabetic chronic kidney disease [CKD]), multiplex electrochemiluminescent immunoassay (ECLIA) of soluble tumor necrosis factor receptor 1 (sTNFR1), soluble tumor necrosis receptor 2 (sTNFR2), and kidney injury molecule 1 (KIM-1) combined with clinical data, plasma, algorithm reported as risk for progressive decline in kidney function
0414U	Oncology (lung), augmentative algorithmic analysis of digitized whole slide imaging for 8 genes (ALK, BRAF, EGFR, ERBB2, MET, NTRK1-3, RET, ROS1), and KRAS G12C and PD-L1, if performed, formalin-fixed paraffin embedded (FFPE) tissue, reported as positive or negative for each biomarker

0415U	Cardiovascular disease (acute coronary syndrome [ACS]), IL-16, FAS, FASLig and, HGF, CTACK, EOTAXIN, and MCP-3 by immunoassay combined with age, sex, family history, and personal history of diabetes, blood, algorithm reported as a 5-year (deleted risk) score for ACS
0418U	Oncology (breast), augmentative algorithmic analysis of digitized whole slide imaging of 8 histologic and immunohistochemical features, reported as a recurrence score
0437U	Psychiatry (anxiety disorders), mRNA, gene expression profiling by RNA sequencing of 15 biomarkers, whole blood, algorithm reported as predictive risk score
0441U	Infectious disease (bacterial, fungal, or viral infection), semiquantitative biomechanical assessment (via deformability B5 cytometry), whole blood, with algorithmic analysis and result reported as an index
0442U	Infectious disease (respiratory infection), Myxovirus resistance protein A (MxA) and C-reactive protein (CRP), fingerstick whole blood specimen, each biomarker reported as present or absent
0446U	Autoimmune diseases (systemic lupus erythematosus [SLE]), analysis of 10 cytokine soluble mediator biomarkers by immunoassay, plasma, individual components reported with an algorithmic risk score for current disease activity
0447U	Autoimmune diseases (systemic lupus erythematosus [SLE]), analysis of 11 cytokine soluble mediator biomarkers by immunoassay, plasma, individual components reported with an algorithmic prognostic risk score for developing a clinical flare
~~0450U~~	~~Oncology (multiple myeloma), liquid chromatography with tandem mass spectrometry (LCMS/MS), monoclonal paraprotein sequencing analysis, serum, results reported as baseline presence or absence of detectable clonotypic peptides~~ (Deleted 10/01/2025)
~~0451U~~	~~Oncology (multiple myeloma), LCMS/MS, peptide ion quantification, serum, results compared with baseline to determine monoclonal paraprotein abundance~~ (Deleted 10/01/2025)
0458U	Oncology (breast cancer), S100A8 and S100A9, by enzyme linked immunosorbent assay (ELISA), tear fluid with age, algorithm reported as a risk score
0462U	Melatonin levels test, sleep study, 7 or 9 sample melatonin profile (cortisol optional), enzyme-linked immunosorbent assay (ELISA), saliva, screening/preliminary
0506U	Gastroenterology (Barrett's esophagus), esophageal cells, DNA methylation analysis by next-generation sequencing of at least 89 differentially methylated genomic regions, algorithm reported as likelihood for Barrett's esophagus
0510U	Oncology (pancreatic cancer), augmentative algorithmic analysis of 16 genes from previously sequenced RNA wholetranscriptome data, reported as probability of predicted molecular subtype
0512U	Oncology (prostate), augmentative algorithmic analysis of digitized whole-slide imaging of histologic features for microsatellite instability (MSI) status, formalin-fixed paraffinembedded (FFPE) tissue, reported as increased or decreased probability of MSI-high (MSI-H)
0513U	Oncology (prostate), augmentative algorithmic analysis of digitized whole-slide imaging of histologic features for microsatellite instability (MSI) and homologous recombination deficiency (HRD) status, formalinfixed paraffin-embedded (FFPE) tissue, reported as increased or decreased probability of each biomarker
0542U	Nephrology (renal transplant), urine, nuclear magnetic resonance (NMR) spectroscopy measurement of 84 urinary metabolites, combined with patient

		data, quantification of BK virus (human polyomavirus 1) using real-time PCR and serum creatinine, algorithm reported as a probability score for allograft injury status
	0558U	Oncology (colorectal), quantitative enzyme-linked immunosorbent assay (ELISA) for secreted colorectal cancer protein marker (BF7 antigen), using serum, result reported as indicative of response/no response to therapy or disease progression/regression
	0559U	Oncology (breast), quantitative enzyme-linked immunosorbent assay (ELISA) for secreted breast cancer protein marker (BF9 antigen), serum, result reported as indicative of response/no response to therapy or disease progression/regression
	0579U	Nephrology (diabetic chronic kidney disease), enzyme linked immunosorbent assay (ELISA) of apolipoprotein A4 (APOA4), CD5 antigen-like (CD5L) combined with estimated glomerular filtration rate (GFR), age, plasma, algorithm reported as a risk score for kidney function decline
	0599U	Oncology (pancreatic cancer), multiplex immunoassay of ICAM1, TIMP1, CTSD, THBS1, and CA 19-9, serum, diagnostic algorithm reported as positive or negative
	0616U	Neurology (dementia), DNA methylation analysis of more than 30,000 sites, whole blood, algorithm reported as positive or negative risk
	0617U	Cardiovascular (atherosclerotic cardiovascular disease), [ASCVD]), DNA methylation analysis of more than 20,000 sites, whole blood, algorithm reported as positive or negative risk
	0618U	Psychiatry (bipolar disorder), DNA methylation analysis of more than 10,000 sites, whole blood, algorithm reported as positive or negative risk
	0619U	Pulmonary (chronic obstructive pulmonary disease [COPD]), DNA methylation analysis of more than 18,000 sites, whole blood, algorithm reported as positive or negative risk
	0620U	Oncology (hepatocellular carcinoma), DNA methylation analysis of more than 5,000 sites, whole blood, algorithm reported as positive or negative risk
	0621U	Infectious disease (Lyme borreliosis), DNA methylation analysis of more than 10,000 sites, whole blood, algorithm reported as positive or negative risk
	0622U	Psychiatry (major depressive disorder), DNA methylation analysis of more than 20,000 sites, whole blood, algorithm reported as positive or negative risk
	0623U	Autoimmune (multiple sclerosis), DNA methylation analysis of more than 5,000 sites, whole blood, algorithm reported as positive or negative risk
	0624U	Hepatology (nonalcoholic steatohepatitis [NASH]), DNA methylation analysis of 5,000 sites, whole blood, algorithm reported as positive or negative risk
	0625U	Endocrinology (osteoporosis), DNA methylation analysis of more than 5,000 sites, whole blood, algorithm reported as positive or negative risk
	0626U	Neurology (Parkinson disease), DNA methylation analysis of more than 20,000 sites, whole blood, algorithm reported as positive or negative risk
	0627U	Psychiatry (schizophrenia), DNA methylation analysis of more than 15,000 sites, whole blood, algorithm reported as positive or negative risk
	0635U	Autoimmune (atopic dermatitis), mRNA, nextgeneration sequencing (NGS), gene expression profiling of 487 genes, noninvasive skinsurface scraping, algorithm reported as likelihood of response to therapy
	81479	Unlisted molecular pathology procedure
	81599	Unlisted multianalyte assay with algorithmic analysis
HCPCS	None	

Date of Origin: *November 2021*