Molecular Biomarker Testing for Noncancer Indications

Humana

Medicaid Medical Coverage Policy

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Description

Molecular biomarker testing may be performed to analyze gene, chromosome or protein alterations in individuals with inherited disorders or acquired diseases. They may be used as a screening tool, to assist in confirming a diagnosis in those who exhibit disease signs and symptoms or to aid with treatment decisions. Examples of conditions that may be evaluated by molecular biomarker testing include, but are not limited to:

- Cardiovascular disease – Growth stimulation expressed gene 2 (ST2) is a biomarker being investigated for its contribution to several medical conditions, including cardiovascular diseases. ST2 is a member of the interleukin-1 (IL-1) receptor family and is secreted by cardiac muscle cells under conditions of mechanical stress. It is currently being studied as a determinant in death rates for individuals with heart failure and predicting a negative cardiovascular event (eg, Cardio IQ ST2]) **(Refer to Coverage Limitations section)**

- Chronic kidney disease – *APOL1* gene testing has been proposed to confirm the presence of apolipoprotein L1 gene risk variants to help determine a potential donor's risk of developing chronic kidney disease risk following kidney donation (eg, Apolipoprotein L1 [APOL1] Renal Risk Variant Genotyping Test) **(Refer to Coverage Limitations section)**

- GM2 gangliosidoses are a group of three related genetic disorders (Tay–Sachs disease, AB variant and Sandhoff disease) that result from a deficiency of the enzyme beta-hexosaminidase. When beta hexosaminidase is no longer functioning properly, the lipids accumulate in the nervous tissue of the brain and cause central nervous system dysfunction including neurodevelopment alterations, neuroinflammation and neuronal apoptosis

- Methylene tetrahydrofolate reductase (MTHFR) enzyme is encoded by the *MTHFR* gene. This enzyme plays a role in processing amino acids (the building blocks of proteins) which is important for a chemical reaction involving forms of the vitamin folate and is required for the multistep process that converts the amino acid homocysteine to another amino acid, methionine. The body uses methionine to make proteins and other important compounds. Variations in the *MTHFR* gene have been studied as risk factors for numerous conditions, including behavioral disorders, cardiovascular disease, thrombophilia, stroke, hypertension, pharmacological management or risk testing and pregnancy-related complications; however, its role remains unclear. **(Refer to Coverage Limitations section)**

- Noninvasive prenatal screening (NIPS) using multiple markers (also referred to as triple screen or quad screen) may be performed during the second trimester and includes testing maternal serum levels of alpha-fetoprotein (AFP), ß-human chorionic gonadotropin (hCG), inhibin-A (DIA), pregnancy-associated plasma protein A (PAPP-A) and/or unconjugated estriol (uE3) to combine screening for chromosome abnormalities and neural tube defects. This panel is usually done around 15 to 20 gestational weeks when abnormal levels could indicate that further evaluation may be needed with invasive testing (eg, amniocentesis)

Gene expression profiling (GEP) is a laboratory test that measures the activity or expression, of ribonucleic acid (RNA) of hundreds to thousands of genes at one time to give an overall picture of gene activity. GEP tests are typically performed on tumor tissue but may also be performed on other specimens such as blood. These tests often use microarray technology though other methodologies, such as next generation sequencing (NGS), whole transcriptome sequencing and reverse transcription polymerase chain reaction (RT-PCR), are also used. GEP has been proposed for indications beyond the cancer space including longevity prediction, pain management, psychiatric conditions, psoriasis and pulmonary diseases. **(Refer to Coverage Limitations section)** Noncancer indications for GEP include, but may not be limited to:

- Coronary artery disease – mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood

- Endometrial implantation prediction – suggested for individuals with recurrent implantation failure to synchronize embryo transfer with the optimal window of implantation (eg, Igenomix Endometrial Receptivity Analysis)

- Longevity – proposed as a method to predict duration of an individual's life (eg, MindX Longevity)

- Pain management – suggested to determine appropriate medication for pain relief tailored to the individual (eg, MindX Pain)

- Psychiatric conditions – proposed to assess risk of mental health disorders such as mood disorders (depression/bipolar), post-traumatic stress disorder (PTSD) and risk of suicide. Also purported to establish a diagnosis and assist with treatment decisions personalized to the individual (eg, MindX Memory/Alzheimers Blood Test, MindX Mood, MindX Stress, MindX Suicidality and MindXOne Blood Test – Anxiety)

- Pulmonary disease – identifies usual interstitial pneumonia (UIP) in transbronchial biopsies to purportedly increase the diagnostic confidence for idiopathic pulmonary fibrosis in patients with interstitial lung disease (ILD) (eg, Envisia Genomic Classifier)

Multianalyte assays with algorithmic analyses (MAAAs) are laboratory measurements that use a mathematic formula to analyze multiple markers that may be associated with a particular disease state and are designed to evaluate disease activity or an individual's risk for disease. The laboratory performs an algorithmic analysis using the results of the assays and sometimes other individual information, such as gender and age and converts the information into a numeric score, which is conveyed on a laboratory report. Generally, MAAAs are exclusive (and/or proprietary) to a single laboratory which owns the algorithm. **(Refer to Coverage Limitations section)** MAAAs for noncancer indications include, but may not be limited to:

- Autism spectrum disorder – a saliva-based test that measures 14 specific microRNAs (miRNAs) in the saliva to purportedly diagnose autism spectrum disorder (ASD) in children 18 months through 6 years of age (eg, Clarifi ASD)

- Barrett's esophagus – test that analyze P16, RUNX3, HPP1 and FBN1 methylation to purportedly determine the risk of progression to high-grade dysplasia or esophageal cancer in an individual diagnosed with precancerous Barrett's esophagus (eg, Esopredict)

- Cardiac artery disease:

    - Blood, saliva or buccal swab test using targeted, variant genotyping of 9 genes (12 variants) and an algorithm that is reported as a genetic risk score for a coronary event as an aid to predicting risk of coronary heart disease (CHD) for individuals with no prior history of cardiovascular events (eg, CARDIO inCode-Score)

    - Buccal swab of DNA for targeted variant genotyping, along with lifestyle and clinical data used to achieve an algorithm, reported as polygenic risk to acquired heart disease (eg, CardioRisk+)

    - Whole blood analysis of 5 single-nucleotide polymorphisms (SNPs) and 3 DNA methylation markers, qPCR and digital PCR, along with an algorithm reported as a 4-tiered risk score for a 3-year risk of symptomatic CHD (eg, Epi+Gen CHD)

    - Whole blood analysis of 10 single-nucleotide polymorphisms (SNPs) and 6 DNA methylation markers, qPCR and digital PCR, along with an algorithm reported as detected or not detected for CHD (eg, PrecisionCHD)

- Diabetes – a risk assessment multianalyte serum assay purported to determine an individual's risk of developing type II diabetes within 5 years. The test measures 7 circulating biomarkers: glucose, insulin, glycosylated hemoglobin A1c (HbA1c), C-reactive protein (CRP), ferritin, interleukin 2 receptor alpha (IL-2Rα) and adiponectin. These measurements are applied to an algorithm, combined with an individual's age and sex, to determine the individual's risk of developing diabetes. (eg, PreDx Diabetes Risk Score)

- Inflammatory bowel disease – a blood-based, prognostic biomarker test that uses mRNA gene expression profiling of 17 genes which is reported as a continuous risk score and classification system for IBD aggressiveness (eg, PredictSURE IBD Test)

- Kawasaki disease – a serum assay that includes interferon alpha-inducible protein 27 (IFI27) and mast cell-expressed membrane protein 1 (MCEMP1) along with RNA and reverse transcription polymerase chain reaction (RT-qPCR) to report a risk score for the pediatric febrile illness (eg, KawasakiDx)

- Scoliosis – a prognostic test that analyzes genetic markers purportedly associated with spinal curve progression and assigns a numerical value regarding the likelihood of curve progression based on the test results and other clinical information (eg, ScoliScore)

Coverage Determination

Alzheimer Disease
Humana members may be eligible under the Plan for **CSF testing for Aβ** (eg, Lumipulse G [0358U]) **and Tau proteins** when the individual is diagnosed with AD and is being considered for an FDA approved Aβ monoclonal antibody drug (eg, lecanemab-irmb [Leqembi], donanemab-azbt [Kisunla]).[44]

GM2 Gangliosidoses (Beta-Hexosaminidase Enzyme)
Humana members may be eligible under the Plan for **beta-hexosaminidase enzyme testing for GM2 gangliosidoses** (83080) when the following criteria are met[24,25]:

- Pre- and post-test genetic counseling; **AND**
    - Carrier screening for couples (or individuals) who are suspected carriers and are planning pregnancy or seeking prenatal care and no prior genetic testing results are available for interpretation; **OR**
    - Individual to be tested has clinical characteristics of one of the following:
        - Tay-sachs disease (eg, infantile acute onset of axial hypotonia, cherry-red spot, exaggerated startle response, regression in developmental milestones, seizures); **OR**
        - Stanhoff disease (eg, juvenile subacute onset of ataxia, intellectual disability, motor regression, myoclonus, progressive clumsiness, psychotic episodes); **OR**

- A/B variant (eg, adult, chronic cerebellar ataxia, dysarthric speech, dysphagia, manic depression, muscle atrophy/weakness, psychotic episodes); **OR**

- Preimplantation or prenatal genetic diagnosis, for family in which GM2 gangliosidoses has been identified

Noninvasive Prenatal Screening
Humana members may be eligible under the Plan for **NIPS for chromosomal abnormalities** using multiple marker screening (AFP, DIA, free or total hCG, PAPP-A and/or uE3 levels [eg, 81509, 81510, 81511, 81512]). See coverage limitations* section.[2,3,35,37,41]

Coverage Limitations

***Individual serum levels (eg, AFP, DIA, free or total hCG, PAPP-A and/or uE3 levels) reported with multianalyte assays with algorithmic analysis (MAAA) for fetal congenital anomalies (eg, 81509, 81510, 81511, 81512) are not separately reimbursable.**

Humana members may **NOT** be eligible under the Plan for **GEP for any noncancer indication** including, but may not be limited to:

- Alzheimer disease prediction (MindX Blood Test Memory/Alzheimers [0289U])
- Coronary artery disease prediction (81493)
- Endometrial implantation prediction (Igenomix Endometrial Receptivity Analysis [0253U])
- Longevity prediction (MindX Blood Test Longevity [0294U])
- Pain management (MindX Blood Test Pain [0290U])
- Psychiatric conditions including:
    - MindX Blood Test Mood (0291U)
    - MindX Blood Test Stress (0292U)
    - MindX Blood Test Suicidality (0293U)
- Pulmonary disease (idiopathic pulmonary fibrosis, interstitial lung diseases) (Envisia Genomic Classifier [81554])

A review of the current medical literature shows that there is **no evidence** to determine these services are standard medical treatments. There is an absence of current, widely-used treatment guidelines or

acceptable clinical literature examining benefit and long-term clinical outcomes establishing the value of these services in clinical management.

Humana members may **NOT** be eligible under the Plan for the following **MAAAs for predicting disease risk or progression** including, but may not be limited to the following:

- Autism spectrum disorder (Clarifi ASD [0170U])
- Barrett's esophagus (Esopredict [0398U])
- Cardiac artery disease:
  - CARDIO inCode-Score (0401U)
  - CardioRisk+ (0466U)
  - Epi+Gen CHD (0439U)
  - PrecisionCHD (0440U)
- Diabetes (PreDx Diabetes Risk Score [81506])
- Inflammatory bowel disease (PredictSURE IBD Test [0203U])
- Kawasaki disease (KawasakiDx [0389U])
- Rheumatoid arthritis (81490)
- Scoliosis (eg, 0004M)

A review of the current medical literature shows that there is **no evidence** to determine these services are standard medical treatments. There is an absence of current, widely-used treatment guidelines or acceptable clinical literature examining benefit and long-term clinical outcomes establishing the value of these services in clinical management.

Humana members may **NOT** be eligible under the Plan for **molecular biomarker testing** for any indications other than those listed above including, but may not be limited to:

- *APOL1* gene testing (eg, Apolipoprotein L1 [APOL1] Renal Risk Variant Genotyping (0355U)
- *MTHFR* gene testing (81291)
- ST2 (growth stimulation expressed gene 2) (eg, Cardio IQ ST2 [83006])

A review of the current medical literature shows that there is **no evidence** to determine these services are standard medical treatments. There is an absence of current, widely-used treatment guidelines or

acceptable clinical literature examining benefit and long-term clinical outcomes establishing the value of these services in clinical management.

Coding Information

Any codes listed on this policy are for informational purposes only. Do not rely on the accuracy and inclusion of specific codes. Inclusion of a code does not guarantee coverage and/or reimbursement for a service or procedure.

CPT® Code(s)	Description	Comments
81291	MTHFR (5,10-methylenetetrahydrofolate reductase) (eg, hereditary hypercoagulability) gene analysis, common variants (eg, 677T, 1298C)	
81479	Unlisted molecular pathology procedure	
81490	Autoimmune (rheumatoid arthritis), analysis of 12 biomarkers using immunoassays, utilizing serum, prognostic algorithm reported as a disease activity score	
81493	Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score	
81506	Endocrinology (type 2 diabetes), biochemical assays of seven analytes (glucose, HbA1c, insulin, hs-CRP, adiponectin, ferritin, interleukin 2-receptor alpha), utilizing serum or plasma, algorithm reporting a risk score	
81509	Fetal congenital abnormalities, biochemical assays of three proteins (PAPP-A, hCG [any form], DIA), utilizing maternal serum, algorithm reported as a risk score	
81510	Fetal congenital abnormalities, biochemical assays of three analytes (AFP, uE3, hCG [any form]), utilizing maternal serum, algorithm reported as a risk score	
81511	Fetal congenital abnormalities, biochemical assays of four analytes (AFP, uE3, hCG [any form], DIA) utilizing maternal serum, algorithm reported as a risk score (may include additional results from previous biochemical testing)	
81512	Fetal congenital abnormalities, biochemical assays of five analytes (AFP, uE3, total hCG, hyperglycosylated hCG, DIA) utilizing maternal serum, algorithm reported as a risk score	
81554	Pulmonary disease (idiopathic pulmonary fibrosis [IPF]), mRNA, gene expression analysis of 190 genes, utilizing transbronchial biopsies, diagnostic algorithm reported as categorical result (eg,	

	positive or negative for high probability of usual interstitial pneumonia [UIP])	
81599	Unlisted multianalyte assay with algorithmic analysis	
83006	Growth stimulation expressed gene 2 (ST2, Interleukin 1 receptor like-1)	
83080	b-Hexosaminidase, each assay	
84999	Unlisted chemistry procedure	
0004M	Scoliosis, DNA analysis of 53 single nucleotide polymorphisms (SNPs), using saliva, prognostic algorithm reported as a risk score	
0170U	Neurology (autism spectrum disorder [ASD]), RNA, next-generation sequencing, saliva, algorithmic analysis, and results reported as predictive probability of ASD diagnosis	
0203U	Autoimmune (inflammatory bowel disease), mRNA, gene expression profiling by quantitative RT-PCR, 17 genes (15 target and 2 reference genes), whole blood, reported as a continuous risk score and classification of inflammatory bowel disease aggressiveness	
0253U	Reproductive medicine (endometrial receptivity analysis), RNA gene expression profile, 238 genes by next-generation sequencing, endometrial tissue, predictive algorithm reported as endometrial window of implantation (eg, pre-receptive, receptive, post-receptive)	
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	
0355U	APOL1 (apolipoprotein L1) (eg, chronic kidney disease), risk variants (G1, G2)	
0358U	Neurology (mild cognitive impairment), analysis of B-amyloid 1-42 and 1-40, chemiluminescence enzyme immunoassay, cerebral spinal fluid, reported as positive, likely positive, or negative	
0389U	Pediatric febrile illness (Kawasaki disease [KD]), interferon alpha-inducible protein 27 (IFI27) and mast cell-expressed membrane protein 1 (MCEMP1), RNA, using quantitative reverse transcription polymerase chain reaction (RT-qPCR), blood, reported as a risk score for KD	
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	
0401U	Cardiology (coronary heart disease [CHD]), 9 genes (12 variants), targeted variant genotyping, blood, saliva, or buccal swab, algorithm reported as a genetic risk score for a coronary event	
0439U	Cardiology (coronary heart disease [CHD]), DNA, analysis of 5 single-nucleotide polymorphisms (SNPs) (rs11716050 [LOC105376934], rs6560711 [WDR37], rs3735222 [SCIN/LOC107986769], rs6820447 [intergenic], and rs9638144 [ESYT2]) and 3 DNA methylation markers (cg00300879 [transcription start site {TSS200} of CNKSR1], cg09552548 [intergenic], and cg14789911 [body of SPATC1L]), qPCR and digital PCR, whole blood, algorithm reported as a 4-tiered risk score for a 3-year risk of symptomatic CHD	
0440U	Cardiology (coronary heart disease [CHD]), DNA, analysis of 10 single-nucleotide polymorphisms (SNPs) (rs710987 [LINC010019], rs1333048 [CDKN2B-AS1], rs12129789 [KCND3], rs942317 [KTN1-AS1], rs1441433 [PPP3CA], rs2869675 [PREX1], rs4639796 [ZBTB41], rs4376434 [LINC00972], rs12714414 [TMEM18], and rs7585056 [TMEM18]) and 6 DNA methylation markers (cg03725309 [SARS1], cg12586707 [CXCL1], cg04988978 [MPO], cg17901584 [DHCR24-DT], cg21161138 [AHRR], and cg12655112 [EHD4]), qPCR and digital PCR, whole blood, algorithm reported as detected or not detected for CHD	
0466U	Cardiology (coronary artery disease [CAD]), DNA, genomewide association studies (564856 single-nucleotide polymorphisms [SNPs], targeted variant genotyping), patient lifestyle and	

	clinical data, buccal swab, algorithm reported as polygenic risk to acquired heart disease	
CPT® Category III Code(s)	**Description**	**Comments**
No code(s) identified		
HCPCS Code(s)	**Description**	**Comments**
No code(s) identified		

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Appendix

Appendix A
Pre- and Post-Test Genetic Counseling Criteria

Pre- and post-test genetic counseling performed by any of the following qualified medical professionals
Genetic counselor who is board-certified or board-eligible by the American Board of Medical Genetics and Genomics (ABMGG) or American Board of Genetic Counseling, Inc (ABGC) and is not employed by a commercial genetic testing laboratory; **OR**

Genetic clinical nurse (GCN) or advanced practice nurse in genetics (APNG) who is credentialed by the Genetic Nursing Credentialing Commission (GNCC) or the American of Nurses Credentialing Center (ANCC) and is not employed by a commercial genetic testing laboratory; **OR**
Medical geneticist who is board-certified or board-eligible by ABMGG; **OR**
Treating physician who has evaluated the individual to be tested and has completed a family history of three generations

Appendix B
Family Relationships[8]

Degree of Relationship	Relative of the Individual to be Tested
First-degree	Parents, siblings, children
Second-degree	Grandparents, grandchildren, uncles, aunts, nephews, nieces, half-siblings
Third-degree	Great-grandparents, great-grandchildren, great uncles, great aunts, first cousins
Fourth-degree	Great-great-grandparents, great-great-grandchildren, first cousins once-removed (children of the individual's first cousins)

Change Summary

05/06/2025 New Policy.