FEP Medical Policy Manual

FEP 2.04.159 Laboratory Testing Investigational Services

Annual Effective Policy Date: April 1, 2025

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Related Policies:

2.01.68 - Laboratory Tests Post Transplant and for Heart Failure
2.04.07 - Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance
2.04.10 - Identification of Microorganisms Using Nucleic Acid Probes
2.04.119 - Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis
2.04.120 - Gene Expression Profiling for Uveal Melanoma
2.04.123 - Serum Biomarker Panel Testing for Systemic Lupus Erythematosus and Other Connective Tissue Diseases
2.04.13 - Genetic Testing for Alzheimer Disease
2.04.142 - Molecular Testing in the Management of Pulmonary Nodules
2.04.146 - Gene Expression Profiling for Cutaneous Melanoma
2.04.150 - Serologic Genetic and Molecular Screening for Colorectal Cancer
2.04.152 - Maternal Serum Biomarkers for Prediction of Adverse Obstetric Outcomes
2.04.26 - Fecal Analysis in the Diagnosis of Intestinal Dysbiosis
2.04.33 - Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
2.04.36 - Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer
2.04.52 - Molecular Testing for the Management of Pancreatic Cysts and Solid Pancreaticobiliary Lesions
2.04.54 - Gene Expression-Based Assays for Cancers of Unknown Primary
2.04.61 - Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer
2.04.62 - Multimarker Serum Testing Related to Ovarian Cancer
2.04.63 - Use of Common Genetic Variants (Single Nucleotide Variants) to Predict Risk of Nonfamilial Breast Cancer
2.04.65 - Biomarker Testing in Risk Assessment and Management of Cardiovascular Disease
2.04.66 - Serum Biomarker Human Epididymis Protein 4
2.04.68 - Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer
2.04.73 - Intracellular Micronutrient Analysis
2.04.93 - Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
2.04.97 - Microarray-Based Gene Expression Profile Testing for Multiple Myeloma Risk Stratification

Laboratory Testing Investigational Services

Description

There are numerous commercially available genetic and molecular diagnostic, prognostic, and therapeutic tests for individuals with certain diseases or asymptomatic individuals with future risk. This review relates to genetic and molecular diagnostic tests not addressed in a separate review. If a separate evidence review exists, then conclusions reached there supersede conclusions here. The main criterion for inclusion in this review is the limited evidence on the clinical utility for the test. As these tests do not have clinical utility, the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

OBJECTIVE

The objective of this review is to provide a list of diagnostic, prognostic, therapeutic, or future risk assessment genetic or molecular diagnostic tests with insufficient or non-evaluable clinical utility that are otherwise not addressed in a separate evidence review.

POLICY STATEMENT

All tests listed in this policy are considered **investigational** as there is insufficient evidence to determine that the technology results in an improvement in the net health outcome (see Policy Guidelines).

POLICY GUIDELINES

Genetic testing is considered **investigational** when BCBSA criteria are not met, including when there is insufficient evidence to determine that the technology results in an improvement in the net health outcome. The following tests are considered investigational:

Test Name	Laboratory	PLA code
Polygenic Risk Score	Many	N/A
MicroGenDx	MicroGen Diagnostics	0112U
Apolipoprotein L1 (*APOL1*) Renal Risk Variant Genotyping	Quest Diagnostics	0355U
Thyroid GuidePx	Protean Biodiagnostics	0362U
Oncuria Detect	DiaCarta Clinical Lab	0365U
Oncuria Monitor	DiaCarta Clinical Lab	0366U
Oncuria Predict	DiaCarta Clinical Lab	0367U
ColoScape™ Colorectal Cancer Detection Test	DiaCarta Clinical Lab	0368U
Qlear UTI	LifeScan Labs of Illinois, Thermo Fisher Scientific	0371U
Qlear UTI - Reflex ABR	LifeScan Labs of Illinois, Thermo Fisher Scientific	0372U
Respiratory Pathogen with ABR (RPX)	Lab Genomics LLC, Thermo Fisher Scientific	0373U
Urogenital Pathogen with Rx Panel (UPX)	Lab Genomics LLC, Thermo Fisher Scientific	0374U
ArteraAI Prostate Test[a]	Artera Inc.	0376U

Liposcale Advanced Lipoprotein Test	CIMA Sciences LLC	0377U
PersonalisedRX	Lab Genomics LLC, Agena Bioscience, Inc.	0380U
NaviDKD Predictive Diagnostic Screening for Kidney Health	Journey Biosciences, Inc.	0384U
PromarkerD Diabetic Kidney Disease Risk Assessment	Sonic Reference Laboratory, Proteomics International	0385U
Esopredict™ (formerly Envisage)	Previse (formerly Capsulomics, Inc.)	0386U
KawasakiDx™ (formerly PEPredictDx)	mProbe, Inc. (formerly OncoOmicsDx Laboratory)	0390U
BTG Early Detection of Pancreatic Cancer	Breakthrough Genomics, Inc.	0405U
CyPath Lung	Precision Pathology Services	0406U
Avantect Pancreatic Cancer Test	ClearNote Health	0410U
SmartVascular Dx	SmartHealth DX	0415U
Prometheus Celiac PLUS	Prometheus Laboratories	No specific code
Prometheus Crohn's Prognostic	Prometheus Laboratories	No specific code
DNA Methylation Pathway Profile	Mosaic Diagnostics (formerly Great Plains Laboratory)	No specific code
Prometheus IBD sgi Diagnostic	Prometheus Laboratories	No specific code
know error	Strand Diagnostics	No specific code

[a] Plans with state mandates for biomarker testing should be aware that the ArteraAI Prostate Cancer test has received a class 2A recommendation from the National Comprehensive Cancer Network (NCCN) despite a lack of prospective studies addressing clinical utility. See Supplemental Information section for additional information.

Please refer to the list of related evidence reviews for an assessment of other molecular and genetic tests not listed in this policy.

Genetics Nomenclature Update

The Human Genome Variation Society nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical evidence review updates starting in 2017 (see Table PG1). The Society's nomenclature is recommended by the Human Variome Project, the Human Genome Organization, and by the Human Genome Variation Society itself.

The American College of Medical Genetics and Genomics and the Association for Molecular Pathology standards and guidelines for interpretation of sequence variants represent expert opinion from both organizations, in addition to the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG2 shows the recommended standard terminology to describe variants identified that cause Mendelian disorders.

Table PG1. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG2. American College of Medical Genetics and Genomics and the Association for Molecular Pathology Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

Genetic Counseling

Experts recommend formal genetic counseling for patients who are at-risk for inherited disorders and who wish to undergo genetic testing. Interpreting the results of genetic tests and understanding risk factors can be difficult for some patients; genetic counseling helps individuals understand the impact of genetic testing, including the possible effects the test results could have on the individual or their family members. It should be noted that genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing; further, genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

Screening (other than the preventive services listed in the brochure) is not covered. Please see Section 6 General exclusions.

Benefits are available for specialized diagnostic genetic testing when it is medically necessary to diagnose and/or manage a patient's existing medical condition. Benefits are not provided for genetic panels when some or all of the tests included in the panel are not covered, are experimental or investigational, or are not medically necessary.

FDA REGULATORY STATUS

Some Plans may have contract or benefit exclusions for genetic testing. Some Plans may have state mandates for biomarker testing.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of this test.

RATIONALE

Summary of Evidence

For individuals with various indications for diagnostic, prognostic, therapeutic, or future risk assessment testing who receive the genetic and molecular tests addressed in this review, the evidence on clinical utility is insufficient or non-evaluable. For each test addressed, a brief description is provided for informational purposes. No formal evidence review was conducted. To sufficiently evaluate clinical utility, features of well-defined test, intended use, and clinical management pathway characteristics are summarized. If it is determined that enough evidence has accumulated to reevaluate its potential clinical utility, the test will be removed from this review and addressed separately. The lack of demonstrated clinical utility of these tests is based on the following factors: (1) there is no or extremely limited published data addressing the test; and/or (2) it is unclear where in the clinical pathway the test fits (replacement, triage, add-on); and/or (3) it is unclear how the test leads to changes in management that would improve health outcomes and/or avoiding existing burdensome and invasive testing; and/or (4) thresholds for decision making have not been established; (5) and/or the outcome from the test result does not result in a clinically meaningful improvement relative to the outcomes(s) obtained without the test.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Gastroenterology

In 2023, the American College of Gastroenterology published a clinical practice update for the diagnosis and management of celiac disease.[27,] A recommendation for genetic testing using a multigene panel test (eg, Celiac PLUS) was not included.

In 2018, the American College of Gastroenterology practice guidelines on Crohn disease state that genetic and routine serologic testing is not indicated to establish the diagnosis of Crohn's disease.[28,]

American Urological Association et al

In 2019, the American Urological Association (AUA) published joint guidelines with the Canadian Urological Association (CUA) and the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) on the management of recurrent uncomplicated urinary tract infections in women.[29,] Regarding the use of polymerase chain reaction (PCR) and next-generation sequencing (NGS) techniques for the identification of bacterial species, the guideline states that "more evidence is needed before these technologies become incorporated into the guideline, as there is concern that adoption of this technology in the evaluation of lower urinary tract symptoms may lead to over treatment with antibiotics."

In 2016, the AUA published joint guidelines with the Society of Urologic Oncology on the diagnosis and treatment of non-muscle invasive bladder cancer.[30,] For use of urinary biomarkers after diagnosis, the guidelines state: "a clinician should not use urinary biomarkers in place of cystoscopic evaluation" (Strong Recommendation; Evidence Strength: Grade B); that "in a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance (Expert Opinion); and that "in a patient with NMIBC, a clinician may use biomarkers to assess response to intravesical BCG (UroVysion FISH) and adjudicate equivocal cytology (UroVysion FISH and ImmunoCyt) (Expert Opinion)."

National Comprehensive Cancer Network

National Comprehensive Cancer Network clinical practice guidelines on bladder cancer (v.4.2024) state the following regarding urine molecular tests for urothelial tumor markers:[31,] "Many of these tests have a better sensitivity for detecting bladder cancer than urinary cytology, but specificity is lower. Considering this, evaluation of urinary urothelial tumor markers may be considered during surveillance of high-risk [non-muscle invasive bladder cancer (NMIBC)]. However, it remains unclear whether these tests offer additional useful information for detection and management of non-muscle invasive bladder tumors. Therefore, the panel considers this to be a category 2B recommendation."

NCCN clinical practice guidelines on colon cancer (v.5.2024) state that "it has not been established if molecular markers (other than MSI-H/dMMR) are useful in treatment determination (predictive markers) and prognosis."[32,]

NCCN clinical practice guidelines on prostate cancer (v.4.2024) state that "there are advanced risk stratification tools (ie, gene expression biomarkers, AI digital pathology) that have been variably demonstrated to independently improve risk stratification beyond NCCN or CAPRA risk stratification" and that "these tools are recommended to be used when they have the potential ability to change disease management. These tools should not be ordered reflexively. The most common treatment decisions in localized prostate cancer to use these tests include the use and/or intensity of active surveillance versus radical therapy, [radiotherapy](RT) versus RT + short-term (ST)-[androgen deprivation therapy](ADT), and RT + ST-ADT versus long-term (LT)-ADT. The most common treatment decisions in biochemically recurrent prostate cancer post-RP to use these tests include secondary RT versus secondary RT + ADT. These tools are not recommended for patients with very-low-risk prostate cancer. There are an extensive number of these tools created with substantial variability in quality of reporting and model design, endpoint selection, and quality and caliber of validation. It is recommended to use models that have high-quality and robust validation, ideally with high-quality, long-term clinical trial data, which usually comes from randomized trials and across multiple clinical trials."[33,]For the ArteraAI Prostate test 2A recommendation, continuous scores may be used to provide more accurate risk stratification to inform shared decision-making; however, NCCN notes that "specific score cut points have not been published to date for specific treatment decisions." Predictive biomarker testing with ArteraAI in individuals with intermediate-risk prostate cancer can help to identify patients with a more favorable prognostic risk who "may consider the use of RT alone" without ST-ADT.

National Human Genome Research Institute et al

In 2021, the National Human Genome Research Institute's ClinGen Complex Disease Working Group updated the Genetic Risk Prediction (GRIPS) Reporting Statement in collaboration with the Polygenic Score (PGS) Catalog.[34,] The 22-item reporting framework developed to define the minimal information needed to interpret and evaluate polygenic risk scores is summarized in Table 1.

Table 2. Polygenic Risk Score Reporting Statement

Reporting Standard	
Background	Study Type
	Risk Model Purpose & Predicted Outcome
Study Population and Data	Study Design & Recruitment
	Participant Demographic and Clinical Characteristics
	Ancestry
	Genetic Data
	Non-Genetic Variables
	Outcome of Interest
	Missing Data
Risk Model Development & Application	Polygenic Risk Score Construction & Estimation
	Risk Model Type
	Integrated Risk Model(s) Description & Fitting
Risk Model Evaluation	PRS Distribution
	Risk Model Predictive Ability
	Risk Model Discrimination
	Risk Model Calibration
	Subgroup Analyses
Limitations & Clinical Implications	Risk Model Interpretation
	Limitations
	Generalizability
	Risk Model Intended Uses
Data Transparency & Availability	

PRS: polygenic risk score.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
March 2025	New policy	Policy updated with literature review through September 30, 2024; references added. Description for CPT code 0377U corrected in Policy Guidelines. Guidelines updated. Policy statement unchanged.