Laboratory Testing Investigational Services

Medicare Advantage Medical Policy #MA-116
Original Effective Date: 08/01/2025
Current Effective Date: 08/01/2025

Applies to all products administered or underwritten by the Health Plan, unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Health Plan considers all tests listed in this policy to be **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 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
Apifiny®‡	Armune BioScience, Inc	0021U
BDX-XL2	Biodesix®‡, Inc	0080U
IsoPSA®‡	Cleveland Diagnostics, Inc	0359U
Nodify CDT®‡	Biodesix, Inc	0360U
AMBLor®‡ melanoma prognostic test	Avero®‡ Diagnostics	0387U
OncobiotaLUNG	Micronoma™‡	0395U
CyPath®‡ Lung	Precision Pathology Services	0406U
PROphet®‡ NSCLC Test	OncoHost, Inc	0436U
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®C	Strand Diagnostics	No specific code

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 PG3 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.

Background/Overview

This policy applies if there is not a separate evidence review that outlines specific criteria for testing. If a separate evidence review does exist, then the criteria for medical necessity therein supersede the guidelines herein.

This policy addresses laboratory services considered to be investigational. These tests are often available on a clinical basis before the required and necessary evidence base to support clinical validity and utility is established. Because these tests are often proprietary, there may be no independent test evaluation data available in the early stages to support the laboratory's claims regarding test performance and utility. 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.

FDA or Other Governmental Regulatory Approval

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/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

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 medical policy 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.

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.

Additional Information
Not applicable.

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. 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.

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. 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. 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: "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."

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. 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 1. 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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05276466[a]	Assessment of Urinary Polymerase Chain Reaction (PCR) and Next Generation	100	Dec 2023

	Sequencing (NGS) Technology in the Evaluation and Management of Females With Chronic Bladder Pain and Cystitis-like Symptoms		
NCT05287438[a]	Next Generation Sequencing Versus Traditional Cultures for Clinically Infected Penile Implants: Impact of Culture Identification on Outcomes	40	Oct 2024

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

References

1. Quest Diagnostics. Apolipoprotein L1 (APOL1) Renal Risk Variant Genotyping. December 16, 2022; https://www.questdiagnostics.com/healthcare-professionals/clinical-education-center/faq/faq287#accordion-48070ca605-item-e92bca3e39.
2. Protean Biodiagnostics. Thyroid GuidePx. n.d.; https://www.proteanbiodx.com/thyroidguidepx.
3. Murakami K, Kamat AM, Dai Y, et al. Application of a multiplex urinalysis test for the prediction of intravesical BCG treatment response: A pilot study. Cancer Biomark. 2022; 33(1): 151-157. PMID 34511488
4. DiaCarta. ColoScape Colorectal Cancer Detection Test. 2018; https://www.diacarta.com/services/coloscape.
5. Lab Genomics. Respiratory Panel (RP) Rapid Molecular Diagnostic Test. 2018; https://labgenomic.com/wp-content/uploads/2018/11/RPPanelPamphlet1.pdf.
6. The University of Chicago Genetic Services Laboratories. Single Gene Repeat Expansion Analysis. 2023; https://dnatesting.uchicago.edu/tests/single-gene-repeat-expansion-analysis.
7. Lab Genomics. Drug Metabolism. n.d.; https://labgenomic.com/drug-metabolism/.
8. Journey Biosciences. NaviDKD: A Powerful Predictive Screening. 2023; https://www.journeybio.life/solution#start-your-journey.
9. Sonic Reference Laboratory. PromarkerD Diabetic Kidney Disease Risk Assessment. 2023; https://www.sonicreferencelab.com/featured-testing/diabetic-kidney-disease-risk-assessment/.
10. mProbe, Inc. Kawasaki Disease. 2023; https://www.mprobe.com/kawasakidx.
11. Breakthrough Genomics. Welcome to Breakthrough Genomics. 2023; https://btgenomics.com/.
12. Precision Pathology Services. Why Use CyPath Lung. 2022; https://cypath.precisionpath.us/cypath-physician/.
13. ClearNote Health. Avantect Pancreatic Cancer Test. 2023; https://www.avantect.com/avantect-test/.
14. SmartHealth Dx. SmartVascular Dx. 2023; https://www.smarthealthdx.com/smartvascular-dx/.
15. Prometheus Laboratories. Prometheus Celiac Plus. 2023; https://prometheuslabs.com/disease-tests/celiac-plus/.
16. Prometheus Laboratories. Prometheus Crohn's Prognostics. 2023; https://prometheuslabs.com/disease-tests/crohns-prognostic/.

17. Mosaic Diagnostics. DNA Methylation Pathway Profile. 2023; https://mosaicdx.com/test/dna-methylation-pathway-profile/.
18. Genova Diagnostics. GI effects. n.d.; https://www.gdx.net/products/gi-effects.
19. Prometheus Laboratories. Prometheus IBD sgi Diagnostic. 2023; https://prometheuslabs.com/disease-tests/ibd-sgi-diagnostic/.
20. Strand Diagnostics. Know Error: Be DNA Certain. 2020; https://knowerror.com/index.html.
21. Singh S, Ananthakrishnan AN, Nguyen NH, et al. AGA Clinical Practice Guideline on the Role of Biomarkers for the Management of Ulcerative Colitis. Gastroenterology. Mar 2023; 164(3): 344-372. PMID 36822736
22. Lichtenstein GR, Loftus EV, Isaacs KL, et al. ACG Clinical Guideline: Management of Crohn's Disease in Adults. Am J Gastroenterol. Apr 2018; 113(4): 481-517. PMID 29610508
23. Anger J, Lee U, Ackerman AL, et al. Recurrent Uncomplicated Urinary Tract Infections in Women: AUA/CUA/SUFU Guideline. J Urol. Aug 2019; 202(2): 282-289. PMID 31042112
24. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer: AUA/SUO Guideline. J Urol. Oct 2016; 196(4): 1021-9. PMID 27317986
25. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Bladder Cancer [Version 4.2024]. May 9, 2024; https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf.
26. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer [Version 5.2024]. August 22, 2024; https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf.
27. Wand H, Lambert SA, Tamburro C, et al. Improving reporting standards for polygenic scores in risk prediction studies. Nature. Mar 2021; 591(7849): 211-219. PMID 33692554

Policy History

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Current Effective Date: 08/01/2025
05/20/2025 Utilization Management Committee review/approval. New policy.
Next Scheduled Review Date: 05/2025

Coding

The five character codes included in the Health Plan Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2025 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	0021U, 0080U, 0359U, 0360U, 0387U, 0395U, 0406U, 0436U, 86152, 85153
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

NOTICE: If the Patient's health insurance contract contains language that differs from the Health Plan's Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Health Plan recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.

NOTICE: Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage.

Medicare Advantage Members
Established coverage criteria for Medicare Advantage members can be found in Medicare coverage guidelines in statutes, regulations, National Coverage Determinations (NCD)s, and Local Coverage Determinations (LCD)s. To determine if a National or Local Coverage Determination addresses coverage for a specific service, refer to the Medicare Coverage Database at the following link: https://www.cms.gov/medicare-coverage-database/search.aspx. You may wish to review the Guide to the MCD Search here: https://www.cms.gov/medicare-coverage-database/help/mcd-benehelp.aspx.

When coverage criteria are not fully established in applicable Medicare statutes, regulations, NCDs or LCDs, internal coverage criteria may be developed. This policy is to serve as the summary of evidence, a list of resources and an explanation of the rationale that supports the adoption of this internal coverage criteria.

InterQual®
Interqual® is utilized as a source of medical evidence to support medical necessity and level of care decisions. InterQual® criteria are intended to be used in connection with the independent professional medical judgment of a qualified health care provider. InterQual® criteria are clinically based on best practice, clinical data, and medical literature. The criteria are updated continually and released annually. InterQual® criteria are a first-level screening tool to assist in determining if the proposed services are clinically indicated and provided in the appropriate level or whether further evaluation is required. The utilization review staff does the first-level screening. If the criteria are met, the case is approved; if the criteria are not met, the case is referred to the medical director.