2.04.159	Laboratory Testing Investigational Services		
Original Policy Date:	October 1, 2025	**Effective Date:**	October 1, 2025
Section:	2.0 Medicine	**Page:**	Page 1 of 17

Policy Statement

I. 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).

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Genetic testing is considered **investigational** when Blue Shield of California 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/CPT 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

Test Name	Laboratory	PLA/CPT code
DNA Methylation Pathway Profile	Mosaic Diagnostics (formerly Great Plains Laboratory)	No specific code
Prometheus® IBD sgi Diagnostic®	Prometheus Laboratories	No specific code
ToxProtect	Genotox Laboratories LTD	0007U
Cytochrome P450 1A2 Genotype	Mayo Clinic	0031U
Onco4D™	Animated Dynamics, Inc	0083U
Vita Risk®	Arctic Medical Laboratories	0205U
Colvera®	Clinical Genomics Pathology Inc	0229U
PancreaSeq® Genomic Classifier	Molecular and Genomic Pathology Laboratory, University of Pittsburgh Medical Center	0313U
AMBLor® melanoma prognostic test	Avero® Diagnostics	0387U
LungOI	Imagene	0414U
RightMed® Oncology Gene Report	OneOme® LLC	0460U
RightMed® Oncology Medication Report	OneOme® LLC	0461U
Shield™	Guardant Health, Inc	0537U
ClarityDx Prostate	Protean BioDiagnostics	0550U
ChemoFx	Helomics Corporation	81535, 81536
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

Variant Classification	Definition
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.

Coding

See the Codes table for details.

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.

Related Policies

- Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer
- Biomarker Testing in Risk Assessment and Management of Cardiovascular Disease
- Fecal Analysis in the Diagnosis of Intestinal Dysbiosis
- Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer **(to be published)**
- Gene Expression Profiling for Cutaneous Melanoma **(to be published)**
- General Approach to Evaluating the Utility of Genetic Panels
- General Approach to Genetic Testing
- Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer
- Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
- Genetic Testing for Alzheimer Disease
- Identification of Microorganisms Using Nucleic Acid Probes
- Intracellular Micronutrient Analysis
- Laboratory Tests Post Transplant and for Heart Failure
- Maternal Serum Biomarkers for Prediction of Adverse Obstetric Outcomes
- Molecular Genomic Profiling for Cancers of Unknown Primary
- Molecular Testing in the Management of Pulmonary Nodules **(to be published)**
- Multibiomarker Disease Activity Blood Test for Rheumatoid Arthritis **(to be published)**
- Multimarker Serum Testing Related to Ovarian Cancer
- Multitarget Polymerase Chain Reaction Testing for Diagnosis of Bacterial Vaginosis

- Noninvasive Techniques for the Evaluation and Monitoring of Patients With Chronic Liver Disease **(to be published)**
- Serologic Genetic and Molecular Screening for Colorectal Cancer
- Serum Biomarker Human Epididymis Protein 4
- Serum Biomarker Panel Testing for Systemic Lupus Erythematosus and Other Connective Tissue Diseases **(to be published)**
- Urinary Biomarkers for Cancer Screening, Diagnosis, and Surveillance
- Use of Common Genetic Variants (Single Nucleotide Variants) to Predict Risk of Nonfamilial Breast Cancer **(to be published)**

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

Regulatory Status

Clinical Laboratory Improvement Amendments (CLIA) and FDA Regulatory Overview
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

Background
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.

Literature Review
Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Laboratory Testing Investigational Services

Clinical Context and Test Purpose

The purpose of various commercially available genetic and molecular diagnostic, prognostic, and therapeutic tests for individuals with relevant indications is to inform a clinical management decision that improves the net health outcome.

No formal evidence review was conducted. To sufficiently evaluate clinical utility, the following PICO characteristics must be well-defined.

Populations

The relevant population of interest are individuals with various indications for diagnostic, prognostic, therapeutic, or future risk assessment testing.

To sufficiently evaluate clinical utility, the intended use population should be clearly defined, including disease state, stage or severity, prior treatment, and symptomatic status. For genetic diseases, details regarding inheritance and penetrance provide valuable context.

Interventions

This review addresses the following tests:

Table 1. Laboratory Testing Services[a]

Test Name	Laboratory
Polygenic Risk Score	Many
MicroGenDx[1,]	MicroGen Diagnostics
Apolipoprotein L1 (*APOL1*) Renal Risk Variant Genotyping[2,]	Quest Diagnostics
Thyroid GuidePx®[3,]	Protean Biodiagnostics
Oncuria® Detect[4,5,]	DiaCarta Clinical Lab
Oncuria® Monitor[4,5,]	DiaCarta Clinical Lab
Oncuria® Predict[4,5,]	DiaCarta Clinical Lab
ColoScape™ Colorectal Cancer Detection Test[6,]	DiaCarta Clinical Lab
Qlear UTI[7,]	LifeScan Labs of Illinois, Thermo Fisher Scientific
Qlear UTI – Reflex ABR[7,]	LifeScan Labs of Illinois, Thermo Fisher Scientific
Respiratory Pathogen with ABR (RPX)[8,]	Lab Genomics LLC, Thermo Fisher Scientific
Urogenital Pathogen with Rx Panel (UPX)[9,]	Lab Genomics LLC, Thermo Fisher Scientific
ArteraAI Prostate Test[10,]	Artera Inc.
Liposcale® Advanced Lipoprotein Test[11,]	CIMA Sciences LLC
PersonalisedRX[12,]	Lab Genomics LLC, Agena Bioscience, Inc.
NaviDKD® Predictive Diagnostic Screening for Kidney Health[13,]	Journey Biosciences, Inc.
PromarkerD Diabetic Kidney Disease Risk Assessment[14,]	Sonic Reference Laboratory, Proteomics International
Esopredict™ (formerly Envisage)[15,]	Previse (formerly Capsulomics, Inc.)
KawasakiDx™ (formerly PEPredictDx)[16,]	mProbe, Inc. (formerly OncoOmicsDx Laboratory)
BTG Early Detection of Pancreatic Cancer[17,]	Breakthrough Genomics, Inc.
CyPath® Lung[18,]	Precision Pathology Services
Avantect Pancreatic Cancer Test[19,]	ClearNote Health
SmartVascular Dx[20,]	SmartHealth DX
Prometheus® Celiac PLUS[21,]	Prometheus Laboratories
Prometheus® Crohn's Prognostic[22,]	Prometheus Laboratories

Test Name	Laboratory
DNA Methylation Pathway Profile[23,]	Mosaic Diagnostics (formerly Great Plains Laboratory)
GI Effects® (Stool)[24,]	Genova Diagnostics
Prometheus® IBD sgi Diagnostic®[25,]	Prometheus Laboratories
know error®[26,]	Strand Diagnostics

[a] See Policy Guidelines and Codes table for additional details.

To sufficiently evaluate clinical utility, the characteristics of the test should be well-defined including thresholds, cutoffs, or classifications used for categorization. The intended use of the test should be clearly stated, including its position in the clinical pathway. Use of the test to replace an existing test or testing pathway (replacement), use before an existing test or testing pathway (triage), or use after an existing test or testing pathway (add-on) should be clearly specified.

Comparators
The clinical practice alternative to which the test is being compared should be clearly stated, including any applicable reference standards and any known disadvantages of the comparator that the test under evaluation aims to overcome.

Outcomes
The general outcomes of interest are symptoms, quality of life, medication use, change in disease status, and morbidity and mortality. Follow-up duration may be informed by the natural history of the disease.

Health outcomes measure length of life, quality of life, and the ability to function and occur as a consequence of the interventions taken as a result of the test. Clinical management decisions and physiologic measures that are not validated surrogates are not health outcomes. The beneficial outcomes resulting from a true test result and the harmful outcomes resulting from a false test result should be clearly stated. Clinical management recommendations for a test result that is discordant with another test applied in the clinical pathway should also be defined.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

The studies using the tests listed in this policy are currently in a developmental phase, with limited evidence of clinical utility for diagnosis, prognosis, or risk assessment. 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 change in a way we find value in, relative to the outcomes(s) obtained without the test.

With the clinical utility not established, evidence review of clinical validity was not performed.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

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

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

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 (e.g., 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 (i.e., 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

Reporting Standard	
	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 3.

Table 3. 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 Sequencing (NGS) Technology in the Evaluation and Management of Females With Chronic Bladder Pain and Cystitis-like Symptoms	100	Dec 2023
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. MicroGen Diagnostics. MicroGenDx: Information for Healthcare Professionals. 2023; https://microgendx.com/microgen-diagnostics-specialties/. Accessed September 30, 2024.
2. 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. Accessed September 30, 2024.
3. Protean Biodiagnostics. Thyroid GuidePx. n.d.; https://www.proteanbiodx.com/thyroidguidepx. Accessed September 30, 2024.
4. Nonagen Bioscience. Introducing Oncuria: A Next-Generation Oncology Diagnostic. 2022; https://www.nonagen.com/products. Accessed September 30, 2024.
5. 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
6. DiaCarta. ColoScape Colorectal Cancer Detection Test. 2018; https://www.diacarta.com/services/coloscape. Accessed September 30, 2024.

7. ThermoFisher Scientific. Urinary Tract Infection (UTI) Testing Research Solutions. 2022; https://www.thermofisher.com/us/en/home/clinical/clinical-genomics/pathogen-detection-solutions/realtime-pcr-solution-urinary-tract-microbiota-detection.html. Accessed September 30, 2024.
8. Lab Genomics. Respiratory Panel (RP) Rapid Molecular Diagnostic Test. 2018; https://labgenomic.com/wp-content/uploads/2018/11/RPPanelPamphlet1.pdf. Accessed September 30, 2024.
9. Lab Genomics. Urinary Pathogen Test (UPX) Rapid Molecular Diagnostic Test. 2018; https://labgenomic.com/wp-content/uploads/2018/12/UTI-Brochure-FINAL.pdf. Accessed September 30, 2024.
10. ArteraAI. ArteraAI Prostate Test. n.d.; https://artera.ai/arteraai-prostate-cancer-test. Accessed September 30, 2024.
11. CIMA Sciences LLC. Liposcale Advanced Lipoprotein Test. 2024; https://cimasciences.com/liposcale/. Accessed on September 30, 2024.
12. Lab Genomics. Drug Metabolism. n.d.; https://labgenomic.com/drug-metabolism/. Accessed September 30, 2024.
13. Journey Biosciences. NaviDKD: A Powerful Predictive Screening. 2023; https://www.journeybio.life/solution#start-your-journey. Accessed September 30, 2024.
14. Sonic Reference Laboratory. PromarkerD Diabetic Kidney Disease Risk Assessment. 2023; https://www.sonicreferencelab.com/featured-testing/diabetic-kidney-disease-risk-assessment/. Accessed September 30, 2024.
15. Previse. Esopredict: Information for Healthcare Providers. 2023; https://previsedx.com/our-test/esopredict-for-providers/. Accessed September 30, 2024.
16. mProbe, Inc. Kawasaki Disease. 2023; https://www.mprobe.com/kawasakidx. Accessed September 30, 2024.
17. Breakthrough Genomics. Welcome to Breakthrough Genomics. 2023; https://btgenomics.com/. Accessed September 30, 2024.
18. Precision Pathology Services. Why Use CyPath Lung. 2022; https://cypath.precisionpath.us/cypath-physician/. Accessed September 30, 2024.
19. ClearNote Health. Avantect Pancreatic Cancer Test. 2023; https://www.avantect.com/avantect-test/. Accessed September 30, 2024.
20. SmartHealth Dx. SmartVascular Dx. 2023; https://www.smarthealthdx.com/smartvascular-dx/. Accessed September 30, 2024.
21. Prometheus Laboratories. Prometheus Celiac Plus. 2023; https://prometheuslabs.com/disease-tests/celiac-plus/. Accessed September 30, 2024.
22. Prometheus Laboratories. Prometheus Crohn's Prognostics. 2023; https://prometheuslabs.com/disease-tests/crohns-prognostic/. Accessed September 27, 2024.
23. Mosaic Diagnostics. DNA Methylation Pathway Profile. 2023; https://mosaicdx.com/test/dna-methylation-pathway-profile/. Accessed September 30, 2024.
24. Genova Diagnostics. GI effects. n.d.; https://www.gdx.net/products/gi-effects. Accessed September 30, 2024.
25. Prometheus Laboratories. Prometheus IBD sgi Diagnostic. 2023; https://prometheuslabs.com/disease-tests/ibd-sgi-diagnostic/. Accessed September 26, 2024.
26. Strand Diagnostics. Know Error: Be DNA Certain. 2020; https://knowerror.com/index.html. Accessed September 30, 2024.
27. 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
28. 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

29. 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
30. 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
31. 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. Accessed September 27, 2024.
32. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Colon Cancer [Version 5.2024]. August 22, 2024; https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed September 24, 2024.
33. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Prostate Cancer [Version 4.2024]. May 17, 2024; https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed September 30, 2024.
34. 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

Documentation for Clinical Review

- No records required

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	0007U	Drug test(s), presumptive, with definitive confirmation of positive results, any number of drug classes, urine, includes specimen verification including DNA authentication in comparison to buccal DNA, per date of service Includes ToxProtect, Genotox Laboratories LTD
	0031U	CYP1A2 (cytochrome P450 family 1, subfamily A, member 2)(e.g., drug metabolism) gene analysis, common variants (i.e., *1F, *1K, *6, *7) Includes Includes Cytochrome P450 1A2 Genotype, Mayo Clinic, Mayo Clinic
	0083U	Oncology, response to chemotherapy drugs using motility contrast tomography, fresh or frozen tissue, reported as likelihood of sensitivity or resistance to drugs or drug combinations Includes Onco4D™, Animated Dynamics, Inc, Animated Dynamics, Inc
	0112U	Infectious agent detection and identification, targeted sequence analysis (16S and 18S rRNA genes) with drug-resistance gene Includes MicroGenDX qPCR & NGS For Infection, MicroGenDX, MicroGenDX
	0205U	Ophthalmology (age-related macular degeneration), analysis of 3 gene variants (2 CFH gene, 1 ARMS2 gene), using PCR and MALDI-TOF, buccal swab, reported as positive or negative for neovascular age-related macular-degeneration risk associated with zinc supplements Includes Vita Risk®, Arctic Medical Laboratories, Arctic Medical Laboratories

Type	Code	Description
	0229U	BCAT1 (Branched chain amino acid transaminase 1) and IKZF1 (IKAROS family zinc finger 1) (e.g., colorectal cancer) promoter methylation analysis Includes Colvera®, Clinical Genomics Pathology Inc
	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 (i.e., negative, low probability of neoplasia or positive, high probability of neoplasia) Includes PancreaSeq® Genomic Classifier, Molecular and Genomic Pathology Laboratory, University of Pittsburgh Medical Center
	0355U	APOL1 (apolipoprotein L1) (e.g., chronic kidney disease), risk variants (G1, G2) Includes Apolipoprotein L1 *(APOL1)* Renal Risk Variant Genotyping, Quest Diagnostics®, Quest Diagnostics®
	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 Includes Thyroid GuidePx®, Protean BioDiagnostics, Qualisure Diagnotics
	0365U	Oncology (bladder), 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1, and VEGFA), by immunoassays, urine, diagnostic algorithm, including patient's age, race, and gender, reported as a probability of harboring urothelial cancer Includes Oncuria® Detect, DiaCarta Clinical Lab, DiaCarta, Inc
	0366U	Oncology (bladder), analysis of 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, algorithm reported as a probability of recurrent bladder cancer Includes Oncuria® Monitor, DiaCarta Clinical Lab, DiaCarta, Inc
	0367U	Oncology (bladder), analysis of 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, diagnostic algorithm reported as a risk score for probability of rapid recurrence of recurrent or persistent cancer following transurethral resection Includes Oncuria® Predict, DiaCarta Clinical Lab, DiaCarta, Inc
	0368U	Oncology (colorectal cancer), evaluation for mutations of APC, BRAF, CTNNB1, KRAS, NRAS, PIK3CA, SMAD4, and TP53, and methylation markers (MYO1G, KCNQ5, C9ORF50, FLI1, CLIP4, ZNF132 and TWIST1), multiplex quantitative polymerase chain reaction (qPCR), circulating cell-free DNA (cfDNA), plasma, report of risk score for advanced adenoma or colorectal cancer Includes ColoScape™ Colorectal Cancer Detection, DiaCarta Clinical Lab, DiaCarta, Inc
	0371U	Infectious agent detection by nucleic acid (DNA or RNA), genitourinary pathogen, semiquantitative identification, DNA from 16 bacterial organisms and 1 fungal organism, multiplex amplified probe technique via quantitative polymerase chain reaction (qPCR), urine Includes Qlear UTI, Lifescan Labs of Illinois, Thermo Fisher Scientific
	0372U	Infectious disease (genitourinary pathogens), antibiotic-resistance gene detection, multiplex amplified probe technique, urine, reported as an antimicrobial stewardship risk score

Type	Code	Description
		Includes Qlear UTI - Reflex ABR, Lifescan Labs of Illinois, Thermo Fisher Scientific
	0373U	Infectious agent detection by nucleic acid (DNA and RNA), respiratory tract infection, 17 bacteria, 8 fungus, 13 virus, and 16 antibiotic-resistance genes, multiplex amplified probe technique, upper or lower respiratory specimen ***(Deleted code effective 7/1/2025)***
	0374U	Infectious agent detection by nucleic acid (DNA or RNA), genitourinary pathogens, identification of 21 bacterial and fungal organisms and identification of 21 associated antibiotic-resistance genes, multiplex amplified probe technique, urine ***(Deleted code effective 7/1/2025)***
	0376U	Oncology (prostate cancer), image analysis of at least 128 histologic features and clinical factors, prognostic algorithm determining the risk of distant metastases, and prostate cancer-specific mortality, includes predictive algorithm to androgen deprivation-therapy response, if appropriate Includes ArteraAI Prostate Test, Artera Inc®, Artera Inc®
	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) Includes Liposcale®, CIMA Sciences, LLC
	0384U	Nephrology (chronic kidney disease), carboxymethyllysine, methylglyoxal hydroimidazolone, and carboxyethyl lysine by liquid chromatography with tandem mass spectrometry (LC-MS/MS) and HbA1c and estimated glomerular filtration rate (GFR), with risk score reported for predictive progression to high-stage kidney disease Includes NaviDKD™ Predictive Diagnostic Screening for Kidney Health, Journey Biosciences, Inc, Journey Biosciences, Inc
	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 Includes PromarkerD, Sonic Reference Laboratory, Proteomics International Pty Ltd
	0387U	Oncology (melanoma), autophagy and beclin 1 regulator 1 (AMBRA1) and loricrin (AMLo) by immunohistochemistry, formalin-fixed paraffin-embedded (FFPE) tissue, report for risk of progression Includes AMBLor® melanoma prognostic test, Avero® Diagnostics
	0390U	Obstetrics (preeclampsia), kinase insert domain receptor (KDR), Endoglin (ENG), and retinol-binding protein 4 (RBP4), by immunoassay, serum, algorithm reported as a risk score Includes PEPredictDx, OncoOmicsDx Laboratory, mProbe
	0405U	Oncology (pancreatic), 59 methylation haplotype block markers, next-generation sequencing, plasma, reported as cancer signal detected or not detected Includes BTG Early Detection of Pancreatic Cancer, Breakthrough Genomics, Breakthrough Genomics
	0406U	Oncology (lung), flow cytometry, sputum, 5 markers (meso-tetra [4-carboxyphenyl] porphyrin [TCPP], CD206, CD66b, CD3, CD19), algorithm reported as likelihood of lung cancer

Type	Code	Description
		Includes CyPath® Lung, Precision Pathology Services, bioAffinity Technologies, Inc
	0410U	Oncology (pancreatic), DNA, whole genome sequencing with 5-hydroxymethylcytosine enrichment, whole blood or plasma, algorithm reported as cancer detected or not detected Includes Avantect™ Pancreatic Cancer Test, ClearNote™ Health, ClearNote™ Health
	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 Includes LungOI, Imagene
	0415U	Cardiovascular disease (acute coronary syndrome [ACS]), IL-16, FAS, FASLigand, 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 Includes SmartHealth Vascular Dx™, Morningstar Laboratories, LLC, SmartHealth DX
	0460U	Oncology, whole blood or buccal, DNA single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, with variant analysis and reported phenotypes Includes RightMed® Oncology Gene Report, OneOme® LLC, OneOme® LLC
	0461U	Oncology, pharmacogenomic analysis of single-nucleotide polymorphism (SNP) genotyping by real-time PCR of 24 genes, whole blood or buccal swab, with variant analysis, including impacted gene-drug interactions and reported phenotypes Includes RightMed® Oncology Medication Report, OneOme® LLC, OneOme® LLC
	0494U	Red blood cell antigen (fetal RhD gene analysis), next-generation sequencing of circulating cell-free DNA (cfDNA) of blood in pregnant individuals known to be RhD negative, reported as positive or negative Includes Rh Test, Natera™
	0512U	Oncology (prostate), augmentative algorithmic analysis of digitized whole-slide imaging of histologic features for microsatellite instability (MSI) status, formalin-fixed paraffin-embedded (FFPE) tissue, reported as increased or decreased probability of MSI-high (MSI-H) Includes Tempus p-MSI, Tempus AI, Inc, Tempus AI, Inc
	0513U	Oncology (prostate), augmentative algorithmic analysis of digitized whole-slide imaging of histologic features for microsatellite instability (MSI) and homologous recombination deficiency (HRD) status, formalin-fixed paraffin-embedded (FFPE) tissue, reported as increased or decreased probability of each biomarker Includes Tempus p-Prostate, Tempus AI, Inc, Tempus AI, Inc
	0536U	Red blood cell antigen (fetal RhD), PCR analysis of exon 4 of RHD gene and housekeeping control gene GAPDH from whole blood in pregnant individuals at 10+ weeks gestation known to be RhD negative, reported as fetal RhD status Includes Prenatal Detect RhD, Devyser Genomic Laboratories, Devyser AB

Type	Code	Description
	0537U	Oncology (colorectal cancer), analysis of cell-free DNA for epigenomic patterns, next-generation sequencing, >2500 differentially methylated regions (DMRs), plasma, algorithm reported as positive or negative Includes Shield™, Guardant Health, Inc, Guardant Health, Inc
	0550U	Oncology (prostate), enzyme-linked immunosorbent assays (ELISA) for total prostate-specific antigen (PSA) and free PSA, serum, combined with age, previous negative prostate biopsy status, digital rectal examination findings, prostate volume, and image and data reporting of the prostate, algorithm reported as a risk score for the presence of high-grade prostate cancer Includes ClarityDx Prostate, Protean BioDiagnostics, Protean BioDiagnostics
	0573U	Oncology (pancreas), 3 biomarkers (glucose, carcinoembryonic antigen, and gastricsin), pancreatic cyst lesion fluid, algorithm reported as categorical mucinous or non-mucinous Includes Amplified Sciences PanCystPro™, Amplified Sciences, Inc
	81535	Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; first single drug or drug combination
	81536	Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; each additional single drug or drug combination (List separately in addition to code for primary procedure)
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
10/01/2025	New policy.

Definitions of Decision Determinations

Healthcare Services: For the purpose of this Medical Policy, Healthcare Services means procedures, treatments, supplies, devices, and equipment.

Medically Necessary: Healthcare Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield of California, are: (a) consistent with Blue Shield of California medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the member; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the member's illness, injury, or disease.

Investigational or Experimental: Healthcare Services which do not meet ALL of the following five (5) elements are considered investigational or experimental:

A. The technology must have final approval from the appropriate government regulatory bodies.
   - This criterion applies to drugs, biological products, devices and any other product or procedure that must have final approval to market from the U.S. Food and Drug Administration ("FDA") or any other federal governmental body with authority to regulate the use of the technology.
   - Any approval that is granted as an interim step in the FDA's or any other federal governmental body's regulatory process is not sufficient.
   - The indications for which the technology is approved need not be the same as those which Blue Shield of California is evaluating.

B. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.
   - The evidence should consist of well-designed and well-conducted investigations published in peer-reviewed journals. The quality of the body of studies and the consistency of the results are considered in evaluating the evidence.
   - The evidence should demonstrate that the technology can measure or alter the physiological changes related to a disease, injury, illness, or condition. In addition, there should be evidence, or a convincing argument based on established medical facts that such measurement or alteration affects health outcomes.

C. The technology must improve the net health outcome.
   - The technology's beneficial effects on health outcomes should outweigh any harmful effects on health outcomes.

D. The technology must be as beneficial as any established alternatives.
   - The technology should improve the net health outcome as much as, or more than, established alternatives.

E. The improvement must be attainable outside the investigational setting.
   - When used under the usual conditions of medical practice, the technology should be reasonably expected to satisfy Criteria C and D.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** Blue font: Verbiage Changes/Additions
New Policy **Policy Statement:** N/A	**Laboratory Testing Investigational Services 2.04.159** **Policy Statement:** I. 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).