Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

Nonprofit corporations and independent licensees of the Blue Cross and Blue Shield Association

***Current Policy Effective Date: 5/1/25**
(See policy history boxes for previous effective dates)

Title: Miscellaneous and Genetic and Molecular Diagnostic Tests

Description/Background

There are numerous commercially available genetic and molecular, diagnostic and prognostic tests for individuals with certain diseases. This evidence review evaluates miscellaneous 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 validity for the test. As a result, these tests do not have clinical utility, and the evidence is insufficient to determine that technology results in an improvement in the net health outcome.

TESTS ADDRESSED IN THIS EVIDENCE REVIEW

Table 1 lists tests assessed in this evidence review. Three types of tests are related to testing of an affected (symptomatic) individual's germline to benefit the individual (excluding reproductive testing): diagnostic testing and prognostic testing. The fourth type of test reviewed is testing of an asymptomatic individual to determine future risk of disease.

Table 1. Genetic and Molecular Diagnostic Tests Assessed This Evidence Review

Test Name	Manufacturer	Date Added	Diagnostic	Prognostic	Future Risk
Prometheus® Celiac PLUS	Prometheus Laboratories	Oct 2014	•		•
Prometheus® Crohn's Prognostic	Prometheus Laboratories	Oct 2014		•	
DNA Methylation Pathway Profile	Great Plains Laboratory (now Mosaic Dxcs)	Jan 2015	•		
GI Effects® (Stool)	Genova Dxcs	Jan 2015	•		
Prometheus® IBD sgi Diagnostic™	Prometheus Laboratories	Oct 2014	•		
Know error®	Strand Dxcs	July 2016	•		
Envisia Genomic Classifier	Veracyte	Nov 2021	•		

Dxcs: Diagnostics; Gxcs: Genetics.
[a] No therapeutic test have been identified for this policy.

DIAGNOSTIC TESTS

Multiple Conditions

Single-nucleotide variants (SNVs) are the most common type of genetic variation, and each SNV represents a difference in a single nucleotide in the DNA sequence. Most commonly, SNVs are found in the DNA between genes and can act as biologic markers of genes and disease association. When SNVs occur within a gene or a gene regulatory region, they can play a more direct role in disease by affecting the gene's function. SNVs may predict an individual's response to certain drugs, susceptibility to environmental factors, and the risk of developing certain diseases.

DNA specimen provenance assays can be used to confirm that tissue specimens are correctly matched to the patient of origin. Specimen provenance errors may occur in up to 1% to 2% of pathology tissue specimens (1) and have serious negative implications for patient care if the error is not corrected.(2) Analysis of DNA microsatellites from tissue specimens can be performed by analyzing long tandem repeats (LTR) and comparing the LTRs of the tissue specimen with LTRs from a patient sample.

Test Description: DNA Methylation Pathway Profile

The DNA Methylation Pathway Profile (Mosaic Diagnostics) analyzes SNVs associated with certain biochemical processes, including methionine metabolism, detoxification, hormone imbalances, and vitamin D function. Intended uses for the test include clarification of a diagnosis suggested by other testing and as an indication for supplements and diet modifications.

Test Description: Know Error DNA Specimen Provenance Assay

The Know Error system (Strand Diagnostics) compares the LTRs of tissue samples with LTRs from a buccal swab of the patient. The intended use of the test is to confirm tissue of origin and avoid specimen provenance errors due to switching of patient samples, mislabeling, or sample contamination.

Test Description: Idiopathic Pulmonary Fibrosis Diagnostic Test (Envisia™ - Veracyte™)

The Envisia Genomic Classifier is the first commercially available genomic test. A transbronchial biopsy specimen is obtained for mRNA sequencing of 190 genes and is combined with a machine learning algorithm to identify usual interstitial pneumonia patterns which provides a probabilistic estimate of the likelihood of idiopathic pulmonary fibrosis (IPF). Envisia is intended to be used as a complement to high-resolution chest CT (HRCT) to differentiate IPF from other interstitial lung diseases in patients who do not have a definite usual interstitial pneumonia and are suspected of having idiopathic pulmonary fibrosis. The Envisia genomic classifier is intended to provide a categorical usual interstitial pneumonia or non-usual interstitial pneumonia result that along with clinical and radiographic information may guide treatment without the need for surgical lung biopsy.

Celiac Disease

Previously called sprue, celiac sprue, gluten-sensitive enteropathy, gluten intolerance, nontropical sprue, or idiopathic steatorrhea, celiac disease is an immune-based reaction to gluten (water insoluble proteins in wheat, barley, rye) that primarily affects the small intestine. Celiac disease occurs almost exclusively in individuals who carry at least 1 human leukocyte

antigen DQ2 or DQ8 allele; the negative predictive value of having neither allele exceeds 98%.(3) Serum antibodies to tissue transglutaminase, endomysium, and deamidated gliadin peptide (DGP) support a diagnosis of celiac disease, but diagnostic confirmation requires duodenal biopsy taken when patients are on a gluten-containing diet.(4)

Test Description: Celiac PLUS

Celiac PLUS (Prometheus Laboratories) is a panel of 2 genetic and 5 serologic markers associated with celiac disease. Per the manufacturer, Celiac PLUS is a diagnostic test that also stratifies the future risk of celiac disease.(5) Genetic markers (human leukocyte antigen DQ2 and DQ8) are considered predictive of the risk of developing celiac disease;(6) serologic markers (immunoglobulin A [IgA] anti-tissue transglutaminase antibody, IgA anti-endomysial antibodies, IgA anti-DGP antibodies, IgG anti-DGP, and total IgA) are considered diagnostic for celiac disease. Celiac PLUS is intended for patients at risk for disease (e.g., with an affected first-degree relative) or with symptoms suggestive of disease.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder that affects 10% to 20% of the general population in the United States and worldwide. Symptoms include abdominal pain and/or bloating associated with disordered bowel habit (constipation, diarrhea, or both). Pathophysiology is poorly understood but may be related to chronic low-grade mucosal inflammation and disturbances in GI flora.(7) Recommended treatments include dietary restriction and pharmacologic symptom control.(8-10) As living microorganisms that promote health when administered to a host in therapeutic doses,(11) probiotics are being investigated as a treatment for IBS. Several systematic reviews of randomized controlled trials (RCTs) have found evidence to support efficacy,(7,12-15) but results from recent randomized controlled trials have been mixed.(16-21) This discrepancy may be due in part to the differential effects of different probiotic strains and doses.

Test Description: GI Effects Comprehensive Stool Profile

The GI Effects Comprehensive Stool Profile (Genova Diagnostics) is a multianalyte stool assay.(22) The test uses polymerase chain reaction (PCR) to quantify 26 commensal gut bacteria and standard biochemical and culture methods to measure levels of other stool components (e.g., lipids, fecal occult blood) and potential pathogens (ova and parasites, opportunistic bacteria, yeast). The test is purported to optimize management of gut health and to differentiate IBS from inflammatory bowel disease (IBD).

Inflammatory Bowel Disease

IBD is an autoimmune condition characterized by inflammation of the bowel wall and has clinical symptoms of abdominal pain, diarrhea, and associated symptoms. Crohn disease (CD) and ulcerative colitis are the two main entities under the category of IBD. The diagnosis is typically made by endoscopy or colonoscopy with biopsy and histologic analysis. This requires a semi-invasive procedure; as a result, a blood test to diagnose IBD could avoid the need for the procedures.

Test Description: IBD sgi Diagnostic

IBD sgi Diagnostic (Prometheus Laboratories) is a panel of 17 serologic (n=8), genetic (n=4), and inflammatory biomarkers (n=5). A proprietary algorithm produces an IBD score; results are reported as consistent with IBD (consistent with ulcerative colitis, consistent with CD, or

inconclusive for UC vs CD) or not consistent with IBD. The test is intended for use in patients with clinical suspicion of IBD.

THERAPEUTIC TESTS
Previously reviewed therapeutic tests are no longer commercially available; no commercially available therapeutic test is reviewed in this policy.

PROGNOSTIC TESTS

Crohn Disease
Recent studies have identified serologic (23) and genetic (24,25) correlates of aggressive CD that is characterized by fistula formation, fibrostenosis, and the need for surgical intervention. Prometheus has developed a blood test that aims to identify patients with CD who are likely to experience an aggressive disease course.

Test Description: Crohn's Prognostic
Crohn's Prognostic (Prometheus Laboratories) is a panel of 6 serologic (n=3) and genetic (n=3) biomarkers. Limited information about the test is available on the manufacturer's website.

TESTS FOR FUTURE RISK OF DISEASE
Previously reviewed tests for future risk of disease are no longer commercially available; no commercially available test for the future risk of disease is reviewed in this policy.

MISCELLANEOUS LABORATORY TESTING
This conceptual framework is to assist in the evaluation of the utility of miscellaneous laboratory testing. In providing a framework for evaluating miscellaneous laboratory tests, this review may not determine the clinical utility of laboratory testing for specific disorders. Rather, it is meant to provide guidelines that can be applied to a wide range of laboratory tests.

This conceptual framework applies only if there is not a separate policy (see Related Policies) that outlines specific criteria for laboratory testing. If a separate policy exists, then the criteria in that policy supersedes the guidelines herein.

Regulatory Status

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. The Centers for Medicare and Medicaid Services (CMS) regulates clinical laboratory testing to ensure laboratory compliance with the Clinical Laboratory Improvement Amendment of 1988, showing accuracy and reliability in conducting assays. The Federal Trade Commission (FTC) oversees advertising of tests and products. The Food and Drug Administration (FDA) regulates tests sold as "diagnostic devices," that is, tests manufactured by one company and then sold as a kit to a laboratory. However, the FDA does not regulate "home brew" tests, that is, tests that are both manufactured and performed by the same laboratory.

Medical Policy Statement

Diagnostic and prognostic genetic testing of (1) an affected (symptomatic) individual's germline to benefit the individual (excluding reproductive testing) **or** (2) of an asymptomatic individual to determine future risk of disease is considered experimental/investigational for the following:

- Prometheus® Celiac PLUS
- Prometheus® Crohn's Prognostic
- DNA Methylation Pathway Profile
- GI Effects® (Stool)
- Prometheus® IBD sgi Diagnostic®
- Know Error™
- Envisia™ Genomic Classifier (Veracyte™)

All miscellaneous laboratory diagnostic tests[a] listed in this policy are considered investigational. There is insufficient evidence to determine that the technology results in an improvement in net health outcomes.

[a] *If a separate policy exists, then the criteria in that policy supersedes the guidelines herein.*

Policy Guidelines

Genetic Counseling

Genetic counseling is primarily aimed at individuals who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Inclusionary and Exclusionary Guidelines

N/A

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

N/A

Other codes (investigational, not medically necessary, etc.):

81265*	81266*	81382	81479	81554	82397
82784	83520	84999	86021	86140	86255
87045	87046	87075	87102	87177	87209
87328	87329	87336	87798	88346	88350

** These codes are considered experimental/investigational when used to bill for the Know Error test.*

Established codes may be considered investigational for the purpose of this policy

Note: Code(s) may not be covered by all contracts or certificates. Please consult customer or provider inquiry resources at BCBSM or BCN to verify coverage.

Rationale

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.

DIAGNOSTIC TESTING

Clinical Context and Test Purpose
The purpose of diagnostic testing in individuals for genetic or heritable pathogenic variants in a symptomatic individual is to establish a molecular diagnosis defined by the presence of known pathologic variant(s). For genetic testing, a symptomatic individual is defined as an individual with a clinical phenotype that correlates with a known pathologic variant.

The specific clinical context of each test is described briefly in the following sections. The following PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are individuals with symptoms of a particular disease for which a definitive diagnosis cannot be made using other diagnostic methods.

Interventions
The interventions of interest are miscellaneous genetic or molecular diagnostic tests, specifically: DNA Methylation Pathway Profile, Know Error, Celiac PLUS, GI Effects (Stool), and IBD sgi Diagnostic.

Comparators
The comparator of interest is standard care without genetic or molecular diagnostic testing.

Outcomes
The outcomes of interest are overall survival (OS), disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The timing of follow-up for irritable bowel syndrome (IBS), inflammatory bowel disease, and celiac disease ranges from weeks for the diagnosis to years for assessment of health outcomes.

Study Selection Criteria
For the evaluation of clinical validity of miscellaneous genetic or molecular tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

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 testing.

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 (RCTs).

No studies examining clinical utility were identified.

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.

It is not possible to construct a chain of evidence for clinical utility due to the lack of clinical validity.

Diagnostic Testing for Multiple Conditions: DNA Methylation Pathway Profile

Review of Evidence
No full-length, peer-reviewed studies of the DNA Methylation Pathway Profile were identified.

Section Summary: DNA Methylation Pathway Profile
No studies were identified that evaluated this test. Factors that support a chain of evidence for prognostic or diagnostic utility are lacking.

Diagnostic Testing for Multiple Conditions: Know Error Specimen Provenance Assay

Review of Evidence
Evidence for the clinical validity of the Know Error Specimen Provenance Assay is lacking. There is some evidence on the application of short tandem repeat testing for specimen provenance assays in general,(27) but these data are not specific to the Know Error test.

Section Summary: Know Error Specimen Provenance Assays
There is a lack of published evidence on the use of the Know Error test to confirm tissue of origin. Studies are needed that compare the use of Know Error with standard laboratory quality measures and that demonstrate a reduction in specimen provenance errors associated with the use of Know Error.

Diagnostic Testing for Celiac Disease: Celiac PLUS

Review of Evidence
Celiac PLUS tests for genetic and serologic factors known to be associated with celiac disease. All 7 test components are included in an evidence-based diagnostic algorithm developed by the American College of Gastroenterology.(28) However, algorithmic testing is individualized according to the baseline risk of disease and is done sequentially, rather than simultaneously as in Celiac PLUS.

No studies of the combined serologic and genetic Celiac PLUS test were identified. Information about clinical validity of obtaining several serologic and genetic tests at once (i.e., Celiac PLUS) is lacking; improved sensitivity and reduced specificity may be expected.

Section Summary: Celiac Disease
No studies examining the clinical utility of Celiac PLUS were identified. Factors that support a chain of evidence for prognostic or diagnostic utility are lacking.

Diagnostic Testing for Irritable Bowel Syndrome: GI Effects Comprehensive Stool Profile

Review of Evidence
No studies were identified that assessed the accuracy of the GI Effects fecal panel for diagnosing IBS or for documenting “gut health,” a concept that may be difficult to define given large interindividual variability in gut flora.(29)

Section Summary: Diagnostic Testing for Irritable Bowel Syndrome
Evidence for the clinical validity and utility of the GI Effects Comprehensive Stool Profile is lacking. Because probiotics are not currently a standard treatment of IBS, the impact of test results on disease management is uncertain; i.e., a chain of evidence for clinical utility of the test cannot be established.

Diagnostic Testing for Inflammatory Bowel Disease: IBD sgi Diagnostic

Review of Evidence
The IBD sgi Diagnostic product monograph includes an extensive bibliography that documents

associations of the 18 component markers, individually and in combination, with ulcerative colitis (UC) and/or Crohn disease (CD).(30)

In a review of the monograph, Shirts et al (2012) (31) observed that serologic tests for ASCA-IgA, ASCA-IgG, and atypical perinuclear anti-neutrophil cytoplasmic antibody are standard of care in the diagnostic workup of IBD,(32,33) although not all investigators include these tests in recommended diagnostic strategies.(34-37) These 3 markers are included in the 17-marker panel. Based on a 2006 meta-analysis of 60 studies (total N=11,608), pooled sensitivity and specificity of the 3-test panel were 63% and 93%, respectively, for diagnosing IBD.(38) Because the product monograph does not compare the 18-marker panel with the 3-marker panel, incremental improvement in diagnosis with the 18-marker panel is unknown. Shirts et al (2012) calculated an area under the curve (AUC) for the 3-marker panel of 0.899.

Published evidence supports associations of each marker in the 18-marker panel, alone and in combination, with IBD diagnosis. Based on manufacturer data, the accuracy for IBD diagnosis of the 18-marker panel exceeds that of each component marker, but the relevant comparison—with a panel of 3 markers that has good discrimination for IBD—was not included; subsequent analysis suggests that the panels may perform similarly. Performance characteristics for the 18-marker panel to distinguish ulcerative colitis from CD were not provided.

Section Summary: Inflammatory Bowel Disease sgi Diagnostic
No studies examining the clinical utility of IBD sgi Diagnostic were identified. Although manufacturer data support clinical validity of the test for diagnosing IBD, this evidence is insufficient to support a chain of evidence for clinical utility due to lack of details about study methodology and lack of replication of the findings. For distinguishing ulcerative colitis from CD, clinical validity has not been established; therefore, a chain of evidence for clinical utility for this purpose cannot be established.

Diagnostic Testing to Identify Interstitial Pneumonia Patterns: Envisia
Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. There is insufficient evidence in the peer reviewed medical literature regarding how the use of genomic testing would change patient management or improve health outcomes. There are no guidelines recommending the use of genomic testing (e.g., Envisia) as a complement to high-resolution chest CT to differentiate idiopathic pulmonary fibrosis from other interstitial lung diseases in patients who do not have a definite usual interstitial pneumonia. Unbiased, large, prospective, multicenter studies are needed to determine the clinical utility .

PROGNOSTIC TESTING

Clinical Context and Test Purpose
The purpose of prognostic testing of diagnosed disease is to predict natural disease course (e.g., aggressiveness, risk of recurrence, death). This type of testing uses gene expression of affected tissue to predict the course of disease.

The specific clinical context of each test is described briefly in the following sections. The following PICOs were used to select literature to inform this review.

Populations
The relevant population of interest is individuals diagnosed with a disease (e.g., CD).

Interventions
The interventions of interest are miscellaneous prognostic tests, specifically Crohn's Prognostic for CD.

Comparators
The comparator of interest is standard care without prognostic testing.

Outcomes
The outcomes of interest are overall survival, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The timing of follow-up ranges from months for aggressiveness of the disease to years for risk of recurrence or death.

Study Selection Criteria
For the evaluation of clinical validity of miscellaneous genetic or molecular tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Prognostic Testing for Crohn Disease with Crohn’s Prognostic

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
No studies of the 6-marker Crohn’s Prognostic test were identified.

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 testing.

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.

Direct evidence for clinical utility is lacking.

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.

It is not possible to construct a chain of evidence for clinical utility due to the lack of clinical validity.

Section Summary: Crohn's Prognostic
Direct and indirect evidence for clinical utility of the Crohn's Prognostic test to identify individuals likely to have an aggressive disease course are currently lacking.

SUMMARY OF EVIDENCE

For each test addressed, a literature review was conducted. The literature review was not comprehensive, but sufficient to establish lack of clinical utility. If it is determined that enough evidence has accumulated to reevaluate its potential clinical utility, the test will be removed from this evidence 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) there is insufficient evidence demonstrating the clinical validity of the test.

Diagnostic Testing

For individuals with symptoms of various conditions thought to be hereditary or with a known genetic component who receive diagnostic testing with a miscellaneous genetic or molecular test (e.g., DNA Methylation Pathway Profile, Celiac PLUS, GI Effects [Stool], IBD sgi Diagnostic, Know Error), the evidence is limited. Relevant outcomes are overall survival (OS), disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Prognostic Testing

For individuals who are diagnosed with various conditions (e.g., Crohn's prognostic) there are no published studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Therapeutic Tests

Previously reviewed therapeutic tests are no longer commercially available; no commercially available therapeutic test is reviewed in this policy.

MISCELLANEOUS LABORATORY TESTS

Individuals and providers need assurance that the tests they are utilizing lead to good health decisions and do not lead to patient harm. The risks of unverified miscellaneous laboratory testing include false-positive and false-negative results; which can lead to unnecessary treatment (with associated side effects), delay in or missed diagnosis and appropriate treatment(s). A useful laboratory test provides information to make a clinical management decision that improves the net health outcome.

There are a multitude of laboratory tests that lack clear evidence of safety and efficacy. Although the FDA approves and clears many types of laboratory tests for blood, saliva or tissue if they are used by many different hospitals and labs, for almost 50 years the FDA has given leeway to individual labs to develop and use their own tests-in house, as long as the labs meet certain standards.

Multiple factors can affect the accuracy/safety/efficacy of a laboratory test including:

- The test manufacturer
- What the test is used for and if it is known for being reliable
- A tests sensitivity and specificity to a specific disease
- Testing conditions, methods and equipment used to complete the test
- Storage and transportation of the blood samples
- Timing of the test in relation to the disease being evaluated
- Timing of food, beverages, and medications

For many years, the FDA has engaged in conversations regarding the oversight of laboratory testing. Concerns exist regarding the safety and efficacy of laboratory testing regarding prognostic, diagnostic, and therapeutic use. The FDA has maintained that these risks can be mitigated by ensuring the safety and effectiveness of these tests through oversite. On September 29, 2023, the FDA announced a proposed rule aimed at helping to ensure that in vitro diagnostic products (IVDs) are devices under the Federal Food, Drug, and Cosmetic Act including when the manufacturer of the IVD is a laboratory.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

A search of ClinicalTrials.gov did not identify any ongoing or unpublished trials that might influence this review.

Supplemental Information

PRACTICE GUIDELINES AND POSITION STATEMENTS

National Comprehensive Cancer Network

The NCCN (v. 5.2024) guidelines for colon cancer state that “it has not been established if molecular markers…are useful in treatment determination (predictive markers) and prognosis."(39)

American College of Gastroenterology

Celiac Disease

The American College of Gastroenterology (2023) published a clinical practice update for the diagnosis and management of celiac disease.(40) A recommendation for genetic testing using a multigene panel test (e.g., Celiac PLUS) was not included.

Inflammatory Bowel Syndrome

The American College of Gastroenterology (2018) practice guidelines on Crohn disease (41) states that genetic and routine serologic testing is not indicated to establish the diagnosis of Crohn's disease.

Government Regulations

National:

There is no national determination on this topic.

Local:

MolDX: Envisia™, Veractye™, Idiopathic Pulmonary Fibrosis Diagnostic Test (L37919); Original Effective Date: 5/13/19; Revision Effective Date: 6/29/23

This policy provides limited coverage for the Envisia™ Genomic Classifier (Veracyte™, Inc., South San Francisco, CA), a tissue based multi-analyte assay with algorithm analysis test (hereafter called Envisia) for interstitial lung disease (ILD) patients who are suspected of having idiopathic pulmonary fibrosis (IPF) and who do not have a definitive usual interstitial pneumonia (UIP) pattern by high resolution computed tomography (HRCT) or other known cause of ILD. IPF suspicion increases significantly in patients greater than 60 years of age when HRCT is not definitive, and comorbidities in this population make clinicians reluctant to perform surgical lung biopsy to obtain a diagnosis due to significant procedure morbidity and mortality. Envisia™ testing is performed on less-invasive bronchoscopy transbronchial biopsy (TBB) samples and is intended to provide a categorical UIP or non-UIP result that along with clinical and radiographic information may guide treatment without the need or risk of surgical lung biopsy.

Billing and Coding: MolDX: know error®. A55172. Original Effective Date 02/16/2017; Revision Effective Date 01/01/2023. Retired 5/30/24

The know error® DNA Specimen Provenance Assay is a forensic assay to confirm that a surgical specimen belongs to the patient evaluated for treatment. Although MolDX agrees the healthcare community should define and follow strict procedures regarding patient and patient specimen identification and handling, tests performed to measure the quality of a process do not provide information to diagnose or treat a patient illness or injury as defined in the Medicare benefit category. Therefore, the know error® DNA Specimen Provenance Assay is a statutorily excluded test. Although an Advance Beneficiary Notice (ABN) is not required for a statutory exclusion, providers supplying this test (directly or through a purchased service) should ensure patients understand the test is not a covered benefit.

To receive a DNA Specimen Provenance Assay service denial, please submit the following claim information:

- CPT code 84999 – unlisted chemistry procedure

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

- Analysis of Human DNA in Stool Samples as a Technique for Colorectal Cancer Screening
- BCR-ABL1 Testing in Chronic Myelogenous Leukemia and Acute Lymphoblastic Leukemia
- Cardiovascular Risk Panels
- Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)

- Circulating Tumor DNA for Management of Non-Small-Cell Lung Cancer (Liquid Biopsy)
- CPT Category III Codes-Noncovered Services
- Evaluation of Biomarkers for Alzheimer's Disease
- Gene Analysis for Corneal Dystrophy
- Gene Expression Profile Analysis for Risk Stratification for Prostate Cancer Management
- Gene Expression Profile Testing and Circulating Tumor DNA Testing for Predicting Recurrence in Colon Cancer (e.g., ColoPrint, Conon PRS, GeneFx, OncoDefender, Oncotype Dx Colon Cancer Test)
- Gene Expression Profiling for Cutaneous Melanoma
- Gene Expression Profiling for Uveal Melanoma
- Genetic and Laboratory Testing for Use of 5-Fluorouracil in Patients with Cancer
- Genetic Cancer Susceptibility Panels Using Next Generation Sequencing
- Genetic, Molecular and Other Tests-Experimental/Investigational Status
- Genetic Testing - Analysis of MGMT Promoter Methylation in Malignant Gliomas
- Genetic Testing-Assays of Genetic Expression in Tumor Tissue as a Technique to Help Guide Decision-Making in Patients With Breast Cancer
- Genetic Testing - *BRAF* Mutation in Selecting Melanoma Patients for Targeted Therapy
- Genetic Testing - Carrier Screening for Genetic Diseases
- Genetic Testing - Chromosomal Microarray (CMA) Analysis and Next-Generation Sequencing Panels, for the Evaluation of Children with Developmental Delay/Intellectual Disability, Autism Spectrum Disorder, and/or Congenital Anomalies
- Genetic Testing - Chromosomal Microarray Testing for the Evaluation of Early Pregnancy Loss and Intrauterine Fetal Demise
- Genetic Testing - Experimental/Investigational Status
- Genetic Testing - Fetal RHD Genotyping Using Maternal Plasma
- Genetic Testing - Human Leukocyte Antigen Testing for Celiac Disease
- Genetic Testing - Human Platelet Antigen Genotyping
- Genetic Testing - *JAK2, MPL* and *CALR* Testing for Myeloproliferative Neoplasms
- Genetic Testing - Microarray Testing for Cancers of Unknown Primary (CUP) Origin
- Genetic Testing - Molecular Markers in Fine Needle Aspirates (FNA) of the Thyroid
- Genetic Testing - Molecular Testing for the Diagnosis and Management of Pancreatic Cysts, Barrett Esophagus, and Solid Pancreaticobiliary Lesions (e.g., PathFinderTG®, PancraGEN, BarreGEN)
- Genetic Testing - NGS of Multiple Genes (Panel) for Malignant Conditions
- Genetic Testing - Noninvasive Prenatal Screening For Fetal Aneuploidies, Microdeletions, Single-Gene Disorders, and Twin Zygosity Using Cell-Free Fetal DNA
- Genetic Testing - Preimplantation
- Genetic Testing - Somatic Biomarker Testing (Including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Non-Small-Cell Lung Cancer (*EGFR, ALK, BRAF, ROS1, RET, MET, KRAS, HER2, PD-L1, TMB*)
- Genetic Testing - Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders
- Genetic Testing and Counseling
- Genetic Testing for Alpha1-Antitrypsin Deficiency
- Genetic Testing for Alzheimer's Disease
- Genetic Testing for Amyotrophic Lateral Sclerosis

- Genetic Testing for Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia (ARVC/D)
- Genetic Testing for Bloom Syndrome
- Genetic Testing for Cardiac Ion Channelopathies (e.g., Congenital Long QT Syndrome, Brugada Syndrome, etc.)
- Genetic Testing for Cystic Fibrosis
- Genetic Testing for Cytochrome P450 Polymorphisms
- Genetic Testing for Dilated Cardiomyopathy
- Genetic Testing for Duchenne and Becker Muscular Dystrophy
- Genetic Testing for Epilepsy
- Genetic Testing for Familial Cutaneous Malignant Melanoma *(CDKN2A)*
- Genetic Testing for *FLT3, NPM1*, *CEBPA, IDH1 and IDH2* Variants in Acute Myeloid Leukemia
- Genetic Testing for *FMR1* and *FMR2* Variants (Including Fragile X and Fragile XE Syndromes)
- Genetic Testing for Hereditary Hearing Loss
- Genetic Testing for Hereditary Hemochromatosis
- Genetic Testing for Heterozygous Familial Hypercholesterolemia
- Genetic Testing for Huntington Disease
- Genetic Testing for Inherited Hypertrophic Cardiomyopathy
- Genetic Testing for Inherited Thrombophilias
- Genetic Testing for *KRAS, NRAS*, and *BRAF* Mutation Analysis in Metastatic Colorectal Cancer
- Genetic Testing for Li-Fraumeni Syndrome
- Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
- Genetic Testing for Macular Degeneration
- Genetic Testing for Marfan Syndrome, Ehlers-Danlos, Thoracic Aortic Aneurysms and Dissections, and Connective Tissue Related Disorders
- Genetic Testing for Mitochondrial Disorders
- Genetic Testing for Myotonic Dystrophy
- Genetic Testing for Noonan Spectrum Disorder
- Genetic Testing for Pharmacogenetic Pain Management
- Genetic Testing for Prader-Willi and Angelman Syndromes (Chromosome 15 Abnormalities)
- Genetic Testing for PTEN Hamartoma Tumor Syndrome
- Genetic Testing for Retinal Dystrophies
- Genetic Testing for Rett Syndrome
- Genetic Testing for Specified Conditions Using Testing Panels
- Genetic Testing for Statin-Induced Myopathy
- Genetic Testing for Tay-Sachs Disease
- Genetic Testing for the Diagnosis of Inherited Peripheral Neuropathies
- Genetic Testing of CADASIL Syndrome
- Genetic Testing (Single Nucleotide Variants) to Predict Risk of Nonfamilial Breast Cancer
- Genotype-Guided Warfarin Dosing
- Germline Genetic Testing for *BRCA1, BRCA2*, and *PALB2* for Hereditary Breast/Ovarian Cancer Syndrome and Other High-Risk Cancers

- Germline Genetic Testing for Gene Variants Associated with Breast Cancer in Individuals at Moderate and High Breast Cancer Risk (e.g., *CHEK2, ATM, BARD1*, etc.)
- Identification of Microorganisms Using Nucleic Acid Probes
- Laboratory Tests Post Transplant (Kidney and Heart) and for Heart Failure
- Measurement of Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) and Secretory Type II Phospholipase A2 (sPLA2-IIA) in the Assessment of Cardiovascular Risk
- Molecular Testing in the Management of Pulmonary Nodules
- Multimarker Serum Testing Related to Ovarian Cancer (e.g., OVA1®, Overa™, OvaWatch and ROMA™ testing)
- Noninvasive Techniques for the Evaluation and Monitoring of Patients with Chronic Liver Disease
- Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease
- Pharmacogenomic and Metabolite Markers for Patients Treated with Thiopurines
- Proteomic Testing for Targeted Therapy in Non-Small-Cell Lung Cancer (NSCLC), e.g., VeriStrat®
- Serological Genetic and Molecular Screening for Colorectal Cancer
- Serum Biomarker Human Epididymis Protein 4 (*HE4*)
- Serum Markers for the Diagnosis of Inflammatory Bowel Disease
- Somatic Biomarker Testing (including Liquid Biopsy) for Targeted Treatment and Immunotherapy in Metastatic Colorectal Cancer *(KRAS, NRAS,BRAF, MMR/MSI, HER2, and TMB)*
- Urinary Biomarkers for Bladder Cancer

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through 11/21/24, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
7/1/18	4/17/18	4/17/18	Joint policy established
3/1/19	12/11/18		• Routine maintenance • Removed Decision Dx Melanoma from policy; added related policy Gene Expression Profiling for Cutaneous Melanoma
3/1/20	12/17/19		• Routine maintenance
3/1/21	12/15/20		• Removed – no longer marketed o TransPredict Fc Gamma 3A o DecisionDX-Thymoma • FirstSight added (new proprietary lab - liquid bx for CRC)
3/1/22	12/14/21		• Routine maintenance • (Envisia) 81554 added as EI • LCD added for Envisia
5/1/22	2/15/22		• FirstSight, *SEPT9* (i.e., epi proColon) and Gene expression profiling (i.e., ColonSentry, Bescreened) for colon cancer screening transferred to "Serological Genetic and Molecular Screening for Colorectal Cancer" • Title changed from: Miscellaneous Genetic and Molecular Diagnostic Tests
5/1/23	2/21/23		• Routine maintenance (slp) • Vendor Managed: N/A
5/1/24	2/20/24		• Routine maintenance (slp) • Vendor Managed: N/A • BCBSA archived 2.04.121 - Incorporated the information into 2.04.159 with additions of PLA codes • ImmunoGenomic Profile and ResponseDX: Colon removed – no longer marketed

			• MPS updated –
			  ○ therapeutic tests are no longer marketed
			  ○ Addition of MPS statement r/t Misc testing

7/1/24	4/16/24		• Off cycle review • Codes added as EI – 81265, 81266 (Know Error testing) • LCA added for Know Error
5/1/25	2/18/25		• Routine maintenance (slp) • Vendor Managed: N/A

Next Review Date: 1st Qtr, 2026

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: MISCELLANEOUS AND GENETIC AND MOLECULAR DIAGNOSTIC TESTS

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Not Covered
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.