



Louisiana

Miscellaneous Genetic and Molecular Diagnostic Tests

Policy # 00577

Original Effective Date: 01/01/2018

Current Effective Date: 11/09/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Note: Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes is addressed in medical policy 00190.

Note: KRAS, NRAS and BRAF Variant Analysis (including Liquid Biopsy) in Metastatic Colorectal Cancer is addressed in medical policy 00233.

Note: Serum Antibodies for the Diagnosis of Inflammatory Bowel Disease is addressed separately in medical policy 00238.

Note: Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer is addressed in medical policy 00291.

Note: Identification of Microorganisms Using Nucleic Acid Probes is addressed separately in medical policy 00488.

Note: Gene Expression Profiling for Uveal Melanoma is addressed in medical policy 00548.

Note: Gene Expression Profiling for Cutaneous Melanoma is addressed in medical policy 00622.

Services Are Considered Investigational

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

Based on review of available data, the Company considers all tests listed in this policy and grouped according to the categories of genetic testing listed below to be **investigational***:

- Testing of an affected (symptomatic) individual's germline to benefit the individual (excluding reproductive testing)
- Diagnostic testing

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- Prognostic testing
- Therapeutic testing
- Testing an asymptomatic individual to determine future risk of disease.

Policy Guidelines

Genetic testing is considered **investigational** when BCBSA criteria are not met, including when there is insufficient evidence to determine whether the technology improves the net health outcome.

Genetic Counseling

Genetic counseling is primarily aimed at patients 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 very 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.

Background/Overview

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	Therapeutic	Future Risk
Celiac PLUS	Prometheus	Oct 2014	●			●
Crohn's Prognostic	Prometheus	Oct 2014		●		

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Test Name	Manufacturer	Date Added	Diagnostic	Prognostic	Therapeutic	Future Risk
				●		
DNA Methylation Pathway Profile	Great Plains Laboratory	Jan 2015	●			
GI Effects ^{®‡} (Stool)	Genova Dxcs	Jan 2015	●			
IBD sgi Diagnostic ^{™‡}	Prometheus	Oct 2014	●			
ImmunoGenomic ^{®‡} Profile	Genova Dxcs	Aug 2015				●
Know Error ^{™‡}	Strand Dxcs	July 2016	●			
ResponseDx Colon	Cancer GXcs	Jan 2015			●	

Dxcs: Diagnostics; Gxcs: Genetics.

a. For example, ColoVantage^{®‡} and Epi proColon^{®‡}.

b. ARUP, Quest, Clinical Genomics and Epigenomics.

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 and have serious negative implications for patient care if the error is not corrected. Analysis of DNA microsatellites from tissue specimens can be performed by analyzing

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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 (Great Plains Laboratory) 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 test (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.

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 patients who carry at least 1 human leukocyte antigen DQ2 or DQ8; the negative predictive value of having neither allele exceeds 98%. Serum antibodies to tissue transglutaminase, endomysium, and deamidated gliadin peptide support a diagnosis of celiac disease but diagnostic confirmation requires duodenal biopsy taken when patients are on a gluten-containing diet.

Test Description: Celiac PLUS

Celiac PLUS (Prometheus Therapeutics & Diagnostics) 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. Genetic markers (human leukocyte antigen DQ2 and DQ8) are considered predictive of the risk of developing celiac disease; serologic markers (immunoglobulin A [IgA] anti-tissue transglutaminase antibody, IgA anti-endomysial antibodies, IgA anti-deamidated gliadin peptide antibodies, IgG anti-deamidated gliadin peptide, and total IgA) are considered diagnostic for celiac disease. Celiac PLUS is intended for patients at risk for the disease (eg, with an affected first-degree relative) or with symptoms suggestive of the disease.

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Irritable Bowel Syndrome

IBS is a functional gastrointestinal (GI) disorder that affects 10% to 20% of the general population in the U. S. 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. Recommended treatments include dietary restriction and pharmacologic symptom control. As living microorganisms that promote health when administered to a host in therapeutic doses, probiotics are being investigated as a treatment for IBS. Several systematic reviews of randomized controlled trials have found evidence to support efficacy, but results from recent randomized controlled trials have been mixed. 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. 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 (eg, 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 2 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 Therapeutics & Diagnostics) is a panel of 17 serologic (n=8), genetic (n=4), and inflammatory (n=5) biomarkers. A proprietary algorithm produces an IBD score; results are reported as consistent with IBD (consistent with ulcerative colitis, consistent with CD, or inconclusive for ulcerative colitis vs CD) or not consistent with IBD. The test is intended for use in patients with clinical suspicion of IBD.

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Therapeutic Tests

Test description: ResponseDX: Colon

Response Genetics currently markets 2 colon cancer genetic panels to guide treatment selection, as well as separate tests for 11 genes associated with colon cancer prognosis and/or treatment response. The Driver Profile panel comprises PCR variant testing in *KRAS*, *BRAF*, and mismatch repair genes (microsatellite instability), plus *NRAS* exon 2 and 3 sequencing. These gene tests are reviewed elsewhere (see medical policies 00190 and 00233), and this panel is not considered here. The ResponseDX: Colon test comprises the 4 tests in the Driver Profile plus: *EGFR* expression; *PI3K* exon 1, 9, and 20 sequencings; *TS* expression; *ERCC1* expression; *UGT1A1* SNV testing (rs8175347, rs4148323); *VEGFR2* expression; and *MET* amplification by fluorescence in situ hybridization.

Prognostic Tests

Crohn Disease

Recent studies have identified serologic and genetic 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 Therapeutics & Diagnostics) 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

Immunologic Disorders

Test Description: ImmunoGenomic Profile

The ImmunoGenomic Profile (Genova Diagnostics) is a buccal swab test that evaluates SNVs in 6 genes associated with immune function and inflammation: interleukin (IL)-10, IL-13, IL-1b, IL-4, IL-6, and tumor necrosis factor α . According to the company website, variations in these genes "can

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affect balance between cell (Th-1) and humoral (Th-2) immunity, trigger potential defects in immune system defense, and stimulate mechanisms underlying chronic, overactive inflammatory responses." "The test uncovers potential genetic susceptibility to: Asthma, Autoimmune Disorders, Certain Cancers, Allergy, Infectious Diseases, Bone Inflammation, Arthritis, Inflammatory Bowel Disease, Heart Disease, Osteopenia, and *Helicobacter pylori* infection (cause of ulcers)."

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

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. Genetic tests evaluated in this evidence review are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed under 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 these tests.

Rationale/Source

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 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 the effect on health outcomes.

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.

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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 (eg, DNA Methylation Pathway Profile, Know Error, Celiac PLUS, GI Effects [Stool], IBD sgi Diagnostic), the evidence is limited. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The evidence is insufficient to determine the effects of the technologies on health outcomes.

Prognostic Testing

For individuals who are diagnosed with various conditions who receive prognostic testing with a miscellaneous genetic or molecular test (eg, Crohn's Prognostic), there are no published studies. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The evidence is insufficient to determine the effects of the technologies on health outcomes.

Therapeutic Testing

For individuals who are diagnosed with various conditions (eg colorectal cancer) who receive therapeutic testing with a miscellaneous genetic or molecular test (eg, ResponseDX: Colon), no evidence was identified. Relevant outcomes are OS, disease-specific survival, change in disease status, and morbid events. The evidence is insufficient to determine the effects of the technologies on health outcomes.

Testing for Future Risk of Disease

For individuals with a family history of various conditions thought to be hereditary or with a known genetic component who receive testing for future risk of disease with a miscellaneous genetic or molecular test (eg, ImmunoGenomic Profile), no evidence was identified. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The evidence is insufficient to determine the effects of the technologies on health outcomes.

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Supplemental Information

Practice Guidelines and Position Statements

National Comprehensive Cancer Network

The NCCN (v.4.2020) guidelines for colon cancer state that it has "not been established if molecular markers are useful in treatment determination (predictive markers) and prognosis."

American College of Gastroenterology

Celiac Disease

In 2019, the American College of Gastroenterology published a clinical practice update for the diagnosis and monitoring of celiac disease. A recommendation for genetic testing using a multigene panel test (eg, Celiac PLUS) was not included.

Inflammatory Bowel Disease

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

Medicare National Coverage

There is no national coverage determination for the tests in this review. 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 ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT03311152	Diagnostic Accuracy of the Circulating Cell-free DNA-based Epigenetic	440	Feb 2022

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	Biomarker mSEPT9 for Hepatocellular Carcinoma Detection Among Cirrhotic Patients: the SEPT9-CROSS Study		
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NCT: national clinical trial

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- 10/05/2017 Medical Policy Committee review
- 10/18/2017 Medical Policy Implementation Committee approval. New policy.
- 01/12/2018 Coding update
- 10/04/2018 Medical Policy Committee review
- 10/17/2018 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 12/03/2018 Coding update
- 08/14/2019 Coding update
- 10/03/2019 Medical Policy Committee review
- 10/09/2019 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
- 03/23/2020 Coding update
- 09/23/2020 Coding update
- 10/01/2020 Medical Policy Committee review
- 10/07/2020 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 10/2021

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Louisiana

Miscellaneous Genetic and Molecular Diagnostic Tests

Policy # 00577

Original Effective Date: 01/01/2018

Current Effective Date: 11/09/2020

Coding

The five character codes included in the Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines are obtained from Current Procedural Terminology (CPT®)‡, copyright 2019 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.

The responsibility for the content of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines is with Blue Cross and Blue Shield of Louisiana and no endorsement by the AMA is intended or should be implied. The AMA disclaims responsibility for any consequences or liability attributable or related to any use, nonuse or interpretation of information contained in Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines. Fee schedules, relative value units, conversion factors and/or related components are not assigned by the AMA, are not part of CPT, and the AMA is not recommending their use. The AMA does not directly or indirectly practice medicine or dispense medical services. The AMA assumes no liability for data contained or not contained herein. Any use of CPT outside of Blue Cross Blue Shield of Louisiana Medical Policy Coverage Guidelines should refer to the most current Current Procedural Terminology which contains the complete and most current listing of CPT codes and descriptive terms. Applicable FARS/DFARS apply.

CPT is a registered trademark of the American Medical Association.

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

Code Type	Code
CPT	0079U, 81266, 81327, 81479, 84999 Add code eff 10/1/2020: 0203U
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into

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standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

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

‡ Indicated trademarks are the registered trademarks of their respective owners.

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

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

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