



# Louisiana

## Miscellaneous Genetic and Molecular Diagnostic Tests

**Policy #** 00577

**Original Effective Date:** 01/01/2018

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*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 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.*

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

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### **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, prognostic testing, and therapeutic 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	•			•
ColonSentry <sup>®†</sup>	GeneNews <sup>a</sup>	Aug 2015				•
Crohn's Prognostic	Prometheus	Oct 2014		•		
DecisionDx-Thymoma	Castle	Jan 2015		•		
DNA Methylation Pathway Profile	Great Plains Laboratory	Jan 2015	•			
GI Effects <sup>®†</sup> (Stool)	Genova Dxcs	Jan 2015	•			
IBD sgi Diagnostic <sup>™†</sup>	Prometheus	Oct 2014	•			
ImmunoGenomic <sup>®†</sup> Profile	Genova Dxcs	Aug 2015				•
Know Error <sup>™†</sup>	Strand Dxcs	July 2016	•			
ResponseDx Colon <sup>d</sup>	Response GXcs	Jan 2015			•	
SEPT9 methylated DNA <sup>b</sup>	Severalc	Oct 2014	•			
TransPredict Fc gamma 3A <sup>d</sup>	Transgenomic	Oct 2014			•	

Castle: Castle Biosciences; Dxcs: Diagnostics; Gxcs: Genetics; HHT: hereditary hemorrhagic telangiectasia.

<sup>a</sup> In a joint venture with Innovative Diagnostic Laboratory.

<sup>b</sup> For example, ColoVantage<sup>®†</sup> and Epi proColon<sup>®†</sup>.

<sup>c</sup> ARUP, Quest, Clinical Genomics and Epigenomics.

<sup>d</sup> Not clear if this test is currently offered.

### **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 deoxyribonucleic acid (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

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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 (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 (NPV) 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 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 (e.g., with an affected first-degree relative) or with symptoms suggestive of the 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. 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

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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 (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 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.

### **Colon Cancer**

Early detection of colorectal cancer (CRC) reduces disease-related mortality, yet many individuals do not undergo recommended screening with fecal occult blood test or colonoscopy. A simpler screening blood test may have the potential to encourage screening and decrease mortality if associated with increased screening compliance. Serum biomarkers that are shed from colorectal tumors have been identified and include Septin 9 hypermethylated DNA (*SEPT9*). The Septin 9 protein is involved in cell division, migration, and apoptosis and acts as a tumor suppressor; when hypermethylated, expression of *SEPT9* is reduced.

A cofounder of the biotechnology firm GeneNews developed a patented platform technology based on the sentinel principle. The sentinel principle posits that because blood interacts with all bodily tissues, “subtle changes occurring in association with injury or disease, within the cells and tissues of the body, may trigger specific changes in gene expression in blood cells reflective of the initiating stimulus.” In this way, blood cells (specifically, leukocytes) may act as sentinels of disease. In studies that led to the formulation of this principle, investigators compared gene expression (total ribonucleic acid [RNA] levels) in blood samples with cataloged genes from 9 different organs (brain, colon, heart, kidney, liver, lung, prostate, spleen, stomach) and estimated that 66% to 82% of genes encoded in the human genome are expressed in human leukocytes.

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### **Test Descriptions: SEPT9 Methylated DNA**

ColoVantage (various manufacturers) blood tests for serum *SEPT9* methylated DNA are offered by several laboratories (ARUP Laboratories, Quest Diagnostics, Clinical Genomics). Epi proColon (Epigenomics) received U.S. Food and Drug Administration (FDA) approval in April 2016. Epigenomics has licensed its Septin 9 DNA biomarker technology to Polymedco and LabCorp. ColoVantage and Epi proColon are both PCR assays; however, performance characteristics vary across tests, presumably due to differences in methodology (e.g., DNA preparation, PCR primers, probes).

### **Test Description: ColonSentry**

ColonSentry (GeneNews; Innovative Diagnostic Laboratory) is a PCR assay that uses a blood sample to detect expression of 7 genes found to be differentially expressed in CRC patients compared with controls: *ANXA3*, *CLEC4D*, *TNFAIP6*, *LMNB1*, *PRRG4*, *VNN1*, and *IL2RB*. Per the company website, these genes are early-warning signs of colon cancer, and test results can indicate the odds of having CRC compared with an average-risk person. An average-risk person is defined as one who is “≥50 years old[, is] asymptomatic for CRC...[, has] no personal history of benign colorectal polyps, colorectal adenomas, CRC, or IBD, and does not have a first-degree relative ... with CRC.” The test is intended for use in adults who are averse to colonoscopy and/or fecal occult blood testing. “Because of its narrow focus, the test is not expected to alter clinical practice for patients who comply with recommended screening schedules.”

## 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.

### **Thymomas and Thymic Carcinomas**

Thymomas and thymic carcinomas are rare epithelial tumors of the thymus. Most are diagnosed in individuals between 40 and 60 years of age. Thymic epithelial tumors range from histologically benign tumors to microscopically or macroscopically invasive low- or high-grade malignant tumors. However, even tumors that are histologically benign can behave aggressively.

### **Test Description: DecisionDx-Thymoma**

DecisionDx-Thymoma (Castle Biosciences) is a gene expression profile test that measures the activity of 23 genes within the thymic tumor. Its intended use is to distinguish between thymic carcinoma and thymoma and to predict tumor aggressiveness by the likelihood that the tumor will metastasize.

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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 sequencing; *TS* expression; *ERCC1* expression; *UGT1A1* SNV testing (rs8175347, rs4148323); *VEGFR2* expression; and *MET* amplification by fluorescence in situ hybridization.

#### **Non-Hodgkin Lymphoma**

Rituximab is a humanized IgG monoclonal antibody against the CD20 antigen, which is commonly expressed on B lymphocytes. It is FDA-approved for the treatment of non-Hodgkin lymphoma, chronic lymphocytic leukemia, and nononcologic uses (e.g., rheumatoid arthritis). Rituximab has demonstrated better response and survival rates in combination chemotherapy regimens in patients with follicular lymphoma, chronic lymphocytic leukemia, and diffuse large B-cell lymphoma than chemotherapy alone, though not all patients responded. Altered binding to lymphocyte-bound rituximab by cytotoxic effector cells (e.g., natural killer cells, macrophages) has been identified as a mechanism of reduced rituximab efficacy. Effector cells with a Val158Phe substitution variant in their surface receptors for IgG molecules (e.g., rituximab) have impaired binding affinity, and cellular cytotoxicity is reduced. A genetic test for the Val158Phe variant of the gene that encodes the IgG receptor on effector cells (*FCGR3A*) has been developed and investigated as a means of predicting response to rituximab.

### 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-1 $\beta$ , IL-4, IL-6, and tumor necrosis factor (TNF)  $\alpha$ . According to the company website, variations in these genes “can 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)**

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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 FDA has chosen not to require any regulatory review of these tests.

### **Centers for Medicare and Medicaid Services (CMS)**

Unless otherwise indicated for the diagnostic, prognostic, therapeutic, and future risk testing, 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.

### **Rationale/Source**

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 FOR MULTIPLE CONDITIONS**

### **Clinical Context and Test Purpose**

The purpose of diagnostic testing in patients for heritable or genetic 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 question addressed in this evidence review is: Does diagnostic testing for heritable or genetic pathogenic variants using the tests described below in symptomatic individuals improve the net health outcome?

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

### ***Patients***

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

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### **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, disease-specific survival, test accuracy and validity, change in disease status, and morbid events.

### **Timing**

The timing of follow-up for IBS, IBD, and celiac disease ranges from weeks for the diagnosis to years for assessment of health outcomes.

### **Setting**

These tests are offered commercially through various manufacturers.

### **Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

### **Diagnostic Testing for Multiple Conditions: DNA Methylation Pathway Profile**

#### *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).

No full-length, peer-reviewed studies of the DNA Methylation Pathway Profile 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 avoid unnecessary 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.

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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: DNA Methylation Pathway Profile**

No studies were identified that evaluated this test.

## **Diagnostic Testing for Multiple Conditions: Know Error Specimen Provenance Assay**

### ***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).

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, but these data are not specific to the Know Error test.

### ***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.

### *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: Know Error Specimen Provenance Assays**

There is a lack of published evidence on the use of the Know Error test to confirm the 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.

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### **Diagnostic Testing for Celiac Disease: Celiac PLUS**

#### ***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).

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. However, algorithmic testing is individualized according to 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.

#### ***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.

#### ***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.

No studies examining the clinical utility of Celiac PLUS 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.

Factors that support a chain of evidence for clinical utility are lacking. A comparison of clinical and/or histopathologic outcomes using either Celiac PLUS or ACG's published diagnostic algorithm would be required to demonstrate improved health outcomes with Celiac PLUS.

#### ***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**

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### ***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).

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.

### ***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.

### ***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.

Clinical trials demonstrating a net health benefit with the GI Effects fecal panel were not 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.

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.

### ***Section Summary: Irritable Bowel Syndrome***

Evidence for the clinical validity and utility of the GI Effects Comprehensive Stool Profile is lacking.

### ***Diagnostic Testing for Inflammatory Bowel Disease: IBD sgi Diagnostic***

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 and/or CD.

In a review of the monograph, Shirts et al (2012) 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, although not all investigators include these tests in recommended diagnostic strategies. These 3 markers are included in the 18-marker panel. Based on a 2006 meta-analysis (MA) of 60 studies (total N=11,608 patients), Reese et al (2006) reported that pooled sensitivity and specificity of the 3-test panel were 63% and 93%, respectively, for diagnosing IBD. Because the product monograph did 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.

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### ***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).

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 has suggested that the panels may perform similarly. Performance characteristics for the 18-marker panel to distinguish ulcerative colitis from CD were not provided.

### ***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.

### ***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.

No studies examining the clinical utility of IBD sgi Diagnostic 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.

### ***Section Summary: Inflammatory Bowel Disease***

No studies examining the clinical utility of IBD sgi Diagnostic were identified. Although manufacturer data supported the clinical validity of the test for diagnosing IBD, this evidence is insufficient to support a chain of evidence for clinical utility. 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 FOR COLORECTAL CANCER SCREENING**

The **U.S. Preventive Services Task Force** has recommended screening for CRC starting at age 50 years and continuing until age 75 years, but many adults do not receive screening for CRC. It is thought that less burdensome methods of screening could increase the number of adults screened and thereby improve outcomes.

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# Louisiana

## Miscellaneous Genetic and Molecular Diagnostic Tests

Policy # 00577

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### **Clinical Context and Test Purpose**

The purpose of diagnostic testing in patients with potential CRC is to establish a molecular diagnosis defined by the presence of a known pathologic variant(s).

The question addressed in this evidence review is: Does CRC screening using the tests described below in individuals diagnosed with a disease improve the net health outcome?

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

### ***Patients***

The relevant population of interest is patients who are being screened for CRC.

### ***Intervention***

The intervention of interest is *SEPT9* methylated DNA testing (e.g., ColoVantage, Epi proColon, ColonSentry).

### ***Comparators***

The comparator of interest is standard of care without genetic screening.

### ***Outcomes***

The outcomes of interest are overall survival, disease-specific survival, test accuracy and validity, change in disease status, and morbid events.

### ***Timing***

The timing of follow-up for CRC screening is weeks for the diagnosis of CRC to years for survival outcomes.

### ***Setting***

These tests are offered commercially through various manufacturers.

### **Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

## **Diagnostic Testing for Colorectal Cancer Screening: *SEPT9* Methylated DNA With ColoVantage and Epi proColon**

### ***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).

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The diagnostic performance of *SEPT9* methylation for colon cancer has been reported in meta-analyses. The systematic reviews identified from 2016 and 2017 included from 14 to 39 studies (see Table 2). Pooled sensitivity ranged from 62% to 71% and pooled specificity ranged from 91% to 93% (see Table 3). The systematic review by Nian et al (2017) found that study designs (case-control [CC] vs cross-sectional [CS]), assays or kits used (Epi proColon vs other), country (Asia or other), sample sizes (>300 or <300), and risk of bias of included studies all contributed to heterogeneity. Most included studies were case-control with the exclusion of difficult to diagnose patients, which may lead to a spectrum bias and overestimation of diagnostic accuracy. Reviewers included 20 studies of Epi proColon test 1.0, 2.0, or a combination of the two. When only looking at studies of Epi ProColon 2.0, sensitivity was 75% compared with 71% in the overall analysis, with a specificity of 93% (see Table 3). Sensitivity and specificity may be additionally affected by the specific algorithm used, with the 1/3 algorithm resulting in higher sensitivity and the 2/3 algorithm resulting in higher specificity.

**Table 2. Systematic Review Characteristics**

Study	Studies Included	N	Study Designs Included	Study Reference Standards Included	11-Item QUADAS Quality Assessment		
					No. of Studies Rated as High or Unclear Risk of Bias		
					No Domains	1-2 Domains	>2 Domains
Nian et al (2017)	25	9927	CC and CS	Colonoscopy	3	14	1
Li et al (2016)	39			Colonoscopy	6	12	21
Yan et al (2016)	14	9870	CC and CS	Colonoscopy	0	13	1

CC: case-control; CS: cross-sectional.

**Table 3. Systematic Review Results**

Study	Test	Sensitivity (95% CI), %	Specificity (95% CI), %
Nian et al (2017)	Various	71 (67 to 75)	92 (89 to 94)
Nian et al (2017)	Epi Procolon 2.0	75 (67 to 77)	93 (88 to 96)
Li et al (2016)	Various	62 (56 to 67)	91 (89 to 93)
Yan et al (2016)	Various	66 (64 to 69)	91 (90 to 91)
Yan et al (2016)	Epi Procolon	63 (58 to 67)	91 (90 to 92)

CI: confidence interval.

The Epi proColon test is the only *SEPT9* DNA test that has received U.S. FDA approval. It was approved in 2016 for use in average-risk patients who decline other screening methods.

The evidence review for the 2016 U.S. Preventive Services Task Force update on CRC screening included studies on blood tests for methylated *SEPT9* DNA. The inclusion criteria were fair- or good-quality English-language studies, asymptomatic screening populations, age of 40 years or older, and at average risk for CRC or not selected for inclusion based on CRC risk factors. The only study on *SEPT9* found to meet these inclusion criteria was PRESEPT (described below).

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PRESEPT (Church et al [2014]) was an international prospective screening study of the first-generation Epi proColon test (see Table 4). Of 1516 patients selected for laboratory analysis, colonoscopy identified 53 (3%) patients with invasive adenocarcinoma, 315 (21%) with advanced adenoma, and 210 (14%) with nonadvanced adenoma. The overall sensitivity, specificity, PPV, and NPV for the detection of invasive adenocarcinoma are shown in Table 5. Sensitivity for any adenoma was 48% and advanced adenoma was 11%.

**Table 4. Study Characteristics**

Study	Study Population	Design	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors
Church et al (2014)	Patients ≥50 y at average risk and scheduled for colonoscopy	Prospective random sampling from 7941 patients at 32 sites	Colonoscopy	6-16 d before colonoscopy	Yes

**Table 5. Study Results**

Study	Initial N	Final N	Excluded Samples	Clinical Validity (95% Confidence Interval), %			
				Sensitivity	Specificity	PPV	NPV
Church et al (2014)	1516	1510	6	48.2 (32.4 to 63.6)	91.5 (89.7 to 93.1)	5	100

NPV: negative predictive value; PPV: positive predictive value.

The purpose of the gaps tables (see Tables 6 and 7) is to display notable gaps identified in each study. This information is synthesized as a summary of the body of evidence following each table and provides the conclusions on the sufficiency of evidence supporting the position statement.

**Table 6. Relevance Gaps**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Duration of Follow-Up <sup>e</sup>
Church et al (2014)		3. First-generation test			

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

<sup>c</sup> Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

<sup>d</sup> Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

<sup>e</sup> Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

**Table 7. Study Design and Conduct Gaps**

Study	Selection <sup>a</sup>	Blinding <sup>b</sup>	Delivery of Test <sup>c</sup>	Selective Reporting <sup>d</sup>	Data Completeness <sup>e</sup>	Statistical <sup>f</sup>
Church et al (2014)	2. Not randomly sampled					

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The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

<sup>b</sup> Blinding key: 1. Not blinded to results of reference or other comparator tests.

<sup>c</sup> Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

<sup>d</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>e</sup> Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

<sup>f</sup> Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported

### ***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.

### ***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.

Studies comparing survival outcomes in patients who undergo CRC screening with *SEPT9* methylated DNA testing or with standard screening were not identified. Such comparative studies with clinically meaningful outcomes (e.g., survival) are necessary to demonstrate incremental improvement in the net health outcome compared with current standard screening approaches (fecal immunochemical test, colonoscopy) and to address lead-time bias for cancers identified through screening.

### ***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.

Because the sensitivity of *SEPT9* methylated DNA is low, a chain of evidence establishing the clinical utility of *SEPT9* methylated DNA cannot be established.

### ***Subsection Summary: Colorectal Cancer Screening With SEPT9 Methylated DNA Testing***

The evidence for clinical validity of CRC screening includes CC studies and prospective screening studies. Systematic reviews have reported that the sensitivity of testing ranges from 62% to 75% and the specificity from 91% to 93%. Studies were generally of low to fair quality. The prospective PRESEPT study with average-risk patients scheduled for colonoscopy estimated the sensitivity and specificity of Epi proColon for detection of invasive adenocarcinoma to be 48% and for an advanced adenoma to be 11%. Based on results from these studies, the clinical validity of *SEPT9* methylated DNA screening is limited by low sensitivity and low PPV of the test.

Detection of only half of preclinical cancers and a small proportion of advanced adenomas limits clinical utility of the test. There is a need for further studies comparing survival outcomes in patients screened with

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SEPT9 methylated DNA testing (ColoVantage, Epi proColon) and with other screening methods. Such comparative studies with clinically meaningful outcomes (e.g., survival) are necessary to demonstrate improvement in the net health outcome compared with current standard screening approaches (fecal immunochemical test, colonoscopy) and to address lead-time bias for cancers identified through screening. Because the evidence on clinical validity has reported that the test has a lower sensitivity than other screening methods, the clinical utility is uncertain. If the test is restricted only to patients who would otherwise not be screened, outcomes might be improved. However, if the test is used as a substitute for other screening tests that have higher sensitivity, outcomes may be worse.

### Diagnostic Testing for Colorectal Cancer Screening With ColonSentry

#### 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).

Two CC studies have been identified. Marshall et al (2010) conducted a genome-wide association study in 189 whole blood samples (98 controls, 91 patients with CRC) and identified 45 differentially expressed gene biomarker candidates using microarray hybridization. Through logistic regression and bootstrapping (subsampling with replacement) in a training set of 232 samples, 7 genes were selected for further development. In a subsequent test set of 410 samples (208 controls, 202 patients with CRC), sensitivity, specificity, positive predictive value (PPV), and NPV were determined (see Tables 8 and 9). Yip et al (2010) conducted a similar CS study of 210 blood samples from patients in Malaysia. The Malaysian population has different ethnic groups with different CRC incidences and CRC in Asian populations is more likely to be nonpolypoid (i.e., flat or depressed) compared with Western populations in whom the test was developed.

Sensitivity for the 2 studies ranged from 61% to 72% and specificity for detecting CRC were 70% to 77%. AUC was 0.76 (95% CI, 0.70 to 0.82).

Table 8. Study Characteristics

Study	Study Population	Design	Reference Standard	Timing of Reference and Index Tests
Marshall et al (2010)	202 patients with CRC and 208 controls	Case-control	NA	NA
Yip et al (2010)	99 patients with CRC and 111 controls	Case-control	NA	NA

NA: not applicable

Table 9. Study Results

Study	Initial N	Final N	Excluded Samples	AUC (95% CI)	Clinical Validity (95% Confidence Interval), %			
					Sensitivity	Specificity	PPV	NPV
Marshall et al (2010)	410			0.80	72	70	70	72

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		(0.76 to 0.84)		
Yip et al (2010)	200		61	77

AUC: area under the curve; NPV: negative predictive value; PPV: positive predictive value.

Gaps in relevance and design and conduct are shown in Tables 10 and 11. Because of its CS design, follow-up of controls to determine which strata developed CRC was not reported, limiting conclusions drawn about the accuracy of the test for risk prediction.

**Table 10. Relevance Gaps**

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Duration of Follow-Up <sup>e</sup>
Marshall et al (2010)	4. Included patients with CRC and healthy controls				
Yip et al (2010)	4. Included patients with CRC and healthy controls				

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment. CRC: colorectal cancer.

<sup>a</sup> Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

<sup>b</sup> Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.

<sup>c</sup> Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.

<sup>d</sup> Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).

<sup>e</sup> Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

**Table 11. Study Design and Conduct Gaps**

Study	Selection <sup>a</sup>	Blinding <sup>b</sup>	Delivery of Test <sup>c</sup>	Selective Reporting <sup>d</sup>	Data Completeness <sup>e</sup>	Statistical <sup>f</sup>
Marshall et al (2010)	2. Selection not random					
Yip et al (2010)	2. Selection not random					

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

<sup>a</sup> Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).

<sup>b</sup> Blinding key: 1. Not blinded to results of reference or other comparator tests.

<sup>c</sup> Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.

<sup>d</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>e</sup> Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.

<sup>f</sup> Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

### **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.

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### *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.

No studies examining the clinical utility of ColonSentry 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.

A chain of evidence supporting the use of ColonSentry for predicting CRC risk cannot be constructed due to lack of clinical validity.

### **Section Summary: Colorectal Cancer Screening With ColonSentry**

ColonSentry is intended to stratify patients with average CRC risk who are averse to current screening approaches to identify those at increased risk and therefore choose a less-invasive screening method. However, 2 CS studies are insufficient to demonstrate the risk predictive ability of the test; i.e., clinical validity has not been established. Direct and indirect evidence of clinical utility is currently lacking.

## **PROGNOSTIC TESTING**

### **Clinical Context and Test Purpose**

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

The question addressed in this evidence review is: Does prognostic testing using the tests described below in individuals diagnosed with a disease improve the net health outcome?

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

### **Patients**

The relevant population of interest is patients diagnosed with a disease (e.g., CD, thymomas, and thymic carcinomas).

### **Interventions**

The interventions of interest are miscellaneous prognostic tests, specifically Crohn's Prognostic for CD and DecisionDx-Thymoma for thymomas and thymic carcinomas.

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### **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.

### **Timing**

The timing of follow-up ranges from months for aggressiveness of the disease to years for risk of recurrence or death.

### **Setting**

These tests are offered commercially through various manufacturers.

### **Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

## **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).

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 avoid unnecessary 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.

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### **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 Disease**

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.

## **Prognostic Testing for Thymomas and Thymic Carcinomas With DecisionDx-Thymoma**

### **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).

No full-length, peer-reviewed studies assessing DecisionDx-Thymoma 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 avoid unnecessary 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: Thymomas and Thymic Carcinomas**

Evidence for the clinical validity and utility of the DecisionDx-Thymoma test to identify individuals likely to have an aggressive disease course is currently lacking.

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### **THERAPEUTIC TESTING**

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are length of life, quality of life, and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

### **Clinical Context and Test Purpose**

The purpose of therapeutic testing in patients who have been diagnosed with conditions like colon cancer and non-Hodgkin lymphoma is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does therapeutic testing using ResponseDX: Colon and TransPredict Fc gamma 3A in individuals diagnosed with colon cancer or non-Hodgkin lymphoma improve the net health outcome?

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

### ***Patients***

The relevant population of interest is patients diagnosed with colon cancer or non-Hodgkin lymphoma.

### ***Interventions***

The interventions of interest are miscellaneous tests for variants that affect response to treatment or environmental exposure, specifically ResponseDX: Colon and TransPredict Fc gamma 3A.

### ***Comparators***

The comparator of interest is standard care without therapeutic testing.

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### Outcomes

The outcomes of interest are overall survival, disease-specific survival, test accuracy and validity, change in disease status, and morbid events.

### Timing

The timing of follow-up ranges from weeks for treatment selection to years for survival outcomes.

### Setting

These tests are offered commercially through various manufacturers.

### Therapeutic Testing for Colon Cancer With ResponseDX: Colon

No full-length, peer-reviewed studies of the ResponseDX: Colon test were identified.

### Section Summary: Colon Cancer

Evidence supporting the use of the ResponseDX Colon test to guide treatment selection in patients with colon cancer is currently lacking.

### Therapeutic Testing for Non-Hodgkin Lymphoma and Rheumatoid Arthritis With TransPredict Fc Gamma 3A

### Systematic Reviews

Two meta-analyses were identified, which came to different conclusions about the association between *FCGR2A* and *FCGR3A* SNVs and response to rituximab.

Ghesquière et al (2017) published a patient-level MA from 2 cohorts of patients with B-cell lymphoma (see Table 12). There was a marginally significant trend toward worse event-free survival for patients with *FCGR3A* (see Table 13). In a MA of patients with rheumatoid arthritis, Lee et al (2014) reported no significant association between *FCGR3A* genotype and response to rituximab or TNF blockers (see Table 13). However, stratification by biologic type indicated an association between the *FCGR3A* VV+VF genotype and nonresponders to rituximab. Statistical heterogeneity was high ( $I^2=82\%$ ).

**Table 12. Systematic Review Characteristics**

Study	Trials	Dates	Participants	N	Design
Ghesquière et al (2017)	2		Patients with B-cell lymphoma	1034	MA of patient-level data from cohort studies
Lee et al (2014)	7	Through Jan 2014	Patients with rheumatoid arthritis	500	

MA: meta-analysis

**Table 13. Systematic Review Results**

Study	Event-Free Survival	Nonresponse to Rituximab	Nonresponse to TNF Blocker
Ghesquière et al (2017)			

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HR (95% CI)	0.87 (0.76 to 0.99)	
p	0.04	
Lee et al (2014)		
OR (95% CI)	0.88 (0.51 to 1.54)	1.337 (0.87 to 2.06)
p	0.66	0.19

CI: confidence interval; HR: hazard ratio; OR: Odds ratio; TNF: tumor necrosis factor

Small studies in patients with non-Hodgkin lymphoma have suggested that the Val158Phe variant of the *FCGR3A* gene might predict response to rituximab therapy, although survival outcomes do not differ by genotype. In subsequent, larger studies in rituximab-treated patients with follicular lymphoma and chronic lymphocytic leukemia, this finding was not replicated. Studies in other types of non-Hodgkin lymphoma have also reported no association between *FCGR3A* genotype and outcomes. MA of studies in rheumatoid arthritis did not find an association between *FCGR3* genotype and response to rituximab.

### Section Summary: Non-Hodgkin Lymphoma

There is mixed evidence on the TransPredict Fc gamma 3A test. Some studies have reported an association with response to rituximab while others have not. 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. No studies examining the clinical utility of TransPredict Fc gamma 3A were identified. Factors supporting a chain of evidence for predicting response to rituximab are lacking primarily because the evidence for clinical validity of the test is lacking.

## FUTURE RISK DISEASE TESTING

### Clinical Context and Test Purpose

The purpose of testing for future risk of disease in asymptomatic patients is that predictive and presymptomatic types of testing can be used to detect gene variants associated with disorders that appear after birth, usually later in life. These tests can be used in individuals with a family history of a genetic disorder, but who themselves have no features of the disorder at the time of testing. Predictive testing can identify variants that increase an individual's risk of developing disorders with a genetic basis (e.g., certain types of cancer or cardiovascular disease). Presymptomatic testing can determine whether a person will develop a genetic disorder, before any signs or symptoms appear, by determining whether an individual has a genetic variant that may lead to the development of the disease.

The question addressed in this evidence review is: Does testing of asymptomatic individuals for future risk of disease using the tests described below in asymptomatic individuals improve the net health outcome?

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

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### **Patients**

The relevant population of interest is patients with a family history of a genetic disorder that might develop later in life but who are currently without symptoms of the disorder.

### **Interventions**

The interventions of interest are miscellaneous genetic or molecular risk assessment tests, specifically ImmunoGenomic Profile.

### **Comparators**

The comparator of interest is standard care without genetic testing for future risk.

### **Outcomes**

The outcomes of interest are overall survival, disease-specific survival, test accuracy and validity, change in disease status, and morbid events.

### **Timing**

The timing of follow-up varies by test and is discussed in the following sections.

### **Setting**

These tests are offered commercially through various manufacturers.

## **Future Risk Disease Testing for Immunologic Disorders With ImmunoGenomic Profile**

### **Technically Reliable**

Assessment of technical reliability focuses on specific tests and operators and requires review of unpublished and often proprietary information. Review of specific tests, operators, and unpublished data are outside the scope of this evidence review and alternative sources exist. This evidence review focuses on the clinical validity and clinical utility.

### **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).

No full-length, peer-reviewed studies of the ImmunoGenomic Profile 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 avoid unnecessary testing.

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### *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.

### *Direct Evidence*

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test.

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

### **Section Summary: Immunologic Disorders**

Evidence for the clinical validity and utility of the ImmunoGenomic Profile to predict the risk of developing arthritis, asthma, allergies, or other chronic inflammatory disorders is currently lacking.

## **SUMMARY OF EVIDENCE**

### **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, Know Error, Celiac PLUS, GI Effects [Stool], IBD sgi Diagnostic), the evidence includes case series, CS studies, diagnostic accuracy studies, and cohort studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. 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. For each test addressed, a literature review was conducted. The literature review was not comprehensive, but sufficient to establish lack of clinical utility. A test will be removed from this evidence review and addressed separately if it is determined that enough evidence has accumulated to reevaluate its potential clinical utility. The evidence is insufficient to determine the effects of the technologies on health outcomes.

For individuals who are being screened for CRC who receive *SEPT9* methylated DNA testing (e.g., ColoVantage, Epi proColon, ColonSentry), the evidence includes CC, CS, and prospective diagnostic accuracy studies along with systematic reviews of those studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The PRESEPT prospective study estimated the sensitivity and specificity of Epi proColon detection of invasive adenocarcinoma at 48% and 92%, respectively. Other studies were generally low to fair quality. Based on results from these studies, the clinical validity of *SEPT9* methylated DNA screening is limited by the low sensitivity of the test given that the sensitivity of the test is lower than imaging screening strategies. Optimal intervals for retesting are not known. The evidence is insufficient to determine the effects of the technologies on health outcomes.

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### Prognostic Testing

For individuals who are diagnosed with various conditions (e.g., CD, thymomas and thymic carcinomas, rheumatoid arthritis) who receive therapeutic testing with a miscellaneous genetic or molecular test (e.g., Crohn's Prognostic, DecisionDx-Thymoma), 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 the effects of the technologies on health outcomes.

### Therapeutic Testing

For individuals who are diagnosed with various conditions (e.g., colon cancer, non-Hodgkin lymphoma) who receive therapeutic testing with a miscellaneous genetic or molecular test (e.g., ResponseDX: Colon, TransPredict Fc gamma 3A), the evidence includes case series, CS studies, diagnostic accuracy studies, and cohort studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. 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. For each test addressed, a literature review was conducted. The literature review was not comprehensive, but sufficient to establish lack of clinical utility. A test will be removed from this evidence review and addressed separately if it is determined that enough evidence has accumulated to reevaluate its potential clinical utility. 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 (e.g., ImmunoGenomic Profile), the evidence includes diagnostic accuracy studies. Relevant outcomes are overall survival, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. 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. For each test addressed, a literature review is conducted. The literature review was not comprehensive, but sufficient to establish lack of clinical utility. A test will be removed from this evidence review and addressed separately if it is determined that enough evidence has accumulated to reevaluate its potential clinical utility. The evidence is insufficient to determine the effects of the technologies on health outcomes.

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### **Policy History**

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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  
 Next Scheduled Review Date: 10/2019

### **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)<sup>®†</sup>, copyright 2017 by the American Medical Association (AMA). CPT is developed by the AMA as a listing of descriptive terms and five character identifying codes and modifiers for reporting medical services and procedures performed by physician.*

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

Code Type	Code
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CPT	81327, 81479, 84999, 87798
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

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

- A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
- B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
  - 1. Consultation with 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.

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