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

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

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

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.

Background/Overview
TESTS ADDRESSED IN THIS EVIDENCE REVIEW
Tests assessed in this evidence review are listed in Table 1. 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 in This Evidence Review

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Manufacturer</th>
<th>Date Added</th>
<th>Diagnostic</th>
<th>Prognostic</th>
<th>Therapeutic</th>
<th>Future Risk</th>
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<td>ColonSentry®</td>
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<td>Aug 2015</td>
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<td>Crohn's Prognostic</td>
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<td>Oct 2014</td>
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Castle: Castle Biosciences; Dxcs: Diagnostics; Gxcs: Genetics.

a In a joint venture with Innovative Diagnostic Laboratory.
b For example, ColoVantage® Epi proColor®.
c ARUP, Quest, Clinical Genomics, 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 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 DNA microsatellites from tissue specimens can be performed by analyzing long tandem repeats (LTRs) 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 allele; the negative predictive value (NPV) of having neither allele exceeds 98%. Serum antibodies to tissue transglutaminase, endomysium, and deamidated gliadin peptide (DGP) support a diagnosis of celiac disease, but diagnostic confirmation requires duodenal biopsy taken when patients are on a gluten-containing diet.

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 [anti-TTG] antibody, IgA anti-endomysial antibodies, IgA anti-DGP antibodies, immunoglobulin G [IgG] anti-DGP, and total IgA) are considered diagnostic for celiac disease. Celiac PLUS is intended for patients at risk for disease (e.g., with an affected first-degree relative) or with symptoms suggestive of disease.

Irritable Bowel Syndrome
Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder that affects 10% to 20% of the general population in the United States and worldwide. Symptoms include abdominal pain and/or bloating associated with disordered bowel habit (constipation, diarrhea, or both). Pathophysiology is poorly understood but may be related to chronic low-grade mucosal inflammation and disturbances in GI flora. 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 (RCTs) have found evidence to support efficacy, but results from recent RCTs 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 two main entities under the category of IBD. The diagnosis is typically made by endoscopy or colonoscopy with biopsy and histologic analysis. This requires a semi-invasive procedure; as a result, a blood test to diagnose IBD could avoid the need for the procedures.

Test Description: IBD sgi Diagnostic
IBD sgi Diagnostic (Prometheus Therapeutics & Diagnostics) is a panel of 17 serologic (n=8), genetic (n=4), and inflammatory biomarkers (n=5). A proprietary algorithm produces an IBD score; results are reported as consistent with IBD (consistent with UC, consistent with CD, or inconclusive for UC vs CD) or not consistent with IBD. The test is intended for use in patients with clinical suspicion of IBD.

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.

Test Descriptions: SEPT9 Methylated DNA
ColoVantage (various manufacturers) blood tests for serum SEPT9 methylated DNA are offered by several laboratories (Associated Regional and University Pathologists [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 ARUP and Quest. 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). Sensitivity as high as 90%, with 88% specificity and 99.9% NPV (4% positive predictive value [PPV]) have been reported for ColoVantage. By comparison, reported sensitivity and specificity for Epi proColon were 68% and 80%, respectively. Serum SEPT9 methylated DNA testing is intended for individuals 50 years of age or older who have an average risk of CRC.
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 “at least 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.

Cutaneous Melanoma
Cutaneous melanoma represents less than 5% of skin malignancies but results in the most skin cancer deaths. The incidence of cutaneous melanoma continues to increase, and it is currently the sixth most common cancer in the United States. Standard treatment options for stage I and II melanoma are excision with or without sentinel lymph node examination. Current risk factors to predict localized tumor aggression include Breslow tumor thickness, tumor ulceration, and mitotic rate of the tumor cells. The likelihood of regional lymph node involvement increases with increasing tumor thickness and negatively impacts the rate of survival significantly.
Test Description: DecisionDx-Melanoma

DecisionDx-Melanoma (Castle Biosciences) is a gene expression profile test with a signature of 31 genes, 28 discriminating genes, and 3 control genes. The test is used to measure the risk of metastasis in patients with stage I and II cutaneous melanoma and classifies tumors into 2 groups of risk of metastasis—low or high (classes 1 and 2, respectively). The test purports to give an independent prediction of tumor metastatic risk, independent of currently used metrics of risk assessment (e.g., Breslow thickness, ulceration status, and mitotic rate; American Joint Committee on Cancer [AJCC] stage, sentinel lymph node biopsy [SLNB] status), so that patients with high-risk stage I or II disease can undergo more aggressive surveillance treatment than they would otherwise receive. The test is intended to provide additional prognostic information to current staging methods (American Joint Committee on Cancer stage, [SLNB]).

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. 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.

Test Description: TransPredict Fc gamma 3A

Formerly PGxPredict:Rituximab, TransPredict Fc gamma 3 (Transgenomic) is a PCR assay that uses a blood sample to detect the Val158Phe variant of the FCGR3A gene. For patients who are homozygous for valine, the test reports a high likelihood of response to rituximab; for all other patients (homozygous for phenylalanine or heterozygous), the test reports an average probability of response. The test is intended for patients with follicular, CD20-positive, B-cell non-Hodgkin lymphoma who are being considered for treatment with rituximab.
FUTURE RISK IN ASYMPTOMATIC INDIVIDUALS

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-1β, IL-4, IL-6, and tumor necrosis factor α. 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

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, 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, and therapeutic tests of future risk, 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

The genetic testing categories are listed in Appendix Table 1. Evidence evaluated for the tests listed in Table 1 is presented after we outline general principles and categories of genetic tests.

The evaluation of a genetic test focuses on 3 main principles: (1) analytic validity (technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent); (2) clinical validity (diagnostic performance of the test [sensitivity, specificity, PPV and NPV] in detecting clinical disease); and (3) clinical utility (i.e., a demonstration that the diagnostic information can be used to improve patient health outcomes).

The review for this group of miscellaneous tests focuses only on clinical validity and utility. A fuller review of all 3 principles will be presented for tests when they are removed from this review to be addressed separately.
DIAGNOSTIC TESTS

Clinical Context and Test Purpose

The purpose of diagnostic testing in patients for genetic or heritable pathogenic variants in a symptomatic individual is to establish a molecular diagnosis defined by the presence of known pathologic variant(s). For genetic testing, a symptomatic individual is defined as an individual with a clinical phenotype that correlates with a known pathologic variant. The criteria under which diagnostic testing for a genetic or heritable disorder may be considered clinically useful are as follows:

- An association of the marker with the disorder has been established;
- Symptoms of the disease are present;
- A definitive diagnosis cannot be made based on history, physical examination, pedigree analysis, and/or standard diagnostic studies or tests;
- Clinical utility of a diagnosis has been established (e.g., by demonstrating that a definitive diagnosis will lead to changes in clinical management of the condition, changes in surveillance, or changes in reproductive decision making, and these changes will lead to improved health outcomes); and
- Establishing the diagnosis by genetic testing will end the clinical workup for other disorders.

The question addressed in this evidence review is: Does diagnostic testing for genetic or heritable 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.

**Interventions**

The interventions of interest are miscellaneous genetic or molecular diagnostic tests, specifically: DNA Methylation Pathway Profile, Celiac PLUS, GI Effects (Stool), IBD sgi Diagnostic, Know Error, and SEPT9 methylated DNA (e.g., ColoVantage, Epi proColon, ColonSentry).

**Comparator**

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

**Outcomes**

The outcome of interest varies by test and is discussed in the following sections.

**Time**

The time of interest varies by test and is discussed in the following sections.
Miscellaneous Genetic and Molecular Diagnostic Tests

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Setting
These tests are offered commercially through various manufacturers.

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

Clinical Validity
Evidence for clinical validity is lacking.

Clinical Utility
Direct and indirect evidence for clinical utility is lacking.

Section Summary: DNA Methylation Pathway Profile
No studies were identified that evaluated this test.

Know Error Specimen Provenance Assay
Clinical Validity
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.

Clinical Utility
Direct evidence for clinical utility is lacking. 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 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.

Celiac Disease
Celiac PLUS
In 2013, the American College of Gastroenterology (ACG) published an evidence-based diagnostic algorithm for patients with high (>5%) or low (<5%) probability of celiac disease. In both groups of patients, IgA anti-TTG antibody is “the preferred single test for detection of celiac disease in individuals over the age of 2 years” (strong recommendation based on a high level of evidence); sensitivity and specificity of the anti-TTG IgA has been reported as both approximately 95%. For patients with high probability of disease, initial diagnostic workup comprises duodenal biopsy and anti-TTG IgA. If both tests are negative, celiac disease is unlikely; if both are positive, celiac disease is diagnosed. If results are discrepant, further workup including human leukocyte antigen DQ2 and DQ8 genotyping and total IgA level to rule out IgA deficiency is recommended. For patients with low probability of disease, initial diagnostic workup comprises anti-TTG IgA
level and total IgA level. With a single exception, combining several serologic tests rather than obtaining IgA anti-TTG alone is not recommended due to substantially reduced specificity for only marginally increased sensitivity (weak recommendation based on moderate evidence). In children younger than 2 years of age, however, combination testing with IgA anti-TTG and anti-DGP (both IgA and IgG) is recommended due to reduced test performance in this age group (strong recommendation based on moderate evidence). A strong recommendation (based on moderate evidence) against routine human leukocyte antigen DQ2 and DQ8 testing in the initial diagnostic workup of celiac disease is made; targeted human leukocyte antigen DQ2 and DQ8 testing is recommended for select clinical situations (e.g., discrepant serology and biopsy results [strong recommendation based on moderate evidence]).

No studies of the combined serologic and genetic Celiac PLUS test were identified.

Clinical Validity
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 ACG. However, algorithmic testing is individualized according to baseline risk of disease and is done sequentially, rather than simultaneously as in Celiac PLUS. 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.

Clinical Utility
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. 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. 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.

Irritable Bowel Syndrome
GI Effects Comprehensive Stool Profile
Two manufacturer-sponsored studies of the GI Effects Comprehensive Stool Profile were published in 2014. Goepp et al conducted a retrospective cohort study to determine the frequency of abnormal fecal biomarkers among patients with IBS symptoms. Records from Genova Diagnostics were reviewed to identify patients with ICD-9 codes for at least 1 of 13 IBS symptoms who had available results of a fecal biomarker panel (N=2256). Quantitative stool culture for Lactobacillus and Bifidobacterium (“beneficial bacteria”) indicated low growth in 73% of patients, parasites in 8%, and elevated eosinophil protein X, elevated calprotectin, and low pancreatic elastase levels in 14%, 12%, and 7%, respectively. The authors
interpreted these biochemical findings to support diagnoses of food allergies, inflammation, and exocrine pancreatic insufficiency, respectively.

Parsons et al conducted a retrospective matched cohort study to compare direct medical costs of care for patients with IBS who underwent fecal biomarker testing with those of matched controls. Investigators searched medical and pharmacy claims from a national pharmacy benefits manager for IBS-related diagnosis codes; patients who also had fecal panel test codes and data for up to 1 year after testing (n=132) were compared with propensity-matched (for age, sex, diagnosis code[s], and baseline medical and pharmacy utilization) controls from the same database who had IBS-related diagnosis codes but no fecal test codes. Outcomes of interest were diagnostic and medical service costs determined from claims data. At baseline, laboratory costs were higher in tested groups than controls. At 30, 90, and 365 days after testing, total medical costs, GI procedural costs including imaging, and laboratory costs were higher in controls. For example, at 90 days after testing, GI procedural costs were $26 less than baseline utilization in the tested cohort and $165 more than baseline in the control cohort.

Clinical Validity
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.

Clinical Utility
Clinical trials demonstrating net health benefit with the GI Effects fecal panel were not identified. 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. Two claims-based, retrospective studies have evaluated abnormal fecal marker prevalence and costs associated with the use of the test. This evidence does not demonstrate a net health benefit with use of the test.

Inflammatory Bowel Disease
IBD sgi Diagnostic
The IBD sgi Diagnostic product monograph includes an extensive bibliography that documents associations of the 17 component markers, individually and in combination, with ulcerative colitis (UC) and/or CD. Development and performance characteristics of the 17-marker panel are described without citation, and it is unclear what standard criterion was used for diagnosis. Overall sensitivities for IBD, UC, and CD are reported as 74%, 98%, and 89%, respectively; specificities are reported as 90%, 84%, and 81%, respectively; receiver operating characteristic analysis showed greater discrimination with the 17-marker panel (area under the curve [AUC], 0.871) compared with any individual marker (greatest AUC=0.690 for IgA anti-Saccharomyces cerevisiae antibodies [ASCA]). Test performance characteristics for distinguishing UC from CD were not provided.
In a 2012 review of the monograph, Shirts et al 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 17-marker panel. Based on a 2006 meta-analysis of 60 studies (total N=11,608 patients), pooled sensitivity and specificity of the 3-test panel were 63% and 93%, respectively, for diagnosing IBD. Because the product monograph does not compare the 17-marker panel with the 3-marker panel, incremental improvement in diagnosis with the 17-marker panel is unknown. Shirts et al calculated an AUC for the 3-marker panel of 0.899.

Clinical Validity
Published evidence supports associations of each marker in the 17-marker panel, alone and in combination, with IBD diagnosis. Based on manufacturer data, the accuracy for IBD diagnosis of the 17-marker panel exceeds that of each component marker, but the relevant comparison— with a panel of 3 markers that has good discrimination for IBD—was not included; subsequent analysis suggests that the panels may perform similarly. Performance characteristics for the 17-marker panel to distinguish UC from CD were not provided.

Clinical Utility
No studies examining the clinical utility of IBD sgi Diagnostic were identified.

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

Colorectal Cancer
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. The primary outcomes of interest are CRC-specific and overall survival (OS).

SEPT9 Methylated DNA: ColoVantage and Epi proColon
There is a fairly large literature on the association of SEPT9 methylation with colon cancer in general. In case-control studies involving more than 3000 patients, overall sensitivity of SEPT9 DNA methylation screening was 60% to 70%, and specificity was 89%. Modifications to ColoVantage methodology increased sensitivity to 90% with little decrement to specificity. A systematic review published in 2016 reviewed 39 studies on the diagnostic performance of SEPT9 methylation for detecting colon cancer. The combined sensitivity was 62% (95% confidence interval [CI], 56% to 67%) and the combined specificity was 91% (95% CI, 89% to 93%). There was no significant impact on the accuracy of testing according to target gene number, tumor stage, geographic region, or method of analysis. Yan et al (2016) reported a meta-analysis
of 14 studies (total N=9870 patients) with similar results (sensitivity, 66%; 95% CI, 64% to 69%; specificity, 91%; 95% CI, 90% to 91%).

Nian et al (2017) published another systematic review including 25 studies (total N=9927 patients) and reported a higher overall sensitivity (71%; 95% CI, 67% to 75%) and similar specificity (92%; 95% CI, 89% to 94%). Study designs (case-control vs cross-sectional), 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. Only 2 studies were rated as having a low risk of bias in all QUADAS-2 domains.

One test has received U.S. FDA approval—the Epi proColon test. It was approved in 2016 for use in average-risk patients who decline other screening methods. Fewer studies have specifically evaluated the performance of the commercially available Epi proColon test. The 2017 review included 18 studies of Epi proColon test 1.0, 2.0, or a combination of the two. The sensitivity and specificity of Epi proColon 2.0 were 75% (95% CI, 67% to 77%) and 91% (95% CI, 80% to 96%), respectively. A 2014 case-control study that compared Epi proColon with fecal immunochemical testing (FIT) for CRC screening enrolled 102 patients with CRC and 199 patients who presented for screening. Colonoscopy was the reference standard. Sensitivity and specificity were 73% and 82% for Epi proColon, respectively, and 68% and 97%, respectively, for FIT. In 290 paired samples, the sensitivity of the 2 tests was similar (~70%), but the specificity of Epi proColon was lower (81% vs 97%). Similar results were observed in a 2015 retrospective case-control study that used a second-generation version of the test.

In 2014, Church et al reported on an international prospective screening study of Epi proColon, called PRESEPT. Patients 50 years of age or older with average risk of CRC who were scheduled for colonoscopy were enrolled (N=7941). Of these, 1516 (19%) were selected for laboratory analysis in stratified random sampling; colonoscopy identified 53 (3%) patients with invasive adenocarcinoma, 315 (21%) with advanced adenoma, 210 (14%) with nonadvanced adenoma, and 938 (62%) with no evidence of disease. Overall sensitivity, specificity, PPV, and NPV for Epi proColon detection of invasive adenocarcinoma were 48%, 92%, 5%, and 100%, respectively. Sensitivity for advanced adenoma was low (11%). As observed by study investigators, detection of only half of preclinical cancers and a small proportion of advanced adenomas limits clinical utility of the test.

Tham et al (2014) reported on a smaller prospective cohort study in Singapore (N=150). Investigators measured methylation levels of 7 genes, including SEPT9, in patients with stage I, II, or III CRC who underwent curative resection. Blood samples were collected 1 week before and 6 months and 1 year after surgery. At a median follow-up of 59 months (range, 5-79 months), 43 (29%) patients developed recurrence. Although a statistically significant association between methylated SEPT9 level at 1 year and recurrence was found, interpretation of this result is limited by lack of correction for multiple comparisons. Additionally, cutoff values for a positive test were determined by median levels rather than prespecified. Receiver operating characteristic curve analysis using optimized cutoffs for SEPT9 methylated DNA at 1 year yielded an AUC of 0.70 (95% CI, 0.58 to 0.82). The AUC for carcinoembryonic antigen at 1 year was similar (AUC=0.69; 95% CI, 0.57 to 0.80).
Orntoft et al (2015) published a case-control study examining whether the prognostic information is impacted by other clinical and demographic variables. One hundred fifty cases of CRC were matched with 150 controls from a database of 4698 individuals undergoing colonoscopy for evaluations of CRC. The variables examined, together with the results of the Epi proColon test, were age, sex, comorbidities, tumor site, and tumor stage. The overall sensitivity of Epi proColon was 73% (95% CI, 64% to 80%). Sensitivity varied by tumor stage. The sensitivity was 37% for stage I tumors; 91% for stage II, 77% for stage III, and 89% for stage IV. In addition to tumor stage, age and comorbidities impacted the accuracy of testing. Elderly patients (>65 years old) had both lower sensitivity and specificity of testing. Patients with arthritis had decreased sensitivity, while patients with coronary artery disease and diabetes had decreased specificity. Diabetes was particularly associated with a positive test, with an odds ratio of 5.2 (95% CI, 1.4 to 19.1) for a positive test compared with patients without diabetes.

The evidence review for the 2016 U.S. Preventive Services Task Force update on CRC screening included studies on blood tests for methylated \textit{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 \textit{SEPT9} found to meet these inclusion criteria was PRESEPT (described above). Therefore, reviewers concluded that “this screening method currently has limited evidence evaluating its use.”

**Clinical Validity**

The evidence for clinical validity of CRC screening includes case-control studies and 2 prospective screening studies. These studies have reported that the sensitivity of testing ranges from 60% to 80% and the specificity from 85% to 95%. The PRESEPT prospective study estimated the sensitivity and specificity of Epi proColon detection of invasive adenocarcinoma to 48% and 92%, respectively. Other studies were generally of low to fair quality. Based on results from these studies, the clinical validity of \textit{SEPT9} methylated DNA screening is limited by low sensitivity and low PPV of the test. The sensitivity of the test is lower than imaging screening strategies. Compared with stool-based strategies, the sensitivity is in the same range and the specificity is lower. Optimal intervals for retesting are not known.

**Clinical Utility**

Studies comparing survival outcomes in patients who undergo CRC screening with \textit{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 (FIT, colonoscopy) and to address lead-time bias for cancers identified through screening. Because the evidence for clinical validity is currently lacking, a chain of evidence establishing the clinical validity of \textit{SEPT9} methylated DNA cannot be established.

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

There is a need for further studies comparing survival outcomes in patients screened with \textit{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 (FIT, colonoscopy) and to
address lead-time bias for cancers identified through screening. Evidence on clinical validity has reported that the test has a lower sensitivity than other screening methods. 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.

**ColonSentry**

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 (120 controls, 112 patients with CRC), 7 genes were selected for further development. Sensitivity, specificity, PPV, and NPV for detecting CRC were 82%, 64%, 68%, and 79%, respectively. The AUC was 0.80 (95% CI, 0.74 to 0.85). In a test set of 410 samples (208 controls, 202 patients with CRC), sensitivity, specificity, PPV, and NPV were 72%, 70%, 70%, and 72%, respectively. AUC was 0.80 (95% CI, 0.76 to 0.84). The authors subsequently applied Bayesian modeling to incorporate the prevalence of CRC in the average-risk population (0.7%) and proposed relative risk categories to stratify average-risk patients for CRC screening further. Because of its cross-sectional 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. In a subsequent publication, the investigators reported test performance stratified by left- and by right-sided cancers and tumor stages.

Yip et al (2010) conducted a similar cross-sectional study of 210 blood samples (111 controls, 99 CRC) from patients in Malaysia. The Malaysian population has different ethnic groups with different CRC incidences (e.g., 0.02% in Chinese Malaysians, 0.01% in ethnic Malays), 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 and specificity for detecting CRC were 61% and 77%, respectively. AUC was 0.76 (95% CI, 0.70 to 0.82). With optimized cut points, sensitivity and specificity were 72% and 71%, respectively. As previously, the cross-sectional design of the study limits conclusions that can be drawn.

**Clinical Validity**

Two cross-sectional studies do not permit full characterization of ColonSentry to predict CRC risk.

**Clinical Utility**

No studies examining the clinical utility of ColonSentry were identified. Factors that support a chain of evidence for predicting CRC risk are lacking primarily because the evidence for clinical validity of the test is lacking.

**Subsection 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 cross-sectional 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 TESTS
Clinical Context and Test Purpose
The purpose of prognostic testing of diagnosed disease is to predict natural disease course (e.g., aggressiveness, risk of recurrence, death). This type of testing uses gene expression of affected tissue to predict the course of disease. The criteria under which prognostic testing may be considered clinically useful are as follows:

- An association of the marker with the natural history of the disease has been established; and
- Clinical utility of identifying the variant has been established, eg, by demonstrating that testing will lead to changes in clinical management of the condition or changes in surveillance.

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.

**Intervention**
The interventions of interest are miscellaneous prognostic tests, specifically: Crohn’s Prognostic, DecisionDx-Thymoma, and DecisionDx-Melanoma.

**Comparator**
The comparator of interest is standard care without prognostic testing.

**Outcomes**
The outcome of interest varies by test and is discussed in the following sections.

**Time**
The time of interest varies by test and is discussed in the following sections.

**Setting**
These tests are offered commercially through various manufacturers.

**Crohn Disease**

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

**Clinical Validity**
Evidence for clinical validity is lacking.
Clinical Utility
Direct and indirect evidence for clinical utility is lacking.

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.

Thymomas and Thymic Carcinomas
DecisionDx-Thymoma
No full-length, peer-reviewed studies assessing DecisionDx-Thymoma were identified.

Clinical Validity
Evidence for clinical validity is lacking.

Clinical Utility
Direct and indirect evidence for clinical utility is lacking.

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.

Cutaneous Melanoma
DecisionDx-Melanoma
Following initial therapy, patients with AJCC stage I or II melanoma typically do not receive surveillance imaging. However, patients with stage III melanoma may be managed with more frequent follow-up and imaging surveillance following therapy. The primary purpose of the DecisionDx-Melanoma test is to identify high-risk patients classified as stage I or II according to the AJCC criteria. The manufacturer website says that physicians can use this information to “consider ‘upstaging’ them for active systemic surveillance or referral to medical oncology for consideration of systemic drug therapy or clinical trials.” Although guidelines have suggested increased surveillance for higher risk patients, there is no direct evidence that increased surveillance reduces mortality. Due to the low mortality in stage I or II melanoma, 10-year survival is the outcome and time-point of interest.

Clinical Validity
To develop the DecisionDx-Melanoma gene panel, Gerami et al (2015) conducted a meta-analysis of published studies that identified differential gene expression in metastatic versus nonmetastatic primary cutaneous melanoma. Of 54 identified genes, investigators selected 20 for further PCR analysis based on chromosomal location. Five genes from the DecisionDx-UM gene panel were added based on analysis of metastatic and nonmetastatic primary cutaneous melanoma, and 2 probes (for both the 3’ and 5’ ends) of the BRCA1-associated protein 1 gene, BAP1, which has been associated with the metastatic potential of uveal melanoma, also were added. Finally, 4 genes with minimal variation in expression level between metastatic and nonmetastatic primary cutaneous melanoma were added as controls. The 31-gene panel
was applied to 3 cohorts using archived formalin-fixed, paraffin-embedded primary cutaneous melanoma tissue. Patients had a minimum follow-up of 5 years unless there was a well-documented metastatic event, including positive SLNB. Information about treatments received was not provided.

The first cohort (development set; see Table 2) included patients with stage I or II primary melanoma from 3 U.S. centers. The second and third cohorts included additional patients with stage 0, I, II, III, or IV disease from 7 U.S. centers (total N=268 patients). Thirty-four (20%) patients without evidence of metastasis had less than 5 years of follow-up. Test performance characteristics of the 3 cohorts are summarized in Table 2. For 78 patients in the third cohort (test set) with AJCC stage I or II cutaneous melanoma who had either a metastatic event or had more than 5 years of follow-up without metastasis, 5-year disease-free survival was 98% for class I patients and 37% for class II patients; PPV and NPV were 67% and 94%, respectively. For 220 patients with AJCC stage I or II cutaneous melanoma in the combined training and test cohorts, DecisionDx-Melanoma classified 84% of patients who did not develop metastasis as class I and 89% of patients who developed metastasis as class II (sensitivity, 90%; specificity, 84%; PPV=72%; NPV=95%). The median duration of follow-up for these 220 patients was not reported.

### Table 2. DecisionDx-Melanoma Test Performance Characteristics in Gerami et al

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Development Set</th>
<th>Training Set</th>
<th>Test Set</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N</td>
<td>107</td>
<td>164</td>
<td>104</td>
</tr>
<tr>
<td>Class 1, n (%)</td>
<td>64 (60)</td>
<td>88 (54)</td>
<td>61 (59)</td>
</tr>
<tr>
<td>Class 2, n (%)</td>
<td>43 (40)</td>
<td>76 (46)</td>
<td>43 (41)</td>
</tr>
<tr>
<td>5-year disease-free survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I, %</td>
<td>100</td>
<td>91</td>
<td>97</td>
</tr>
<tr>
<td>Class II, %</td>
<td>38</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>Sensitivity, %</td>
<td>100</td>
<td>85</td>
<td>89</td>
</tr>
<tr>
<td>Specificity, %</td>
<td>78</td>
<td>80</td>
<td>83</td>
</tr>
<tr>
<td>Positive predictive value, %</td>
<td>58</td>
<td>75</td>
<td>72</td>
</tr>
<tr>
<td>Negative predictive value, %</td>
<td>100</td>
<td>89</td>
<td>93</td>
</tr>
<tr>
<td>Area under the receiver operating curve</td>
<td>0.93</td>
<td>0.91</td>
<td>0.91</td>
</tr>
</tbody>
</table>

In a subsequent study of patients with melanoma who had undergone SLNB, Gerami et al (2015) compared prognostic classification by DecisionDx-Melanoma with biopsy results. A total of 217 patients comprised a convenience sample from a database of 406 patients previously tested with DecisionDx-Melanoma. Patients who had undergone SLNB were eligible for the current study and might have overlapped with patients in the Gerami study discussed above. Most (73%) patients had a negative SLNB, and 27% had a positive SLNB; the SLNB-positive patients were AJCC stage III. Five-year OS for SLNB-negative patients was 70% and 62% for SLNB-positive patients. DecisionDx-Melanoma classified 76 (35%) tumors as low risk (class I) and 141 (65%) tumors as high-risk (class II). Five-year OS for class I patients was 89% and 55% for class II patients. Within the group of SLNB-negative patients, 5-year OS was 91% in class I patients and 55% in class II patients. Within the group of SLNB-positive patients, 5-year OS was 77% in class I patients and 57% in class II patients.
Ferris et al (2017) compared the accuracy of DecisionDx-Melanoma with a web-based AJCC Individualized Melanoma Patient Outcome Prediction Tool. The study included 205 patients who appear to overlap with the patients in the second Gerami (2015) study described above. AJCC-predicted 5-year survival for each patient was obtained using the prediction tool and categorized into low and high risk based on both a 68% predicted 5-year survival and a 79% predicted 5-year survival. The 68% and 79% cutpoints were reported to correspond to 5-year survival in patients with stage IIA and IIB, respectively, although it is unclear whether those cutpoints were prespecified, whether they were based on internal or external estimates of risk, or whether they are commonly used in practice. The prognostic sensitivity and specificity for death (median follow-up, 7 years) of the Decision-Dx Melanoma were 78% and 69%, respectively (CIs not reported). The sensitivity and specificity for the AJCC calculator with the 79% cutpoint were 60% and 74%, respectively. The combination of the DecisionDx-Melanoma and AJCC tools had a sensitivity of 82% and specificity of 62%. The method used to create a binary combination of the 2 tools was not described but, given that sensitivity increased and specificity decreased, the combination was likely categorized as positive if either test was positive. The cross-classification for the DecisionDx-Melanoma and AJCC tools for 5-year OS is shown in Table 3.

### Table 3. Cross-Classification for the DecisionDx-Melanoma and AJCC Tool (79% Cutpoint) for 5-Year Overall Survival

<table>
<thead>
<tr>
<th>Risk Classification (DecisionDx-Melanoma vs AJCC)</th>
<th>N</th>
<th>No. of Events</th>
<th>5-Year Overall Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low/low</td>
<td>105</td>
<td>9</td>
<td>96</td>
</tr>
<tr>
<td>Low/high</td>
<td>13</td>
<td>2</td>
<td>83</td>
</tr>
<tr>
<td>High/low</td>
<td>30</td>
<td>11</td>
<td>71</td>
</tr>
<tr>
<td>High/high</td>
<td>57</td>
<td>28</td>
<td>44</td>
</tr>
</tbody>
</table>

Adapted from Ferris et al (2017).
AJCC: American Joint Committee on Cancer.

### Section Summary: Clinical Validity

Three studies using archived tumor specimens suggested that DecisionDx-Melanoma may provide incremental prognostic information for patients with melanoma compared with current staging methods (AJCC staging, SLNB). However, these studies were small and might have enrolled similar or overlapping patient sets as well as patients outside of the intended use population (AJCC stage I/II); follow-up might have been inadequate to determine disease-free survival in some patients; and because details about treatments received were not provided, the impact of possible confounding by treatment cannot be assessed. These findings require replication in larger, independent cohorts, ideally with homogenous treatment histories.

### Clinical Utility

Direct evidence for clinical utility is limited. Berger et al (2016) published a retrospective study of 156 consecutive patients from 6 institutions who had cutaneous melanoma and were evaluated with the DecisionDx-Melanoma test. This study used chart review to describe changes in management and examined whether these changes were associated with DecisionDx-Melanoma results. The frequency of
clinic visits, imaging tests, referrals, and blood work was measured before and after DecisionDx results were available. For 40 of 42 patients with class I results, there was reduced utilization; for 74 of 79 patients with class II results, there was increased utilization. The difference in management changes by test class was statistically significant (p<0.001).

**Section Summary: Cutaneous Melanoma**

Evidence for the clinical validity and utility of the DecisionDx-Melanoma test to identify individuals likely to have an aggressive disease course is currently lacking. Some evidence on clinical validity has indicated that the gene expression profile can identify groups of patients with different levels of metastatic risk. This evidence is limited by small, select patient samples and a lack of independent validation. There is minimal evidence on clinical utility, with a single retrospective study reporting test results associated with utilization measures. A chain of evidence is not possible given the lack of sufficient clinical validity.

**THERAPEUTIC TESTS**

**Clinical Context and Test Purpose**

There are 3 main types of therapeutic tests to identify genetic variants that alter the response to treatment or an environmental factor. A description of the types of tests and purpose is below:

- Constitutional (germline) testing to detect genetic variants that alter, e.g., the risk of treatment response, adverse events, drug metabolism, or drug effectiveness (e.g., cytochrome P450 testing [also referred to as pharmacogenomics]).
- Tissue-specific or tumor testing to detect variants that predict response to a certain type of treatment, e.g., ALK variant testing in non-small-cell lung cancer to predict response to crizotinib.
- Testing for genetic variants that adversely affect response to exposures in the environment that are ordinarily tolerated (e.g., G6PD deficiency, genetic disorders of immune function, aminoacidopathies).

The criteria under which predictive testing for variants that affect response to treatment or environmental exposure may be considered clinically useful are:

- Constitutional (germline) testing:
  - Association of the marker with a phenotype or a metabolic state that relates to drug efficacy or adverse drug reactions has been established; and
  - Clinical utility has been established, e.g., by demonstrating that results of the genetic test will impact clinical decision making and will be expected to yield improved clinical outcomes for the patient based on drug selection or dosage.
- Tissue-specific or tumor testing:
  - Association of a variant with response to a particular drug has been established; and
  - Clinical utility has been established, e.g., by demonstrating that the patient is a candidate for targeted drug therapy associated with a specific variant.

The question addressed in this evidence review is: Does therapeutic 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.

**Intervention**
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.

**Comparator**
The comparator of interest is standard care without therapeutic testing.

**Outcomes**
The outcome of interest varies by test and is discussed in the following sections.

**Time**
The time of interest varies by test and is discussed in the following sections.

**Setting**
These tests are offered commercially through various manufacturers.

**Colon Cancer**

**ResponseDX: Colon**

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

**Clinical Validity**
Evidence for clinical validity is lacking.

**Clinical Utility**
Direct and indirect evidence for clinical utility is lacking.

**Section Summary: Colon Cancer**
Evidence for the clinical validity and utility of the ResponseDX Colon to guide treatment selection in patients with colon cancer is currently lacking.

**Non-Hodgkin Lymphoma**

**TransPredict Fc Gamma 3A**

In a multicenter study from France, Cartron et al (2002) compared objective response rates (including unconfirmed complete remission) among 49 previously untreated patients with follicular lymphoma who received rituximab. Ten (20%) patients had the homozygous valine genotype of FCGR3A, 17 (35%) patients were homozygous for phenylalanine, and 22 (45%) patients were heterozygotes. At 2 months, the
objective response rate was 100% in valine homozygotes, 70% in phenylalanine homozygotes, and 64% in heterozygotes (p=0.09). At 12 months, objective response rates were 90%, 59%, and 45%, respectively (p=0.06). At both time points, the differences in response rates between valine homozygotes and phenylalanine carriers (homo- and heterozygotes) were statistically significant. With a median follow-up of 35 months, there was no statistical difference in 3-year progression-free survival between valine homozygotes (56%) and phenylalanine carriers (35%).

In a multicenter study from Korea, Kim et al (2006) compared objective response rates in 198 patients with diffuse large B-cell lymphoma who received first-line CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone; n=85) or rituximab plus CHOP (R-CHOP; n=113). Fifty-three (47%) patients were valine homozygous, 6 (5%) patients were phenylalanine homozygous, and 54 (48%) patients were heterozygous. In the R-CHOP group, the complete response rate was statistically greater in valine carriers (88%) than in phenylalanine carriers (50%) and 79% in heterozygotes (p=0.002). In the CHOP group, response rates were similar across genotypes. With a median follow-up of 420 days, no differences in event-free survival or OS across genotypes were found in the treatment groups.

Subsequent, larger studies have not shown an association between FCGR3A genotype and outcomes in patients with follicular lymphoma or chronic lymphocytic leukemia who received rituximab plus chemotherapy. Smaller studies in rituximab-treated patients with diffuse large B-cell lymphoma, mantle cell lymphoma, and posttransplant lymphoproliferative disorder also have reported no association.

Two meta-analyses were identified, which came to different conclusions about the association between FCGR2A and FCGR3A SNVs and response to rituximab. In 2016, Ghesquières et al published a patient-level meta-analysis from 2 large cohorts with B-cell lymphoma (total N=1034 patients). FCGR3A status did not correlate with OS, and there was a marginally significant trend toward worse event-free survival for patients with FCGR3A (hazard ratio, 0.87; 95% CI, 0.76 to 0.99; p=0.04). Febrile neutropenia was more common in patients with FCGR3A variants (39%) compared with patients with FCGR2A SNVs (29%) or no SNVs (32%; p=0.04).

Biologic therapies used to treat lymphoma are also used to treat autoimmune diseases like rheumatoid arthritis. To this end, a 2014 meta-analysis from Korea assessed the association between FCGR3A and IL6 genotype and response to biologic therapies in patients with rheumatoid arthritis. The literature was searched through January 2014, and 3 studies of FCGR3A and rituximab were included (total N=500 patients). Study quality was not assessed. A statistically significant association between FCGR3A genotype and response to rituximab was not observed (odds ratio for nonresponse, valine homozygotes vs all other patients, 0.59; 95% CI, 0.10 to 3.4; p=0.55); statistical heterogeneity was high (I²=82%).

Clinical Validity
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. Meta-analysis of studies in rheumatoid arthritis did not find an association between FCGR3 genotype and response to rituximab.

**Clinical Utility**

No studies examining the clinical utility of TransPredict Fc gamma 3A were identified. Factors that support a chain of evidence for predicting response to rituximab are lacking primarily because the evidence for clinical validity of the test is lacking.

**Section Summary: Non-Hodgkin Lymphoma**

There is mixed evidence on the clinical validity of the TransPredict Fc Gamma 3A test. Some studies have reported an association with response to rituximab while others have not. 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 IN ASYMPTOMATIC INDIVIDUALS**

**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 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 development of the disease. The criteria under which testing for a genetic or heritable disorder may be considered clinically useful are as follows:

- An association of the marker with future disorder has been established; and
- Clinical utility has been established (e.g., by demonstrating that testing will lead to improved health outcomes based on prevention or early detection strategies).

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.

**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.

**Intervention**

The interventions of interest are miscellaneous genetic or molecular risk assessment tests, specifically ImmunoGenomic Profile.
Comparator
The comparator of interest is standard care without genetic testing for future risk.

Outcomes
The outcome of interest varies by test and is discussed in the following sections.

Time
The time of interest varies by test and is discussed in the following sections.

Setting
These tests are offered commercially through various manufacturers.

Immunologic Disorders
ImmunoGenomic Profile
No full-length, peer-reviewed studies of the ImmunoGenomic Profile were identified.

Clinical Validity
Evidence for clinical validity is lacking.

Clinical Utility
Direct and indirect evidence for clinical utility is lacking.

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 Tests
For individuals with symptoms of various conditions thought to be hereditary or with a known genetic component who receive diagnostic testing with a miscellaneous genetic or molecular test (e.g., DNA Methylation Pathway Profile, Celiac PLUS, GI Effects [Stool], IBD sgi Diagnostic, Know Error), the evidence includes case series, cross-sectional studies, diagnostic accuracy studies, and cohort studies. Relevant outcomes are OS, 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.

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FOR INDIVIDUALS WHO ARE BEING SCREENED FOR CRC WHO RECEIVE SEPT9 METHYLATED DNA TESTING (E.G., COLOVANTAGE, EPI PROCOLON, COLONSENTRY), THE EVIDENCE INCLUDES CASE-CONTROL, CROSS-SECTIONAL, AND PROSPECTIVE DIAGNOSTIC ACCURACY STUDIES. RELEVANT OUTCOMES ARE OS, 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. IT IS UNCLEAR WHETHER THE TEST IS MEANT TO BE USED IN ADDITION TO OR IN PLACE OF EXISTING TESTS. BASED ON RESULTS FROM THESE STUDIES, THE CLINICAL VALIDITY OF SEPT9 METHYLATED DNA SCREENING IS LIMITED BY LOW SENSITIVITY OF THE TEST GIVEN THAT THE SENSITIVITY OF THE TEST IS LOWER THAN IMAGING SCREENING STRATEGIES. COMPARED WITH STOOL-BASED STRATEGIES, THE SENSITIVITY IS IN THE SAME RANGE AND THE SPECIFICITY IS LOWER. OPTIMAL INTERVALS FOR RETESTING ARE NOT KNOWN. THE EVIDENCE IS INSUFFICIENT TO DETERMINE THE EFFECTS OF THE TECHNOLOGIES ON HEALTH OUTCOMES.

PROGNOSTIC TESTS

FOR INDIVIDUALS WHO ARE DIAGNOSED WITH VARIOUS CONDITIONS (E.G., CD, THYMOMAS AND THYMIC CARCINOMAS, CELIAC DISEASE) WHO RECEIVE PROGNOSTIC TESTING WITH A MISCELLANEOUS GENETIC OR MOLECULAR TEST (E.G., CROHN'S PROGNOSTIC, DECISIONDX-THYMOMA), 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.

FOR INDIVIDUALS WHO ARE DIAGNOSED STAGE I OR II MELANOMA WHO RECEIVE PROGNOSTIC TESTING WITH DECISIONDX-MELANOMA, THE EVIDENCE INCLUDES DIAGNOSTIC ACCURACY STUDIES AND DECISION IMPACT STUDIES. RELEVANT OUTCOMES ARE OS, TEST ACCURACY AND VALIDITY, DISEASE-SPECIFIC SURVIVAL, CHANGE IN DISEASE STATUS, AND MORBID EVENTS. THE 3 CLINICAL VALIDITY STUDIES ENROLLED SIMILAR OR OVERLAPPING PATIENT SETS AND PATIENTS OUTSIDE OF THE INTENDED USE POPULATION (AJCC STAGE I OR II). THEY REPORTED FOLLOW-UP INADEQUATE TO DETERMINE DISEASE-FREE SURVIVAL IN SOME PATIENTS, AND OFFERED INADEQUATE DETAILS ABOUT TREATMENTS RECEIVED. ONE RETROSPECTIVE STUDY HAS REPORTED THAT TEST RESULTS ARE ASSOCIATED WITH UTILIZATION MEASURES BUT, WITHOUT SUFFICIENT EVIDENCE OF CLINICAL VALIDITY, IT IS NOT KNOWN WHETHER THE CHANGES IN MANAGEMENT WERE APPROPRIATE. THE EVIDENCE IS INSUFFICIENT TO DETERMINE THE EFFECTS OF THE TECHNOLOGIES ON HEALTH OUTCOMES.

THERAPEUTIC TESTS

FOR INDIVIDUALS WHO ARE DIAGNOSED WITH VARIOUS CONDITIONS (E.G., CROHN DISEASE, THYMOMAS AND THYMIC CARCINOMAS, CELIAC DISEASE) WHO RECEIVE THERAPEUTIC TESTING WITH A MISCELLANEOUS GENETIC OR MOLECULAR TEST (E.G., RESPONSEDX: COLON, TRANSPREDICT FC GAMMA 3A), THE EVIDENCE INCLUDES CASE SERIES, CROSS-SECTIONAL STUDIES, DIAGNOSTIC ACCURACY STUDIES, AND COHORT STUDIES. RELEVANT OUTCOMES ARE OS, 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.
Miscellaneous Genetic and Molecular Diagnostic Tests

Policy # 00577
Original Effective Date: 01/01/2018
Current Effective Date: 01/01/2018

Tests 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 OS, 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.

References

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44. Shirts B, von Roon AC, Tebo AE. The entire predictive value of the prometheus IBD sgi diagnostic product may be due to the three least expensive and most available components. Am J Gastroenterol. Nov 2012;107(11):1760-1761. PMID 23160303
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Miscellaneous Genetic and Molecular Diagnostic Tests

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Policy History
Original Effective Date: 01/01/2018
Current Effective Date: 01/01/2018
10/05/2017 Medical Policy Committee review
10/18/2017 Medical Policy Implementation Committee approval. New policy.
01/12/2018 Coding update
Next Scheduled Review Date: 10/2018

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

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<tr>
<td>ICD-10 Diagnosis</td>
<td>All related diagnoses</td>
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*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);
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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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