2.04.121	Miscellaneous Genetic and Molecular Diagnostic Tests		
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Policy Statement

All tests listed in this policy are considered **investigational** and grouped according to the categories of genetic testing outlined in Blue Shield of California Medical Policy: General approach to Genetic Testing:

- 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

Policy Guidelines

Genetic testing is considered **investigational** when Blue Cross Blue Shield Association Technology Evaluation Center (TEC) criteria are not met, including when there is insufficient evidence to determine whether the technology improves the net health outcome.

Genetic Counseling

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

Coding

There is a specific CPT code for *SEPT9* methylation analysis:

- **81327**: *SEPT9 (Septin9)* (e.g., colorectal cancer) methylation analysis

According to laboratory websites, CPT codes listed below are used to report some of the listed tests:

- **Prometheus Celiac PLUS**
  - **81382(x2)**: HLA Class II typing, high resolution (i.e., alleles or allele groups); one locus (e.g., HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
  - **82784**: Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each
  - **83520(x3):** Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
  - **86255**: Fluorescent noninfectious agent antibody; screen, each antibody

- **Prometheus Crohn's Prognostic**
  - **81479**: Unlisted molecular pathology procedure
  - **83520(x3)**: Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
  - **86021(x2)**: Antibody identification; leukocyte antibodies
  - **86255(x2**): Fluorescent noninfectious agent antibody; screen, each antibody

- **Genova GI Effects**
  - **87045:** Culture, bacterial; stool, aerobic, with isolation and preliminary examination (e.g., KIA, LIA), Salmonella and Shigella species
  - **87046(x3):** Culture, bacterial; stool, aerobic, additional pathogens, isolation and presumptive identification of isolates, each plate
  - **87075:** Culture, bacterial; any source, except blood, anaerobic with isolation and presumptive identification of isolates
  - **87798(x20):** Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; amplified probe technique, each organism
  - **87177:** Ova and parasites, direct smears, concentration and identification
  - **87209:** Smear, primary source with interpretation; complex special stain (e.g., trichrome, iron hemotoxylin) for ova and parasites
  - **87328:** Infectious agent antigen detection by immunoassay technique, (e.g., enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; cryptosporidium
  - **87336:** Infectious agent antigen detection by immunoassay technique, (e.g., enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; Entamoeba histolytica dispar group
  - **87329:** Infectious agent antigen detection by immunoassay technique, (e.g., enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; giardia
  - **87102:** Culture, fungi (mold or yeast) isolation, with presumptive identification of isolates; other source (except blood)

- **Prometheus IBD sgi Diagnostic**
  - **81479(x4):** Unlisted molecular pathology procedure
  - **82397(x3):** Chemiluminescent assay
  - **83520(x8):** Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
  - **86140:** C-reactive protein
  - **88346:** Immunofluorescence, per specimen; initial single antibody stain procedure
  - **88350:** Immunofluorescence, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)

- **TransPredict Fc gamma 3a**
  - **81479**: Unlisted molecular pathology procedure

- **Know Error**
  - **84999**: Unlisted chemistry procedure

If any component of the test has been codified in CPT, that specific code would be reported for that component of the test. One unit of the unlisted molecular pathology code 81479 or unlisted chemistry code 84999 is likely used for the remaining components or the entire test.

Description

There are numerous commercially available genetic and molecular diagnostic, prognostic, and therapeutic tests for individuals with certain diseases or asymptomatic individuals with a future risk. This evidence review evaluates miscellaneous genetic and molecular diagnostic tests not addressed in a separate review. If a separate evidence review exists, then conclusions reached there supersede conclusions here. The main criterion for inclusion in this review is the limited evidence on the clinical validity for the test. As a result, these tests do not have clinical utility, and the evidence is insufficient to determine the effect on health outcomes.

Related Policies

- Gene Expression Profiling for Uveal Melanoma
- General Approach to Evaluating the Utility of Genetic Panels
- General Approach to Genetic Testing
- Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes
- Identification of Microorganisms Using Nucleic Acid Probes
- KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer
- Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients with Cancer

Benefit Application

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

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. 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 Food and Drug Administration has chosen not to require any regulatory review of these tests.

Rationale

Background

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®	GeneNews[a]	Aug 2015				•
Crohn's Prognostic	Prometheus	Oct 2014		•		
DecisionDx-Thymoma	Castle	Jan 2015		•		
DNA Methylation Pathway Profile	Great Plains Laboratory	Jan 2015	•			
GI Effects® (Stool)	Genova Dxcs	Jan 2015	•			

Test Name	Manufacturer	Date Added	Diagnostic	Prognostic	Therapeutic	Future Risk
IBD sgi Diagnostic™	Prometheus	Oct 2014	•			
ImmunoGenomic® Profile	Genova Dxcs	Aug 2015				•
Know Error™	Strand Dxcs	July 2016	•			
ResponseDx Colon[d]	Response GXcs	Jan 2015			•	
SEPT9 methylated DNA[b]	Several[c]	Oct 2014	•			
TransPredict Fc gamma 3A[d]	Transgenomic	Oct 2014			•	

Castle: Castle Biosciences; Dxcs: Diagnostics; Gxcs: Genetics; HHT: hereditary hemorrhagic telangiectasia.
[a] In a joint venture with Innovative Diagnostic Laboratory.
[b] For example, ColoVantage® and Epi proColon®.
[c] ARUP, Quest, Clinical Genomics and Epigenomics.
[d] 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 DNA sequence. Most commonly, SNVs are found in the DNA between genes and can act as biologic markers of genes and disease association. When SNVs occur within a gene or a gene regulatory region, they can play a more direct role in disease by affecting the gene's function. SNVs may predict an individual's response to certain drugs, susceptibility to environmental factors, and the risk of developing certain diseases.

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

Test Description: DNA Methylation Pathway Profile

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

Test Description: Know Error DNA Specimen Provenance Assay

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

Celiac Disease

Previously called sprue, celiac sprue, gluten-sensitive enteropathy, gluten intolerance, nontropical sprue, or idiopathic steatorrhea, celiac disease is an immune-based reaction to gluten (water-insoluble proteins in wheat, barley, rye) that primarily affects the small intestine. Celiac disease occurs almost exclusively in patients who carry at least 1 human leukocyte antigen DQ2 or DQ8; the negative predictive value of having neither allele exceeds 98%.[3] 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.[4]

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.[5] Genetic markers (human leukocyte antigen DQ2 and DQ8) are considered predictive of the risk of developing celiac disease[6]; serologic markers (immunoglobulin A [IgA] anti-tissue transglutaminase antibody, IgA anti-endomysial antibodies, IgA anti-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.[7] Recommended treatments include dietary restriction and pharmacologic symptom control.[8-10] As living microorganisms that promote health when administered to a host in therapeutic doses,[11] probiotics are being investigated as a treatment for IBS. Several systematic reviews of randomized controlled trials have found evidence to support efficacy,[7,12-15] but results from recent randomized controlled trials have been mixed.[16-21] This discrepancy may be due in part to the differential effects of different probiotic strains and doses.

Test Description: GI Effects Comprehensive Stool Profile

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

Inflammatory Bowel Disease

IBD is an autoimmune condition characterized by inflammation of the bowel wall and has clinical symptoms of abdominal pain, diarrhea, and associated symptoms. Crohn disease (CD) and ulcerative colitis are the 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.[23] 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."[23] 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 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.[23]

***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 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[24]: *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.[25] 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 inflammatory bowel disease, and does not have a first-degree relative … with CRC."[25] 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."[26]

Prognostic Tests

Crohn Disease

Recent studies have identified serologic[27] and genetic[28,29] 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.

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 evidence reviews 2.04.08 and 2.04.53), 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 Food and Drug Administration–approved for the treatment of non-Hodgkin lymphoma, chronic lymphocytic leukemia, and nononcologic uses (e.g., rheumatoid arthritis).[30] 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-1β, IL-4, IL-6, and tumor necrosis factor α.[31] 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)."

Literature Review

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

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

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 are 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, Know Error, Celiac PLUS, GI Effects (Stool), and IBD sgi Diagnostic.

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

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

Timing
The timing of follow-up for irritable bowel syndrome (IBS), inflammatory bowel disease, and celiac disease ranges from weeks for the diagnosis to years for assessment of health outcomes.

Setting
These tests are offered commercially through various manufacturers.

Technically Reliable
Assessment of technical reliability focuses on specific tests and operators and requires a 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 (RCTs).

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,[32,] 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 RCTs.

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.

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 seven test components are included in an evidence-based diagnostic algorithm developed by the American College of Gastroenterology.[33] However, algorithmic testing is individualized according to the baseline risk of disease and is done sequentially, rather than simultaneously as in Celiac PLUS.

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

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 RCTs.

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 IBS: GI Effects Comprehensive Stool 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 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.[34]

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 RCTs.

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: IBS
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 Crohn disease (CD).[35,]

In a review of the monograph, Shirts et al (2012)[36,] 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,[37,38,] although not all investigators include these tests in recommended diagnostic strategies.[39,40,41,42,] These 3 markers are included in the 18-marker panel. Based on a 2006 meta-analysis of 60 studies (total n=11608 patients), Reese et al (2006) reported that pooled sensitivity and specificity of the 3-test panel were 63% and 93%, respectively, for diagnosing IBD.[43,] 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 for the 3-marker panel of 0.899.

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 RCTs.

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: IBD
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.[44,] It is thought that less burdensome methods of screening could increase the number of adults screened and thereby improve outcomes.

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 are 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 the standard of care without genetic screening.

Outcomes
The outcomes of interest are OS, 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 a 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 CRC 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).

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 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 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 2. 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.[46,]

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)[45]	25	9927	CC and CS	Colonoscopy	3	14	1
Li et al (2016)[47]	39			Colonoscopy	6	12	21
Yan et al (2016)[48]	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)[45]	Various	71 (67 to 75)	92 (89 to 94)
Nian et al (2017)[45]	Epi Procolon 2.0	75 (67 to 77)	93 (88 to 96)
Li et al (2016)[47]	Various	62 (56 to 67)	91 (89 to 93)
Yan et al (2016)[48]	Various	66 (64 to 69)	91 (90 to 91)
Yan et al (2016)[48]	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 the U.S. Food and Drug Administration 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 the Evaluation of SEPT9 Biomarker Performance for Colorectal Cancer Screening found to meet these inclusion criteria was (PRESEPT) (described below).

PRESEPT (Church et al [2014]) was an international prospective screening study of the first-generation Epi proColon test (see Table 4).[49,] 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, positive predictive value, and negative predictive value 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)[49]	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)[49]	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 limitations tables (see Tables 6 and 7) is to display notable limitations 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 the evidence supporting the position statement.

Table 6. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Church et al (2014)[49]		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.
[a] 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.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] 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.
[d] 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).
[e] 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 Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Church et al (2014)[49],	2. Not randomly sampled					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] 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.

[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] 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.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with other tests not reported

Song et al (2018) conducted a prospective study of the colorectal tumor detection rate from methylated *SEPT9* levels by Epi proColon 2.0 using the 2/3 algorithm.[50,] All 1347 individuals who met criteria and were to undergo colonoscopy provided a blood sample prior to evaluation of clinical status. The level of methylated *SEPT9* increased as the severity of disease increased, and the detection rate increased with disease severity. The detection rate was less than 20% for serrated adenoma and tubular adenoma, 41% for tubulovillous adenoma, 54% for stage I CRC, and then increased to 84% as the stage of CRC increased to stage IV CRC. Results suggested potential utility for monitoring treatment response but limited utility as a screening tool.

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 RCTs.

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 the 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: CRC Screening With SEPT9 Methylated DNA Testing
The evidence for the clinical validity of CRC screening includes case-control 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 positive predictive value of the test.

Detection of only half of preclinical cancers and a small proportion of advanced adenomas limits the clinical utility of the test. There is a need for further studies evaluating survival outcomes in patients screened with *SEPT9* methylated DNA testing (ColoVantage, Epi proColon)who have refused established screening methods.. 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 CRC 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 case-control 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.[51,] 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, PPV, and NPV were determined (see Tables 8 and 9). Yip et al (2010) conducted a similar cross-sectional study of 210 blood samples from patients in Malaysia.[24,] 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% to77%. The area under the curve 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)[51,]	202 patients with CRC and 208 controls	Case-control	NA	NA
Yip et al (2010)[24,]	99 patients with CRC and 111 controls	Case-control	NA	NA

CRC: colorectal cancer; 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)[50]	410			0.80 (0.76 to 0.84)	72	70	70	72
Yip et al (2010)[24]	200				61	77		

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

Limitations in relevance and design and conduct are shown in Tables 10 and 11. 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.

Table 10. Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Marshall et al (2010)[50]	4. Included patients with CRC and healthy controls				
Yip et al (2010)[24]	4. Included patients with CRC and healthy controls				

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

[a] 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.
[b]Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] 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.
[d] 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).
[e] 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 Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Marshall et al (2010)[50]	2. Selection not random					
Yip et al (2010)[24]	2. Selection not random					

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b]Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c]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.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] 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.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison with 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 RCTs.

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 because constructed due to lack of clinical validity.

Section Summary: CRC 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, two 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 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 are 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.

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

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

Timing
The timing of follow-up ranges from months for the 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 a 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 RCTs.

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: CD
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 RCTs.

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.

Therapeutic Testing
Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the 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 technology, two domains are examined: the relevance, and 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 RCT is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs 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 are 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.

Outcomes
The outcomes of interest are OS, 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* single nucleotide variants and response to rituximab.

Ghesquières et al (2017) published a patient-level meta-analysis from 2 cohorts of patients with B-cell lymphoma (see Table 12).[52,] There was a marginally significant trend toward worse event-free survival for patients with *FCGR3A* (see Table 13). In a meta-analysis 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).[53,]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
Ghesquières et al (2017)[52,]	2		Patients with B-cell lymphoma	1034	MA of patient-level data from cohort studies
Lee et al (2014)[53,]	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
Ghesquières et al (2017)[52,]			
HR (95% CI)	0.87 (0.76 to 0.99)		
p	0.04		
Lee et al (2014)[53,]			
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. A meta-analysis 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 RCTs. 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.

Patients
The relevant population of interest are 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 Immuno Genomic Profile.

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

Outcomes
The outcomes of interest are OS, 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 a 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.

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 RCTs.

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, cross-sectional studies, diagnostic accuracy studies, and cohort studies. The 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.
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 along with systematic reviews of those studies. The 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. Based on results from these studies, the clinical validity of *SEPT9* methylated DNA screening is limited by the low sensitivity of the test. . Optimal intervals for retesting are not known. The evidence is insufficient to determine the effects of the technologies on health outcomes.

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. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The evidence is insufficient to determine the effects of the technologies on health outcomes.

Therapeutic Testing
For individuals who are diagnosed with various conditions (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, cross-

sectional studies, diagnostic accuracy studies, and cohort studies. The 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.

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. The 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.

Supplemental Information

Practice Guidelines and Position Statements

Diagnostic and Prognostic Tests

Multiple Conditions

No guidelines or statements were identified.

Celiac Disease

The American College of Gastroenterology (2013) published an evidence-based consensus algorithm for the diagnosis and management of celiac disease.[33] A recommendation for genetic testing using a multigene panel test (e.g., Celiac PLUS) was not included. An update of this guideline is in progress.

Inflammatory Bowel Disease

American College of Gastroenterology (2018) practice guidelines on Crohn disease [54] states that genetic and routine serologic testing is not indicated to establish the diagnosis of Crohn's disease.

Colorectal Cancer

National Comprehensive Cancer Network

Current NCCN(v.1.2019)guidelines on colorectal cancer (CRC) screening state that tests for methylated *SEPT9* DNA "may provide an alternative for individuals who refuse other screening modalities. However, the NCCN panel notes that its ability to detect CRC and advanced adenomas is inferior to other recommended screening modalities. The interval for repeated testing is unknown."[55]

American Cancer Society

The American Cancer Society (2018) has recommended that "adults aged 45 y and older with an average risk of CRC undergo regular screening with either a high-sensitivity stool-based test or a structural (visual) examination, depending on patient preference and test availability. As a part of the screening process, all positive results on noncolonoscopy screening tests should be

followed up with timely colonoscopy." [56] The stool-based tests listed as options are a fecalimmunochemical test, fecal occult blood test, and multi-target stool DNA test. The College noted that "...at this time, mSept9 is not included in this guideline as an option for routine CRC screening for average-risk adults."

American College of Physicians

Based on its review of U.S. guidelines, the American College of Physicians (2012) issued a guidance statement on screening for CRC.[57] For average-risk adults ages 50 to 75 years, the College recommended using a stool-based test, flexible sigmoidoscopy, or optical colonoscopy for screening. For high-risk patients, it recommended using optical colonoscopy. No recommendation for genetic or molecular testing of average-risk individuals was included.

U.S. Multi-Society Task Force on Colorectal Cancer

The U.S. Multi-Society Task Force on Colorectal Cancer represents the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy.[58] The Task Force's (2017) clinical guidelines stated that the advantage of *SEPT9* assays for CRC screening is convenience. The disadvantage is "markedly inferior performance characteristics compared with FIT [fecal immunochemical test]." The guidelines also stated that the best frequency for performing the test is unknown and that the task force recommended not using *SEPT9* assays for CRC screening.

Thymomas and Thymic Carcinomas

The NCCN (v.2.2019) guidelines for thymomas and thymic carcinomas do not address the use of gene expression profiling of tumors of the thymus.[59]

Therapeutic Tests

Colon Cancer

The NCCN (v.2.2018) guidelines for colon cancer state that it has "not been established if molecular markers are useful in treatment determination (predictive markers) and prognosis."[60]

Non-Hodgkin Lymphoma

American College of Rheumatology (2016) recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis do not address *FCGR3* testing.[61]

U.S. Preventive Services Task Force Recommendations

Unless otherwise indicated for the diagnostic, prognostic, therapeutic, and future risk testing, no U.S. Preventive Services Task Force recommendations for genetic or molecular tests have been identified.

The U.S. Preventive Services Task Force (2016) updated its recommendations for CRC screening in adults.[44,62] It recommended screening for CRC starting at age 50 years and continuing until age 75 years. The 2016 recommendations differ from the 2008 recommendations in that current guidance does not emphasize specific screening approaches but highlights evidence that CRC screening substantially reduces deaths from the disease among adults ages 50 to 75 years and not enough adults in the U. S. are using effective preventive interventions. The evidence review supporting the recommendations included a search for studies of blood tests for methylated SEPT9 DNA but concluded that the test "currently has limited evidence evaluating its use."

Medicare National Coverage

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.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 14.

Table 14. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03218423[a]	Performance of Epi proColon in Repeated Testing in the Intended Use Population	4500	Jan 2022
NCT03311152	Diagnostic Accuracy of the Circulating Cell-free DNA-based Epigenetic Biomarker mSEPT9 for Hepatocellular Carcinoma Detection Among Cirrhotic Patients: the SEPT9-CROSS Study	440	Feb 2022

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

IE
The following services may be considered investigational.

Type	Code	Description
CPT®	81327	SEPT9 (Septin9) (e.g., colorectal cancer) methylation analysis
	81382	HLA Class II typing, high resolution (i.e., alleles or allele groups); one locus (e.g., HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
	81479	Unlisted molecular pathology procedure
	82397	Chemiluminescent assay
	82784	Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each
	83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
	84999	Unlisted chemistry procedure
	86021	Antibody identification; leukocyte antibodies

Type	Code	Description
	86140	C-reactive protein
	86255	Fluorescent noninfectious agent antibody; screen, each antibody
	87045	Culture, bacterial; stool, aerobic, with isolation and preliminary examination (e.g., KIA, LIA), Salmonella and Shigella species
	87046	Culture, bacterial; stool, aerobic, additional pathogens, isolation and presumptive identification of isolates, each plate
	87075	Culture, bacterial; any source, except blood, anaerobic with isolation and presumptive identification of isolates
	87102	Culture, fungi (mold or yeast) isolation, with presumptive identification of isolates; other source (except blood)
	87177	Ova and parasites, direct smears, concentration and identification
	87209	Smear, primary source with interpretation; complex special stain (e.g., trichrome, iron hemotoxylin) for ova and parasites
	87328	Infectious agent antigen detection by immunoassay technique, (e.g., enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; cryptosporidium
	87329	Infectious agent antigen detection by immunoassay technique, (e.g., enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; giardia
	87336	Infectious agent antigen detection by immunoassay technique, (e.g., enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; Entamoeba histolytica dispar group
	87798	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; amplified probe technique, each organism
	88346	Immunofluorescence, per specimen; initial single antibody stain procedure
	88350	Immunofluorescence, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
HCPCS	None	
ICD-10 Procedure	None	

Policy History

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

Effective Date	Action	Reason
05/29/2015	BCBSA Medical Policy Adoption	Medical Policy Committee
09/01/2016	Policy revision without position change	Medical Policy Committee
02/01/2017	Coding update	Administrative Review
09/01/2017	Policy revision without position change	Medical Policy Committee
09/01/2018	Policy revision without position change	Medical Policy Committee
11/01/2019	Policy revision without position change	Medical Policy Committee

Definitions of Decision Determinations

Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

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