Introduction

There are many genetic tests. High-quality medical studies show certain genetic tests are helpful when diagnosing some conditions or guiding treatment. However, not all genetic tests have been well studied. In some cases, studies have shown that genetic tests aren’t useful in making a diagnosis or changing care. This policy lists a number of genetic tests where there is not enough evidence in published medical studies to show that they bring health benefits. These tests are considered unproven.

Note: The Introduction section is for your general knowledge and is not to be taken as policy coverage criteria. The rest of the policy uses specific words and concepts familiar to medical professionals. It is intended for providers. A provider can be a person, such as a doctor, nurse, psychologist, or dentist. A provider also can be a place where medical care is given, like a hospital, clinic, or lab. This policy informs them about when a service may be covered.
Test Name | Investigational
---|---
- Celiac PLUS
- ColonSentry®
- ColoVantage®
- Crohn’s Prognostic
- DecisionDx-Thymoma
- DNA Methylation Pathway Profile
- Epi proColon®
- GI Effects® (Stool)
- IBD sigma Diagnostic™
- ImmunoGenomic® Profile
- Know Error™
- ResponseDX®: Colon
- SEPT9 methylated DNA
- TransPredict Fc gamma 3a

All of the tests listed in this policy are considered investigational and grouped according to the categories of genetic testing as outlined in Medical Policy 12.04.91 (General Approach to Genetic Testing; see Related Policies above):
- 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 is considered investigational.**

**Note:** See Table 1 in Evidence Review for additional information about test names listed at the left.

### Coding

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<tr>
<td>0069U</td>
<td>Oncology (colorectal), microrna, rt-pcr expression profiling of mir-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score</td>
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<td>81229</td>
<td>Cytogenomic constitutional (genome-wide) microarray analysis; interrogation of genomic regions for copy number and single nucleotide polymorphism (SNP) variants for chromosomal abnormalities</td>
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<td>81327</td>
<td>SEPT9 (Septin9) (eg, colorectal cancer) methylation analysis</td>
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<td>81407</td>
<td>Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of &gt; 50 exons, sequence analysis of multiple genes on one platform)</td>
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<td>81479</td>
<td>Unlisted molecular pathology procedure</td>
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<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
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</table>
Related Information

Genetic testing is considered investigational when 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.

Evidence Review

Description

There are numerous commercially available genetic and molecular diagnostic, prognostic, and therapeutic tests for individuals with certain diseases and or asymptomatic individuals with a future risk. This medical policy evaluates miscellaneous genetic and molecular diagnostic tests not addressed in a separate review. If a separate medical policy exists, then conclusions reached there supersede conclusions in this policy. The main criterion for inclusion in this policy 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. The lack of
clinical utility of these tests is based on criteria outlined in a separate medical policy (see Related Policies).

Background

Tests that are assessed in this medical policy are listed in Table 1. Excluding reproductive testing, there are primarily three reasons why genetic and molecular tests might be useful to a person with a disease: diagnostic testing, prognostic testing, and therapeutic testing. A fourth reason would be testing that is done on an asymptomatic person to determine his/her future risk of developing the disease.

Table 1: Genetic and Molecular Diagnostic Tests in This Medical Policy

<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></td>
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<tr>
<td>DecisionDx-Thymoma</td>
<td>Castle</td>
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<td></td>
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<td></td>
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<tr>
<td>DNA Methylation PathwayProfile</td>
<td>Great Plains Laboratory</td>
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<td>GI Effects® (Stool)</td>
<td>Genova Dxcs</td>
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<td></td>
<td>•</td>
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<td></td>
<td></td>
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<tr>
<td>IBD sgi Diagnostic™</td>
<td>Prometheus</td>
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<td></td>
<td></td>
<td>•</td>
<td></td>
<td></td>
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<tr>
<td>ImmunoGenomic® Profile</td>
<td>Genova Dxcs</td>
<td>Aug 2015</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Know Error™</td>
<td>Strand Dxcs</td>
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<tr>
<td>ResponseDx Colon®</td>
<td>Response GXcs</td>
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<td></td>
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<td>SEPT9 methylated DNA</td>
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<td>TransPredict Fc</td>
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<tr>
<td>Test Name</td>
<td>Manufacturer</td>
<td>Date Added</td>
<td>Diagnostic</td>
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</tbody>
</table>

Castle: Castle Biosciences; Dxcs: Diagnostics; Gxcs: Genetics; HHT: hereditary hemorrhagic telangiectasia.
\textsuperscript{a} In a joint venture with Innovative Diagnostic Laboratory.
\textsuperscript{b} For example, ColoVantage\textsuperscript{®} and Epi proColon\textsuperscript{®}.
\textsuperscript{c} ARUP, Quest, Clinical Genomics and Epigenomics.
\textsuperscript{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\textsuperscript{1} and have serious negative implications for patient care if the error is not corrected.\textsuperscript{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%. 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 antibody, IgA anti-endomysial antibodies, IgA anti-deamidated gliadin peptide [DGP] antibodies, IgG anti-DGP, and total IgA) are considered diagnostic for celiac disease. Celiac PLUS is intended for patients at risk for the disease (eg, with an affected first-degree relative) or with symptoms suggestive of 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.\textsuperscript{8-10} As living microorganisms that promote health when administered to a host in therapeutic doses,\textsuperscript{11} probiotics are being investigated as a treatment for IBS. Several systematic reviews of randomized controlled trials (RCTs) have found evidence to support efficacy,\textsuperscript{7,12-15} but results from recent RCTs have been mixed.\textsuperscript{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.\textsuperscript{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 (eg, lipids, fecal occult blood) and potential pathogens (ova and parasites, opportunistic bacteria, yeast). The test is purported to optimize management of gut health and to differentiate IBS from inflammatory bowel disease (IBD).

**Inflammatory Bowel Disease**

IBD is an autoimmune condition characterized by inflammation of the bowel wall and has clinical symptoms of abdominal pain, diarrhea, and associated symptoms. Crohn disease (CD) and ulcerative colitis are the 2 main entities under the category of IBD. The diagnosis is typically made by endoscopy or colonoscopy with biopsy and histologic analysis. This requires a semi-invasive procedure; as a result, a blood test to diagnose IBD could avoid the need for the procedures.

**Test Description: IBD sgi Diagnostic**

IBD sgi Diagnostic (Prometheus Therapeutics & Diagnostics) is a panel of 17 serologic (n=8), genetic (n=4), and inflammatory biomarkers (n=5). A proprietary algorithm produces an IBD score; results are reported as consistent with IBD (consistent with ulcerative colitis, consistent with CD, or inconclusive for UC vs CD) or not consistent with IBD. The test is intended for use in patients with clinical suspicion of IBD.
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 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 (ARUP Laboratories, Quest Diagnostics, Clinical Genomics). Epi proColon (Epigenomics) received U.S. Food and Drug Administration (FDA) approval in April 2016. Epigenomics has licensed its Septin 9 DNA biomarker technology to Polymedco and LabCorp. ColoVantage and Epi proColon are both PCR assays; however, performance characteristics vary across tests, presumably due to differences in methodology (eg, DNA preparation, PCR primers, probes).

Test Description: ColonSentry

ColonSentry (GeneNews; Innovative Diagnostic Laboratory) is a PCR assay that uses a blood sample to detect expression of 7 genes found to be differentially expressed in CRC patients compared with controls: ANXA3, CLEC4D, TNFAIP6, LMNB1, PRRG4, VNN1, and IL2RB. Per the company website, these genes are early-warning signs of colon cancer, and test results can indicate the odds of having CRC compared with an average-risk person. An average-risk
person is defined as one who is “≥ 50 years old, is asymptomatic for CRC, has no personal history of benign colorectal polyps, colorectal adenomas, CRC, or inflammatory bowel disease, 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\(^{27}\) 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 medical policy 2.04.08), and this panel is not considered here. The ResponseDX: Colon test comprises the 4 tests in the Driver Profile plus: EGFR expression; PI3K exon 1, 9, and 20 sequencing; TS expression; ERCC1 expression; UGT1A1 SNV testing (rs8175347, rs4148323); VEGFR2 expression; and MET amplification by fluorescence in situ hybridization.

Non-Hodgkin Lymphoma

Rituximab is a humanized IgG monoclonal antibody against the CD20 antigen, which is commonly expressed on B lymphocytes. It is FDA-approved for the treatment of non-Hodgkin lymphoma, chronic lymphocytic leukemia, and nononcologic uses (eg, 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 (eg, 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 (eg, 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.

Tests for Future Risk of Disease

Immunologic Disorders

Test Description: ImmunoGenomic Profile

The ImmunoGenomic Profile (Genova Diagnostics) is a buccal swab test that evaluates SNVs in 6 genes associated with immune function and inflammation: interleukin (IL)-10, IL-13, IL-1, 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).

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 diagnostic test (eg, 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 overall survival (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 medical policy and addressed separately if it is determined that enough evidence has accumulated for us to reevaluate its potential clinical utility. The evidence is insufficient at this time to determine the effects of the technologies on health outcomes.
For individuals who are being screened for colorectal cancer who receive SEPT9 methylated DNA testing (eg, ColoVantage, Epi proColon, ColonSentry), the evidence includes case-control, cross-sectional, and prospective diagnostic accuracy studies along with systematic reviews of those 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. Based on results from these studies, the clinical validity of SEPT9 methylated DNA screening is limited by the low sensitivity of the test given that the sensitivity of the test is lower than imaging screening strategies. Optimal intervals for retesting are not known. The evidence is insufficient to determine the effects of the technologies on health outcomes.

**Prognostic Testing**

For individuals who are diagnosed with various conditions (eg, Crohn disease, thymomas and thymic carcinomas, rheumatoid arthritis) who receive prognostic testing with a miscellaneous genetic or molecular test (eg, 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.

**Therapeutic Testing**

For individuals who are diagnosed with various conditions (eg, colon cancer, non-Hodgkins lymphoma) who receive therapeutic testing with a miscellaneous genetic or molecular test (eg, 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 for us to reevaluate its potential clinical utility. The evidence is insufficient at this time to determine the effects of the technologies on health outcomes.
Testing for Future Risk of Disease

For individuals with a family history of various conditions thought to be hereditary or with a known genetic component who receive testing for future risk of disease with a miscellaneous genetic or molecular test (eg, ImmunoGenomic Profile), 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 for us to reevaluate its potential clinical utility. The evidence is insufficient at this time to determine the effects of the technologies on health outcomes.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

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<th>NCT No.</th>
<th>Trial Name</th>
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NCT: national clinical trial.
\(^a\) Denotes industry-sponsored or cosponsored trial.
Practice Guidelines and Position Statements

*Diagnostic 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. A recommendation for genetic testing using a multigene panel test (eg, Celiac PLUS) was not included.

**Irritable Bowel Syndrome**

American College of Gastroenterology practice guidelines on ulcerative colitis (2010) and Crohn disease (2009) did not contain recommendations for multimarker panels that include genetic tests to facilitate diagnosis or prognosis.

**Colorectal Cancer**

*National Comprehensive Cancer Network*

Current National Comprehensive Cancer Network (NCCN) guidelines on colorectal cancer (CRC) screening (v.1.2017) 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 colorectal cancer and advanced adenomas is inferior to other recommended screening modalities. The interval for repeated testing is unknown.

*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. The stool-based tests listed as options are a fecal immunochemical test, fecal occult blood test, and multi-target stool D 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 (ACP) issued a guidance statement in 2012 on screening for CRC. 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 of Colorectal Cancer**

The U.S. Multi-Society Task Force of Colorectal Cancer represents the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy. The Task Force’s 2017 clinical guidelines state 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.

**Prognostic Tests**

**Crohn Disease**

No guidelines or statements were identified.

**Thymomas and Thymic Carcinomas**

NCCN guidelines for thymomas and thymic carcinomas (v.1.2015) do not address the use of gene expression profiling of tumors of the thymus.
**Therapeutic Tests**

**Colon Cancer**

Current NCCN guidelines for colon cancer (v.2.2017) state that it has “not been established if molecular markers are useful in treatment determination (predictive markers) and prognosis.”

**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.

**U.S. Preventive Services Task Force**

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

The U.S. Preventive Services Task Force updated its recommendations for CRC screening in adults in 2016. 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 United States 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.”

**National Medicare Coverage**

Unless otherwise indicated for the diagnostic, prognostic, and 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.
Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Genetic tests evaluated in this policy are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

References


### History

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<thead>
<tr>
<th>Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>11/10/14</td>
<td>New Policy. Policy created with literature review through September 21, 2014. All tests listed in this policy are considered investigational, and are grouped according to the categories of genetic testing as outlined in medical policy No. 12.04.91.</td>
</tr>
<tr>
<td>03/10/15</td>
<td>Annual Review. Policy updated with literature review through December 9, 2014; references 7-27, 45, 47, 65, and 67 added. Genetic tests added as shown in Table 1. No change to policy statement.</td>
</tr>
<tr>
<td>10/13/15</td>
<td>Annual Review. Policy updated with literature review through July 15, 2015; references 49-58 and 62-64, 81 added. Genetic tests added to Table 1 are ColonSentry and ImmunoGenomic Profile. Appendix Table 1 added with Categories of Genetic Tests included in the policy. Policy statement unchanged. Coding update: CPT codes 81382, 82397, 82784, 86140 and 86255 removed; these are not reviewed in the scope of this policy.</td>
</tr>
<tr>
<td>04/01/16</td>
<td>Update Related Policies. Remove 12.04.38 as it was deleted and replaced with 12.04.517.</td>
</tr>
<tr>
<td>05/19/16</td>
<td>Coding update. Added 84999.</td>
</tr>
<tr>
<td>10/01/16</td>
<td>Annual Review, approved September 13, 2016. Policy updated with literature review through July 5, 2016; references added. Blood DNA tests for colon cancer (ColonSentry, SEPT9 methylated DNA- ColoVantage, Epi proColon) moved to policy 2.04.141, that is now included in the Related Policies section. Policy statements unchanged.</td>
</tr>
<tr>
<td>Date</td>
<td>Comments</td>
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<tr>
<td>11/01/16</td>
<td>Coding update, approved October 11, 2016. Codes listed within verbiage and test names in Coding section removed; these were informational only. Update Related Policies. Removed 2.04.141 as it was replaced with 12.04.141. Added 12.04.141 to Related Policies section.</td>
</tr>
<tr>
<td>07/07/17</td>
<td>Policy moved into new format, no changes to policy statement.</td>
</tr>
<tr>
<td>09/01/17</td>
<td>Annual Review, approved August 22, 2017. Policy updated with literature review through July 5, 2017; references 51, 57-58, 64, 67, and 86 added. Several guidelines updated with current versions. Policy statements updated to organize types of tests with language that corresponds to related policy; all tests remain investigational. Removed CPT codes 83520 and 86021.</td>
</tr>
<tr>
<td>10/01/18</td>
<td>Annual Review, approved September 20, 2018. Policy updated with literature review through May 2018; references 46 and 54 added; some references removed. Date of literature review from 2017 corrected. DecisionDx Melanoma was removed from this policy and a new policy on genetic testing for melanoma was created. ColoSentry, ColoVantage, Epi proColon, and SEPT9 were moved back into this policy statement from policy 12.04.141; otherwise no other changes to policy statements. Added CPT codes 81327 and 0069U.</td>
</tr>
</tbody>
</table>

**Disclaimer:** This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. The Company adopts policies after careful review of published peer-reviewed scientific literature, national guidelines and local standards of practice. Since medical technology is constantly changing, the Company reserves the right to review and update policies as appropriate. Member contracts differ in their benefits. Always consult the member benefit booklet or contact a member service representative to determine coverage for a specific medical service or supply. CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). ©2018 Premera All Rights Reserved.

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Premera:
- Provides free aids and services to people with disabilities to communicate effectively with us, such as:
  - Qualified sign language interpreters
  - Written information in other formats (large print, audio, accessible electronic formats, other formats)
- Provides free language services to people whose primary language is not English, such as:
  - Qualified interpreters
  - Information written in other languages

If you need these services, contact the Civil Rights Coordinator.

If you believe that Premera has failed to provide these services or discriminated in another way on the basis of race, color, national origin, age, disability, or sex, you can file a grievance with:

Civil Rights Coordinator - Complaints and Appeals
PO Box 91102, Seattle, WA 98111
Toll free 855-332-4535, Fax 425-918-5592, TTY 800-842-5357
Email AppealsDepartmentInquiries@Premera.com

You can find a grievance in person or by mail, fax, or email. If you need help filling a grievance, the Civil Rights Coordinator is available to help you.

You can also file a civil rights complaint with the U.S. Department of Health and Human Services, Office for Civil Rights, electronically through the Office for Civil Rights Complaint Portal, available at https://ocrportal.hhs.gov/ocr/portal/lobby.jsf, or by mail or phone at:

U.S. Department of Health and Human Services
200 Independence Avenue SW, Room S09F, HHH Building
Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

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