This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient’s contract at the time the services are rendered.

### Populations

Individuals:
- With various conditions thought to be hereditary or with a known genetic component

### Interventions

Interventions of interest are:
- Testing with a miscellaneous genetic or molecular diagnostic test

### Comparators

Comparators of interest are:
- Usual care without genetic or molecular diagnostic testing

### Outcomes

Relevant outcomes include:
- Test accuracy
- Test validity
- Symptoms
- Change in disease status
- Morbid events

* Celiac PLUS, ColonSentry, Crohn’s Prognostic, DecisionDx-Melanoma, DecisionDx-Thymoma, DNA Methylation Pathway Profile, GI Effects (Stool), IBD sgi Diagnostic, ImmunoGenomic Profile, ResponseDX: Colon, SEPT9 methylated DNA (e.g., ColoVantage, Epi proColon), TransPredict Fc gamma 3A; Know Error.

### Description

There are numerous commercially available genetic and molecular diagnostic tests. This protocol evaluates miscellaneous genetic and molecular diagnostic tests not addressed in a separate protocol. If a separate protocol exists, then conclusions reached there supersede conclusions in this protocol. The main criterion for inclusion in this protocol is that there is limited evidence on the clinical validity for the test. As a result, these tests do not have clinical utility and the evidence is insufficient to determine the effect on health outcomes.

### Summary of Evidence

For individuals with various conditions thought to be hereditary or with a known genetic component who receive testing with a miscellaneous genetic or molecular diagnostic test (e.g., Celiac PLUS, ColonSentry, Crohn’s Prognostic, DecisionDx-Melanoma, DecisionDx-Thymoma, DNA Methylation Pathway Profile, GI Effects (Stool), IBD sgi Diagnostic, ImmunoGenomic Profile, ResponseDX: Colon, SEPT9 methylated DNA [e.g., ColoVantage, Epi proColon], TransPredict Fc gamma 3A; Know Error), the evidence consists of case series, cross-sectional studies, diagnostic accuracy studies, and cohort studies. Relevant outcomes are test accuracy and validity, symptoms, change in disease status, and morbid events. The lack of clinical utility of these tests is based on criteria outlined in the General Approach to Genetic Testing Protocol. Also, one or more of the following factors are present: (1) there is no or extremely limited published data addressing the test; and/or (2) there is insufficient evidence demonstrating clinical validity of the test. For each test addressed herein, 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 protocol 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.

Policy

All tests listed in this protocol are considered investigational and grouped according to the categories of genetic testing outlined in the General Approach to Genetic Testing Protocol:

- Diagnostic testing
- Risk assessment
- Prognostic testing
- Genetic variants that alter response to treatment or to an environmental factor.

Policy Guidelines

Genetic Counseling

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

Background

Tests Addressed in This Protocol

Tests that are assessed in this protocol are listed in Table 1.

Table 1: Genetic and Molecular Diagnostic Tests in This Protocol

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Manufacturer</th>
<th>Date Added</th>
<th>Diagnosis</th>
<th>Risk Assessment</th>
<th>Prognosis</th>
<th>Treatment Response</th>
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<tr>
<td>Celiac PLUS</td>
<td>Prometheus</td>
<td>Oct 2014</td>
<td></td>
<td>●</td>
<td>●</td>
<td></td>
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<tr>
<td>ColonSentry®</td>
<td>GeneNews</td>
<td>Aug 2015</td>
<td></td>
<td>●</td>
<td>●</td>
<td></td>
</tr>
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<td>Crohn's Prognostic</td>
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<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>Jan 2015</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>DecisionDx-Thymoma</td>
<td>Castle</td>
<td>Jan 2015</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>DNA Methylation Pathway Profile</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI Effects® (Stool)</td>
<td>Genova Dxcs</td>
<td>Jan 2015</td>
<td></td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD sgi Diagnostic™</td>
<td>Prometheus</td>
<td>Oct 2014</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>ImmunoGenomic® Profile</td>
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<td>Aug 2015</td>
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<tr>
<td>Know Error™</td>
<td>Strand Dxcs</td>
<td>July 2016</td>
<td></td>
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<tr>
<td>ResponseDX®: Colon</td>
<td>Response Gxcs</td>
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<td>SEPT9 methylated DNA</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
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<td>Transgenomic</td>
<td>Oct 2014</td>
<td></td>
<td>●</td>
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</table>

Castle: Castle Biosciences; Dxcs: Diagnostics; Gxcs: Genetics.
Diagnostic Tests

Multiple Conditions

Single-nucleotide polymorphisms (SNPs) are the most common type of genetic variation, and each SNP represents a difference in a single nucleotide in the DNA sequence. Most commonly, SNPs are found in the DNA between genes and can act as biological markers of genes and disease association. When SNPs occur within a gene or a gene regulatory region, they can play a more direct role in disease by affecting the gene’s function. SNPs may predict an individual’s response to certain drugs, susceptibility to environmental factors, and the risk of developing certain diseases.

DNA specimen provenance assays can be used to confirm that tissue specimens are correctly matched to the patient of origin. Specimen provenance errors may occur in up to 1% to 2% of pathology tissue specimens, and have serious negative implications for patient care if the error is not corrected.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 to LTRs from a patient sample.

TEST DESCRIPTION: DNA METHYLATION PATHWAY PROFILE

The DNA Methylation Pathway Profile (Great Plains Laboratory, Lenexa, KS) analyzes SNPs 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, Indianapolis, IN) 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

Celiac disease (previously called sprue, celiac sprue, gluten-sensitive enteropathy, gluten intolerance, nontropical sprue, idiopathic steatorrhea) 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 one human leukocyte antigen (HLA) DQ2 or DQ8 allele; negative predictive value (NPV) of having neither allele exceeds 98%.3 Serum antibodies to tissue transglutaminase (TTG), 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.4

TEST DESCRIPTION: CELIAC PLUS

Celiac PLUS (Prometheus Therapeutics & Diagnostics, San Diego) is a panel of two genetic and five 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, HLA DQ2 and DQ8, are considered predictive of the risk of developing celiac disease;6 serologic markers—immunoglobulin A (IgA) anti-TTG antibody, IgA anti-endomysial antibodies, IgA anti-DGP antibodies, IgG anti-DGP, and total IgA—are considered diagnostic for celiac disease. Celiac PLUS is intended for patients at risk for disease (e.g., with an affected first-degree relative) or with symptoms suggestive of disease.

Irritable Bowel Syndrome

Irritable bowel syndrome (IBS) is a functional gastrointestinal (GI) disorder that affects 10% to 20% of the
general population in the United States and worldwide. Symptoms include abdominal pain and/or bloating associated with disordered bowel habit (constipation, diarrhea, or both). Pathophysiology is poorly understood but may be related to chronic low-grade mucosal inflammation and disturbances in GI flora. Recommended treatments include dietary restriction and pharmacologic symptom control. Probiotics—living microorganisms that promote health when administered to a host in therapeutic doses—are being investigated as a treatment for IBS. Several systematic reviews of randomized controlled trials (RCTs) have found evidence to support efficacy, but results from recent RCTs have been mixed. This discrepancy may be due in part to differential effects of different probiotic strains and doses.

TEST DESCRIPTION: GI EFFECTS COMPREHENSIVE STOOL PROFILE

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

Inflammatory Bowel Disease

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

TEST DESCRIPTION: IBD SGI DIAGNOSTIC

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

Colon Cancer

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

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, Berlin) received FDA approval in the United States in April 2016. Epigenomics has licensed its Septin 9 DNA biomarker technology to ARUP and Quest. ColoVantage and Epi proColon are both PCR assays; however, performance characteristics vary across tests, presumably due to differences in methodology (e.g., DNA preparation, PCR primers, probes). Sensitivity as high as 90%, with 88% specificity and 99.9% NPV (4% positive predictive value [PPV]) have been reported for ColoVantage. By comparison, reported sensitivity and specificity for Epi proColon were 68% and 80%, respectively. Serum SEPT9 methylated DNA testing is intended for individuals 50 years of age or older who have an average risk of colorectal cancer.
Risk Assessment

Celiac Disease

TEST DESCRIPTION: IMMUNOGENOMIC PROFILE

The ImmunoGenomic Profile (Genova Diagnostics, Asheville, NC) is a buccal swab test that evaluates SNPs in six genes associated with immune function and inflammation: interleukin (IL)-10, IL-13, IL-1β, IL-4, IL-6, and tumor necrosis factor α. According to the company website, variations in these genes can affect balance between cell (TH-1) and humoral (TH-2) immunity, trigger potential defects in immune system defense, and stimulate mechanisms underlying chronic, overactive inflammatory responses.

The test uncovers potential genetic susceptibility to: Asthma, Autoimmune Disorders, Certain Cancers, Allergy, Infectious Diseases, Bone Inflammation, Arthritis, Inflammatory Bowel Disease, Heart Disease, Osteopenia, and Helicobacter pylori infection (cause of ulcers)....

Colorectal Cancer

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 catalogued genes from nine 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 DESCRIPTION: COLONSENTRY

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

Prognostic Tests

Crohn Disease

Recent studies have identified serologic and genetic correlates of aggressive CD that is characterized by fistula formation, fibrostenosis, and the need for surgical intervention. Prometheus has developed a blood test that aims to identify patients with CD who are likely to experience an aggressive disease course.

TEST DESCRIPTION: CROHN’S PROGNOSTIC

Crohn’s Prognostic (Prometheus Therapeutics & Diagnostics, San Diego, CA) is a panel of six serologic (n=three) and genetic (n=three) biomarkers. Limited information about the test is available on the manufacturer’s website.
Cutaneous Melanoma

Cutaneous melanoma represents less than 5% of skin malignancies but results in the most skin cancer deaths. The incidence of cutaneous melanoma continues to increase, and it is currently the sixth most common cancer in the United States. Standard treatment options for stage 1 and 2 melanoma are excision with or without sentinel lymph node examination. Current risk factors to predict localized tumor aggression include Breslow tumor thickness, tumor ulceration, and mitotic rate of the tumor cells. The likelihood of regional lymph node involvement increases with increasing tumor thickness, and significantly negatively impacts the rate of survival.

TEST DESCRIPTION: DECISIONDX-MELANOMA

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

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-THYMOA

DecisionDx-Thymoma (Castle Biosciences, Friendswood, TX) 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 likelihood that the tumor will metastasize.

Tests for Genetic Variants That Alter Response to Treatment or to an Environmental Factor

Colon Cancer

TEST DESCRIPTION: RESPONSEDX: COLON

Response Genetics (Los Angeles, CA) currently markets two 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 mutation testing in KRAS, BRAF, and mismatch repair genes (microsatellite instability), plus NRAS exon 2 and 3 sequencing. These gene tests are reviewed elsewhere (see the Genetic Testing for FAP and Lynch Syndrome Protocol and the KRAS, NRAS, and BRAF Mutation Analysis in Metastatic Colorectal Cancer Protocol), and this panel is not considered here. The ResponseDX: Colon test comprises the four tests in the Driver Profile plus: EGFR expression; PI3K exon 1, 9, and 20 sequencing; T5 expression; ERCC1 expression; UGT1A1 SNP testing (rs8175347, rs4148323); VEGFR2 expression; and MET amplification by fluorescence in situ hybridization. Evidence for clinical validity and clinical utility of the ResponseDX: Colon test was sought.

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 treatment of non-Hodgkin lymphoma, chronic lymphocytic leukemia, and nononcologic uses (e.g., rheumatoid arthritis). Although rituximab has demonstrated improved 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 (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 mutation 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 mutation 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:** TRANS_PREDICT Fc GAMMA 3A

TransPredict Fc gamma 3A (formerly PGxPredict: Rituximab; Transgenomic, Omaha, NE) is a PCR assay that uses a blood sample to detect the Val158Phe mutation 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.

**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 protocol 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 this test.

**Related Protocols**

- General Approach to Evaluating the Utility of Genetic Panels
- General Approach to Genetic Testing
- Genetic Testing for FAP and Lynch Syndrome
- KRAS, NRAS, and BRAF Mutation Analysis in Metastatic Colorectal Cancer

Services that are the subject of a clinical trial do not meet our Technology Assessment Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.

**References**

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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


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