**MEDICAL POLICY – 12.04.121**

**Miscellaneous Genetic and Molecular Diagnostic Tests**

BCBSA Ref. Policy: 2.04.121  
Effective Date: Oct. 1, 2016  
Last Revised: July 7, 2017  
Replaces: 2.04.121

**RELATED MEDICAL POLICIES:**  
12.04.91 General Approach to Genetic Testing  
12.04.141 Circulating Tumor DNA and Circulating Tumor Cells for Cancer Diagnosis and Management (Liquid Biopsy)  
12.04.517 CYP450 Genotyping to Determine Drug Metabolizer Status

Select a hyperlink below to be directed to that section.

**POLICY CRITERIA | CODING | RELATED INFORMATION**  
**EVIDENCE REVIEW | REFERENCES | HISTORY**

∞ Clicking this icon returns you to the hyperlinks menu above.

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**Introduction**

There are many genetic tests. High-quality medical studies show certain genetic tests are valuable 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.

**Policy Coverage Criteria**

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Investigational</th>
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<tbody>
<tr>
<td>Celiac PLUS</td>
<td>All of the tests listed in this policy are considered</td>
</tr>
<tr>
<td>Crohn Prognostic</td>
<td></td>
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Test Name
- DecisionDx-Melanoma™
- DecisionDx-Thymoma
- DNA Methylation
- Pathway Profile
- GI Effects® (Stool)
- IBD sgi Diagnostic™
- ImmunoGenomic® Profile
- Know Error™
- ResponseDX®: Colon
- TransPredict Fc gamma 3A

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

Genetic testing is considered investigational when criteria are not met, including when there is insufficient evidence to determine whether the technology improves health outcomes.

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

### Coding

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<thead>
<tr>
<th>Code</th>
<th>Description</th>
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<td>CPT</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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<tr>
<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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<td>83520</td>
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<tr>
<td>84999</td>
<td>Unlisted chemistry procedure</td>
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<tr>
<td>86021</td>
<td>Antibody identification; leukocyte antibodies</td>
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Note: CPT codes, descriptions and materials are copyrighted by the American Medical Association (AMA). HCPCS codes, descriptions and materials are copyrighted by Centers for Medicare Services (CMS).
Evidence Review

Description

There are numerous commercially available genetic and molecular diagnostic tests. 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 therein supersede conclusions in this review. The main criterion for inclusion in this review 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. 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.

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>Diagnosis</th>
<th>Risk Assessment</th>
<th>Prognosis</th>
<th>Treatment Response</th>
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<td>Celiac PLUS</td>
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<tr>
<td>DecisionDx-Melanoma™</td>
<td>Castle</td>
<td>Jan 2015</td>
<td>•</td>
<td>•</td>
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<tr>
<td>Test Name</td>
<td>Manufacturer</td>
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<td>Castle</td>
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<td>IBD sgi Diagnostic™</td>
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<td>Know Error™</td>
<td>Strand Dxcs</td>
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<td>ResponseDX®: Colon</td>
<td>Response Gxcs</td>
<td>Jan 2015</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>TransPredict Fc gamma 3A</td>
<td>Transgenomic</td>
<td>Oct 2014</td>
<td></td>
<td></td>
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</tbody>
</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.
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.

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 to LTRs from a patient sample.

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 1 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 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, HLA DQ2 and DQ8, are considered predictive of the risk of developing celiac disease; 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 (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. 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 (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).

Current approaches to diagnosing IBD include endoscopy, mucosal biopsy, serology, and radiology. Differential diagnosis includes other GI inflammatory disorders and infectious etiologies. Differentiating ulcerative colitis (UC) from Crohn disease (CD) is necessary for appropriate treatment planning; in cases with atypical presentations, this differentiation can be
difficult. Prometheus® has developed a blood test that aims to more accurately diagnose IBD and differentiate UC from CD.

**Inflammatory Bowel Disease (IBD)**

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

**Risk Assessment**

**Celiac Disease**

**Test Description: ImmunoGenomic Profile**

The ImmunoGenomic Profile (Genova Diagnostics, Asheville, NC) is a buccal swab test that evaluates SNPs in 6 genes associated with immune function and inflammation: interleukin (IL)-10, IL-13, IL-1β, IL-4, IL-6, and tumor necrosis factor α. According to the company website, variations in these genes...

...can affect balance between cell (TH-1) and humoral (TH-2) immunity, trigger potential defects in immune system defense, and stimulate mechanisms underlying chronic, overactive inflammatory responses...
The test uncovers potential genetic susceptibility to: Asthma, Autoimmune Disorders, Certain Cancers, Allergy, Infectious Diseases, Bone Inflammation, Arthritis, Inflammatory Bowel Disease, Heart Disease, Osteopenia, and Helicobacter pylori infection (cause of ulcers)....

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 6 serologic (n=3) and genetic (n=3) 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 is a gene expression profile test with a signature of 31 genes, 28 discriminating genes and 3 control genes. The test is used to measure risk of metastasis in
patients with stage I and II cutaneous melanoma and classifies tumors into 2 groups of risk of metastasis • low or high (classes 1 and 2, respectively). The test purports to give an independent prediction of tumor metastatic risk, independent of currently used metrics of risk assessment (eg, 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-Thymoma**

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 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 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 Related Policies), 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 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 (eg, rheumatoid arthritis).\(^{35}\) 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 (eg, 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 (eg, 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: TransPredict 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.

**General Principles of Genetic Tests**

The test should be cleared or approved by the U.S. Food and Drug Administration (FDA) or performed in a Clinical Laboratory Improvement Amendment–certified laboratory.
Peer-reviewed literature on test performance and indications for the test should be available. Evaluation of genetic tests focuses on 3 main principles:

1. Analytic validity (technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent)

2. Clinical validity (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease)

3. Clinical utility (how results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes)

Categories of Genetic Tests

Medical criteria listed after each category defines the circumstances in which testing for a genetic or heritable disorder may be considered clinically useful.

Diagnostic Tests

Diagnostic testing for genetic or heritable mutations in a symptomatic individual refers to molecular diagnosis defined by the presence of a known pathologic mutation. For purposes of genetic testing, a symptomatic individual is defined as an individual with a clinical phenotype that correlates with a known pathologic mutation.

Criteria

- An association of the marker with the disorder has been established; AND
- Symptoms of the disease are present; AND
- A definitive diagnosis cannot be made based on history, physical examination, pedigree analysis, and/or standard diagnostic studies/tests; AND
- Clinical utility of a diagnosis has been established, eg, by demonstrating that a definitive diagnosis will lead to changes in clinical management of the condition, changes in
surveillance, or changes in reproductive decision making, and the changes will lead to improved health outcomes; AND

- Establishing the diagnosis by genetic testing will end the clinical work-up for other disorders.

**Risk Assessment**

Risk assessment for genetic and heritable mutations is done for:

- Predictive and presymptomatic types of testing are used to detect gene mutations 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 mutations that increase an individual’s risk of developing disorders with a genetic basis, such as 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 mutation that may lead to development of the disease.

**Criteria**

- Predictive and presymptomatic testing:
  - An association of the marker with future disorder has been established; AND
  - Clinical utility has been established, eg, by demonstrating that testing will lead to improved health outcomes based on prevention or early detection strategies.

**Prognostic Tests**

Prognostic testing of diagnosed disease is done to predict natural disease course, eg, aggressiveness, risk of recurrence, death). This type of testing uses gene expression of affected tissue to predict the course of disease.
Criteria

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

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

There are three main types of tests to identify genetic variants that alter response to treatment or to an environmental factor:

- Constitutional (germline) testing to detect genetic variants that alter risk of treatment response, adverse events, drug metabolism, drug effectiveness, etc., eg, cytochrome p450 testing (also referred to as pharmacogenomics).
- Tissue-specific or tumor testing to detect mutations that predict response to a certain type of treatment, eg, ALK mutation testing in non-small-cell lung cancer to predict response to crizotinib.
- Testing for genetic mutations that adversely affect response to exposures in the environment that are ordinarily tolerated, eg, G6PD deficiency, genetic disorders of immune function, aminoacidopathies).

Criteria

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

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 (eg, Celiac PLUS, Crohn’s Prognostic, DecisionDx-Melanoma, DecisionDx-Thymoma, DNA Methylation Pathway Profile, GI Effects (Stool), IBD sgi Diagnostic, ImmunoGenomic Profile, ResponseDX: Colon, , 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 policymedical policy 112.04.91 (see Related Policies). Also, 1 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 medical policy 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.

Practice Guidelines and Position Statements

*Diagnostic Tests: Multiple Conditions*

No guidelines or statements were identified.
**Diagnostic Tests: Celiac Disease**

In 2013, American College of Gastroenterology (ACG) 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.

**Diagnostic Tests: Irritable Bowel Syndrome**

**American Gastroenterological Association**

A 2014 evidence-based American Gastroenterological Association (AGA) guideline for pharmacologic management of IBS did not review probiotic treatment.

**American College of Gastroenterology**

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

**British Dietetic Association**

A 2012 evidence-based British Dietetic Association guideline for dietary management of IBS in adults recommended considering probiotics "secondary to other second-line advanced dietary interventions," such as reduced intake of fermentable carbohydrates (grade of recommendation: B [based on 4 randomized controlled trial and 1 observational study with high risk of bias]).

**National Institute for Health and Care Excellence**

A 2008 evidence-based National Institute for Health and Care Excellence guideline for diagnosis and management of IBS in primary care stated that testing for fecal ova and parasites is unnecessary to confirm the diagnosis in patients who meet IBS diagnostic criteria. The guideline also stated: “People with IBS who choose to try probiotics should be advised to take the product for at least 4 weeks while monitoring the effect. Probiotics should be taken at the dose recommended by the manufacturer.” This guideline is currently being updated.
Risk Assessment: Multiple Conditions

No guidelines or statements were identified.

Prognostic Tests: Crohn Disease

No guidelines or statements were identified.

Prognostic Tests: Cutaneous Melanoma

NCCN guidelines for melanoma (v.3.2015) state that “while there is interest in newer prognostic molecular techniques such as gene expression profiling to differentiate melanomas at low-versus high-risk for metastasis, routine genetic testing of primary melanoma (before or following sentinel lymph node biopsy) is not recommended outside of a clinical trial.”

Prognostic Tests: 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.

Tests for Genetic Variants: Colon Cancer

Although current NCCN guidelines for colon cancer (v.2.2015) consider the clinical utility of genetic testing for specific genes to guide treatment selection (eg, “EGFR testing has no demonstrated predictive value; therefore routine EFGFR testing is not recommended”), gene panels for colon cancer are not addressed.
Tests for Genetic Variants: Non-Hodgkin Lymphoma

National Comprehensive Cancer Network

Current NCCN guidelines for non-Hodgkin lymphomas (v.2.2015) do not include a recommendation for genetic testing (eg, TransPredict Fc gamma 3A) to predict response to rituximab therapy.\textsuperscript{68,69}

American College of Rheumatology

Current (2012) American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis do not address FCGR3 testing.\textsuperscript{70}

U.S. Preventive Services Task Force

Unless otherwise indicated for the diagnostic, risk assessment, prognostic, and genetic variant tests that alter response to treatment or an environmental factor, no U.S. Preventive Services Task Force (USPSTF) recommendations for genetic or molecular tests have been identified.

National Medicare Coverage

Unless otherwise indicated for the diagnostic, risk assessment, prognostic, and genetic variant tests that alter response to treatment or an environmental factor, there is no national coverage determination (NCD). In the absence of an NCD, 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 standards of the Clinical Improvement Act (CLIA). Genetic tests reviewed 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


52. Weng WK, Levy R. Immunoglobulin G Fc receptor polymorphisms do not correlate with response to chemotherapy or clinical course in patients with follicular lymphoma. Leuk Lymphoma. Sep 2009;50(9):1494-1500. PMID 19672774


### History

<table>
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<th>Date</th>
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<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>
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<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 changes made to the policy.</td>
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<tr>
<td>Date</td>
<td>Comments</td>
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<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>
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<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>
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<tr>
<td>05/19/16</td>
<td>Coding update. Added 84999.</td>
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<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>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>
</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). ©2017 Premera All Rights Reserved.

**Scope:** Medical policies are systematically developed guidelines that serve as a resource for Company staff when determining coverage for specific medical procedures, drugs or devices. Coverage for medical services is subject to the limits and conditions of the member benefit plan. Members and their providers should consult the member benefit booklet or contact a customer service representative to determine whether there are any benefit limitations applicable to this service or supply. This medical policy does not apply to Medicare Advantage.
Discrimination is Against the Law

Premera Blue Cross complies with applicable Federal civil rights laws and does not discriminate on the basis of race, color, national origin, age, disability, or sex. Premera does not exclude people or treat them differently because of race, color, national origin, age, disability or sex.

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, or 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 file a grievance in person or by mail, fax, or email. If you need help filing 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 509F, HHH Building
  Washington, D.C. 20201, 1-800-368-1019, 800-537-7697 (TDD)

Complaint forms are available at

Getting Help in Other Languages

This Notice has Important Information. This notice may have important information about your application or coverage through Premera Blue Cross. There may be key dates in this notice. You may need to take action by certain deadlines to keep your health coverage or help with costs. You have the right to get this information and help in your language at no cost.

Call 800-722-1471 (TTY: 800-842-5357).

Arabic:
لا يключа هذه الإشعار خدماتًا محددة، وقد يحتوي هذا الإشعار معلوماتًا مهمة ينصح بإستلامها أو مراجعتها.

 đạt raat saaCIY 44 et yaj 20 201 80 0 80 2 7 22 1 47 17 17 (TTY: 80 0 8 42 5 3 5 5 5 5 5).

Français (French):

Appelez le 800-722-1471 (TTY: 800-842-5357).

Italiano (Italian):
Questo avviso contiene informazioni importanti. Questo avviso può contenere informazioni importanti sulla tua domanda o copertura attraverso Premera Blue Cross. Potrebbero esserci date chiave in questo avviso. Potrebbe essere necessario tuo intervento entro una scadenza determinata per consentirti di mantenere la tua copertura o sovvenzione. Hai il diritto di ottenere queste informazioni e assistenza nella tua lingua gratuitamente.

Chiamate 800-722-1471 (TTY: 800-842-5357).

Kreyol ayisyen (Creole):

Deutsche (German):

中文 (Chinese):
本通知有重要的訊息。本通知可能有關於您透過 Premera Blue Cross 提交的申請或保險的重要資訊。本通知內可能有重要日期。您可能需要在截止日期之前採取行動，以保留您的健康保險或費用補貼。您有權利免費以您的母語得到本訊息和幫助。請撥電話 800-722-1471 (TTY: 800-842-5357).