Protocol

Miscellaneous Genetic and Molecular Diagnostic Tests

(204121)

Medical Benefit		**Effective Date**: 10/01/20	**Next Review Date**: 07/21
Preauthorization	No	**Review Dates**: 07/17, 07/18, 07/19, 07/20	

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.

RELATED PROTOCOLS

General Approach to Evaluating the Utility of Genetic Panels

General Approach to Genetic Testing

Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes

KRAS, NRAS, and BRAF Variant Analysis in Metastatic Colorectal Cancer

Laboratory and Genetic Testing for Use of 5-Fluorouracil in Patients With Cancer

Populations	Interventions	Comparators	Outcomes
Individuals: • With symptoms of various conditions thought to be hereditary or with a known genetic component	Interventions of interest are: • Diagnostic testing with a miscellaneous genetic or molecular test	Comparators of interest are: • Standard care without genetic or molecular diagnostic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Change in disease status • Morbid events
Individuals: • Who are being screened for colorectal cancer	Interventions of interest are: • Testing with a SEPT9 methylated DNA test	Comparators of interest are: • Standard care without SEPT9 methylated DNA testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Change in disease status • Morbid events
Individuals: • Who are diagnosed with various conditions (e.g., Crohn disease, thymomas and thymic carcinomas, rheumatoid arthritis)	Interventions of interest are: • Prognostic testing with a miscellaneous genetic or molecular test	Comparators of interest are: • Standard care without genetic or molecular prognostic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Change in disease status • Morbid events

Populations	Interventions	Comparators	Outcomes
Individuals: • Who are diagnosed with various conditions (e.g., colon cancer, non-Hodgkin lymphoma)	Interventions of interest are: • Therapeutic testing with a miscellaneous genetic or molecular test	Comparators of interest are: • Standard care without genetic or molecular therapeutic testing	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Change in disease status • Morbid events
Individuals: • With a family history of various conditions thought to be hereditary or with a known genetic component	Interventions of interest are: • Testing for future risk of disease with a miscellaneous genetic or molecular test	Comparators of interest are: • Standard care without genetic or molecular diagnostic testing for future risk	Relevant outcomes include: • Overall survival • Disease-specific survival • Test accuracy • Test validity • Change in disease status • Morbid events

DESCRIPTION

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

SUMMARY OF EVIDENCE

DIAGNOSTIC TESTING

For individuals with symptoms of various conditions thought to be hereditary or with a known genetic component who receive diagnostic testing with a miscellaneous genetic or molecular test (e.g., DNA Methylation Pathway Profile, Know Error, Celiac PLUS, GI Effects [Stool], IBD sgi Diagnostic), the evidence includes case series, cross-sectional studies, diagnostic accuracy studies, and cohort studies. The relevant outcomes are 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 evidence review and addressed separately if it is determined that enough evidence has accumulated to reevaluate its potential clinical utility. The evidence is insufficient to determine the effects of the technologies on health outcomes.

For individuals who are being screened for colorectal cancer who receive SEPT9 methylated DNA testing (e.g., ColoVantage, Epi proColon, ColonSentry), the evidence includes case-control, cross-sectional, and prospective diagnostic accuracy studies along with systematic reviews of those studies. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The Prospective Evaluation of Septin 9 Performance for Colorectal Cancer Screening, estimated the sensitivity and specificity of Epi proColon detection of invasive adenocarcinoma at 48% and 92%, respectively. Other studies were generally low to fair quality. Based on results from these studies, the clinical validity of SEPT9 methylated DNA screening is

limited by the low sensitivity of the test. . Optimal intervals for retesting are not known. The evidence is insufficient to determine the effects of the technologies on health outcomes.

PROGNOSTIC TESTING

For individuals who are diagnosed with various conditions (e.g., Crohn disease, thymomas, and thymic carcinomas, rheumatoid arthritis) who receive therapeutic testing with a miscellaneous genetic or molecular test (e.g., Crohn's Prognostic, DecisionDx-Thymoma), there are no published studies. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The evidence is insufficient to determine the effects of the technologies on health outcomes.

THERAPEUTIC TESTING

For individuals who are diagnosed with various conditions (e.g., colon cancer, non-Hodgkin lymphoma) who receive therapeutic testing with a miscellaneous genetic or molecular test (e.g., ResponseDX: Colon, TransPredict Fc gamma 3A), the evidence includes case series, cross-sectional studies, diagnostic accuracy studies, and cohort studies. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The lack of demonstrated clinical utility of these tests is based on the following factors: (1) there is no or extremely limited published data addressing the test; and/or (2) there is insufficient evidence demonstrating the clinical validity of the test. For each test addressed, a literature review was conducted. The literature review was not comprehensive but sufficient to establish lack of clinical utility. A test will be removed from this evidence review and addressed separately if it is determined that enough evidence has accumulated to reevaluate its potential clinical utility. The evidence is insufficient to determine the effects of the technologies on health outcomes.

TESTING FOR FUTURE RISK OF DISEASE

For individuals with a family history of various conditions thought to be hereditary or with a known genetic component who receive testing for future risk of disease with a miscellaneous genetic or molecular test (e.g., ImmunoGenomic Profile), the evidence includes diagnostic accuracy studies. The relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The lack of demonstrated clinical utility of these tests is based on the following factors: (1) there is no or extremely limited published data addressing the test; and/or (2) there is insufficient evidence demonstrating the clinical validity of the test. For each test addressed, a literature review is conducted. The literature review was not comprehensive but sufficient to establish lack of clinical utility. A test will be removed from this evidence review and addressed separately if it is determined that enough evidence has accumulated to reevaluate its potential clinical utility. The evidence is insufficient to determine the effects of the technologies on health outcomes.

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:

- Testing of an affected (symptomatic) individual's germline to benefit the individual (excluding reproductive testing)
- Diagnostic testing
- Prognostic testing
- Therapeutic testing
- Testing an asymptomatic individual to determine future risk of disease.

POLICY GUIDELINES

GENETIC 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.

MEDICARE ADVANTAGE

For Medicare Advantage testing for SEPT9 (SEPTIN9) is unlikely to impact therapeutic decision-making in the clinical management of the patient and is considered **not medically necessary**.

The oncology (gastrointestinal neuroendocrine tumors) real-time PCR expression analysis of 51 genes, utilizing whole peripheral blood, algorithm reported as a nomogram of tumor disease index for its use in treating neuroendocrine tumors is considered **not medically necessary.**

Note: The oncology (gastrointestinal neuroendocrine tumors) real-time PCR expression analysis of 51 genes is not included in Table 1.

BACKGROUND

TESTS ADDRESSED IN THIS PROTOCOL

Table 1 lists tests assessed in this protocol. Three types of tests are related to testing of an affected (symptomatic) individual's germline to benefit the individual (excluding reproductive testing): diagnostic testing, prognostic testing, and therapeutic testing. The fourth type of test reviewed is testing of an asymptomatic individual to determine future risk of disease.

Table 1. Genetic and Molecular Diagnostic Tests Assessed This Protocol

Test Name	Manufacturer	Date Added	Diagnostic	Prognostic	Therapeutic	Future Risk
Celiac PLUS	Prometheus	Oct 2014	•			•
ColonSentry®	GeneNews[a]	Aug 2015				•
Crohn's Prognostic	Prometheus	Oct 2014		•		
DecisionDx-Thymoma	Castle	Jan 2015		•		
DNA Methylation Pathway Profile	Great Plains Laboratory	Jan 2015	•			
GI Effects® (Stool)	Genova Dxcs	Jan 2015	•			
IBD sgi Diagnostic™	Prometheus	Oct 2014	•			
ImmunoGenomic® Profile	Genova Dxcs	Aug 2015				•
Know Error™	Strand Dxcs	July 2016	•			
ResponseDx Colon	Response GXcs	Jan 2015			•	
SEPT9 methylated DNA[b]	Several[c]	Oct 2014	•			
TransPredict Fc gamma 3A[d]	Transgenomic	Oct 2014			•	

Castle: Castle Biosciences; Dxcs: Diagnostics; Gxcs: Genetics.
[a] In a joint venture with Innovative Diagnostic Laboratory.
[b] For example, ColoVantage® and Epi proColon®.
[c] ARUP, Quest, Clinical Genomics and Epigenomics.
[d] Not clear if this test is currently offered.

DIAGNOSTIC TESTS

Multiple Conditions

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

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

Test Description: DNA Methylation Pathway Profile

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

Test Description: Know Error DNA Specimen Provenance Assay

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

Celiac Disease

Previously called sprue, celiac sprue, gluten-sensitive enteropathy, gluten intolerance, nontropical sprue, or idiopathic steatorrhea, celiac disease is an immune-based reaction to gluten (water-insoluble proteins in wheat, barley, rye) that primarily affects the small intestine. Celiac disease occurs almost exclusively in patients who carry at least one human leukocyte antigen DQ2 or DQ8; the negative predictive value of having neither allele exceeds 98%.[3] Serum antibodies to tissue transglutaminase, endomysium, and deamidated gliadin peptide support a diagnosis of celiac disease but diagnostic confirmation requires duodenal biopsy taken when patients are on a gluten-containing diet.[4]

Test Description: Celiac PLUS

Celiac PLUS (Prometheus Therapeutics & Diagnostics) is a panel of two genetic and five serologic markers associated with celiac disease. Per the manufacturer, Celiac PLUS is a diagnostic test that also stratifies the future risk of celiac disease.[5] Genetic markers (human leukocyte antigen DQ2 and DQ8) are considered predictive of the risk of developing celiac disease[6]; serologic markers (immunoglobulin A [IgA] anti-tissue transglutaminase antibody, IgA anti-endomysial antibodies, IgA anti-deamidated gliadin peptide antibodies, IgG anti-deamidated gliadin peptide, and total IgA) are considered diagnostic for celiac disease. Celiac PLUS is intended for patients at risk for the disease (e.g., with an affected first-degree relative) or with symptoms suggestive of the disease.

Irritable Bowel Syndrome

IBS is a functional gastrointestinal (GI) disorder that affects 10% to 20% of the general population in the U.S. and worldwide. Symptoms include abdominal pain and/or bloating associated with disordered bowel habit (constipation, diarrhea, or both). Pathophysiology is poorly understood but may be related to chronic low-grade mucosal inflammation and disturbances in GI flora.[7] Recommended treatments include dietary restriction and phar-

macologic symptom control.[8-10] As living microorganisms that promote health when administered to a host in therapeutic doses,[11] probiotics are being investigated as a treatment for IBS. Several systematic reviews of randomized controlled trials have found evidence to support efficacy,[7,12-15] but results from recent randomized controlled trials have been mixed.[16-21] This discrepancy may be due in part to the differential effects of different probiotic strains and doses.

Test Description: GI Effects Comprehensive Stool Profile

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

Inflammatory Bowel Disease

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

Test Description: IBD sgi Diagnostic

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

Colon Cancer

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

A co-founder of the biotechnology firm GeneNews developed a patented platform technology based on the sentinel principle.[23] The sentinel principle posits that because blood interacts with all bodily tissues, "subtle changes occurring in association with injury or disease, within the cells and tissues of the body, may trigger specific changes in gene expression in blood cells reflective of the initiating stimulus."[23] In this way, blood cells (specifically, leukocytes) may act as sentinels of disease. In studies that led to the formulation of this principle, investigators compared gene expression (total RNA levels) in blood samples with cataloged genes from 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.[23]

Test Descriptions: SEPT9 Methylated DNA

ColoVantage (various manufacturers) blood tests for serum SEPT9 methylated DNA are offered by several laboratories (ARUP Laboratories, Quest Diagnostics; Clinical Genomics). Epi proColon (Epigenomics) received U.S. Food and Drug Administration approval in April 2016. Epigenomics has licensed its Septin 9 DNA biomarker technology to Polymedco and LabCorp. ColoVantage and Epi proColon are both PCR assays; however, performance characteristics vary across tests, presumably due to differences in methodology (e.g., DNA preparation, PCR primers; probes).

Test Description: ColonSentry

ColonSentry (GeneNews; Innovative Diagnostic Laboratory) is a PCR assay that uses a blood sample to detect the expression of seven genes found to be differentially expressed in CRC patients compared with controls24,: ANXA3, CLEC4D, TNFAIP6, LMNB1, PRRG4, VNN1, and IL2RB. Per the company website, these genes are early-warning signs of colon cancer, and test results can indicate the odds of having CRC compared with an average-risk person.[25] An average-risk person is defined as one who is "≥50 years old [is] asymptomatic for CRC…[has] no personal history of benign colorectal polyps, colorectal adenomas, CRC, or inflammatory bowel disease, and does not have a first-degree relative … with CRC."[25] The test is intended for use in adults who are averse to colonoscopy and/or fecal occult blood testing. "Because of its narrow focus, the test is not expected to alter clinical practice for patients who comply with recommended screening schedules."[26]

PROGNOSTIC TESTS

Crohn Disease

Recent studies have identified serologic[27] and genetic[28,29] correlates of aggressive CD that is characterized by fistula formation, fibrostenosis, and the need for surgical intervention. Prometheus has developed a blood test that aims to identify patients with CD who are likely to experience an aggressive disease course.

Test Description: Crohn's Prognostic

Crohn's Prognostic (Prometheus Therapeutics & Diagnostics) is a panel of six 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 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 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 the Genetic Testing for Lynch Syndrome and Other Inherited Colon Cancer Syndromes Protocol and the KRAS, NRAS, BRAF Variant Analysis (Including Liquid Biopsy) 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 sequencings; TS expression; ERCC1 expression; UGT1A1 SNV testing (rs8175347, rs4148323); VEGFR2 expression; and MET amplification by fluorescence in situ hybridization.

Non-Hodgkin Lymphoma

Rituximab is a humanized IgG monoclonal antibody against the CD20 antigen, which is commonly expressed on B lymphocytes. It is Food and Drug Administration-approved for the treatment of non-Hodgkin lymphoma, chronic lymphocytic leukemia, and nononcologic uses (e.g., rheumatoid arthritis).[30] Rituximab has demonstrated

better response and survival rates in combination chemotherapy regimens in patients with follicular lymphoma, chronic lymphocytic leukemia, and diffuse large B-cell lymphoma than chemotherapy alone, though not all patients responded. Altered binding to lymphocyte-bound rituximab by cytotoxic effector cells (e.g., natural killer cells, macrophages) has been identified as a mechanism of reduced rituximab efficacy. Effector cells with a Val158Phe substitution variant in their surface receptors for IgG molecules (e.g., rituximab) have impaired binding affinity, and cellular cytotoxicity is reduced. A genetic test for the Val158Phe variant of the gene that encodes the IgG receptor on effector cells (FCGR3A) has been developed and investigated as a means of predicting response to rituximab.

TESTS FOR FUTURE RISK OF DISEASE

Immunologic Disorders

Test Description: ImmunoGenomic Profile

The ImmunoGenomic Profile (Genova Diagnostics) is a buccal swab test that evaluates SNVs in 6 genes associated with immune function and inflammation: interleukin (IL)-10, IL-13, IL-1b, IL-4, IL-6, and tumor necrosis factor α.[31] According to the company website, variations in these genes "can affect balance between cell (Th-1) and humoral (Th-2) immunity, trigger potential defects in immune system defense, and stimulate mechanisms underlying chronic, overactive inflammatory responses." "The test uncovers potential genetic susceptibility to: Asthma, Autoimmune Disorders, Certain Cancers, Allergy, Infectious Diseases, Bone Inflammation, Arthritis, Inflammatory Bowel Disease, Heart Disease, Osteopenia, and Helicobacter pylori infection (cause of ulcers)."

REGULATORY STATUS

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

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

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

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