Medical Policy

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Title: Miscellaneous Genetic and Molecular Diagnostic Tests

Professional
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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 diagnosed with various conditions	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	Interventions of interest are: • Therapeutic testing with 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 a future risk. This evidence review evaluates miscellaneous genetic and molecular diagnostic tests not addressed in a separate review. If a separate policy exists, then conclusions reached there supersede conclusions here. The main criterion for inclusion in this review is that 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.

Objective

The objective of this evidence review is to determine whether diagnostic, prognostic, therapeutic, or future risk assessment testing using one of several miscellaneous genetic or molecular diagnostic tests improves the net health outcome in individuals with, or with a risk of, one of the various genetic conditions.

Background

Tests Addressed in This Evidence Review

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

Table 1. Genetic and Molecular Diagnostic Tests Assessed This Evidence Review

Test Name	Manufacturer	Date Added	Diagnostic	Prognostic	Therapeutic	Future Risk
Celiac PLUS	Prometheus	Oct 2014	●			●
Crohn's Prognostic	Prometheus	Oct 2014		●		
DNA Methylation Pathway Profile	Great Plains Laboratory	Jan 2015	●			
GI Effects (Stool)	Genova Dxcs	Jan 2015	●			
IBD sgi Diagnostic	Prometheus	Oct 2014	●			

Test Name	Manufacturer	Date Added	Diagnostic	Prognostic	Therapeutic	Future Risk
ImmunoGenomic Profile	Genova Dxcs	Aug 2015				●
Know Error	Strand Dxcs	July 2016	●			
ResponseDx Colon	Cancer GXcs	Jan 2015			●	

Dxcs: Diagnostics; Gxcs: Genetics.
a. For example, ColoVantage® and Epi proColon®.
b. ARUP, Quest, Clinical Genomics and Epigenomics.

DIAGNOSTIC TESTS

Multiple Conditions

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

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

Test Description: DNA Methylation Pathway Profile

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

Test Description: Know Error DNA Specimen Provenance Assay

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

Celiac Disease

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

peptide support a diagnosis of celiac disease but diagnostic confirmation requires duodenal biopsy taken when patients are on a gluten-containing diet.[4,]

Test Description: Celiac PLUS
Celiac PLUS (Prometheus Therapeutics & Diagnostics) is a panel of 2 genetic and 5 serologic markers associated with celiac disease. Per the manufacturer, Celiac PLUS is a diagnostic test that also stratifies 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 pharmacologic symptom control.[8,9,10,] 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,[7,12,13,14,15,] but results from recent randomized controlled trials have been mixed.[16,17,18,19,20,21,] This discrepancy may be due in part to the differential effects of different probiotic strains and doses.

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

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

Test Description: IBD sgi Diagnostic
IBD sgi Diagnostic (Prometheus Therapeutics & Diagnostics) is a panel of 17 serologic (n=8), genetic (n=4), and inflammatory (n=5) biomarkers. A proprietary algorithm produces an IBD score; results are reported as consistent with IBD (consistent with ulcerative colitis, consistent

with CD, or inconclusive for ulcerative colitisvs CD) or not consistent with IBD. The test is intended for use in patients with clinical suspicion of IBD.

THERAPEUTIC TESTS

Test description: ResponseDX: Colon

Response Genetics currently markets 2 colon cancer genetic panels to guide treatment selection, as well as separate tests for 11 genes associated with colon cancer prognosis and/or treatment response. The Driver Profile panel comprises PCR variant testing in *KRAS*, *BRAF*, and mismatch repair genes (microsatellite instability), plus *NRAS* exon 2 and 3 sequencing. These gene tests are reviewed elsewhere (see evidence reviews in the BCBSKS medical policies *Genetic Testing for Lynch Syndrome and Other inherited Colon Cancer Syndromes,* and *KRAS, NRAS, BRAF Variant Analysis(Including Liquid Biopsy) in Metastatic Colorectal Cancer*), 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 sequencings; *TS* expression; *ERCC1* expression; *UGT1A1* SNV testing (rs8175347, rs4148323); *VEGFR2* expression; and *MET* amplification by fluorescence in situ hybridization.

PROGNOSTIC TESTS

Crohn Disease

Recent studies have identified serologic[23,] and genetic[24,25,] 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.

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.[26,] 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 U.S. Food and Drug Administration has chosen not to require any regulatory review of these tests.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

POLICY

A. All of the tests listed in this policy are considered **experimental / investigational** and grouped according to the categories of genetic testing outlined in the BCBSKS *General Approach to Genetic Testing* medical policy evidence review:

1. Testing of an affected (symptomatic) individual's germline to benefit the individual (excluding reproductive testing)
2. Diagnostic testing
3. Prognostic testing
4. Therapeutic testing
5. 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.

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through May 25, 2021.

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

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

Diagnostic Testing

Clinical Context and Test Purpose

The purpose of diagnostic testing in patients for heritable or genetic pathogenic variants in a symptomatic individual is to establish a molecular diagnosis defined by the presence of known pathologic variant(s). For genetic testing, a symptomatic individual is defined as an individual with a clinical phenotype that correlates with a known pathologic variant.

The question addressed in this evidence review is: Does diagnostic testing for heritable or genetic pathogenic variants using the tests described below in symptomatic individuals improve the net health outcome?

The specific clinical context of each test is described briefly in the following sections. The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with symptoms of a particular disease for which a definitive diagnosis cannot be made using other diagnostic methods.

Interventions

The interventions of interest are miscellaneous genetic or molecular diagnostic tests, specifically: DNA Methylation Pathway Profile, Know Error, Celiac PLUS, GI Effects (Stool), and IBD sgi Diagnostic.

Comparators

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

Outcomes

The outcomes of interest are overall survival (OS), disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The timing of follow-up for irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and celiac disease ranges from weeks for the diagnosis to years for assessment of health outcomes.

Study Selection Criteria

For the evaluation of clinical validity of miscellaneous genetic or molecular tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Clinically Useful
A test is clinically useful if the use of the results inform management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials (RCTs).

No studies examining clinical utility were identified.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

It is not possible to construct a chain of evidence for clinical utility due to the lack of evidence on clinical validity.

DIAGNOSTIC TESTING FOR MULTIPLE CONDITIONS: DNA METHYLATION PATHWAY PROFILE
Review of Evidence
No full-length, peer-reviewed studies of the DNA Methylation Pathway Profile were identified.

Section Summary: DNA Methylation Pathway Profile
No studies were identified that evaluated this test.

DIAGNOSTIC TESTING FOR MULTIPLE CONDITIONS: KNOW ERROR SPECIMEN PROVENANCE ASSAY
Review of Evidence
Evidence for the clinical validity of the Know Error Specimen Provenance Assay is lacking. There is some evidence on the application of short tandem repeat testing for specimen provenance assays in general,[27,] but these data are not specific to the Know Error test.

Section Summary: Know Error Specimen Provenance Assays
There is a lack of published evidence on the use of the Know Error test to confirm the tissue of origin. Studies are needed that compare the use of Know Error with standard laboratory quality measures and that demonstrate a reduction in specimen provenance errors associated with the use of Know Error.

DIAGNOSTIC TESTING FOR CELIAC DISEASE: CELIAC PLUS
Review of Evidence
Celiac PLUS tests for genetic and serologic factors known to be associated with celiac disease. All 7 test components are included in an evidence-based diagnostic algorithm developed by the American College of Gastroenterology.[28,] However, algorithmic testing is individualized according to the baseline risk of disease and is done sequentially, rather than simultaneously as in Celiac PLUS.

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

Section Summary: Celiac Disease
No studies examining the clinical validity or clinical utility of Celiac PLUS were identified. Factors that support a chain of evidence for prognostic or diagnostic utility are lacking.

DIAGNOSTIC TESTING FOR IRRITABLE BOWEL SYNDROME: GI EFFECTS COMPREHENSIVE STOOL PROFILE

Review of Evidence

No studies were identified that assessed the accuracy of the GI Effects fecal panel for diagnosing IBS or for documenting "gut health," a concept that may be difficult to define given large interindividual variability in gut flora.[29,]

Section Summary: Diagnostic Testing for Irritable Bowel Syndrome
Evidence for the clinical validity and utility of the GI Effects Comprehensive Stool Profile is lacking. Because probiotics are not currently a standard treatment of IBS, the impact of test results on disease management is uncertain; ie, a chain of evidence for clinical utility of the test cannot be established.

DIAGNOSTIC TESTING FOR INFLAMMATORY BOWEL DISEASE: IBD SGI DIAGNOSTIC

Review of Evidence

The IBD sgi Diagnostic product monograph includes an extensive bibliography that documents associations of the 18 component markers, individually and in combination, with ulcerative colitis and/or Crohn disease (CD).[5,]

In a review of the monograph, Shirts et al (2012)[30,] observed that serologic tests for ASCA-IgA, ASCA-IgG, and atypical perinuclear anti-neutrophil cytoplasmic antibody are standard of care in the diagnostic workup of IBD,[31,32,] although not all investigators include these tests in recommended diagnostic strategies.[33,34,35,36,] These 3 markers are included in the 18-marker panel. Based on a 2006 meta-analysis of 60 studies (N=11608 patients), Reese et al (2006) reported that pooled sensitivity and specificity of the 3-test panel were 63% and 93%, respectively, for diagnosing IBD.[37,] Because the product monograph did not compare the 18-marker panel with the 3-marker panel, incremental improvement in diagnosis with the 18-marker panel is unknown. Shirts et al (2012) calculated an area under the curve for the 3-marker panel of 0.899.

Published evidence supports associations of each marker in the 18-marker panel, alone and in combination, with IBD diagnosis. Based on manufacturer data, the accuracy for IBD diagnosis of the 18-marker panel exceeds that of each component marker, but the relevant comparison with a panel of 3 markers that has good discrimination for IBD was not included; subsequent analysis has suggested that the panels may perform similarly. Performance characteristics for the 18-marker panel to distinguish ulcerative colitis from CD were not provided.

Section Summary: IBD sgi Diagnostic
No studies examining the clinical utility of IBD sgi Diagnostic were identified. Although manufacturer data supported the clinical validity of the test for diagnosing IBD, this evidence is insufficient to support a chain of evidence for clinical utility. For distinguishing ulcerative colitis from CD, clinical validity has not been established; therefore, a chain of evidence for clinical utility for this purpose cannot be established.

PROGNOSTIC TESTING

Clinical Context and Test Purpose

The purpose of prognostic testing of diagnosed disease is to predict natural disease course (eg, aggressiveness, the risk of recurrence, death). This type of testing uses gene expression of affected tissue to predict the disease course.

The question addressed in this evidence review is: Does prognostic testing using the tests described below in individuals diagnosed with a disease improve the net health outcome?

The specific clinical context of each test is described briefly in the following sections. The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients diagnosed with a disease (eg, CD).

Interventions

The interventions of interest are miscellaneous prognostic tests, specifically Crohn's Prognostic for CD.

Comparators

The comparator of interest is standard care without prognostic testing.

Outcomes

The outcomes of interest are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The timing of follow-up ranges from months for the aggressiveness of the disease to years for risk of recurrence or death.

Study Selection Criteria

For the evaluation of clinical validity of miscellaneous genetic or molecular tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

PROGNOSTIC TESTING FOR CROHN DISEASE WITH CROHN'S PROGNOSTIC

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
No studies of the 6-marker Crohn's Prognostic test were identified.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Direct evidence for clinical utility is lacking.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

It is not possible to construct a chain of evidence for clinical utility due to the lack of clinical validity.

Section Summary: Crohn's Prognostic
Direct and indirect evidence for clinical utility of the Crohn's Prognostic test to identify individuals likely to have an aggressive disease course are currently lacking.

Therapeutic Testing
Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Clinical Context and Test Purpose
The purpose of therapeutic testing in patients who have been diagnosed with conditions like colon cancer is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does therapeutic testing using ResponseDX: Colon in individuals diagnosed with colon cancer improve the net health outcome?

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients diagnosed with colon cancer.

Interventions
The interventions of interest are miscellaneous tests for variants that affect response to treatment or environmental exposure, specifically ResponseDX: Colon.

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

Outcomes
The outcomes of interest are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The timing of follow-up ranges from weeks for treatment selection to years for survival outcomes.

Study Selection Criteria
For the evaluation of clinical validity of miscellaneous genetic or molecular tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

THERAPEUTIC TESTING FOR COLON CANCER WITH RESPONSEDX: COLON
Review of Evidence
No full-length, peer-reviewed studies of the ResponseDX: Colon test were identified.

Section Summary: Colon Cancer
Evidence supporting the use of the ResponseDX Colon test to guide treatment selection in patients with colon cancer is currently lacking.

FUTURE RISK DISEASE TESTING
Clinical Context and Test Purpose
The purpose of testing for future risk of disease in asymptomatic patients is that predictive and presymptomatic types of testing can be used to detect gene variants associated with disorders that appear after birth, usually later in life. These tests can be used in individuals with a family history of a genetic disorder but who themselves have no features of the disorder at the time of

testing. Predictive testing can identify variants that increase an individual's risk of developing disorders with a genetic basis (eg, certain types of cancer or cardiovascular disease). Presymptomatic testing can determine whether a person will develop a genetic disorder, before any signs or symptoms appear, by determining whether an individual has a genetic variant that may lead to the development of the disease.

The question addressed in this evidence review is: Does testing of asymptomatic individuals for future risk of disease using the tests described below in asymptomatic individuals improve the net health outcome?

The specific clinical context of each test is described briefly in the following sections. The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest is patients with a family history of a genetic disorder that might develop later in life but who are currently without symptoms of the disorder.

Interventions
The interventions of interest are miscellaneous genetic or molecular risk assessment tests, specifically ImmunoGenomic Profile.

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

Outcomes
The outcomes of interest are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The timing of follow-up varies by test and is discussed in the following sections.

Study Selection Criteria
For the evaluation of clinical validity of miscellaneous genetic or molecular tests, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard (describe the reference standard)
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

FUTURE RISK DISEASE TESTING WITH IMMUNOGENOMIC PROFILE
Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence
No full-length, peer-reviewed studies of the ImmunoGenomic Profile were identified.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy, or testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Direct evidence for clinical utility is lacking.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

It is not possible to construct a chain of evidence for clinical utility due to the lack of clinical validity

Section Summary: ImmunoGenomic Profile
Evidence for the clinical validity and utility of the ImmunoGenomic Profile to predict the risk of developing arthritis, asthma, allergies, or other chronic inflammatory disorders is currently lacking.

Summary of Evidence
For each test addressed, a literature review was conducted. The literature review was not comprehensive, but sufficient to establish lack of clinical utility. If it is determined that enough evidence has accumulated to reevaluate its potential clinical utility, the test will be removed from this evidence review and addressed separately. 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.

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 (eg, DNA Methylation Pathway Profile, Know Error, Celiac PLUS, GI Effects [Stool], IBD sgi Diagnostic), the evidence is limited. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Prognostic Testing
For individuals who are diagnosed with various conditions who receive prognostic testing with a miscellaneous genetic or molecular test (eg, Crohn's Prognostic), 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 that the technology results in an improvement in the net health outcome.

Therapeutic Testing
For individuals who are diagnosed with various conditions (eg colorectal cancer) who receive therapeutic testing with a miscellaneous genetic or molecular test (eg, ResponseDX: Colon), no evidence was identified. Relevant outcomes are OS, disease-specific survival, change in disease status, and morbid events.The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

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), no evidence was identified. Relevant outcomes are OS, disease-specific survival, test accuracy and validity, change in disease status, and morbid events. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

SUPPLEMENTAL INFORMATION
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

National Comprehensive Cancer Network
The NCCN (v. 2.2021) guidelines for colon cancer state that it has "not been established if molecular markers are useful in treatment determination (predictive markers) and prognosis."[38,]

AMERICAN COLLEGE OF GASTROENTEROLOGY
Celiac Disease
In 2019, the American College of Gastroenterology published a clinical practice update for the diagnosis and monitoring of celiac disease.[39,] A recommendation for genetic testing using a multigene panel test (eg, Celiac PLUS) was not included.

Inflammatory Bowel Disease
In 2018, the American College of Gastroenterology practice guidelines on Crohn disease [40,] state that genetic and routine serologic testing is not indicated to establish the diagnosis of Crohn's disease.

Ongoing and Unpublished Clinical Trials
Some currently ongoing and unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03311152	Diagnostic Accuracy of the Circulating Cell-free DNA-based Epigenetic Biomarker mSEPT9 for Hepatocellular Carcinoma Detection Among Cirrhotic Patients: the SEPT9-CROSS Study	440	Feb 2022

NCT: national clinical trial

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS

81382	HLA Class II typing, high resolution (i.e., alleles or allele groups); one locus (e.g., HLA-DRB1, -DRB3/4/5, -DQB1, -DQA1, -DPB1, or -DPA1), each
81479	Unlisted molecular pathology procedure
81554	Pulmonary disease (idiopathic pulmonary fibrosis [IPF]), mRNA, gene expression analysis of 190 genes, utilizing transbronchial biopsies, diagnostic algorithm reported as categorical result (eg, positive or negative for high probability of usual interstitial pneumonia [UIP]) (eff 01/01/2021)
82397	Chemiluminescent assay
82784	Gammaglobulin (immunoglobulin); IgA, IgD, IgG, IgM, each
83520	Immunoassay for analyte other than infectious agent antibody or infectious agent antigen; quantitative, not otherwise specified
84999	Unlisted chemistry procedure
86021	Antibody identification; leukocyte antibodies
86140	C-reactive protein;
86255	Fluorescent noninfectious agent antibody; screen, each antibody
87045	Culture, bacterial; stool, aerobic, with isolation and preliminary examination (e.g., KIA, LIA), Salmonella and Shigella species
87046	Culture, bacterial; stool, aerobic, additional pathogens, isolation and presumptive identification of isolates, each plate
87075	Culture, bacterial; any source, except blood, anaerobic with isolation and presumptive identification of isolates
87102	Culture, fungi (mold or yeast) isolation, with presumptive identification of isolates; other source (except blood)
87177	Ova and parasites, direct smears, concentration and identification

87209	Smear, primary source with interpretation; complex special stain (e.g., trichrome, iron hemotoxylin) for ova and parasites
87328	Infectious agent antigen detection by immunoassay technique, (e.g., enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; cryptosporidium
87329	Infectious agent antigen detection by immunoassay technique, (e.g., enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; giardia
87336	Infectious agent antigen detection by immunoassay technique, (e.g., enzyme immunoassay [EIA], enzyme-linked immunosorbent assay [ELISA], immunochemiluminometric assay [IMCA]) qualitative or semiquantitative, multiple-step method; Entamoeba histolytica dispar group
87798	Infectious agent detection by nucleic acid (DNA or RNA), not otherwise specified; amplified probe technique, each organism
88346	Immunofluorescence, per specimen; initial single antibody stain procedure
88350	Immunofluorescence, per specimen; each additional single antibody stain procedure (List separately in addition to code for primary procedure)
0017M	Oncology (diffuse large B-cell lymphoma [DLBCL]), mRNA, gene expression profiling by fluorescent probe hybridization of 20 genes, formalin-fixed paraffin-embedded tissue, algorithm reported as cell of origin (eff 01/01/2021)

ICD-10 Diagnoses

Experimental / Investigational for all diagnoses related to this medical policy.

REVISIONS

01-07-2016	Policy added to the bcbsks.com web site on 12-08-2015 with an effective date of 01-07-2016.
08-17-2016	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Removed CPT code: 88347.
	Updated References section.
01-01-2017	In Coding section: ▪ Added CPT code: 81327 *(New code, effective January 1, 2017)*.
10-25-2017	Updated Description section.
	In Policy section: ▪ Added new Item A 1, "Testing of an affected (symptomatic) individual's germline to benefit the individual (excluding reproductive testing)". ▪ Previous Item A 1 is new Item A 2. ▪ Removed previous Item A 2, "Risk assessment". ▪ Removed previous Item A 4, "Genetic variants that alter response to treatment or to an environmental factor". ▪ Added new Item A 4, "Therapeutic testing". ▪ Added new Item A 5, "Testing an asymptomatic individual to determine future risk of disease".
	Updated Rationale section.

	In Coding section: ▪ Removed CPT code: 81401.
	Updated References section.
12-20-2017	Updated Description section.
	Updated Rationale section.
10-12-2018	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Added CPT codes: 88346, 88349.
	Updated References section.
	Removed Appendix section.
01-01-2019	In Coding section: ▪ Revised nomenclature to CPT code: 81327.
08-28-2019	Updated Description section.
	Updated Rationale section.
	Updated References section.
05-14-2021	Updated Description section.
	In Policy section: • Item A: added "outlined in the BCBSKS *General Approach to Genetic Testing* medical policy evidence review:"
	Updated Rationale section.
	Updated References section.
09-10-2021	Updated Rationale section.
	In the Coding section: Added CPT codes: 81554; 0017M Deleted CPT codes: 81327
	Updated References section.

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