Medical Policy

Miscellaneous Genetic and Molecular Diagnostic Tests

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Policy Number: 712
BCBSA Reference Number: 2.04.121
NCD/LCD: N/A

Related Policies
General Approach to Genetic Testing, #735
General Approach to Evaluating the Utility of Genetic Panels, #734

Policy

Commercial Members: Managed Care (HMO and POS), PPO, and Indemnity Medicare HMO BlueSM and Medicare PPO BlueSM Members

All of the tests listed in this policy are considered INVESTIGATIONAL.

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Manufacturer</th>
<th>Diagnosis</th>
<th>Risk Assessment</th>
<th>Prognosis</th>
<th>Treatment Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celiac PLUS</td>
<td>Prometheus®</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ColonSentry®</td>
<td>GeneNews</td>
<td></td>
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<td>Crohn’s Prognostic</td>
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</tr>
<tr>
<td>Decision Dx-Melanoma™</td>
<td>Castle</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
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<tr>
<td>Decision Dx-Thymoma</td>
<td>Castle</td>
<td></td>
<td></td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>DNA Methylation</td>
<td>Great Plains</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathway Profile</td>
<td>Laboratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI Effects® (Stool)</td>
<td>Genova Dxcs®</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBD sgi Diagnostic™</td>
<td>Prometheus®</td>
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<tr>
<td>ImmunoGenomic®</td>
<td>Genova Dxcs®</td>
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<td>✓</td>
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<td>Profile</td>
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<tr>
<td>Response Dx®: Colon</td>
<td>Response Gxcs</td>
<td></td>
<td></td>
<td>✓</td>
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<tr>
<td>SEPT9 methylated DNA</td>
<td>Several</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Prior Authorization Information
Pre-service approval is required for all inpatient services for all products.
See below for situations where prior authorization may be required or may not be required for outpatient services.
Yes indicates that prior authorization is required.
No indicates that prior authorization is not required.
N/A indicates that this service is primarily performed in an inpatient setting.

<table>
<thead>
<tr>
<th>Outpatient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial Managed Care (HMO and POS)</td>
</tr>
<tr>
<td>Commercial PPO and Indemnity</td>
</tr>
<tr>
<td>Medicare HMO Blue℠</td>
</tr>
<tr>
<td>Medicare PPO Blue℠</td>
</tr>
</tbody>
</table>

CPT Codes / HCPCS Codes / ICD Codes
Inclusion or exclusion of a code 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 as it applies to an individual member.

Providers should report all services using the most up-to-date industry-standard procedure, revenue, and diagnosis codes, including modifiers where applicable.

CPT Codes

| 81327 | SEPT9 (Septin9) (eg, colorectal cancer) methylation analysis |

Description
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 workup 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:
  o An association of the marker with future disorder has been established; AND
  o 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 3 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:
  o Association of the marker with a phenotype/metabolic state that relates to drug efficacy or adverse drug reactions has been established; AND
  o 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:
Association of a mutation with response to a particular drug has been established; AND
Clinical utility has been established (see evidence review 2.04.91), eg, by demonstrating that
the patient is a candidate for targeted drug therapy that is associated with a specific mutation.

Summary
There are numerous commercially available genetic and molecular diagnostic tests. This evidence review
evaluates the clinical utility of many miscellaneous genetic and molecular diagnostic tests that are not
addressed in a separate review. If a separate evidence review exists, then conclusions reached in it
supersede those in this here. Criteria by which it is determined that a test will be included in the
miscellaneous genetic and molecular diagnostic tests policy are the following:

The evidence is insufficient to determine the effects of using the tests addressed in this review on health
outcomes. The lack of clinical utility of these tests is based on criteria outlined in evidence review (#735
General Approach to Genetic Testing). Also, 1 or more of the following factors are present:

- There is no or extremely limited published data addressing the test.
- There is insufficient evidence demonstrating clinical validity of the test.

For each test addressed in this evidence review, a literature review is conducted. The literature review will
not be 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.

Policy History

<table>
<thead>
<tr>
<th>Date</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2017</td>
<td>Clarified coding information for the 2017 code changes.</td>
</tr>
<tr>
<td>8/2016</td>
<td>New references added from BCBSA National medical policy.</td>
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</table>

Information Pertaining to All Blue Cross Blue Shield Medical Policies
Click on any of the following terms to access the relevant information:
Medical Policy Terms of Use
Managed Care Guidelines
Indemnity/PPO Guidelines
Clinical Exception Process
Medical Technology Assessment Guidelines

References
1. Pfeifer JD, Zehnbauer B, Payton J. The changing spectrum of DNA-based specimen
21173135
2013;112(3-4):248-256. PMID 24029703
Dis Sci. Sep 2014;59(9):2199-2206. PMID 24705698


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


69. 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):14941500. PMID 19672774
73. Fabisiewicz A, Paszkiewicz-Kozik E, Osowiecki M, et al. FcgammaRIIIA and FcgammaRIIa polymorphisms do not influence survival and response to rituximab, cyclophosphamide,


