Medical Policy
Genotyping for 9p21 Single Nucleotide Polymorphisms to Predict Risk of Cardiovascular Disease or Aneurysm

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- Policy: Medicare
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Policy Number: 340
BCBSA Reference Number: 2.04.71

Related Policies
- Measurement of Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) in the Assessment of Cardiovascular Risk, #558
- Novel Lipid Risk Factors in Risk Assessment and Management of Cardiovascular Disease, #283
- Gene Expression Testing to Predict Coronary Artery Disease, #349
- Genetic Testing for Lipoprotein-a Variants as a Decision Aid for Aspirin Treatment, #339
- KIF6 Genotyping for Predicting Cardiovascular Risk and or Effectiveness of Statin Therapy, #129
- Homocysteine Testing in the Screening, Diagnosis, and Management of Cardiovascular Disease, #016

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

Genotyping for 9p21 single nucleotide polymorphisms is INVESTIGATIONAL, including, but not limited to identifying:
- Patients who may be at increased risk of cardiovascular disease
- Patients who are at risk of cardiovascular manifestations (e.g., MI, ischemic stroke, peripheral arterial disease, coronary artery calcification), or
- Patients who may be at increased risk for aneurysmal disease (abdominal aortic aneurysms, or intracranial aneurysms or polypoidal choroidal vasculopathy).

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>Commercial Managed Care (HMO and POS)</th>
<th>Outpatient</th>
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<tr>
<td>This is not a covered service.</td>
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<td>Commercial PPO and Indemnity</td>
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<td>Medicare HMO BlueSM</td>
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<td>Medicare PPO BlueSM</td>
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CPT Codes / HCPCS Codes / ICD-9 Codes

The following codes are included below for informational purposes. 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

<table>
<thead>
<tr>
<th>CPT codes:</th>
<th>Code Description</th>
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<tr>
<td>81400</td>
<td>Molecular pathology procedure, Level 1 (e.g., identification of single germline variant [e.g., SNP] by techniques such as restriction enzyme digestion or melt curve analysis)</td>
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Description

A number of highly correlated single nucleotide polymorphisms (SNPs) found in the chromosome 9 region p21 locus (9p21) have been significantly associated with myocardial infarction (MI), particularly early onset MI, and other manifestations of cardiovascular disease (CVD). Associations with abdominal aortic aneurysm and with intracranial aneurysm have also been reported. Genotyping for 9p21 SNPs may be offered as an approach to identify patients who may be at increased risk of some of these outcomes.

Genome-wide association studies using single nucleotide polymorphism (SNP) arrays detected a common genetic variant affecting the risk of coronary heart disease. These risks are defined as inadequate circulation to cardiac muscle and surrounding tissue potentially resulting in MI, unstable angina pectoris, coronary revascularization, or death in Caucasians. All of the SNPs were located at chromosome 9p21.3 shortened for simplicity to 9p21.

Several studies have extended the 9p21 association to other vascular diseases including ischemic stroke; thus 9p21 may be reported as associated with CVD outcomes, defined as including CHD outcomes plus ischemic stroke. Associations have also been reported with abdominal aortic aneurysm and with intracranial arterial aneurysm.

Many researchers expected that just a handful of genetic mutations would explain most cases of any given major disease, but the mutations detected in each disease turned out to account for a small fraction of the overall incidence. Natural selection seems to be much more efficient than expected at ridding the population of dangerous genes, even of those that act well after the age of reproduction. That leaves thousands of different mutations, each very rare in the population, as the probable culprit. Because most of the mutations are rare, they are extremely hard to find.

Examples of 9p21 genotyping tests which are laboratory-developed tests to predict cardiac risk are the 9p21-EarlyMICheck™ Genotype Test from Berkeley HeartLab and the deCODE MI™ from deCodeME genetics. All 9p21 genetic tests for predicting cardiac risk are considered investigational regardless of the commercial name, the manufacturer, or FDA approval status.
Summary
The association of 9p21 SNP alleles with CHD/CAD outcomes (clinical validity) is well-established and consistent in multiple independent populations, with evidence of increasing severity of outcomes with increasing risk allele dosage. The clinical validity for 9p21 and ischemic stroke or abdominal aortic aneurysm is less well-studied and less certain. Despite the clinical validity evidence for CHD/CAD outcomes, however, clinical utility, i.e. that the use of the test to change medical management improves CHD/CAD health outcomes, is not established. No studies have shown that 9p21 genotyping significantly improves risk reclassification after initial classification by traditional risk factors, nor have studies shown that addition of 9p21 genotyping to traditional risk factors improves risk assessment, an intermediate outcome. Thus, 9p21 genotyping for all applications is investigational.

Policy History
<table>
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<tr>
<th>Date</th>
<th>Action</th>
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<tbody>
<tr>
<td>6/2015</td>
<td>New references added from BCBSA National medical policy.</td>
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<td>7/2014</td>
<td>New references added from BCBSA National medical policy.</td>
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<tr>
<td>5/2013</td>
<td>New references from BCBSA National medical policy.</td>
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<td>2/2013</td>
<td>BCBSA national policy review. No change to policy statement. Effective 2/4/2013.</td>
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<tr>
<td>1/1/2012</td>
<td>New policy, effective 1/1/2012, describing ongoing non-coverage.</td>
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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. Wellcome Trust Case Control Consortium: Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 2007; 447(7145):661-78.
52. Sheridan SL, Crespo E. Does the routine use of global coronary heart disease risk scores translate into clinical benefits or harms? A systematic review of the literature. BMC Health Serv Res 2008; 8:60.


