The following Protocol contains medical necessity criteria that apply for this service. It is applicable to Medicare Advantage products unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Preauthorization is not required but is recommended if, despite the position of this Protocol, you feel this service is medically necessary. 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.

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 (AAA) 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.

Background

In 2007, genome-wide association studies (GWAS) using SNP arrays resulted in the near simultaneous reporting of the first common genetic variant that affects the risk of coronary heart disease (CHD; defined as inadequate circulation to cardiac muscle and surrounding tissue resulting in MI, unstable angina pectoris, coronary revascularization, or death) in Caucasians. (1-4) The SNPs commonly reported across these studies were supplemented with more SNPs with similar estimates of CHD risk in the same and additional studies. These SNPs were confirmed in case control replication studies in a variety of study populations, showing that the identified SNPs were associated with CHD and even more specifically with MI. (5) All of the SNPs were found within a locus spanning a 58-kilobase region at chromosome 9p21.3 (thus the locus is sometimes represented more specifically as 9p21.3; for simplicity, 9p21 will be used for the rest of this document), are highly correlated ($r^2>0.8$) and thus are said to be in linkage disequilibrium (nonrandom association of alleles). In all studies, the association of any identified SNP with CHD risk was shown to be independent of traditional risk factors. (5)

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 AAA and with intracranial arterial aneurysm. (6)

Several genes are found at the 9p21 locus, including ANRIL, which encodes a large noncoding RNA that may have regulatory functions, and CDKN2A and CDKN2B, which encode cyclin-dependent kinase inhibitors. (6) The mechanisms by which the SNPs lead to increased CHD risk have been largely unknown. Recently, Harismendy et al identified several potential enhancer regulatory DNA sequences in the 9p21 region. (7) They reported that the SNP rs10747278, consistently associated with increased risk of CHD, occurs in one of these enhancer sequences and that the risk allele disrupts a transcription factor binding site involved in the inflammatory response (STAT1). The interaction of STAT1 with part of the inflammatory signaling pathway, interferon-gamma, is impaired in 9p21 risk carriers. Congrains et al genotyped 18 SNPs across the CVD-associated region and encompassing ANRIL and CDKN2A/B to determine the impact of 9p21 variants on gene expression. (8) The authors reported that
“several SNPs in 9p21 locus affect the expression of ANRIL, which is further in control of the regulation of CDKN2A/B and cell growth. Cell proliferation mediates the progression of atherosclerosis and is also directly or indirectly involved in the pathogenesis of diseases associated with this locus.”

Availability

The Berkeley HeartLab offers the 9p21 Genotype Test, which detects the rs10757278 A>G and rs1333049 G>C SNPs within the 9p21 locus of chromosome. The information on the website (available online at: http://www.bhlinc.com/clinicians/test-descriptions/9p21) indicates that the SNPs have been shown to predict increased risk for early onset MI, for AAA, and for MI/CHD in general. It is suggested that the test may help identify patients at increased risk for these conditions, alerting providers to characterize and reduce other contributing risk factors.

Cardiac risk genotyping panels offered by other laboratories may include and individually report 9p21 SNP results. For example, the deCODE MI™ (deCODE Genetics, Reykjavik) test genotypes 9p21.3 rs10757278 in addition to seven other SNPs from other chromosomal loci to estimate the risk of CHD and MI.

Regulatory Status

There is no manufactured test kit for 9p21 genotyping that has been reviewed by the U.S. Food and Drug Administration. 9p21 genotyping tests are laboratory-developed tests, offered by clinical laboratories licensed under Clinical Laboratory Improvement Amendment for high-complexity testing.

Related Protocol

Novel Biomarkers in Risk Assessment and Management of Cardiovascular Disease

Policy (Formerly Corporate Medical Guideline)

The use of genotyping for 9p21 single nucleotide polymorphisms (SNPs) is considered investigational, including, but not limited to, identification of patients who may be at increased risk of cardiovascular disease or its manifestations (e.g., MI, ischemic stroke, peripheral arterial disease, coronary artery calcification) or identification of patients who may be at increased risk of aneurysmal disease (AAAs, intracranial aneurysms, polypoidal choroid vasculopathy).

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

References

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


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<tr>
<th>Protocol</th>
<th>Genotyping for 9p21 Single Nucleotide Polymorphisms to Predict Risk of Cardiovascular Disease or Aneurysm</th>
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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.


