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

Policy # 00299
Original Effective Date: 06/15/2011
Current Effective Date: 07/13/2020

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers genotyping for *9p21* single nucleotide polymorphisms (SNPs) for all clinical uses including but not limited to, identification of patients who may be at increased risk of cardiovascular disease (CVD) or its manifestations (e.g., myocardial infarction [MI], ischemic stroke, peripheral arterial disease, coronary artery calcification), or identification of patients who may be at increased risk for aneurysmal disease (abdominal aortic aneurysms [AAAs], intracranial aneurysms, polypoidal choroidal vasculopathy) to be **investigational.***

Background/Overview

A number of highly correlated SNPs found at the 9p21 locus have been significantly associated with risk of MI, particularly early onset MI, and other manifestations of CVD. Associations between *9p21* SNPs and risk of AAA, intracranial aneurysms, and other vascular disorders have also been reported. Genotyping for *9p21* SNPs has been investigated to identify patients at risk of cardiovascular disorders.

In 2007, multiple investigators nearly simultaneously reported the first common genetic variant affecting 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 whites through genome-wide association studies (GWAS) using SNP arrays. Additional studies identified other SNPs with similar estimates of CHD risk. 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. 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). The association of any identified SNP with CHD risk was shown to be independent of traditional risk factors.

Several studies have extended the 9p21 association to other vascular diseases including ischemic stroke; thus 9p21 may be reported as being associated with CVD (defined as CHD and cerebrovascular disease) outcomes. Associations have also been reported with AAA and with intracranial arterial aneurysm and other vascular diseases.

Several genes are found at the 9p21 locus, including ANRIL, which encodes a large noncoding ribonucleic acid (RNA) which may have regulatory functions, and *CDKN2A* and *CDKN2B*, which encode cyclin-dependent kinase inhibitors. The mechanisms by which the SNPs lead to increased CHD risk have been largely unknown. In 2011, Harismendy et al. identified several potential enhancer regulatory deoxyribonucleic acid (DNA) sequences in the 9p21 region. They reported that the SNP rs10747278, consistently associated with increased risk of CHD, occurs in 1 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. 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."

Commercially Available Tests

Several laboratories offer 9p21 genotyping. For example, the Berkeley HeartLab (Quest Diagnostics) offers the 9p21 Genotype Test, which detects the rs10757278 A>G and rs1333049 G>C SNPs within the 9p21 locus of chromosome 9. Baylor Miraca Genetics Laboratories offers genotyping of the rs10757278 A>G polymorphism at *9p21*.

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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 7 other SNPs from other chromosomal loci to estimate the risk of CHD and MI.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). 9p21 genotyping tests are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the U.S. FDA has chosen not to require any regulatory review of this test.

Rationale/Source

A number of highly correlated single-nucleotide polymorphisms (SNPs) found at the 9p21 locus have been significantly associated with risk of myocardial infarction (MI), particularly early-onset MI, and other manifestations of cardiovascular disease. Associations between *9p21* SNPs and risk of abdominal aortic aneurysm, intracranial aneurysms, and other vascular disorders have also been reported. Genotyping for *9p21* SNPs has been investigated to identify patients at risk of cardiovascular disorders.

The association of SNPs at the 9p21 locus with coronary artery/heart disease (CAD/CHD) 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 the association of *9p21* polymorphisms with ischemic stroke, aneurysms, or other vascular disorders is less well-studied and less certain. Despite evidence that *9p21* polymorphisms are associated with CAD/CHD incidence and outcomes, the clinical utility of *9p21* genotyping has not been established. Studies have not conclusively demonstrated that *9p21* genotyping significantly improves risk reclassification after initial classification by traditional risk factors or that the addition of *9p21* genotyping to traditional risk factors improves risk assessment. No studies were identified that evaluate whether use of *9p21* genotyping is associated with changes in patient management,

improvements in clinical outcomes, or both. Thus, *9p21* genotyping for all applications is investigational.

Supplemental Information

American College of Cardiology and the American Heart Association
In 2013, the American College of Cardiology and the American Heart Association Task Force on Practice Guidelines issued guidelines on the assessment of cardiovascular risk, which did not address assessment of *9p21* polymorphisms.

Evaluation of Genomic Applications in Practice and Prevention Working Group
The Evaluation of Genomic Applications in Practice and Prevention Working Group (EWG) published a recommendation on "…genomic profiling to assess cardiovascular risk to improve cardiovascular health," which included a recommendation on 9p21 profiling alone based on Palomaki et al. In general, EWG found "…insufficient evidence to recommend testing for the 9p21 genetic variant or 57 other variants in 28 genes ... to assess risk for cardiovascular disease (CVD) in the general population, specifically heart disease and stroke. The EWG found that the magnitude of net health benefit from use of any of these tests alone or in combination is negligible. The EWG discourages clinical use unless further evidence supports improved clinical outcomes. Based on the available evidence, the overall certainty of net health benefit is deemed 'Low'."

U.S. Preventive Services Task Force Recommendations
No U.S. Preventive Services Task Force recommendations for *9p21* genotyping to identify risk for cardiovascular disease have been identified.

Medicare National Coverage
There is no national coverage determination (NCD). In the absence of an NCD, coverage decisions are left to the discretion of local Medicare carriers.

References

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Policy History

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06/02/2011	Medical Policy Committee review
06/15/2011	Medical Policy Implementation Committee approval. New policy.
06/14/2012	Medical Policy Committee review
06/20/2012	Medical Policy Implementation Committee approval. Title changed from "Genotyping for 9p21 Single Nucleotide Polymorphisms to Predict Risk of Cardiovascular Disease or Aneurysm" to "Genotyping for 9p21 Genetic Polymorphisms to Predict Cardiovascular Disease Risk". Coverage eligibility unchanged.
02/19/2013	Coding updated
06/06/2013	Medical Policy Committee review

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06/25/2013	Medical Policy Implementation Committee approval. Identification of patients at risk for aneurysmal disease added to the policy title and investigational statement, and additional cardiovascular disease added to policy statement (peripheral vascular disease, coronary artery calcification, polypoidal choroidal vasculopathy).
06/05/2014	Medical Policy Committee review
06/18/2014	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2015	Medical Policy Committee review
06/17/2015	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
08/03/2015	Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
06/02/2016	Medical Policy Committee review
06/20/2016	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
01/01/2017	Coding update: Removing ICD-9 Diagnosis Codes
06/01/2017	Medical Policy Committee review
06/21/2017	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
07/05/2018	Medical Policy Committee review
07/11/2018	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/06/2019	Medical Policy Committee review
06/19/2019	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
06/04/2020	Medical Policy Committee review
06/10/2020	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 06/2021

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Coding

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Codes used to identify services associated with this policy may include (but may not be limited to) the following:

Code Type	Code
CPT	81479
HCPCS	No codes
ICD-10 Diagnosis	All related diagnoses

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into

standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with the Blue Cross and Blue Shield Association technology assessment program (TEC) or other nonaffiliated technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or
    3. Reference to federal regulations.

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NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

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