



Louisiana

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

Policy # 00299

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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-

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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.

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.

Centers for Medicare and Medicaid Services (CMS)

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

Rationale/Source

Analytic Validity

In the case of 9p21 mutations, analytic validity refers to a test’s technical accuracy in detecting a mutation that is present or in excluding a mutation that is absent. Limited information is available on the analytic validity of the available 9p21 genotyping methods. The deCODE MI test is based on the Centaurus™[‡] Assay (Nanogen Inc., San Diego, CA), which is a real-time polymerase chain reaction (PCR)–based assay

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that uses fluorescence detection of PCR products by spectrometry. Published literature describing the development of the Centaurus Assay reported 100% concordance with a criterion standard. Real-time PCR-based methods are generally considered to have high accuracy.

Clinical Validity

9p21 polymorphisms have been associated with multiple types of CVD. The strength of association between the polymorphisms and each disease type (ie, clinical validity) is discussed separately.

9p21 Polymorphisms and Coronary Heart Disease

Meta-Analyses

Palomaki et al. conducted the first formal systematic review of the 9p21 literature to estimate the strength of the association between established 9p21 SNP variants and heart disease and to examine clinical utility. This review was commissioned by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (EWG). Of the 25 published studies identified, 16 were initially included; a follow-up search identified another 6. The 22 studies analyzed 47 data sets that reported 9p21 SNP genotypes in association with outcomes of CHD (including MI) or CAD (the result of the accumulation of atheromatous plaques within the walls of the coronary arteries that supply the myocardium, and the most frequent cause of CHD) were included in this review. Ischemic stroke and aneurysm outcomes were excluded from this analysis; all CHD/CAD outcomes were combined. Data sets were limited to Asian and white populations.

Three publications were cohort studies, the rest case-control studies; level 1 and level 2 evidence, respectively, using EWG methods. Five SNPs in the 9p21 locus (rs1333049, rs10757274, rs2383207, rs2891168, and rs10757278) covered all studies/data sets. First, the review demonstrated that the choice of SNP was relatively unimportant; in combining the data from 2 studies, 4 SNPs provided nearly identical odds ratios (ORs). Thus, the results from only 1 SNP per study were used.

Across all studies, consensus genotype frequencies in controls were 27%, 50%, and 23% for 0, 1, and 2 at-risk alleles, respectively. The random-effects summary OR across all studies/data sets was 1.25 (95% confidence interval [CI], 1.21 to 1.29; $p < 0.001$; $I^2 = 10\%$) for individuals with 2 at-risk SNP alleles compared to individuals with 1 at-risk allele. When the same analysis was restricted to individuals younger than 55 years of age, the summary OR increased to 1.35 (95% CI, 1.3-1.4). Limiting the data sets to only those with upper age cutoff levels greater than 70 years, the summary OR was 1.19 (95% CI, 1.13-1.25; $P < 0.001$). For individuals (all data sets) with no at-risk alleles compared to individuals with 1 at-risk allele the summary OR was 0.80 (95% CI, 0.77-0.82; $p < 0.001$). No differences were found between Asians and whites.

Since this study, several additional meta-analyses of 9p21 genotyping have been published. Schunkert et al. and the CARDIoGRAM Consortium conducted a meta-analysis of 14 GWAS of CAD. The 9p21 association per risk allele with CAD, as measured by SNP rs4977574, was 1.29 (95% CI, 1.23–1.36; $p = 1.35 \times 10^{-22}$). In an earlier report of this analysis, the association was stronger among cases less than 50 years of age at an OR of 1.45 ($p = 0.0015$). The Coronary Artery Disease Genetics Consortium meta-

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analyzed 4 large GWAS of CAD and reported an allele risk of 1.20 (95% CI, 1.16–1.25; $p = 1.62 \times 10^{-25}$) for 9p21 SNP rs4977574 and CAD. These results compare well with Palomaki et al.

Zhou et al conducted a meta-analysis of 7 case control studies (N=7123 total) and found associations between early-onset CAD and rs2383207 (OR=0.79; 95% CI, 0.71 to 0.88; $p < 0.001$), rs10757278 (OR=1.28; 95% CI, 1.15 to 1.42; $p < 0.001$), rs10757274 (OR=1.17; 95% CI, 1.08 to 1.33; $p = 0.02$), and rs2383206 (OR=1.17; 95% CI, 1.10 to 1.25; $p < 0.001$). In a meta-analysis of 21 studies that included patients with information on CAD, MI status and 9p21 genotype (N=33,673), Chan et al also found associations with CAD and the 9p21 locus and reported an OR of 1.15 (95% CI, 1.04 to 1.26) for heterozygous carriers and an OR of 1.23 (95% CI, 1.08 to 1.39) for homozygous carriers. However, when underlying CAD was present in both case subjects ($n=17,791$) and control subjects ($n=15,882$), the prevalence of MI was not significantly associated with the 9p21 risk allele (OR=0.99; 95% CI, 0.95 to 1.03). In a meta-analysis of 21 case control studies evaluating the association between 9p21 SNPs and CHD in an east Asian population, including 25,945 cases and 31,777 controls, Dong et al found a significant association between the allele rs1333049 and CHD (OR=1.30; 95% CI, 1.25 to 1.35; $p < 0.001$). A 2014 meta-analysis of case-control studies had similar findings.

Individual Studies: 9p21 Polymorphisms and Risk of CHD/CAD

Several studies analyzing individual patient cohorts or case-control populations for association of 9p21 and CHD/CAD have been published since the Palomaki et al. review. Most results again compare well with Palomaki et al. Scheffold et al. evaluated a population of male patients with acute MI compared to an otherwise comparable population of males without an event and reported a slightly higher allele risk for several 9p21 SNPs (OR approximate range, 1.6-1.9). The estimates increased when the population was limited to those cases with a family history of MI (OR approximate range, 1.9-2.8); the authors point out that the combination risk factor of family history plus 9p21 status is similar in value to those of traditional risk factors such as hypertension, diabetes mellitus, and current smoking.

Beckie et al. studied the allelic frequencies and haplotype structure of genetic variants on chromosome 9p21 in a cohort of black and white women with early-onset CHD. The authors report interethnic diversity in the SNP risk alleles and the haplotype structure of chromosome 9p21 SNP variants, suggesting that different variants may influence CHD in whites and blacks. Shiffman also reported no association of rs10757274 and incident MI in African American men (N = 228) and women (N = 405) aged ≥ 65.2 years.

Wang et al. studied CAD in a Chinese Han cohort with and without type 2 diabetes. An adjusted (gender, hypertension, hyperlipidemia, smoking) analysis of the homozygous risk genotype for rs1333049 showed an increased risk of early-onset CAD among diabetic (OR: 2.367, 95% CI: 1.258–4.453, $P = 0.008$), but not among non-diabetic patients (OR: 1.632, 95% CI: 0.995–2.654, $P = 0.057$).

Individual Studies: 9p21 Allele Dosage and Disease Severity, Progression, and Risk of Death

Dandona et al. reported a strong direct association between the proportion of early onset patients with angiographically-determined 3-vessel disease and increasing gene dosage of 9p21 SNP rs1333049 (OR

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per risk allele copy, 1.45, 95% CI 1.18-1.79; $p = 4.26 \times 10^{-4}$). Patel et al. also reported greater 9p21 risk allele frequency with increasing angiographically-defined CAD severity ($p = 0.003$). In a case-control study with a 10-year follow-up of cases ($N = 1,508$), Ardissino et al. reported that rs1333040 was significantly associated with coronary atherosclerosis progression, heterozygous hazard ratio (HR) 1.5 (95% CI: 1.17 to 2.02) and homozygous HR 2.2 (95% CI: 1.3 to 2.7). There was no significant association with cardiovascular death or the recurrence of MI.

Szpacowicz et al evaluated the association of the 9p21 SNPs rs1333049, rs10757278, and rs4977574 with 5-year all-cause mortality in a cohort of 589 patients who underwent percutaneous coronary intervention for ST-elevation MI. Results were published in 2014, after retraction of a previous publication due to reporting of an incorrect allele being associated with mortality. In the cohort as a whole, there was no significant association between genotype and mortality. Among the subgroup of 238 patients with high risk of death (GRACE risk score, ≥ 155), the heterozygotes or homozygotes with a high-risk genotype had higher risk of mortality (for rs10757278: HR=2.2; 95% CI, 1.15 to 4.2; for rs4977574: HR=2.7; 95% CI, 1.3 to 5.4; for rs1333049, HR=2.3; 95% CI, 1.2 to 4.5).

9p21 Polymorphisms and Ischemic Stroke

Meta-Analyses

Several studies have reported, with mixed results, on the association of 9p21 with ischemic stroke. Anderson et al conducted a meta-analysis of 8 studies, focusing on two 9p21 SNPs, rs1537378 and rs10757278.³² Inclusion of all data resulted in a high degree of heterogeneity; restriction to only those studies with sufficient information to allow stroke subtype-specific analysis ($n=5$) resulted in an overall OR estimate of 1.15 (95% CI, 1.08 to 1.23; $p < 0.001$), and a large artery subtype estimate from 3 cohorts of 1.20 (95% CI, 1.08 to 1.33; $p < 0.001$), suggesting that the risk is largely restricted to the large artery subtype.

In a meta-analysis by Traylor et al of 15 studies that included 12,389 subjects with ischemic stroke and 62,004 controls, the 9p21 locus was only associated with large-vessel stroke.

Dichgans et al analyzed data from the CARDIoGRAM/C4D consortium study previously described in conjunction with data from the METASTROKE consortium to evaluate whether CAD and ischemic stroke share genetic risk in respect to common genetic variants. The authors found that the 9p21 locus was significantly associated with both CAD and the phenotype of large artery stroke (p for association with large artery stroke, 3.85×10^{-6} ; p for the joint phenotype of CAD and large artery stroke, 2.9×10^{-35}).

Ni and Zhang reported results of a meta-analysis of genetic association studies between 9p21 polymorphisms and ischemic stroke, which included 21 studies with 34,128 patients and 153,428 controls. The rs10757278 polymorphism was significantly associated with increased overall ischemic stroke risk (per-allele OR for ischemic stroke, 1.11; 95% CI, 1.07 to 1.15; $p < 10^{-5}$) and increased large-vessel stroke risk (per-allele OR for large vessel stroke, 1.15; 95% CI, 1.10 to 1.19), but not with small vessel, cardioembolic, or other types of stroke.

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Individual Studies

Since publication of the previous meta-analyses, a number of individual studies have evaluated the association between 9p21 polymorphisms and ischemic stroke. For example, in a retrospective study evaluating the association between macro- and microscopic infarcts on neuropathology, Chou et al reported that the 9p21 SNP at the CDKN2A/B locus (rs2383207) was significantly associated with the presence of macroscopic infarct on pathology (OR=1.26; 95% CI, 1.02 to 1.55; p=0.031).

Other studies have focused on particular population subsets, with mixed findings. Olsson et al published a case control study of the association of 9p21 and ischemic stroke in individuals younger than 70 years. In this study, the low-risk allele of 9p21 SNP rs7857345 showed significant association with decreased risk of large vessel disease after adjusting for traditional risk factors (OR=0.58; 95% CI, 0.39 to 0.86). However, not all tested 9p21 SNPs were significant. Dutta et al studied CAD mortality at older ages in association with 9p21 variants, reporting a positive association with mortality but no significant association with deaths due to stroke (HR=1.07; 95% CI, 0.81 to 1.41; p=0.63). Yue et al reported significant associations between the SNPs rs2383207, rs3731245, and rs1537378 were significantly associated with cerebral infarction in a Chinese Han population (OR=1.18; 95% CI, 1.01 to 1.37; OR=1.29; 95% CI, 1.06 to 1.56; OR=1.30; 95% CI, 1.05 to 1.60, respectively).

9p21 Polymorphisms and Aneurysms

The 9p21 locus has been associated with risk of both intracranial and AAAs. In 2013, Alg et al reported results from a systematic review and meta-analysis of all genetic association studies of sporadic intracranial aneurysm to identify genetic risk factors for intracranial aneurysm. The authors included 66 cohort or case control studies of intracranial aneurysms that examined a total of 41 SNPs, not limited to the 9p21 locus, in 29 genes. Among polymorphisms with the strongest associations with intracranial aneurysm were the 9p21 SNPs rs10757278 (OR=1.29; 95% CI, 1.21 to 1.38) and rs1333040 (OR=1.24; 95% CI, 1.20 to 1.29). There has been a greater focus on the association of 9p21 with AAA. Several studies report 9p21 allele-specific estimates of risk in the range of 1.2 to 1.8. Biros et al combined the results of a cohort study including 3371 men, 513 with AAA, with the results of previous studies and reported a combined estimate of about 1.3 for both 9p21 SNPs rs10757278 and rs1333049. This is lower than other well-characterized risk factor estimates for AAA such as age (OR = \approx 1.7 per 7 years), family history (OR = \approx 1.9), and smoking (OR = \approx 5). Wei et al reported slightly higher risk of AAA associated with homozygosity for the rs10757278 and rs1333040 risk alleles in a Chinese Han population, after controlling for other AAA risk factors (OR=2.31; 95% CI, 1.22 to 4.36; OR=2.14; 95% CI, 1.13 to 4.05, respectively).

Association of 9p21 with Other Conditions

A few studies have explored the association of 9p21 variants with a variety of other conditions such as peripheral arterial disease, coronary artery calcification, aortic calcification, polypoidal choroidal vasculopathy (characterized by aneurismal dilations at the border of the choroidal vascular network), arterial stiffness in hypertensive individuals, and brain arteriovenous malformation. In contrast, Folsom et al found no association between SNPs at the 9p21 locus with arterial elasticity and retinal microvascular diameter.

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While some studies reported positive associations, the strength of the associations was modest and none suggested clinical use.

Section Summary

The clinical validity of the association between 9p21 polymorphisms and CHD/CAD incidence and outcomes is well-established and consistent in multiple independent populations, with evidence of increasing severity of outcomes with increasing risk allele dosage. The magnitude of increased risk is modest, with ORs for CVD generally in the 1 to 2 range. The clinical validity for the association between 9p21 polymorphisms and ischemic stroke, and other vascular disorders is less well-studied and less certain.

Clinical Utility

Clinical utility is demonstrated when the evidence shows that using a test changes medical management for at least some patients, and these changes lead to improved outcomes. Most of the evidence related to the clinical utility of 9p21 testing is related to its role in risk-stratifying patients for CHD; a smaller body of evidence exists for its utility in other conditions.

Clinical Utility of 9p21 Genotyping for CHD

Palomaki et al addressed clinical utility of 9p21 genotyping with a reclassification analysis, evaluating whether genotyping helped reclassify individuals more accurately than traditional risk factors according to their known outcomes, which was measured by calculating the net reclassification index (NRI) with data from 3 studies/4 data sets. For the 4 data sets, the proportions of cases reclassified by 9p21 genotype after initial classification by traditional risk factors were 0.5%, 0.7%, 2.5%, and -0.1%; of controls, 0.3%, 4.2%, -0.1%, and 0%; corresponding NRIs were 0.8%, 4.9%, 2.5%, and -0.2%; none of the NRIs were statistically significant. In addition, the study showing the largest NRI achieved most of the risk reclassification because of reduced risk in subjects without events, which would have less chance of improving outcomes. Moreover, in 2 individual studies the NRI actually worsened when 9p21 risk alleles were added to algorithms that also included family history as a CAD risk factor.

Dutta et al also conducted a reclassification analysis, evaluating risk first with Framingham score, then with 9p21 SNP-determined risk added to the Framingham score. In their cohort of community-dwelling elderly subjects followed for 20 years after DNA collection (N=1095), SNP risk predictors identified an additional 6% (n=5) of the 81 CAD deaths within 10 years in the high-risk group, compared with the 21% (n=17) identified by Framingham score. However, an NRI was not reported for a full evaluation of the results. In a similar analysis, Shiffman et al found that adding a 9p21 SNP risk variant to the Framingham score did not improve the area under the curve (AUC) and that the net number of subjects who were reclassified to more appropriate risk categories was 25 or fewer out of 3651 whites, with an NRI of 0.02 or less (p≥0.4). Adding C-reactive protein and KIF6 resulted in a larger number of correctly reclassified white men (n=93, p=0.04), but did not improve risk prediction for white women.

Studies have also used the OR associated with a subject's 9p21 genotype to modify a risk assessment based on traditional risk factors. For example, based on the results of Palomaki et al, a subject with a 10-

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year CHD risk of 10% based on traditional risk factors who has two 9p21 at-risk alleles would have his risk estimate increased to about 14% ($10\% \times 1.2 \times 1.2$) compared with a subject with no at-risk alleles. Davies et al, however, found that the addition of 9p21 to traditional risk factors was not significant as measured by AUC (0.8013 with traditional risk factors alone vs 0.8044 with traditional risk factors plus 9p21; $p=0.097$). Other similar attempts to add 9p21 alone as a risk factor have not demonstrated significance in addition to traditional risk factors. An improved risk calculation, if shown, would be an intermediate outcome. The expectation is that improved risk assessment might influence patient and provider decisions about preventive interventions and behavioral change. However, as Palomaki et al note, only 37% of U.S. physicians reported regular use of a heart disease risk score, and the evidence that such risk scores translate into net clinical benefits is minimal. Thus, the clinical utility of 9p21 genotyping cannot be assumed even if risk assessment is improved.

Do et al tested several 9p21 SNPs in 3820 cases and 4294 matched controls from the multiethnic INTERHEART study of risk factors for acute nonfatal MI, and also collected dietary information. As expected, the SNPs were significantly associated with MI, with ORs of approximately 1.2. An analysis of interactions found no significant effect of physical activity or smoking, but a significant interaction with the prudent diet (including raw vegetables, fruits, green leafy vegetables, nuts, desserts, dairy products; as opposed to diets characterized by soy sauce, tofu, pickled foods, green leafy vegetables, eggs, and low sugar, or by eggs, meats, fried and salty foods, sugar, nuts, and desserts) score, the most significant interaction being with raw vegetable intake. A second, similar analysis in the prospective FINRISK study, a series of population-based CVD risk factor surveys conducted every 5 years in Finland, found a similar interaction with diet and additionally found that the effect was diminished in the high prudent diet consumption group. Thus, the risk effect of the SNP variants may be most pronounced when diet is poor. Although not yet direct evidence of clinical utility, the results suggest the modification of low-level genetic risk with diet.

Gransbo et al evaluated the incremental impact of a 9p21 SNP (rs497757) on CVD risk prediction. The authors used data from the Malmo Diet and Cancer study, a prospective, population-based cohort study that included 28,449 subjects, with the primary outcome of incident CVD. NRI was calculated when the presence of the rs4977574 SNP was added to a prediction model that used traditional risk factors (age, sex, hypertension, lipid-lowering therapy, diabetes, smoking, body mass index). While there was a significant association between the rs4977574 SNP and incident CVD, the addition of the 9p21 genotype did little to improve risk prediction in additive multivariate models. Although statistically significant, the NRI was small (1.2%, $p=0.043$).

Clinical Utility of 9p21 Genotyping for Other CVDs

Downing et al evaluated the impact of adding 9p21 polymorphism (rs10757269) in a risk-factor-based model predicting peripheral artery disease. Among 393 subjects in the prospective Genetic Determinants of Peripheral Artery Disease study who met study inclusion criteria, the rs10757269 allele was associated with the presence of peripheral artery disease (defined as ankle-brachial index <0.9) after controlling for traditional cardiovascular risk factors and other biomarkers (OR=1.92; 95% CI, 1.29 to 2.85). The addition

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of *9p21* genotype to a previously validated peripheral artery disease risk model (including age, sex, race, smoking history, body mass index, hypertension stage, diabetes status, history of CVD, heart failure, CAD) lead to improved risk classification (NRI=33.5%, p=0.001).

Section Summary

The clinical utility of *9p21* mutation testing has not been established. The contribution of *9p21* genotyping to overall cardiovascular risk assessment, above that of traditional risk factors, is small and not likely to be clinically important. Studies of risk reclassification do not report that *9p21* testing results in substantial numbers of patients being reclassified to clinically relevant categories. No studies were identified that evaluate whether the use of *9p21* genotyping is associated with changes in patient management, improvements in clinical outcomes, or both.

Summary of Evidence

The association of SNPs at the *9p21* locus with CAD/CHD incidence and 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 ischemic stroke, aneurysms, or other vascular disorders is less well-studied and less certain. Despite evidence that *9p21* polymorphisms are associated with CAD/CHD 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 the 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.

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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 |
| 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. |
| Next Scheduled Review Date: | 07/2019 |

Coding

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| 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);
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