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

**Effective:** July 1, 2021

**Next Review:** May 2022  
**Last Review:** May 2021

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**IMPORTANT REMINDER**

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

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**DESCRIPTION**

Single nucleotide variants (SNVs, also known as single nucleotide polymorphisms [SNPs]) found in the 9p21 locus have been associated with myocardial infarction (MI) and other manifestations of cardiovascular disease (CVD). Genotyping for 9p21 SNPs may be offered as an approach to identify patients who may be at increased risk of some of these outcomes.

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**MEDICAL POLICY CRITERIA**

The use of genotyping for 9p21 single nucleotide variants is considered **investigational** for all indications, including but not limited to identification of:

A. Patients who may be at increased risk of cardiovascular disease or its manifestations (e.g., myocardial infarction, ischemic stroke, peripheral arterial disease, coronary artery calcification); or

B. Patients who may be at increased risk for aneurysmal disease (e.g., abdominal aortic aneurysms, intracranial aneurysms, polypoidal choroidal vasculopathy).

**NOTE:** A summary of the supporting rationale for the policy criteria is at the end of the policy.
SNVs occur normally throughout a person’s DNA. They occur once in every 300 nucleotides on average, which means there are roughly 10 million SNVs in the human genome. Most commonly, these variations are found in the DNA between genes. They can act as biological markers, helping scientists locate genes that are associated with disease. When SNVs occur within a gene or in a regulatory region near a gene, they may play a more direct role in disease by affecting the gene’s function.

SNVs are not absolute indicators of disease development. Most SNVs have no effect on health or development. SNVs do not cause disease, but they can help determine the likelihood that someone will develop a particular illness. Some of these genetic differences, however, have proven to be very important in the study of human health. Researchers have found SNVs that may help predict an individual’s response to certain drugs, susceptibility to environmental factors such as toxins, and risk of developing specific diseases. SNVs can also be used to track the inheritance of disease genes within families. Future studies will work to identify SNVs associated with complex diseases such as heart disease, diabetes, and cancer.

9P21 AND CARDIOVASCULAR DISEASE

In 2007, genome-wide association studies using single nucleotide variant (SNV) arrays resulted in the near simultaneous reporting of the first common genetic variant that affects the risk of coronary heart disease (CHD) in Caucasians at chromosome 9p21.3 (also known as 9p21). CHD is defined as inadequate circulation to cardiac muscle and surrounding tissue resulting in myocardial infarction (MI), unstable angina pectoris, coronary revascularization, or death.[1-4] Estimates of CHD risk were confirmed in case-control replication studies in a variety of study populations, showing that the identified SNVs were associated with CHD and even more specifically with MI.[5] In all studies, the association of any identified SNV with CHD risk was shown to be independent of traditional risk factors.[6]

Several studies have extended the 9p21 association to other vascular diseases including ischemic stroke; thus, 9p21 may be reported as associated with cardiovascular disease (CVD) outcomes, defined as including CHD outcomes plus ischemic stroke. Associations have also been reported with abdominal aortic aneurysm 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 SNVs lead to increased CHD risk have been largely unknown. Harismendy (2011) identified several potential enhancer regulatory DNA sequences in the 9p21 region.[7] They reported that the SNV 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 (2012) genotyped 18 SNVs across the CVD-associated region and determined 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."

COMMERCIAL TESTING

Quest Diagnostics offers the CardiolQ 9p21 Genotype test, which detects the rs10757278 A>G and rs1333049 G>C SNVs within the 9p21 locus of chromosome. The information on the website indicates that the SNVs are associated with the risk of coronary heart disease.\(^9\) It is suggested that the test is suitable for individuals with an intermediate risk of CHD, but is not appropriate for use in African Americans.

Cardiac risk genotyping panels offered by other laboratories may include and individually report 9p21 SNV results. For example, the deCODE MI™ (deCODE Genetics) test genotypes 9p21.3 rs10757278 in addition to seven other SNVs from other chromosomal loci to estimate the risk of coronary heart disease and MI. Quest Diagnostics offers the Cardio IQ® 9p21 Genotype test for rs10757278 (A>G) and rs1333049 (G>C)

REGULATORY STATUS

There is no manufactured test kit for 9p21 genotyping that has been reviewed by the U.S. Food and Drug Administration (FDA). Clinical laboratories may develop and validate tests in-house for 9p21 (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). The laboratory offering the service must be licensed by CLIA for high-complexity testing.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature\(^{[10]}\) is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term “variant” is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as “mutation.” Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

Validation of the clinical use of any genetic test focuses on three main principles:

1. Analytic validity, which refers to the technical accuracy of the test in detecting a variant that is present or in excluding a variant that is absent;
2. Clinical validity, which refers to the diagnostic performance of the test (i.e., sensitivity, specificity, positive and negative predictive values) in detecting clinical disease; and
3. Clinical utility, which refers to how the results of the diagnostic test will be used to change disease management and whether these changes in management lead to clinically important improvements in health outcomes.

This evidence review evaluates well-designed studies regarding the ability of test results to:

- Guide decisions in the clinical setting related to either treatment, management, or prevention; and;
- Improve health outcomes as a result of those decisions.

9P21 VARIANTS AND CORONARY HEART DISEASE (CHD)
Clinical utility is demonstrated when the evidence shows that using a test to change medical management for at least some patients significantly improves outcomes. Most of the evidence regarding the clinical utility of 9p21 testing is related to its role in risk-stratifying patients for coronary heart disease; a smaller body of evidence exists for its utility in other conditions. Direct evidence for how patient management is changed with 9p21 testing is not addressed in the literature.

**Systematic Reviews**

A systematic review and meta-analysis by Xu (2020) examined the association between the rs10757274 SNV, located in the CDKN2B-AS1 gene, and coronary artery disease (CAD).[11] The analysis included data from 11 case-control studies (n=52,209, cases: 7,990, controls: 44,219), Five inheritance models were evaluated and all showed significant association between the SNV and CAD (allele model p<0.001, dominant model p<0.001, recessive model p<0.001, heterozygote codominant p=0.002, homozygote codominant p<0.001). There was significant heterogeneity between the studies for all models.

Patel (2019) published a meta-analysis of data from the GENIUS-CHD Consortium to examine the association between 9p21 rs1333049 and subsequent cardiac events in participants with established CHD.[12] The analysis included data from 93,115 participants, and the primary outcome in the analysis was CHD death or myocardial infarction (MI). No significant association was found between this outcome and 9p21 (odds ratio [OR] 1.02, 95% confidence interval [CI] 0.99 to 1.05).

Chen (2015) performed a meta-analysis to evaluate the association between the rs10757278 variant (or its proxy rs1333049) on chromosome 9p21 with MI susceptibility in individuals of Caucasian and Chinese ancestry, pooling data from 17 large case-control studies (n=14,924 cases and 28,039 controls).[13] The investigators reported a significant association between rs10757278 and MI with a modest OR of 1.29 (95% CI 1.22 to 1.36, p=6.09×10^{-22}) in the pooled population. Further subgroup analysis found significant association between rs10757278 variant and MI in Asian (OR 1.21, 95% CI 1.16 to 1.27, p=1.82×10^{-17}) and Caucasian populations (OR 1.34, 95% CI 1.28 to 1.40, p=8.51×10^{-39}). Since this is the first report of a strong association between rs10757278 and MI, directly conflicting with previously published reports, addition studies of this size are needed.

In a systematic review and meta-analysis, Patel (2014) compared the association between variants at the chromosome 9p21 locus and risk of first versus subsequent CHD events.[14] The authors identified 31 cohorts reporting on 193,372 individuals. Among the 16 cohorts of individuals without prior CHD (n=168,209), there were 15,664 first CHD events. Variants in 9p21 were associated with first event with a pooled hazard ratio (HR) of 1.19 (95% CI 1.17 to 1.22) per risk allele. In individuals with established CHD (n=25,163) there were 4,436 subsequent events providing >99% and 91% power to detect a per-allele HR of 1.19 or 1.10, respectively. The pooled HR for subsequent events was 1.01 (95% CI 0.97 to 1.06) per risk allele. There was strong evidence of heterogeneity between the effect estimates for first and subsequent events (p-value for heterogeneity=5.6x10^{-11}). The authors concluded that 9p21 shows differential association with risk of first versus subsequent CHD events.

In a meta-analysis of 21 studies that included patients with information on CAD, MI status and 9p21 genotype (n=33,673), Chan (2013) also found associations with CAD and the 9p21 locus.[15] The authors suggest that the 9p21 has a stronger association with CAD compared to MI.
Another meta-analysis, by Dong (2013) of 21 case-control studies evaluated the association between 9p21 SNVs and CHD in an East Asian population, including 25,945 cases and 31,777 controls, and found a significant association between the rs1333049 and CHD (OR 1.30, 95% CI 1.25 to 1.35, \( p<0.001 \)).\[16\]

Zhou (2012) conducted a meta-analysis of seven case-control studies (n=7,123 total). Authors suggest the genetic variation on the 9p21 chromosome may contribute to early-onset CAD, however the effect size was small.\[17\] Another 2014 meta-analysis by different authors evaluating case-control studies had similar findings.\[18\]

Schunkert (2011) conducted a meta-analysis of 14 genome-wide association studies of CAD.\[19\] Authors concluded that their large-scale meta-analysis identified the association of CAD with 13 novel chromosomal loci. Authors suggested these newly identified loci affect CAD risk carriers and may improve treatment of this common disease.

The Coronary Artery Disease Genetics Consortium meta-analyzed four large genome-wide association studies of CAD and identified five loci newly associated with CAD.\[20\] Authors suggested their findings may implicate new pathways for CAD susceptibility. These results compare well with those of Palomaki (2010), who conducted the first formal systematic review of the 9p21 literature to estimate the strength of the association between established 9p21 SNVs and coronary heart disease and to examine clinical utility.\[21\] Authors reviewed the published literature for effect size, heterogeneity, publication bias, strength of evidence, and evidence of clinical utility of the test. Authors analyzed 47 data sets from 22 articles were analyzed including 35,872 cases and 95,837 controls. The authors concluded that the association between 9p21 SNVs and heart disease, which varied by age at disease onset, was statistically significant; however, the magnitude of the association was small.

This group also addressed clinical utility 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 three studies (four data sets).\[21\] 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 individuals without events, which would have less chance of improving outcomes. Moreover, in two individual studies the NRI actually worsened when 9p21 risk alleles were added to algorithms that also included family history as a CAD risk factor.\[22, 23\] Therefore based on this meta-analysis, evidence for clinical utility of 9p21 testing is insufficient.

**Randomized Controlled Trials**

While there have been no randomized trials focused on genetic testing for 9p21 SNVs, Anand (2016) published the results of a single-blind, randomized trial of a digital health intervention designed to reduce the burden of MI in South Asian people living in Ontario and British Columbia, a group with a relatively high burden of premature MI.\[24\] The main outcome of the study was a change in MI risk score, which included clinical risk measures as well as genetic risk as determined by 9p21 risk alleles. The intervention used emails or text messages to promote diet and physical activity changes but found no significant differences between groups after one year. Additionally, the follow-up results did not appear to be influenced by participants' knowledge of their genetic risk.

**Nonrandomized Studies**
Several studies analyzing individual patient cohorts or case-control populations for association of 9p21 and CHD/CAD have been published since the systematic reviews described above.[25-32] Most have found statistically significant, but small associations, with substantial heterogeneity between subgroups.

Evidence for the clinical utility of 9p21 variant testing is not addressed in the literature. Risk assessment may influence patient and provider decisions about preventive interventions and behavioral change. However, as Palomaki (2010)[21] noted, only 37% of U.S. physicians reported regular use of a heart disease risk score,[33] and the evidence that such risk scores translate into net clinical benefits is minimal.[34] Thus, the clinical utility of 9p21 genotyping cannot be assumed even if risk assessment is improved. As noted, the evidence related to the clinical utility of 9p21 testing is related to its role in risk-stratifying patients for coronary heart disease; a smaller body of evidence exists for its utility in other conditions.[22, 23, 35-39]

**Section Summary**

The clinical utility of 9p21 testing, or how patient management may change as a result of this testing, has not been established. The contribution of 9p21 to overall cardiovascular risk, 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. Additionally, a study testing a digital health intervention found no improvements in MI risk associated with knowledge of 9p21 genetic risk.

**9P21 ASSOCIATION WITH ISCHEMIC STROKE**

Several analytical and clinical validity studies have reported, with mixed results, on the association of 9p21 with ischemic stroke. There are no clinical utility studies which address how 9p21 test results are used to improved health outcomes in patients at risk for ischemic stroke.

**Systematic Reviews**

Anderson (2010) conducted a meta-analysis of eight studies, focusing on two 9p21 SNVs, s1537378 and rs10757278.[40] Authors concluded that the variants on 9p21 were associated with ischemic stroke.

In a meta-analysis by Traylor (2012) of 15 studies that included 12,389 individuals with ischemic stroke and 62,004 controls, the 9p21 locus was only associated with large-vessel stroke.[41]

Ni (2014) reported results of a meta-analysis of genetic association studies between 9p21 variants and ischemic stroke, which included 21 studies with 34,128 patients and 153,428 controls.[42] The rs10757278 variant 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.

**Randomized Controlled Trials**

There have been no randomized trials of genetic testing 9p21 SNVs for stroke risk.

**Nonrandomized Studies**
Since publication of the recent meta-analyses, several nonrandomized studies have evaluated the association between 9p21 variants and ischemic stroke.

Lu (2015) published a case-control analysis of six SNVs on 9p21 and their association with ischemic stroke and carotid plaque in 528 patients with ischemic stroke (375 with carotid plaque and 153 without carotid plaque) and 258 controls. The SNVs rs2383206 (OR 1.472, p=0.021) and rs4977574 (OR 1.519, p=0.013) were significantly associated with ischemic stroke without carotid plaque compared to controls. SNVs rs2383206 and rs4977574 were also modestly associated with a risk of carotid plaque among patients with ischemic stroke above age 65 (OR 2.329, p=0.018 and OR 1.997, p=0.049, respectively). However, all six SNVs tested were in linkage disequilibrium with each other and were no longer significantly associated after correction for multiple testing.

Bi (2015) published a case-control analysis of four SNVs on 9p21 and their association with ischemic stroke in 116 cases and 118 controls. The authors reported that the SNVs rs10757278, rs1537378 and rs1333047 conveyed anywhere between a 1.64- to 2.0-fold increased risk of ischemic stroke. However, these results were marginally significant and once corrected for multiple testing, would not have fallen within the limit considered significant. In addition, there was also a significant association between rs10757278 and lipid levels.

Yue (2015) reported that the significant statistical associations between the SNVs 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).

Dichgans (2014) analyzed data from the CARDIOGRAM/C4D consortium study described above 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 (PLAS 3.85x10^-6, Spearman's rho coefficient for large artery stroke/CAS 0.85, p=2.9E^-35).

**Section Summary**

Studies on the clinical and analytical validity of 9p21 association with ischemic stroke reported mixed results. Further, the clinical utility of 9p21 variant testing for ischemic stroke has not been established.

**9P21 ASSOCIATION WITH ANEURYSM**

The 9p21 locus has been associated with risk of both intracranial and abdominal aortic aneurysms. There are no clinical utility studies on the association of 9p21 with aneurysm.

**Systematic Review**

Yu (2020) published a meta-analysis of the association between CDKN2B-AS polymorphisms and intracranial aneurysm, which included five studies: two with Caucasian populations and three with Asian populations. The results of the analysis indicated that the rs10757272, rs1333040, and rs6475606 polymorphisms was significantly associated with aneurysm (OR 1.21, 95% CI 1.13 to 1.29 p<0.001; OR 1.26, 95% CI 1.07 to 1.48, p=0.005; and OR 1.48, 95% CI 1.14 to 1.93, p=0.005, respectively). There was no significant difference found between Caucasian and Asian populations on subgroup analysis.
Alg (2013) 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\[49\]. The authors included 66 cohort or case-control studies of intracranial aneurysms that examined a total of 41 SNVs, not limited to the 9p21 locus, in 29 genes. Among variants with the strongest associations with intracranial aneurysm were the 9p21 SNVs rs10757278 (OR 1.29, 95% CI 1.21 to 1.38) and rs1333040 (OR 1.24, 95% CI 1.20 to 1.29).

**Randomized Controlled Trials**

There have been no randomized trials of 9p21 SNV testing for aneurysm risk.

**Nonrandomized Studies**

Research on the association of 9p21 with abdominal aortic aneurysm (AAA) includes several studies that reported 9p21 allele-specific estimates of risk in the range of 1.2 to 1.8.\[25, 50-53\] Biros (2010) combined the results of their study with the results of previous studies and reported a combined estimate of about 1.3 for both 9p21 SNVs (rs10757278 and rs1333049).\[53\] This estimate is lower than other well-characterized risk factor estimates for AAA such as age, family history, and smoking.\[54\] Wei (2014) 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).\[55\]

**Section Summary**

The evidence that addresses the clinical validity of 9p21 for both intracranial and abdominal aortic aneurysms is limited. Further, the clinical utility of 9p21 variant testing for aneurysm has not been established.

**9P21 ASSOCIATION WITH OTHER CONDITIONS**

Analytical and clinical validity studies have been reported, with mixed results, on the association of 9p21 with other conditions. There are no clinical utility studies on the association of 9p21 with the other conditions described below.

A few studies have explored the association of 9p21 variants with a variety of other conditions such as peripheral arterial disease,\[56\] coronary artery calcification,\[57-59\] aortic calcification,\[58\] polypoidal choroidal vasculopathy (characterized by aneurismal dilations at the border of the choroidal vascular network),\[60\] cardiovascular mortality in the absence of coronary lesions,\[61\] and arterial stiffness in hypertensive individuals.\[62\] The strength of the associations was modest and none suggested clinical use.

In contrast, Folsom (2013) found no association between SNVs at the 9p21 locus with arterial elasticity and retinal microvascular diameter.\[63\]

Downing (2014) evaluated the impact of adding 9p21 variant (rs10757269) in a risk-factor-based model predicting peripheral artery disease.\[64\] 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 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, and history of cardiovascular disease, congestion heart failure, and CAD) led to improved risk classification (net reclassification index 33.5%, p=0.001).

**Section Summary**

Evidence that addresses the analytical and clinical validity, as well as the clinical utility of 9p21 association with other conditions, including but not limited to peripheral artery disease, coronary artery calcification, aortic calcification, polypoidal choroidal vasculopathy, and arterial stiffness is insufficient.

**PRACTICE GUIDELINE SUMMARY**

**AMERICAN COLLEGE OF CARDIOLOGY (ACC)/AMERICAN HEART ASSOCIATION (AHA)**

In 2013, the American College of Cardiology Foundation 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 variants.[65]

The 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease included recommendations regarding the assessment of cardiovascular risk did not discuss testing for 9p21 variants.[66]

**EGAPP WORKING GROUP (EWG)**

The EGAPP 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 (2010).[21] In general, the 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 discouraged clinical use unless further evidence supports improved clinical outcomes. Based on the available evidence, the overall certainty of net health benefit was deemed “Low.”[67]

**SUMMARY**

There is not enough research to show that testing for 9p21 SNV alleles can improve health outcomes for patients with any conditions. Also, there are no practice guidelines based on research that recommend this testing for any purpose. Therefore, 9p21 genotyping for all applications is considered investigational.

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**CODES**

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