

MEDICAL POLICY

POLICY TITLE	GENOTYPING FOR 9p21 SINGLE NUCLEOTIDE POLYMORPHISMS TO PREDICT RISK OF CARDIOVASCULAR DISEASE OR ANEURYSM
POLICY NUMBER	MP 2.311

CLINICAL BENEFIT	☐ MINIMIZE SAFETY RISK OR CONCERN. ☒ MINIMIZE HARMFUL OR INEFFECTIVE INTERVENTIONS. ☐ ASSURE APPROPRIATE LEVEL OF CARE. ☐ ASSURE APPROPRIATE DURATION OF SERVICE FOR INTERVENTIONS. ☐ ASSURE THAT RECOMMENDED MEDICAL PREREQUISITES HAVE BEEN MET. ☐ ASSURE APPROPRIATE SITE OF TREATMENT OR SERVICE.
Effective Date:	RETIRED 7/1/2026

[POLICY
RATIONALE
CODING INFORMATION](#)

[PRODUCT VARIATIONS
DEFINITIONS
REFERENCES](#)

[DESCRIPTION/BACKGROUND
DISCLAIMER
POLICY HISTORY](#)

I. POLICY

The use of genotyping for 9p21 single nucleotide polymorphisms (SNPs) is considered **investigational** for all clinical uses, including but not limited to identification of 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 identification of patients who may be at increased risk of aneurysmal disease (abdominal aortic aneurysm, intracranial aneurysm or polypoidal choroidal vasculopathy). There is insufficient evidence to support a general conclusion concerning the health outcomes or benefits associated with this procedure.

Policy Guidelines

There is no specific CPT code for this test. If the specific analyte is listed in codes 81200-81355 or 81400- 81408, that CPT code would be reported along with the unlisted code 81479 for the analytes that are not listed. If none of the analytes are listed in the more specific CPT codes, unlisted code 81479 would be reported for the whole test.

The Quest website reports that their Cardio IQ® 9p21 Genotype test is reported with code 81479.

II. PRODUCT VARIATIONS

[TOP](#)

This policy is only applicable to certain programs and products administered by Capital Blue Cross and subject to benefit variations as discussed in Section VI. Please see additional information below.

MEDICAL POLICY

POLICY TITLE	GENOTYPING FOR 9p21 SINGLE NUCLEOTIDE POLYMORPHISMS TO PREDICT RISK OF CARDIOVASCULAR DISEASE OR ANEURYSM
POLICY NUMBER	MP 2.311

FEP PPO - Refer to FEP Medical Policy Manual. The FEP Medical Policy manual can be found at: <https://www.fepblue.org/benefit-plans/medical-policies-and-utilization-management-guidelines/medical-policies>

III. DESCRIPTION/BACKGROUND

[TOP](#)

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 (CVD). Associations with 9p21 SNPs and risk of abdominal aortic aneurysm, intracranial aneurysm 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 cardiovascular disease (CVD; defined as CHD and cerebrovascular disease) outcomes. Associations have also been reported with abdominal aortic aneurysm and with intracranial arterial aneurysm and other vascular diseases.

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. The mechanisms by which the SNPs lead to increased CHD risk have been largely unknown. Harismendy et al identified several potential enhancer regulatory DNA sequences in the 9p21 region. 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

MEDICAL POLICY

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POLICY NUMBER	MP 2.311

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."

A 2014 systemic review and meta-analysis of 31 cohorts including 193,372 persons confirmed the association between 9p21 variants and the likelihood of a first CHD event (HR 1.19 per risk allele, 95% CI 1.17-1.22). However, 9p21 variants were not associated with an increased likelihood of subsequent CHD events among persons with known CHD (HR 1.01 per risk allele, 95% CI 0.97-1.06).

Regulatory Status

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. Food and Drug Administration has chosen not to require any regulatory review of this test.

III. RATIONALE

[TOP](#)

Summary of Evidence

The association of single-nucleotide polymorphisms 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

MEDICAL POLICY

POLICY TITLE	GENOTYPING FOR 9P21 SINGLE NUCLEOTIDE POLYMORPHISMS TO PREDICT RISK OF CARDIOVASCULAR DISEASE OR ANEURYSM
POLICY NUMBER	MP 2.311

IV. DEFINITIONS

[TOP](#)

N/A

V. DISCLAIMER

[TOP](#)

Capital Blue Cross' medical policies are used to determine coverage for specific medical technologies, procedures, equipment, and services. These medical policies do not constitute medical advice and are subject to change as required by law or applicable clinical evidence from independent treatment guidelines. Treating providers are solely responsible for medical advice and treatment of members. These policies are not a guarantee of coverage or payment. Payment of claims is subject to a determination regarding the member's benefit program and eligibility on the date of service, and a determination that the services are medically necessary and appropriate. Final processing of a claim is based upon the terms of contract that applies to the members' benefit program, including benefit limitations and exclusions. If a provider or a member has a question concerning this medical policy, please contact Capital Blue Cross' Provider Services or Member Services.

VI. CODING INFORMATION

[TOP](#)

Note: This list of codes may not be all-inclusive, and codes are subject to change at any time. The identification of a code in this section does not denote coverage as coverage is determined by the terms of member benefit information. In addition, not all covered services are eligible for separate reimbursement.

The following CPT code is investigational when used to report genotyping for 9p21 single nucleotide polymorphisms to predict risk of cardiovascular disease or aneurysm as outlined in the policy statement:

Procedure Codes									
81479									

VII. REFERENCES

[TOP](#)

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MEDICAL POLICY

POLICY TITLE	GENOTYPING FOR 9P21 SINGLE NUCLEOTIDE POLYMORPHISMS TO PREDICT RISK OF CARDIOVASCULAR DISEASE OR ANEURYSM
POLICY NUMBER	MP 2.311

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MEDICAL POLICY

POLICY TITLE	GENOTYPING FOR 9P21 SINGLE NUCLEOTIDE POLYMORPHISMS TO PREDICT RISK OF CARDIOVASCULAR DISEASE OR ANEURYSM
POLICY NUMBER	MP 2.311

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MEDICAL POLICY

POLICY TITLE	GENOTYPING FOR 9P21 SINGLE NUCLEOTIDE POLYMORPHISMS TO PREDICT RISK OF CARDIOVASCULAR DISEASE OR ANEURYSM
POLICY NUMBER	MP 2.311

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MEDICAL POLICY

POLICY TITLE	GENOTYPING FOR 9P21 SINGLE NUCLEOTIDE POLYMORPHISMS TO PREDICT RISK OF CARDIOVASCULAR DISEASE OR ANEURYSM
POLICY NUMBER	MP 2.311

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MEDICAL POLICY

POLICY TITLE	GENOTYPING FOR 9p21 SINGLE NUCLEOTIDE POLYMORPHISMS TO PREDICT RISK OF CARDIOVASCULAR DISEASE OR ANEURYSM
POLICY NUMBER	MP 2.311

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IX. POLICY HISTORY

[TOP](#)

	03/09/2020 Consensus Review. No changes to policy statement. References updated. Variations updated. Coding verified.
	02/11/2021 Consensus Review. Policy statement unchanged. Referenced updated. Cross referenced policy removed as retired. FEP variation updated.
	01/21/2022 Consensus Review. FEP, background, and references updated.

MEDICAL POLICY

POLICY TITLE	GENOTYPING FOR 9P21 SINGLE NUCLEOTIDE POLYMORPHISMS TO PREDICT RISK OF CARDIOVASCULAR DISEASE OR ANEURYSM
POLICY NUMBER	MP 2.311

	12/08/2023 Consensus Review. No changes to coding.
	12/11/2024 Consensus Review. Created policy guidelines. Updated background, rationale, and references. No changes to coding.
	08/13/2025 Consensus Review. Policy statement unchanged.
	03/09/2026 Retirement Review. EviCore Delegation.

[Top](#)

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