MEDICAL POLICY

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

Effective Date:	5/1/2022

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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 conclusion concerning the health outcomes or benefits associated with this procedure.

II. PRODUCT VARIATIONS

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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.

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

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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.

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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 ($r2>0.8$) 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. Recently, 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 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).

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Regulatory Status

There is no manufactured test kit for 9p21 genotyping that has been reviewed by the Food and Drug Administration (FDA). 9p21 genotyping tests are laboratory-developed tests (LTD) offered by clinical laboratories, licensed under CLIA for high-complexity testing.

III. RATIONALE

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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. Thus, *9p21* genotyping for all applications is investigational.

IV. DEFINITIONS

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N/A

V. BENEFIT VARIATIONS

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The existence of this medical policy does not mean that this service is a covered benefit under the member's health benefit plan. Benefit determinations should be based in all cases on the applicable health benefit plan language. Medical policies do not constitute a description of benefits. A member's health benefit plan governs which services are covered, which are excluded, which are subject to benefit limits and which require preauthorization. There are different benefit plan designs in each product administered by Capital Blue Cross. Members and providers should consult the member's health benefit plan for information or contact Capital Blue Cross for benefit information.

VI. DISCLAIMER

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Capital Blue Cross's medical policies are developed to assist in administering a member's benefits, do not constitute medical advice and are subject to change. Treating providers are solely responsible for medical advice and treatment of members. Members should discuss any medical policy related to their coverage or condition with their provider and consult their benefit information to determine if the service is covered. If there is a discrepancy between this medical policy and a member's benefit information, the benefit information will govern. If a provider or a member has a question concerning the application of this medical policy to a specific member's plan of benefits, please contact Capital Blue Cross' Provider Services or Member Services. Capital Blue Cross considers the information contained in this medical policy to be proprietary and it may only be disseminated as permitted by law.

VII. CODING INFORMATION

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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:

CPT Codes®								
81479								

VIII. REFERENCES

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IX. POLICY HISTORY

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MP-2.311	**CAC 11/22/11** New Policy. Adopt BCBSA. Considered investigational.
	MPU 7/18/13 Admin coding review completed
	CAC 9/24/13 Consensus review. References updated but no changes to the policy statements. Rationale added.
	CAC 7/22/14 Consensus review. References and rationale updated. No changes to the policy statements.
	CAC 7/21/15 Consensus review. References and rationale updated. The following additions to the policy statement did not change intent - all indications are investigational • Identification of patients at risk for aneurysmal disease added to policy statement Additional cardiovascular disease added to policy statement (peripheral vascular disease, coronary artery calcification, polypoidal choroidal vasculopathy). Coding reviewed.
	CAC 7/26/16 Consensus review. Policy statement unchanged. FEP variation revised to reference FEP policy. Rationale and Reference sections updated. Coding reviewed.
	Administrative Update 11/23/16 -Variation reformatting.
	CAC 7/25/17 Consensus review. Policy statement unchanged. FEP variation removed (policy archived). Rationale updated. Coding reviewed.
	4/3/18 Consensus review. No change to policy statements. Background and references reviewed. Rationale condensed to include only summary of evidence.
	3/13/19 Consensus review. No changes made to policy.
	3/9/20 Consensus review. No changes to policy statement. References updated. Variations updated. Coding verified.
	2/11/2021 Consensus review. Policy statement unchanged. Referenced updated. Cross referenced policy removed as retired. FEP variation updated.
	1/21/2022 Consensus review. FEP, background, and references updated.

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