

Corporate Medical Policy

Genetic Markers for Assessing Risk of Cardiovascular Disease AHS – M2180

File Name: genetic_markers_for-assessing_risk_of_cardiovascular_disease
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Description of Procedure or Service

Cardiovascular risk assessment comprises the means and processes to predict the probability of developing a cardiovascular disease. These are a group of tests and health factors that have been proven to indicate a person's chance of having a cardiovascular event such as a heart attack or stroke. This policy addresses genetic markers that are associated with cardiovascular disease risk.

Related Policies

Cardiovascular Disease Risk Assessment AHS-G2050
Testing of Homocysteine Metabolism-Related Conditions AHS-M2141
Vitamin B12 and Methylmalonic Acid Testing AHS-G2014

******Note: This Medical Policy is complex and technical. For questions concerning the technical language and/or specific clinical indications for its use, please consult your physician.***

Policy

Genetic Markers for Assessing Risk of Cardiovascular Disease is considered investigational for all applications. BCBSNC does not provide coverage for investigational services or procedures.

Benefits Application

This medical policy relates only to the services or supplies described herein. Please refer to the Member's Benefit Booklet for availability of benefits. Member's benefits may vary according to benefit design; therefore member benefit language should be reviewed before applying the terms of this medical policy.

When Genetic Markers for Assessing Risk of Cardiovascular Disease is covered

Not Applicable

When Genetic Markers for Assessing Risk of Cardiovascular Disease is not covered

1. To predict the risk of developing cardiovascular disease and/or the effectiveness of statin therapy, *KIF6* genotyping is considered investigational.

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2. To assess an individual's risk of developing cardiovascular disease, the following tests are considered investigational:
 - a. Gene expression profiling.
 - b. Genotyping for 9p21 single nucleotide polymorphisms.
 - c. Panels that incorporate genetic risk factors with nongenetic biomarkers.
3. All other genetic tests for assessing cardiovascular disease risk are considered investigational.

Policy Guidelines

Background

Statistics show that cardiovascular disease (including coronary heart disease, stroke, and hypertension) is America's leading health problem and the leading cause of death. According to the 2023 update of the heart disease and stroke statistics report released by the American Heart Association (AHA):

- Approximately 127.9 million people in this country suffer from some form of cardiovascular disease (encompassing coronary heart disease, heart failure, hypertension, and stroke).
- The direct and indirect costs of cardiovascular disease and stroke are about \$407.3 billion and increasing every year.
- Coronary heart disease (CHD) was the leading cause (41.2%) of deaths attributable to CVD in the United States, followed by stroke (17.3%), other CVD (16.8%), high blood pressure (12.9%), heart failure (9.2%), diseases of the arteries (2.6%).
- Heart disease and stroke claim more lives each year in the United States than all forms of cancer and Chronic Lower Respiratory disease combined.
- On average, someone dies of a stroke every 3 minutes 17 seconds in the United States.
- Women have a higher lifetime risk of stroke than men.
- 12.5% of US adults reported cigarette use every day or some days (14.1% of males and 11.0% of females).
- Worldwide, high body mass index was attributed to 2.40 million deaths (AHA, 2023; Tsao et al., 2023).

Cardiovascular Risk Assessment

Traditionally, the most important indicators for cardiac risk are those of a person's health history. These include factors such as family history, age, weight, exercise, and cigarette smoking status (Wilson, 2023). Research has begun examining genetic markers and their ability to predict an individual's risk of developing cardiovascular disease.

Genetic Markers

According to the AHA in 2013, genomics serves several roles in cardiovascular health and disease, including disease prediction, discovery of genetic loci influencing CVD, functional evaluation of these genetic loci to understand mechanisms, and identification of therapeutic targets (Ganesh et al., 2013). The AHA notes that several clinically useful diagnostic tests have been discovered for single-gene

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CVDs. However, it is laborious to develop genetic testing for complex CVD because individual common variants have a smaller impact on risk. Furthermore, the influence of factors such as environmental variables, phenotypic heterogeneity, and pathogenic complexity, makes understanding the genomics behind complex CVDs more difficult. Characterization of the clinical phenotype requires consideration of the clinical details of the diseases and traits under study (Ganesh et al., 2013). Many genetic loci and polymorphisms have been proposed to influence cardiovascular risk. Palotie et al. (2016) identified 49,310 single nucleotide polymorphisms (SNPs), created a genomic risk score (GRS) based on those SNPs, and evaluated the GRS with five population cohorts totaling over 15,000 samples. The GRS was found to result in a hazard ratio of 1.74 for the three Finnish population cohorts (n = 12676) and a hazard ratio of 1.28 for the two Framingham cohorts (n = 3406). The GRS was also found to capture different trajectories of absolute risk, with men in the top 20% attaining 10% cumulative coronary heart disease (CHD) risk 12–18 years earlier than those in the bottom 20% (Palotie et al., 2016).

Gene expression changes, particularly in peripheral blood cells, may provide some information on CVD risk. Gene expression is thought to reflect the pathological state of the current cell, tissue, or organ system, therefore providing molecular insight on the status of cardiac tissue before clinical symptoms start to appear (Elashoff et al., 2011). Genetic variation may lead to vastly differing concentrations of many genetic products. For example, Zhernakova et al. (2018) evaluated the plasma concentrations of 92 cardiovascular disease-related proteins, of which 73 had a genetic association. Cis- and trans- isoforms of the protein quantitative trait loci produced genetic variation; this, combined with microbial variation, is responsible for 17.5% of inter-individual variation in plasma proteins (Zhernakova et al., 2018).

9p21 SNP

Genetic determinants of the development of CHD have been investigated in multiple studies with 46 SNPs across the genome significantly associated with an increased risk of disease (Deloukas et al., 2013). The strongest association with CHD risk was linked to SNPs around locus 9p21 (Palomaki et al., 2010; Patel et al., 2014; Paynter et al., 2009; Samani et al., 2007; Wilson, 2023). However, despite clear association between variants and incident CHD, locus 9p21 SNPs have not been definitively shown to significantly improve CHD risk prediction compared with traditional risk factors (Dutta et al., 2011; Palomaki et al., 2010; Paynter et al., 2009; Virani et al., 2012). Trenkwalder et al. (2019) identified an association between the LPA locus and an increased risk of aortic valve stenosis, particularly in patients without CAD; however, 9p21 was not associated with aortic valve stenosis. The pathophysiologic impact of these genetic variants likely varies depending on other environmental factors or comorbid conditions (Wilson, 2023). Proprietary labs such as Celera Corporation (now owned by Quest Diagnostics) and deCODE Genetics offer tests revolving around analysis of this locus mutation (Quest, 2023).

Palomaki et al. (2010) performed a targeted systematic review of published literature to evaluate the clinical utility of 9p21 single nucleotide polymorphism testing. Forty-seven distinct data sets from 22 articles were analyzed, including 35,872 cases and 95,837 controls. The authors found a statistically significant association between 9p21 SNPs and heart disease that varied by age at disease onset, but the magnitude of the association was small. These risk alleles were found to associate more strongly with cardiovascular events in younger persons than cardiovascular events overall. However, the authors noted that the clinical utility of 9p21-related biomarkers cannot be assumed due to numerous complicating factors such as patient adherence (Palomaki et al., 2010).

Gransbo et al. (2013) evaluated if testing for 9p21 SNP adds useful information to CVD prediction beyond assessment of traditional risk factors. The common SNP variant rs4977574 on chromosome 9p21 was genotyped in 24,777 subjects who were free from CVD prior to the baseline examination. The genotyping of the 9p21 gene was not found to significantly improve predictive accuracy of CVD, although 9p21 significantly predicted CVD in the whole population in additive models. The authors evaluated the attributable risk conferred by 9p21 to be 13%. The investigators concluded that a

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variation of chromosome 9p21 alone “does not add clinically meaningful information in terms of CVD prediction beyond traditional risk factors at any age” (Gransbo et al., 2013).

Dehghan et al. (2016) evaluated the genome-wide association study (GWAS) for incident myocardial infarction (MI) and CHD in prospective cohort studies, which analyzed a total of 64297 individuals, including 3898 MI cases and 5465 CHD cases. A modest association between the 9p21 locus SNP (rs1333049) and MI, as well as marginal association with CHD was found. Among an inception cohort of those who experienced MI during follow-up, this risk allele was associated with a decreased risk of subsequent mortality. The authors concluded that the role of 9p21 locus may be complex and that the protective effect of the risk alleles at 9p21 is unclear; however, the authors note that several other studies have found that the 9p21 locus increases the CHD risk for the first event only and not for subsequent events. Overall, the authors suggest further investigation of genetic causes of complex disorders (Dehghan et al., 2016).

Kessler et al. (2016) reviewed the impact of GWAS on the pathophysiology and therapy of CVD. The researchers found a correlation between the number of individuals participating in the study and the number of genome-wide significant variants detected by the GWAS. Technological advancement has led to denser genotyping, resulting in increased number of loci with genome-wide significant association for CAD. Over 50 genetic variants associated with cardiovascular risk have so far been identified. Almost all risk variants identified by GWAS were found in European individuals with the average European carrying several risk alleles associated with CHD. Most of these risk alleles were found in non-coding parts of the genome, suggesting that these variants affect gene regulation rather than protein structure. For example, the 9p21 locus encodes different isoforms of antisense non-coding RNA in the INK4 locus (ANRIL) which is involved in the preferred synthesis of non-circular/circular forms of the long non-coding RNA, affecting expression of multiple genes (Kessler et al., 2016). The authors state, however, that variants identified represent no more than 10% of the heritable risk. Although important progress was made with GWAS, further understanding of inheritance patterns is needed. The results available so far provide valuable insights into the pathophysiology of CAD and MI, but they are only a starting point for individualized treatment strategies (Kessler et al., 2016).

In summary, no studies were found that outlined changes to preventive and monitoring strategies, patient management, or improvement in clinical outcomes due to genotyping for 9p21 SNPs. There is a lack of published evidence regarding the clinical utility of genetic testing. Based on current literature, the contribution of 9p21 genotyping to overall cardiovascular risk assessment, above that of traditional risk factors, is not likely to be clinically important.

Kinesin family member 6 (KIF6)

Kinesin family member 6 (KIF6) is a protein encoded by the *KIF6* gene. This protein is involved in transport along microtubules, and the primary mutation of Trp719Arg affects its ability to bind its cargo. KIF6 has been studied as a marker for coronary artery disease and effectiveness of statin therapy. Initial studies of two trials with statins found an association between the *KIF6* p.Trp719Arg (rs20455, c.2155T>C) polymorphism and clinical outcomes with statin therapy, showing carriers of the 719Arg allele having greater reduction in clinical events compared with noncarriers (Iakoubova et al., 2008). However, subsequent studies dispute the reported associations.

Hopewell et al. (2011) studied the effects of the *KIF6* Trp719Arg polymorphism (rs20455) on vascular risk and response to statin therapy in 18,348 participants from the Heart Protection Study. Participants received 40 mg simvastatin daily for four to six weeks before being randomly allocated 40 mg simvastatin daily or placebo for five years. The *KIF6* genotype was not significantly associated, among placebo-allocated participants, with the risks of incident major vascular events, major coronary events, revascularizations, or strokes. The investigators concluded that statin therapy significantly reduces the incidence of coronary and other major vascular events to a similar extent, irrespective of *KIF6* genotype. The authors further stated that use of *KIF6* genotyping to guide statin therapy is not warranted (Hopewell et al., 2011).

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Ridker et al. (2011) evaluated the effect of polymorphism at rs20455 encoding the *KIF6* 719Arg allele on outcomes of 8,781 Caucasian trial participants in the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study. Rosuvastatin was equally effective at reducing cardiovascular event rates among carriers and noncarriers of the *KIF6* 719Arg allele, and carriers of the 719Arg allele were not found to have more vascular events or a significant difference in hsCRP or lipid levels. The authors concluded that for rosuvastatin there appears to be no clinical utility to screening for the *KIF6* genotype as a method to determine vascular risk or to predict statin efficacy (Ridker et al., 2011).

Arsenault et al. (2012) investigated if carriers of the *KIF6* 719Arg variant benefit more from statin therapy, in terms of CVD risk reduction, than noncarriers through two large prospective, randomized, double-blinded, controlled trials. A total of 10,001 patients with stable CHD and LDL-C levels <130 mg/dL (3.4 mmol/L) of the Treating to New Targets (TNT) study were randomly assigned to receive either 10- or 80-mg of atorvastatin per day and followed up for a median of 4.9 years. 8,888 patients with a history of myocardial infarction from the Incremental Decrease in End Points Through Aggressive Lipid-Lowering (IDEAL) study were randomly assigned to receive 20–40 mg of simvastatin or 80 mg of atorvastatin and followed up for a median of 4.8 years. The investigators concluded that carriers of the *KIF6* 719Arg allele were not at increased cardiovascular risk and did not obtain consistent cardiovascular benefit from high-dose statin therapy compared with noncarriers (Arsenault et al., 2012).

Charland et al. (2014) investigated the impact of providing *KIF6* test results and risk information directly to 647 tested patients on 6-month statin adherence and persistence compared with concurrent non-tested matched controls. The investigators observed that significantly more tested patients were adherent and persisted on therapy compared to the control group, with tested patients rating out at a 63.4% adherence (defined as ingesting medication on 80% of days), compared to 45% for the control group over six months (Charland et al., 2014). The test group also persisted on therapy more often than the control group (69.1% for the testing group, 53.3% for the control). The investigators concluded that the study provided the first evidence that pharmacogenetic testing may modify patient adherence (Charland et al., 2014).

Ruiz-Ramos et al. (2015) performed a systematic review and meta-analysis of previously published association studies between Trp719Arg polymorphism of *KIF6* and the development of CHD. This electronic search included papers published between 1993 and 2014. Twenty-three studies consisting of 38,906 subjects were identified (17,812 cases, 21,094 controls). A significant association was not found between Caucasian populations and the polymorphism or the CAD subgroup and the polymorphism, though the authors concluded that allele 719Arg may have a protective association to present CHD in all populations and the Trp719Arg polymorphism of the *KIF6* gene is an important risk factor for developing MI (Ruiz-Ramos et al., 2015).

Proprietary Testing

Cardiovascular Risk Panels/Profiles

Cardiovascular risk panels refer to combinations of cardiac markers that are used to assess risk of developing cardiovascular disease, major adverse cardiovascular events, or ischemic cerebrovascular events. Commercially available risk panels use different combinations of lipids, inflammatory, genetic, and metabolic markers. Risk panels report the results of multiple individual tests, whereas quantitative risk scores generally use proprietary algorithms to combine the results of multiple markers into one score. The clinical utility of risk panels is lacking as the impact of results on patient management is unknown.

Quest Diagnostics currently offers cardiogenetic testing for CVD risk. Tests include Cardio IQ® 9p21 and Cardio IQ® KIF6 (Quest, 2023).

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Guidelines and Recommendations

U.S. Preventative Services Task Force (USPSTF)

In a 2018 recommendation, the USPSTF provided a general statement regarding nontraditional risk factors in CVD risk assessment, but did not directly address the use of commercial CVD risk panels:

“The USPSTF concludes that there are insufficient adequately powered clinical trials evaluating the incremental effect of the ankle-brachial index (ABI), high-sensitivity C-reactive protein (hs-CRP) level, or coronary artery calcium (CAC) score in risk assessment and initiation of preventive therapy.

Furthermore, the clinical meaning of improvements in measures of calibration, discrimination, and reclassification risk prediction studies is uncertain” (Lin et al., 2018).

American College of Cardiology (ACC) and the American Heart Association (AHA)

The 2019 ACC and AHA guidelines do not address arterial compliance, lipoprotein-associated phospholipase, long-chain omega-3 fatty acids, 9p21 polymorphisms, *KIF6* genotyping, or endothelial function assessment as methods to assess initial CVD risk (Arnett et al., 2019). The 2013 ACC and AHA guidelines on the assessment of cardiovascular risk did not address assessment of 9p21 polymorphisms or *KIF6* genotyping. However, the 2010 guidelines recommended against genotype testing for “CHD risk assessment in asymptomatic adults” (Goff et al., 2014; Greenland et al., 2010).

American Heart Association (AHA)

A policy statement from the AHA on genetics and cardiovascular disease states “although robust GWAS [genome wide association studies] evidence exists linking common variants to complex CVD, studies are not yet available to inform the clinical benefit of providing such genetic information to patients” (Ashley et al., 2012).

A 2022 statement notes that the use of polygenic risk factors shows promise for the prediction of cardiovascular disease, as “the identification of monogenic risk variants predisposing to cardiovascular conditions has been used clinically to inform surveillance and management plans. Relatively recent advances in population genetics have uncovered the polygenic basis of these and other cardiovascular conditions in most patients. These observations point to the possibility of using genetic profiling to inform clinical practice... Such PRSs [Polygenic Risk Scores] may be appropriately considered in select scenarios, given the current evidence base.”

The AHA statement points to coronary artery disease (CAD) as one of the main areas where polygenic risk factors show promise; the discovery of common genetic variants associated with coronary artery disease has enabled this development of polygenic risk profiling. They also note that “scores have been shown to be strong predictors of subclinical coronary atherosclerosis and independently prognostic of CAD risk.” The statement does not specifically mention individual genes such as 9p21 single nucleotide polymorphisms or *KIF6* genotyping—focusing instead on genome wide association studies (O’Sullivan et al., 2022).

European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidaemias

The ESC published 2021 guidelines on cardiovascular disease prevention in clinical practice. The authors note that the etiology of atherosclerotic cardiovascular disease (ASCVD) has genetic associations; but, genetic information is not currently used to guide preventive practice. The authors cite a “lack of consensus regarding which genes and corresponding single nucleotide polymorphisms should be included, and whether to use risk factor-specific or outcome-specific polygenic risk scores”

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(F. L. J. Visseren et al., 2021).

Endocrine Society (ES)

This guideline was published with the intent to assess and treat dyslipidemia in patients with endocrine disorders.

The guideline remarks that certain “advanced” lipid testing (assessment of markers such as Apo B, lipid fractionation, and Lp(a)) may be helpful in “characterizing” lipid abnormalities, but “add little” to risk prediction beyond the standard lipid profile. The guideline also notes that genetic tests for risk stratification may “modestly” improve risk prediction but are not available in clinical practice. The guideline does remark that Apo B and non-HDL cholesterol should be considered “risk-enhancing” factors (Newman et al., 2020).

Canadian Cardiovascular Society (CCS)

In 2021, the CCS published updated recommendations on the management of dyslipidemia for the prevention of cardiovascular disease in adults. A summary of the society’s recommendations that involve genetic associations relevant to CVD risk assessment is provided below:

- We suggest that CAC (coronary artery calcium) screening might be considered for a subset of low-risk individuals 40 years or older with a family history of premature ASCVD (men 55 years or younger; women 65 years or younger), in addition to identifying known genetic causes of ASCVD such as elevated Lp(a) or FH (Weak Recommendation; Low-Quality Evidence)” (Pearson et al., 2021).

The 2021 guidelines reaffirmed those from 2016, stating that “Screening should be repeated every 5 years for men and women aged 40-75 years using the modified FRS or Cardiovascular Life Expectancy Model (CLEM) to guide therapy to reduce major CV events” (Pearson et al., 2021).

2021 European Society of Cardiology (ESC) and Other Societies on Cardiovascular Disease Prevention in Clinical Practice

In 2021, the Joint Task Force of the ESC and Other Societies on Cardiovascular Disease Prevention in Clinical Practice published an update to guidelines on cardiovascular disease prevention in clinical practice. The Task Force recognized that genetic screening could be useful in some conditions such as familial hypercholesterolemia.

However, the ESC does not recommend genetic screening in the general population or the use of genetics in “preventive approaches.” According to the Task Force, there is no consensus regarding which genes and their corresponding single nucleotide polymorphisms that should be included in a genetic risk score. In terms of polygenic risk scores, they acknowledge potential towards using genetics for prevention, but a lack of clarity towards whether to use “risk factor-specific” or “outcome-specific” polygenic risk scores. Further evaluation of clinical utility is required (Frank L. J. Visseren et al., 2021).

State and Federal Regulations, as applicable

Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

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Billing/Coding/Physician Documentation Information

This policy may apply to the following codes. Inclusion of a code in this section does not guarantee that it will be reimbursed. For further information on reimbursement guidelines, please see Administrative Policies on the Blue Cross Blue Shield of North Carolina web site at www.bcbsnc.com. They are listed in the Category Search on the Medical Policy search page.

Applicable service codes: 81402, 81403, 81404, 81405, 81406, 81407, 81408, 81479, 81493, 0401U

BCBSNC may request medical records for determination of medical necessity. When medical records are requested, letters of support and/or explanation are often useful, but are not sufficient documentation unless all specific information needed to make a medical necessity determination is included.

Scientific Background and Reference Sources

AHA. (2023). *2023 Heart Disease and Stroke Statistics Update Fact Sheet At-a-Glance*.

https://professional.heart.org/-/media/PHD-Files-2/Science-News/2/2023-Heart-and-Stroke-Stat-Update/2023-Statistics-At-A-Glance-final_1_17_23.pdf

Arnett, D. K., Blumenthal, R. S., Albert, M. A., Buroker, A. B., Goldberger, Z. D., Hahn, E. J., Himmelfarb, C. D., Khera, A., Lloyd-Jones, D., McEvoy, J. W., Michos, E. D., Miedema, M. D., Muñoz, D., Smith, S. C., Virani, S. S., Williams, K. A., Yeboah, J., & Ziaecian, B. (2019). 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*, *140*(11), e596-e646.

<https://doi.org/doi:10.1161/CIR.0000000000000678>

Arsenault, B. J., Boekholdt, S. M., Hovingh, G. K., Hyde, C. L., DeMicco, D. A., Chatterjee, A., Barter, P., Deedwania, P., Waters, D. D., LaRosa, J. C., Pedersen, T. R., & Kastelein, J. J. (2012). The 719Arg variant of KIF6 and cardiovascular outcomes in statin-treated, stable coronary patients of the treating to new targets and incremental decrease in end points through aggressive lipid-lowering prospective studies. *Circ Cardiovasc Genet*, *5*(1), 51-57.

<https://doi.org/10.1161/circgenetics.111.960252>

Ashley, E. A., Hershberger, R. E., Caleshu, C., Ellinor, P. T., Garcia, J. G., Herrington, D. M., Ho, C. Y., Johnson, J. A., Kittner, S. J., Macrae, C. A., Mudd-Martin, G., Rader, D. J., Roden, D. M., Scholes, D., Sellke, F. W., Towbin, J. A., Van Eyk, J., & Worrall, B. B. (2012). Genetics and cardiovascular disease: a policy statement from the American Heart Association. *Circulation*, *126*(1), 142-157. <https://doi.org/10.1161/CIR.0b013e31825b07f8>

Charland, S. L., Agatep, B. C., Herrera, V., Schrader, B., Frueh, F. W., Ryvkin, M., Shabbeer, J., Devlin, J. J., Superko, H. R., & Stanek, E. J. (2014). Providing patients with pharmacogenetic test results affects adherence to statin therapy: results of the Additional KIF6 Risk Offers Better Adherence to Statins (AKROBATS) trial. *Pharmacogenomics J*, *14*(3), 272-280.

<https://doi.org/10.1038/tpj.2013.27>

Dehghan, A., Bis, J. C., White, C. C., Smith, A. V., Morrison, A. C., Cupples, L. A., Trompet, S., Chasman, D. I., Lumley, T., Völker, U., Buckley, B. M., Ding, J., Jensen, M. K., Folsom, A. R., Kritchevsky, S. B., Girman, C. J., Ford, I., Dörr, M., Salomaa, V., . . . O'Donnell, C. J. (2016). Genome-Wide Association Study for Incident Myocardial Infarction and Coronary

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Heart Disease in Prospective Cohort Studies: The CHARGE Consortium. *PLOS ONE*, 11(3), e0144997. <https://doi.org/10.1371/journal.pone.0144997>

- Deloukas, P., Kanoni, S., Willenborg, C., Farrall, M., Assimes, T. L., Thompson, J. R., Ingelsson, E., Saleheen, D., Erdmann, J., Goldstein, B. A., Stirrups, K., Konig, I. R., Cazier, J. B., Johansson, A., Hall, A. S., Lee, J. Y., Willer, C. J., Chambers, J. C., Esko, T., . . . Samani, N. J. (2013). Large-scale association analysis identifies new risk loci for coronary artery disease. *Nat Genet*, 45(1), 25-33. <https://doi.org/10.1038/ng.2480>
- Dutta, A., Henley, W., Lang, I. A., Murray, A., Guralnik, J., Wallace, R. B., & Melzer, D. (2011). The coronary artery disease-associated 9p21 variant and later life 20-year survival to cohort extinction. *Circ Cardiovasc Genet*, 4(5), 542-548. <https://doi.org/10.1161/circgenetics.111.960146>
- Elashoff, M. R., Wingrove, J. A., Beineke, P., Daniels, S. E., Tingley, W. G., Rosenberg, S., Voros, S., Kraus, W. E., Ginsburg, G. S., Schwartz, R. S., Ellis, S. G., Tahirkheli, N., Waksman, R., McPherson, J., Lansky, A. J., & Topol, E. J. (2011). Development of a blood-based gene expression algorithm for assessment of obstructive coronary artery disease in non-diabetic patients. *BMC Med Genomics*, 4, 26. <https://doi.org/10.1186/1755-8794-4-26>
- Ganesh, S. K., Arnett, D. K., Assimes, T. L., Basson, C. T., Chakravarti, A., Ellinor, P. T., Engler, M. B., Goldmuntz, E., Herrington, D. M., Hershberger, R. E., Hong, Y., Johnson, J. A., Kittner, S. J., McDermott, D. A., Meschia, J. F., Mestroni, L., O'Donnell, C. J., Psaty, B. M., Vasani, R. S., . . . Waldman, S. A. (2013). Genetics and genomics for the prevention and treatment of cardiovascular disease: update: a scientific statement from the American Heart Association. *Circulation*, 128(25), 2813-2851. <https://doi.org/10.1161/01.cir.0000437913.98912.1d>
- Goff, D. C., Jr., Lloyd-Jones, D. M., Bennett, G., Coady, S., D'Agostino, R. B., Sr., Gibbons, R., Greenland, P., Lackland, D. T., Levy, D., O'Donnell, C. J., Robinson, J. G., Schwartz, J. S., Shero, S. T., Smith, S. C., Jr., Sorlie, P., Stone, N. J., & Wilson, P. W. (2014). 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*, 63(25 Pt B), 2935-2959. <https://doi.org/10.1016/j.jacc.2013.11.005>
- Gransbo, K., Almgren, P., Sjogren, M., Smith, J. G., Engstrom, G., Hedblad, B., & Melander, O. (2013). Chromosome 9p21 genetic variation explains 13% of cardiovascular disease incidence but does not improve risk prediction. *J Intern Med*, 274(3), 233-240. <https://doi.org/10.1111/joim.12063>
- Greenland, P., Alpert, J. S., Beller, G. A., Benjamin, E. J., Budoff, M. J., Fayad, Z. A., Foster, E., Hlatky, M. A., Hodgson, J. M., Kushner, F. G., Lauer, M. S., Shaw, L. J., Smith, S. C., Jr., Taylor, A. J., Weintraub, W. S., Wenger, N. K., Jacobs, A. K., Anderson, J. L., Albert, N., . . . Yancy, C. W. (2010). 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*, 56(25), e50-103. <https://doi.org/10.1016/j.jacc.2010.09.001>
- Hopewell, J. C., Parish, S., Clarke, R., Armitage, J., Bowman, L., Hager, J., Lathrop, M., & Collins, R. (2011). No impact of KIF6 genotype on vascular risk and statin response among 18,348 randomized patients in the heart protection study. *J Am Coll Cardiol*, 57(20), 2000-2007. <https://doi.org/10.1016/j.jacc.2011.02.015>
- Iakoubova, O. A., Tong, C. H., Rowland, C. M., Kirchgessner, T. G., Young, B. A., Arellano, A. R., Shiffman, D., Sabatine, M. S., Campos, H., Packard, C. J., Pfeffer, M. A., White, T. J., Braunwald, E., Shepherd, J., Devlin, J. J., & Sacks, F. M. (2008). Association of the Trp719Arg polymorphism in kinesin-like protein 6 with myocardial infarction and coronary

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- heart disease in 2 prospective trials: the CARE and WOSCOPS trials. *J Am Coll Cardiol*, 51(4), 435-443. <https://doi.org/10.1016/j.jacc.2007.05.057>
- Kessler, T., Vilne, B., & Schunkert, H. (2016). The impact of genome-wide association studies on the pathophysiology and therapy of cardiovascular disease. *EMBO Mol Med*, 8(7), 688-701. <https://doi.org/10.15252/emmm.201506174>
- Lin, J. S., Evans, C. V., Johnson, E., Redmond, N., Coppola, E. L., & Smith, N. (2018). Nontraditional Risk Factors in Cardiovascular Disease Risk Assessment: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *Jama*, 320(3), 281-297. <https://doi.org/10.1001/jama.2018.4242>
- Newman, C. B., Blaha, M. J., Boord, J. B., Cariou, B., Chait, A., Fein, H. G., Ginsberg, H. N., Goldberg, I. J., Murad, M. H., Subramanian, S., & Tannock, L. R. (2020). Lipid Management in Patients with Endocrine Disorders: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*, 105(12). <https://doi.org/10.1210/clinem/dgaa674>
- O'Sullivan, J. W., Raghavan, S., Marquez-Luna, C., Luzum, J. A., Damrauer, S. M., Ashley, E. A., O'Donnell, C. J., Willer, C. J., & Natarajan, P. (2022). Polygenic Risk Scores for Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*, 146(8), e93-e118. <https://doi.org/doi:10.1161/CIR.0000000000001077>
- Palomaki, G. E., Melillo, S., & Bradley, L. A. (2010). Association between 9p21 genomic markers and heart disease: a meta-analysis. *Jama*, 303(7), 648-656. <https://doi.org/10.1001/jama.2010.118>
- Palotie, A., Havulinna, A. S., De Livera, A. M., Tikkanen, E., Sijbrands, E. J., Abraham, G., Schunkert, H., Yetukuri, L., Perola, M., Bhalala, O. G., Byars, S. G., Inouye, M., Samani, N. J., Ripatti, S., & Salomaa, V. (2016). Genomic prediction of coronary heart disease. *European Heart Journal*, 37(43), 3267-3278. <https://doi.org/10.1093/eurheartj/ehw450>
- Patel, R. S., Asselbergs, F. W., Quyyumi, A. A., Palmer, T. M., Finan, C. I., Tragante, V., Deanfield, J., Hemingway, H., Hingorani, A. D., & Holmes, M. V. (2014). Genetic variants at chromosome 9p21 and risk of first versus subsequent coronary heart disease events: a systematic review and meta-analysis. *J Am Coll Cardiol*, 63(21), 2234-2245. <https://doi.org/10.1016/j.jacc.2014.01.065>
- Paynter, N. P., Chasman, D. I., Buring, J. E., Shiffman, D., Cook, N. R., & Ridker, P. M. (2009). Cardiovascular disease risk prediction with and without knowledge of genetic variation at chromosome 9p21.3. *Ann Intern Med*, 150(2), 65-72. <http://dx.doi.org/>
- Pearson, G. J., Thanassoulis, G., Anderson, T. J., Barry, A. R., Couture, P., Dayan, N., Francis, G. A., Genest, J., Grégoire, J., Grover, S. A., Gupta, M., Hegele, R. A., Lau, D., Leiter, L. A., Leung, A. A., Lonn, E., Mancini, G. B. J., Manjoo, P., McPherson, R., . . . Wray, W. (2021). 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. *Can J Cardiol*, 37(8), 1129-1150. <https://doi.org/10.1016/j.cjca.2021.03.016>
- Quest. (2023). *Cardio IQ® 9p21 Genotype* <https://testdirectory.questdiagnostics.com/test/test-detail/90648/cardio-iq-9p21-genotype?p=r&q=cardio%20IA%209p21%20genotype&cc=MASTER>
- Ridker, P., MacFadyen, J., Glynn, R., & Chasman, D. (2011). Kinesin-Like Protein 6 (KIF6) Polymorphism and the Efficacy of Rosuvastatin in Primary Prevention. *Circulation: Cardiovascular Genetics*, 4(3), 312-317. <https://doi.org/10.1161/CIRCGENETICS.110.959353>

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- Ruiz-Ramos, D., Hernández-Díaz, Y., Tovilla-Zárate, C. A., Juárez-Rojop, I., López-Narváez, M. L., González-Castro, T. B., Torres-Hernández, M. E., & Baños-González, M. A. (2015). The Trp719Arg polymorphism of the KIF6 gene and coronary heart disease risk: systematic review and meta-analysis. *Hereditas*, 152, 3. <https://doi.org/10.1186/s41065-015-0004-7>
- Samani, N. J., Erdmann, J., Hall, A. S., Hengstenberg, C., Mangino, M., Mayer, B., Dixon, R. J., Meitinger, T., Braund, P., Wichmann, H. E., Barrett, J. H., König, I. R., Stevens, S. E., Szymczak, S., Tregouet, D. A., Iles, M. M., Pahlke, F., Pollard, H., Lieb, W., . . . Schunkert, H. (2007). Genomewide association analysis of coronary artery disease. *N Engl J Med*, 357(5), 443-453. <https://doi.org/10.1056/NEJMoa072366>
- Trenkwalder, T., Nelson, C. P., Musameh, M. D., Mordi, I. R., Kessler, T., Pellegrini, C., Debiec, R., Rheude, T., Lazovic, V., Zeng, L., Martinsson, A., Gustav Smith, J., Gadin, J. R., Franco-Cereceda, A., Eriksson, P., Nielsen, J. B., Graham, S. E., Willer, C. J., Hveem, K., . . . Samani, N. J. (2019). Effects of the coronary artery disease associated LPA and 9p21 loci on risk of aortic valve stenosis. *Int J Cardiol*, 276, 212-217. <https://doi.org/10.1016/j.ijcard.2018.11.094>
- Tsao, C. W., Aday, A. W., Almarzooq, Z. I., Anderson, C. A. M., Arora, P., Avery, C. L., Baker-Smith, C. M., Beaton, A. Z., Boehme, A. K., Buxton, A. E., Commodore-Mensah, Y., Elkind, M. S. V., Evenson, K. R., Eze-Nliam, C., Fugar, S., Generoso, G., Heard, D. G., Hiremath, S., Ho, J. E., . . . Martin, S. S. (2023). Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. *Circulation*, 147(8), e93-e621. <https://doi.org/10.1161/cir.0000000000001123>
- Virani, S. S., Brautbar, A., Lee, V.-V., MacArthur, E., Morrison, A. C., Grove, M. L., Nambi, V., Frazier, L., Wilson, J. M., Willerson, J. T., Boerwinkle, E., & Ballantyne, C. M. (2012). Chromosome 9p21 single nucleotide polymorphisms are not associated with recurrent myocardial infarction in patients with established coronary artery disease. *Circulation journal : official journal of the Japanese Circulation Society*, 76(4), 950-956. <https://doi.org/10.1253/circj.cj-11-1166>
- Visseren, F. L. J., Mach, F., Smulders, Y. M., Carballo, D., Koskinas, K. C., Bäck, M., Benetos, A., Biffi, A., Boavida, J.-M., Capodanno, D., Cosyns, B., Crawford, C., Davos, C. H., Desormais, I., Di Angelantonio, E., Franco, O. H., Halvorsen, S., Hobbs, F. D. R., Hollander, M., . . . Group, E. S. C. S. D. (2021). 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice: Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies With the special contribution of the European Association of Preventive Cardiology (EAPC). *European Heart Journal*, 42(34), 3227-3337. <https://doi.org/10.1093/eurheartj/ehab484>
- Visseren, F. L. J., Mach, F., Smulders, Y. M., Carballo, D., Koskinas, K. C., Back, M., Benetos, A., Biffi, A., Boavida, J. M., Capodanno, D., Cosyns, B., Crawford, C., Davos, C. H., Desormais, I., Di Angelantonio, E., Franco, O. H., Halvorsen, S., Hobbs, F. D. R., Hollander, M., . . . Group, E. S. C. S. D. (2021). 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J*, 42(34), 3227-3337. <https://doi.org/10.1093/eurheartj/ehab484>
- Wilson, P. (2023). Overview of the possible risk factors for cardiovascular disease - UpToDate. In B. Downey (Ed.), *UpToDate*. <https://www.uptodate.com/contents/overview-of-the-possible-risk-factors-for-cardiovascular-disease>
- Zhernakova, D. V., Le, T. H., Kurilshikov, A., Atanasovska, B., Bonder, M. J., Sanna, S., Claringbould, A., Vösa, U., Deelen, P., Franke, L., de Boer, R. A., Kuipers, F., Netea, M. G., Hofker, M. H., Wijmenga, C., Zhernakova, A., Fu, J., LifeLines cohort, s., & consortium, B. (2018). Individual variations in cardiovascular-disease-related protein levels are driven by

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genetics and gut microbiome. *Nature Genetics*, 50(11), 1524-1532.
<https://doi.org/10.1038/s41588-018-0224-7>

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Policy Implementation/Update Information

- 9/13/22 New policy developed. Genetic Markers for Assessing Risk of Cardiovascular Disease is considered investigational for [all applications}. BCBSNC does not provide coverage for investigational services or procedures. Medical Director review 7/2022. **Notification given 9/13/2022 for effective date 10/18/2022. (tm)**
- 6/30/23 Code 0401U added to Billing/Coding section, effective 7/1/23. (tm)
- 8/15/23 Reviewed by Avalon 2nd Quarter 2023 CAB. Updated Description, Policy Guidelines and References. Not Covered section edited for clarity: previous coverage criteria 1, 2, and 4 combined into new coverage criteria 2 with subcriteria and now reads “To assess an individual’s risk of developing cardiovascular disease, the following tests are considered investigational: a. Gene expression profiling. b. Genotyping for 9p21 single nucleotide polymorphisms. c. Panels that incorporate genetic risk factors with nongenetic biomarkers.” No change to policy intent. Medical Director review 7/2023. (tm)

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