Sentara Health Plans

Genetic Markers for Assessing Risk of Cardiovascular Disease

Policy Number: AHS – M2180 – Genetic Markers for Assessing Risk of Cardiovascular Disease	Prior Policy Name and Number, as applicable:
Policy Revision Date: 12/01/2024 Initial Policy Effective Date: 12/01/2024	

I. Policy Description

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. Terms such as male and female are used when necessary to refer to sex assigned at birth.

II. Related Policies

Policy Number	Policy Title
AHS-G2050	Cardiovascular Disease Risk Assessment
AHS-M2082	Genetic Testing for Lipoprotein(a) Variant(s) as a Decision Aid for Aspirin Treatment and/or CVD Risk Assessment
AHS-M2137	Genetic Testing for Familial Hypercholesterolemia
AHS-M2141	Testing of Homocysteine Metabolism-Related Conditions

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in the "Applicable State and Federal Regulations" section of this policy document.

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of an individual's illness.

1) To predict the risk of developing cardiovascular disease and/or the effectiveness of statin therapy, *KIF6* genotyping **DOES NOT MEET COVERAGE CRITERIA**.

2) To assess an individual's risk of developing cardiovascular disease, the following tests **DO NOT MEET COVERAGE CRITERIA**:
   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 **DO NOT MEET COVERAGE CRITERIA**.

IV. Table of Terminology

Term	Definition
ABI	Ankle-brachial index
ACC	American College of Cardiology
AHA	American Heart Association
Apo B	Apolipoprotein B
ASCVD	Atherosclerotic cardiovascular disease
CAC	Coronary artery calcium
CAD	Coronary artery disease
CCS	Canadian Cardiovascular Society
CHD	Coronary heart disease
CVD	Cardiovascular disease
EAS	European Atherosclerosis Society
ES	Endocrine Society
ESC	European Society of Cardiology
FDA	Food and Drug Administration
GRS	Genomic risk score
GWAS	Genome-wide association study
HDL	High-density lipoprotein
hsCRP	High-sensitivity C reactive protein
IDEAL	Incremental decrease in end points through aggressive lipid-lowering
KIF6	*Kinesin family member 6*
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein cholesterol
LDT	Laboratory developed test
Lp(a)	Lipoprotein A
LPA	Apolipoprotein(a) locus
Lp-PLA2	Lipoprotein-associated phospholipase A2
MI	Myocardial infarction
PRSs	Polygenic risk scores

RNA	Ribonucleic acid
SNPs	Single nucleotide polymorphisms
TNT	Treating to new targets study
VLDL	Very low-density lipoprotein

V. Scientific 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 2024 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 $422.3 billion and increasing every year.
- Coronary heart disease (CHD) was the leading cause (40.3%) of deaths attributable to CVD in the United States, followed by stroke (17.5%), other CVD (17.1%), high blood pressure (13.4%), heart failure (9.1%), 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 three minutes fourteen seconds in the United States.
- 11.5% of US adults reported cigarette use every day or some days (13.1% of males and 10.1% of females).
- Worldwide, high body mass index was attributed to 3.69 million deaths (AHA, 2024; Seth S. Martin, 2024).

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 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, 2024).

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 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).

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. A total of 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 six 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 panel's 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, 2024).

VI. 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).

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 five 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. 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.

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).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: https://www.cms.gov/Medicare-Coverage-Database/search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

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.

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81402	Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])

CPT	Code Description
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81408	Molecular pathology procedure, Level 9 (eg, analysis of >50 exons in a single gene by DNA sequence analysis)
81479	Unlisted molecular pathology procedure
81493	Coronary artery disease, mRNA, gene expression profiling by real-time RT-PCR of 23 genes, utilizing whole peripheral blood, algorithm reported as a risk score Proprietary test: Corus®CAD Lab/Manufacturer: CardioDx, Inc.
0401U	Cardiology (coronary heart disease [CAD]), 9 genes (12 variants), targeted variant genotyping, blood, saliva, or buccal swab, algorithm reported as a genetic risk score for a coronary event Proprietary test: CARDIO inCode-Score (CIC-SCORE) Lab/Manufacturer: GENinCode U.S. Inc
0439U	Cardiology (coronary heart disease [CHD]), DNA, analysis of 5 single-nucleotide polymorphisms (SNPs) (rs11716050 [LOC105376934], rs6560711 [WDR37], rs3735222 [SCIN/LOC107986769], rs6820447 [intergenic], and rs9638144 [ESYT2]) and 3 DNA methylation markers (cg00300879 [transcription start site {TSS200} of CNKSR1], cg09552548 [intergenic], and cg14789911 [body of SPATC1L]), qPCR and digital PCR, whole blood, algorithm reported as a 4-tiered risk score for a 3-year risk of symptomatic CHD Proprietary test: Epi+Gen CHD ™ Lab Manufacturer: Cardio Diagnostics, Inc
0440U	Cardiology (coronary heart disease [CHD]), DNA, analysis of 10 single-nucleotide polymorphisms (SNPs) (rs710987 [LINC010019], rs1333048 [CDKN2B-AS1], rs12129789 [KCND3], rs942317 [KTN1-AS1], rs1441433 [PPP3CA], rs2869675 [PREX1], rs4639796 [ZBTB41], rs4376434 [LINC00972], rs12714414 [TMEM18], and rs7585056 [TMEM18]) and 6 DNA methylation markers (cg03725309 [SARS1], cg12586707 [CXCL1, cg04988978 [MPO], cg17901584

CPT	Code Description
	[DHCR24-DT], cg21161138 [AHRR], and cg12655112 [EHD4]), qPCR and digital PCR, whole blood, algorithm reported as detected or not detected for CHD Proprietary test: PrecisionCHDTM Lab/Manufacturer: Cardio Diagnostics, Inc
0466U	Cardiology (coronary artery disease [CAD]), DNA, genomewide association studies (564856 single-nucleotide polymorphisms [SNPs], targeted variant genotyping), patient lifestyle and clinical data, buccal swab, algorithm reported as polygenic risk to acquired heart disease Proprietary test: CardioRisk+ Lab/Manufacturer: Gene by Gene, Ltd, Open DNS, Ltd

Procedure codes appearing in Medical Policy documents are included only as a general reference tool for each policy. They may not be all-inclusive.

IX. Evidence-based Scientific References

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X. Review/Revision History

Effective Date	Summary
12/01/2024	Reviewed and Updated: Updated the background, guidelines and recommendations, and evidence-based scientific references. Literature review did not necessitate any modifications to coverage criteria. Added CPT code 0466U (effective date 7/1/2024) Updated code description for CPT code 81406 (annual updates; effective 1/1/2024)
12/01/2024	Initial Policy Implementation