Apolipoprotein E for Risk Assessment and Management of Cardiovascular Disease

Effective: April 1, 2026

Next Review: December 2026
Last Review: February 2026

IMPORTANT REMINDER

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

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

DESCRIPTION

Apolipoprotein E (apo E) genotype has been associated with risk for coronary artery disease (CAD) and may affect responses to lipid-lowering medications. Genetic testing of apo E has been proposed for individual CAD risk assessment and to predict the response to statin therapy.

MEDICAL POLICY CRITERIA

Apolipoprotein E genetic testing is considered **investigational** for the risk assessment and management of cardiovascular disease.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

CROSS REFERENCES

1. Measurement of Lipoprotein-Associated Phospholipase A2 (Lp-PLA2) in the Assessment of Cardiovascular Risk, Laboratory, No. 63

BACKGROUND

Numerous lipid and nonlipid biomarkers have been proposed as potential risk markers for cardiovascular disease. Low-density lipoproteins (LDL) have been identified as the major atherogenic lipoproteins and have long been identified by the National Cholesterol Education Project (NCEP) as the primary target of cholesterol-lowering therapy. LDL particles consist of a surface coat composed of phospholipids, free cholesterol, and apolipoproteins surrounding an inner lipid core composed of cholesterol ester and triglycerides. Traditional lipid risk factors such as LDL-cholesterol (LDL-C), while predictive on a population basis, are weaker markers of risk on an individual basis. Only a minority of subjects with elevated LDL and cholesterol levels will develop clinical disease, and up to 50% of cases of coronary artery disease (CAD) occur in subjects with 'normal' levels of total and LDL-C. Thus, there is considerable potential to improve the accuracy of current cardiovascular risk prediction models.

Apolipoprotein E (apo E) is the primary apolipoprotein found in very-low-density lipoproteins (VLDLs) and chylomicrons. Apo E is the primary binding protein for LDL receptors in the liver and is thought to play an important role in lipid metabolism. The apo E gene is polymorphic, consisting of three alleles (e2, e3, and e4) that code for three protein isoforms, known as E2, E3, and E4, which differ from one another by one amino acid. These molecules mediate lipid metabolism through their different interactions with the LDL receptors. The genotype of apo E alleles can be assessed by gene amplification techniques, or the apo E phenotype can be assessed by measuring plasma levels of apo E.

It has been proposed that various apo E genotypes are more atherogenic than others and that apo E measurement may provide information on risk of CAD above traditional risk factor measurement. It has also been proposed that the apo E genotype may be useful in the selection of specific components of lipid-lowering therapy such as drug selection. In the major lipid-lowering intervention trials, including trials of statin therapy, there is considerable variability in response to therapy that cannot be explained by factors such as compliance. Apo E genotype may be one factor that determines an individual's degree of response to interventions such as statin therapy.

EVIDENCE SUMMARY

Human Genome Variation Society (HGVS) nomenclature[1] is used to describe variants found in DNA and serves as an international standard. It is being implemented for genetic testing medical evidence review updates starting in 2017. According to this nomenclature, the term "variant" is used to describe a change in a DNA or protein sequence, replacing previously-used terms, such as "mutation." Pathogenic variants are variants associated with disease, while benign variants are not. The majority of genetic changes have unknown effects on human health, and these are referred to as variants of uncertain significance.

A 2002 BlueCross BlueShield Association Technology Evaluation Center (TEC) Assessment[2] summarized the steps necessary to determine utility of a novel cardiac risk factor. Three steps were required:

- Standardization of the measurement of the risk factor.
- Determination of its contribution to risk assessment. As a risk factor, it is important to determine whether the novel risk factor […] independently contributes to risk assessment compared to established risk factors.

- Determination of how the novel risk assessment will be used in the management of the patient, compared to standard methods of assessing risk, and whether any subsequent changes in patient management result in an improvement in patient outcome.

Similarly, the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III; ATP III) noted that emerging risk factors should be evaluated against the following criteria in order to determine their clinical significance:[3]

- Significant predictive power that is independent of other major risk factors
- A relatively high prevalence in the population (justifying routine measurement in risk assessment)
- Laboratory or clinical measurement must be widely available, well standardized, inexpensive, have accepted population reference values, and be relatively stable biologically
- Preferable, but not necessarily, modification of the risk factor in clinical trials will have shown reduction in risk.

The focus of the following literature appraisal is on evidence related to the clinical utility of testing or the ability of apo E testing to:

- Provide clinically relevant information beyond that provided by traditional lipid measures, and
- Improve health outcomes as a result of patient management decisions that would not otherwise have been made in the absence of apo E testing.

APO E AS A PREDICTOR OF CARDIOVASCULAR DISEASE

A large body of research has established a correlation between lipid levels and the underlying apo E genotype. Numerous studies have focused on the relationship between genotype and physiologic markers of atherosclerotic disease. A number of small- to medium-sized cross-sectional and case-control studies have correlated apo E with surrogate outcomes such as cholesterol levels, markers of inflammation, or carotid intima-media thickness.[4-10] These studies have generally shown a relationship between apo E and these surrogate outcomes. For example, in population studies, the presence of an apo e2 allele was associated with the lowest cholesterol levels and the apo e4 allele was associated with the highest levels.[11, 12] Other studies have suggested that carriers of apo e4 are more likely to develop signs of atherosclerosis independent of total and LDL-cholesterol levels.[13-16]

Some larger observational studies have correlated apo E genotype with clinical disease. For example, the Atherosclerosis Risk in Communities (ARIC) study followed 12,000 middle-aged individuals free of coronary artery disease (CAD) at baseline for 10 years.[17] This study reported that the e3/2 genotype was associated with carotid artery atherosclerosis after controlling for other atherosclerotic risk factors. Volcik (2006) reported that apo E polymorphisms were associated with LDL levels and carotid intima-media thickness but were not predictive of incident CAD.[18] A British birth cohort study found apo e2 genotypes to be associated with both deep and lobar intracerebral hemorrhage (ICH). APO e4 and apo e2/4 genotypes had selective associations with ICH in case-control and age-adjusted analyses.[19] However, Ajnakina (2023) published a study using data from the English Longitudinal Study of Aging (ELSA) that did not find an association between *APO-ε4* status and cardiovascular disease deaths in 7,131 adults aged $\geq$50 years with 10 years of follow-up.[20]

Shao (2022) conducted a meta-analysis of 32 studies to analyze the correlation between APOE polymorphisms and risk of myocardial infarction (MI).[21] The studies included 13,706 cases of MI and 14,817 controls. Pooled analysis using the random-effects model found the apo e4 genotypes were associated with the highest risk of MI (OR 1.24, 95% CI 1.09-1.42) and MI frequency was lowest in people with apo e2 genotypes (OR 0.74, 95% CI 0.64-0.86).

Sofat (2016) published a meta-analysis of three studies of circulating apo E and CVD events.[22] The method for selecting the studies was not described. The three studies included 9,587 participants and 1,413 CVD events. In the pooled analysis, there was no association of apo E with CVD events. The unadjusted odds ratio (OR) for CVD events for a standard deviation increase in apo E concentration was 1.02 (95% CI, 0.96 to 1.09). After adjustment for other cardiovascular risk factors, the OR for CVD for a standard deviation increase in apo E concentration was 0.97 (95% CI 0.82 to 1.15).

A systematic review by Zhao (2017) assessed the link between apo E polymorphisms and premature CAD.[23] Premature CAD (PAD) was defined as CAD in males below age 55 and females below age 65. The review included 18 research reports with a low to moderate risk of bias, for a total of 2,361 cases of PCAD and 2,811 controls. Overall, the e2 allele was not significantly associated with PCAD. However, when results were stratified by race, the e2 allele appeared to increase the risk of PCAD in Asians (OR 1.54, 95% CI 1.09 to 2.17, as compared to the e3 allele), while a protective effect was seen in Caucasians (OR 0.77, 95% CI 0.62 to 0.95, as compared to the e3 allele). Subgroup analysis showed a decreased risk of myocardial infarction associated with e2 compared to e3 (OR 0.70, 95% CI 0.49 to 0.98). Overall, the e4 allele was associated with greater risk of PCAD (OR 1.62, 95% CI 1.27 to 2.06). This increased risk was seen for all racial groups.

An earlier meta-analysis published by Bennet (2007) summarized the evidence from 147 studies on the association of apo E genotypes with lipid levels and cardiac risk.[24] Eighty-two studies included data on the association of apo E with lipid levels, and 121 studies reported the association with clinical outcomes. The authors reported that patients with the apo e2 allele had LDL levels that were approximately 31% less compared with patients with the apo e4 allele. Patients with the apo e3 allele had an approximately 20% decreased risk for coronary events compared with patients with apo e2 (OR 0.80, 95% CI 0.70 to 0.90), and patients with the apo e4 had an estimated 6% higher risk of coronary events that was not statistically significant (OR 1.06, 95% CI 0.99 to 1.13).

No studies were identified that compared the health outcomes of patient management based on apo E genotypes compared with patient management based on conventional risk assessment measures such as LDL. Therefore, it is unclear how the associations reported above can be used to improve health outcomes over current patient management procedures.

APO E AS A PREDICTOR OF RESPONSE TO THERAPY

Apo E has been investigated as a predictor of response to therapy by examining apo E alleles in the intervention arm(s) of lipid-lowering trials. Some data have suggested that patients with an apo e4 allele may respond better to diet-modification strategies.[25-27] King (2022) found that people who were given nutritional advice tailored to their apo e4 genotype modified their diet.[28] Subjects with apo e4 genotypes associated with increased CVD risk who ate higher than recommended levels of saturated fat reduced their fat intake (p=0.012) to recommended levels after hearing genotype-specific dietary advice (p=0.409). Participants with non-risk apo e4 genotypes who ate higher than recommended levels of saturated fat also reduced their fat

intake (p=0.001) after nutritional advice but continued to consume significantly higher than recommended levels of saturated fat (p=0.007). However, the number of participants who had both the risk-associated genotype and the risk-associated diet at baseline was small (n=9). Other studies have suggested that response to statin therapy may vary with apo E genotype and that the e2 allele indicates greater responsiveness to statins.[25, 27, 29-32] There is also evidence that apo e2 correlates with superior response to long-term aspirin therapy in people with existing cardiovascular disease.[33]

No studies were identified that directly compared the health outcomes of patient management that was based on apo E status with those based on conventional measures.

PRACTICE GUIDELINE SUMMARY

No clinical practice guidelines or position statements from U.S. professional associations were identified that recommended the use of apo E in cardiovascular risk assessment, including but not limited to the following:

- The 2021 National Lipid Association (NLA) scientific statement on lipid measurements in cardiovascular disease.[34]
- The 2020 National Lipid Association (NLA) scientific statement on genetic testing in dyslipidemia[35]
- The 2013 American College of Cardiology/American Heart Association guidelines for the assessment of cardiovascular risk in asymptomatic patients.[36]
- The 2019 U.S. Preventive Services Task Force (USPSTF) recommendations on the use of nontraditional risk factors for the assessment of coronary heart disease.
- The American Diabetes Association and the American College of Cardiology Foundation consensus conference publication.[37]

SUMMARY

APO E AS A PREDICTOR OF CARDIOVASCULAR DISEASE

There is some research that shows that apolipoprotein E (apo E) genotype may have an effect on cholesterol levels and risk for coronary artery disease (CAD). However, there is not enough research to show that testing for apo E genotype helps to improve health outcomes for people at risk for CAD. There are no clinical guidelines based on research that recommend testing apo E genotype for cardiovascular risk. Therefore, the use of apo E measurements in the risk assessment and management of cardiovascular disease is considered investigational.

APO E AS A PREDICTOR OF RESPONSE TO THERAPY

There is not enough research to show that genetic testing of apolipoprotein E (apo E) can improve health outcomes for people that are considering starting a statin medication to reduce their cardiovascular risk. Therefore, apo E testing to predict response to lipid-lowering therapy is considered investigational.

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CODES

Codes	Number	Description
CPT	81401	Molecular pathology procedure, Tier 2, Level 2
HCPCS	None	

Date of Origin: *January 2013*