

Medical Policy



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Title: **Apolipoprotein E Genotype or Phenotype in the Management of Cardiovascular Disease**

Professional

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DESCRIPTION

Apolipoprotein E (apo E) is the primary apolipoprotein found in very-low-density lipoproteins 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 3 alleles (e2, e3, and e4) that code for 3 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 apolipoprotein E.

There has been much research interest in investigating lipid metabolism and lipoprotein levels in patients with different apo E genotypes and phenotypes. It has been proposed that various genotypes are more atherogenic than others, and that apo E measurement may provide information on risk of coronary artery disease above traditional risk factor measurement. It has also been proposed that the apo E genotype may be useful in 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.

Apolipoprotein E isoforms have also been investigated as a risk factor for Alzheimer's disease.

POLICY

Determination of the apo E genotype or phenotype is considered **investigational** as a cardiovascular risk factor.

Determination of apo E may be included as a component of a comprehensive cardiovascular risk assessment offered by reference laboratories. Comprehensive risk assessment may include evaluation of small low-density lipoproteins, subclassification of high-density lipoproteins, high-sensitivity C-reactive protein, total plasma homocysteine, apolipoproteins A and B, lipoprotein a, small low-density LDL, and homocysteine levels. The lack of a specific CPT code may make identification of claims for apo E difficult. However, apo E phenotyping as part of cardiovascular risk assessment is likely when CPT code 84181 is submitted from a reference laboratory in conjunction with CPT codes 82172 (used to code for apolipoprotein B), CPT code 83695 (lipoprotein a), CPT code 82664 (used to code for HDL subclasses), CPT code 86141 (used to code for high-sensitivity C-reactive protein), CPT code 83090 (homocysteine), and CPT code 83701 (used to code for small, low-density LDL.)

RATIONALE

A large body of research has focused on the correlation between lipid levels and the underlying apo E genotype. For example, in population studies the presence of an apo e2 allele is associated with the lowest cholesterol levels and the apo e4 allele is associated with the highest levels. (1, 2)

Other studies have focused on the relationship between genotype and clinical disease. The Copenhagen City Heart Study was a large case control study of 940 adults with known ischemic heart disease and 9,241 adults in the general population.(3) In men with a genotype of e4/e4 compared to those with a genotype of e3/e3, the odds ratio of ischemic disease was 1.58. Among women, the odds ratio of those with a genotype of e3/2 compared to those with a genotype of 3/3 was 0.57. The attributable risk of apo E to CAD was relatively small for all genotypes. Other studies have suggested that carriers of apo e4 are more likely to develop atherosclerosis and coronary artery disease (CAD), independent of total and LDL cholesterol levels.(4-6) The Atherosclerosis Risk in Communities (ARIC) followed up 12,000 middle-aged individuals free of CAD at baseline for 10 years. (7) This study reported that the e3/2 genotype was associated with carotid artery atherosclerosis after controlling for other atherosclerotic risk factors.

Despite observations such as those above, apo E is considered to be a relatively poor predictor of CAD, especially when compared to other established and emerging clinical variables.(8) In one study, apo E polymorphism was responsible for only 7% of the interindividual variation in total cholesterol (TC) and low-density lipoprotein (LDL) levels.(9) Apo E was not identified as one of the important “emerging risk factors” in the most recent Adult Treatment Panel (ATP III) recommendations from the National Cholesterol Education Program. (10)

Apo E has also 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 suggest that patients with an apo e4 allele may respond better to diet-modification strategies.(11, 12) 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. (12, 13) At present, it is unclear how this type of information will change clinical management. Dietary modifications are a universal recommendation for those with elevated cholesterol or LDL levels, and statin drugs are the overwhelmingly preferred agents for lipid-lowering therapy. It is unlikely that a clinician will choose alternative therapies, even in the presence of an Apo E phenotype that indicates diminished response.

In summary, the evidence suggests that apo E is not clinically useful in providing additional information on risk for CAD when compared with other established and emerging risk factors. Moreover, improved ability to predict risk and/or treatment response does not by itself result in better health outcomes.(14) To improve outcomes, clinicians must have the tools to translate this information into clinical practice. This requires guidelines that incorporate new risk factors into existing risk prediction models and that have been demonstrated to classify patients into risk categories with greater accuracy. Predictive models also need to be accompanied by treatment guidelines that target interventions toward patients who will get the most benefit. As a tool for drug selection, a similar situation exists. Apo E phenotype may be a predictor of response to statins and may allow clinicians to better gauge an individual's chance of successful treatment. However, to improve health outcomes, clinicians must have the tools to translate specific apo E phenotypes into clinical decision making regarding drug selection.

2005 Update

A literature search was performed for the period of 2003 through June 2005. No published studies were found that would prompt reconsideration of the policy statement, which remains unchanged.

2006–2007 Update

A literature search was formed for the period of July 2005 through December 2006. During this time, studies were published that continued to evaluate the predictive ability of apo E for cardiovascular events. These publications generally conclude that apo E is not a clinically important predictor of cardiovascular risk. (15) Other studies have examined the association of apo E with markers of inflammation, such as C-reactive protein levels (16) or interleukin-10 levels. (17) No published studies were found that would prompt reconsideration of the policy statement, which remains unchanged.

2008 Update

A literature search was completed for the period of January 2007 through March 2008. The majority of studies published during this period continued to evaluate the predictive ability of apo E polymorphisms. A smaller number of studies evaluate response to lipid lowering according by apo E genotype.

There were no large prospective cohort studies that evaluated the ability of apo E polymorphisms to predict future clinical events. The available studies were small to moderate-sized cross-sectional and case-control studies that often used lipid levels or other physiologic markers such as carotid intima-medial thickness (IMT) as surrogate

outcome measures. (18-21) These studies generally confirmed previous findings, i.e., that patients with the apo E*4 allele had higher LDL levels and a higher prevalence of CAD.

A meta-analysis published by Bennet and colleagues (22) summarized the evidence from 147 studies on the association of apo E genotypes with lipid levels and cardiac risk. 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 estimated that patients with the apo E*2 allele had LDL levels that were approximately 31% less compared to patients with the apo E*4 allele. Compared to patients with the apo E*3 allele, patients with apo E*2 had an approximately 20% decreased risk for coronary events (odds ratio [OR] 0.80, 95% CI: 0.70–0.90). Patients with the apo E*4 had an estimated 6% higher risk of coronary events, a result that was of marginal statistical significance (OR 1.06, 95% CI: 0.99–1.13).

One study examined differential response to statin therapy according to apo E genotype. Chiodini and colleagues (23) reanalyzed data from the GISSI study according to apo E genotype. GISSI was a randomized, controlled trial comparing pravastatin with placebo in 3,304 Italian patients with previous myocardial infarction. Patients with the apo E*4 allele treated with statins had a greater response to treatment as evidenced by lower overall mortality (1.85% vs. 5.28%, $p=0.023$), while there was no difference in mortality for patients who were not treated with statins (2.81% vs. 3.67%, $p=0.21$). This study corroborates results reported in previous studies, but does not provide evidence to suggest that changes in treatment should be made as a result of apo E genotype.

None of the studies reviewed provide adequate data to suggest that apo E genotype improves outcomes when used in clinical care. No published studies were found that would prompt reconsideration of the policy statement, which remains unchanged. This determination is considered investigational.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

84181	Protein; Western Blot, with interpretation and report, blood or other body fluid
84999	Unlisted chemistry procedure

Policy Guidelines

There is no specific code for apo E phenotyping or genotyping. For phenotyping, CPT code 84181 (Protein; Western blot) may be used.

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