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. This topic is discussed separately in policy No. 2.04.13.

Policy

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

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

Rationale

Apo E as a Predictor of Cardiovascular Disease

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)

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 carotid intima-media thickness. (3-6) These studies have generally shown a relationship between apo E and these surrogate outcomes. Other studies have suggested that carriers of apo e4 are more likely to develop signs of atherosclerosis independent of total and low-density lipoprotein (LDL) cholesterol levels. (7-9) Some larger observational studies have correlated apo E genotype with 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. (10) 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 coronary artery disease (CAD) was relatively small for all genotypes. The Atherosclerosis Risk in Communities (ARIC) study followed up 12,000 middle-aged individuals free of CAD at baseline for 10 years. (11) This study reported that the e3/2 genotype was associated with carotid artery atherosclerosis after controlling for other atherosclerotic risk factors. Volcik et al. reported that apo E polymorphisms were associated with LDL levels and carotid intima-media thickness, but were not predictive of incident CAD. (12)

A meta-analysis published by Bennet and colleagues (13) 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 e2 allele had LDL levels that were approximately 31% less compared to patients with the apo e4 allele. When compared to patients with the apo e3 allele, patients with apo e2 had an approximately 20% decreased risk for coronary events (odds ratio [OR] 0.80; 95% CI: 0.70–0.90). Patients with the apo e4 had an estimated 6% higher risk of coronary events that was of marginal statistical significance (OR 1.06; 95% CI: 0.99–1.13).

In summary, the evidence suggests that apo E genotype may be associated with lipid levels and CAD, but is probably not useful in providing additional clinically relevant information beyond established risk factors. Apo E is considered a relatively poor predictor of CAD, especially when compared to other established and emerging clinical variables, (14) and does not explain a large percent of the inter-individual variation in total cholesterol (TC) and LDL levels. (15) Moreover, apo E has not been incorporated into standardized cardiac risk assessment models and was not identified as one of the important “emerging risk factors” in the most recent Adult...
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 suggest that patients with an apo e4 allele may respond better to diet-modification strategies. (17, 18) 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. (18, 19)

Chiodini et al. (20) examined differential response to statin therapy according to apo E genotype, by reanalyzing 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 e4 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.

For the most recent 2009 policy update, additional published studies were identified that evaluated apo E genetic status as a predictor of response to lipid lowering therapy. Donnelly et al. (21) reported on 1,383 patients treated with statins from the Genetics of Diabetes Audit and Research in Tayside, Scotland (Go-DARTS) database. The researchers reported on the final LDL levels and percent of patients achieving target LDL according to apo E genetic status. LDL levels following treatment were lower for patients who were homozygous for apo e2 compared to patients homozygous for apo e4 (0.6 +/- 0.5 mmol/L vs. 1.7 +/- 0.3 mmol/L, p < 0.001). All patients who were homozygous for apo e2 reached their target LDL level, compared to 68% of patients homozygous for apo e4 (p < 0.001).

Vossen et al. (22) evaluated response to diet and statin therapy by apo E status in 981 patients with CAD who were enrolled in a cardiac rehabilitation program. These authors reported that patients with an apo e4 allele were more responsive to both diet and statin therapy than were patients with an apo e2 allele. The overall response to treatment was more dependent on baseline LDL levels than apo E genetic status, with 30%–47% of the variation in response to treatment explained by baseline LDL, compared to only 1% of the variation explained by apo E status.

This evidence indicates that apo E genotype may be a predictor of response to statins and may allow clinicians to better gauge an individual’s chance of successful treatment, although not all studies are consistent in reporting this relationship. 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.

None of the available evidence provides adequate data to establish that apo E genotype or phenotype improves outcomes when used in clinical care. No published studies were found that would prompt reconsideration of the policy statement, which remains unchanged.

References:


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