

Evidence Based Guideline

Apolipoprotein E Genotype or Phenotype in Cardiac Disease Risk Assessment

File Name: apolipoprotein_e_genotype_or_phenotype_in_cardiac_disease_risk_assessment
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Description of Procedure or Service

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 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.

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

Evidence Based Guideline for Apolipoprotein E Genotype or Phenotype in Cardiac Disease Risk Assessment

Determination of the apo E genotype or phenotype may not be appropriate as a cardiovascular risk factor.

Medical Evidence regarding Apolipoprotein E Genotype or Phenotype in Cardiac Disease Risk Assessment:

A large body of research has established a correlation between lipid levels and the underlying apolipoprotein E (apo E) genotype. Studies have suggested that carriers of apo eR are more likely to develop signs of atherosclerosis independent of total and low-density lipoprotein (LDL) cholesterol levels. While the evidence suggests that apo E genotype may be associated with lipid levels and CAD, it is probably not useful in providing additional clinically relevant information beyond established risk factors. Apo E is considered a rela-

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tively poor predictor of CAD, especially when compared to other established and emerging clinical variables, and does not explain a large percent of the inter-individual variation in total cholesterol and LDL levels. 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 Treatment Panel (ATP III) recommendations from the National Cholesterol Education Program.

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. 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.

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.

Benefits Application

Please refer to certificate for availability of benefit. This guideline relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore certificate language should be reviewed before applying the terms of the guideline.

Billing/Coding/Physician Documentation Information

This guideline 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 codes: no specific code

For phenotyping, CPT code 84181 may be used.

Scientific Background and Reference Sources

BCBSA Medical Policy Reference Manual [Electronic Version]. 2.04.25, 4/24/09

Eichner JE, Dunn ST, Perveen G et al. Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. *Am J Epidemiol* 2002; 155(6):487-95.

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Donnelly LA, Palmer CN, Whitley AL et al. Apolipoprotein E genotypes are associated with lipid-lowering responses to statin treatment in diabetes: a Go-DARTS study. *Pharmacogenet Genomics* 2008; 18(4):279-87.

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Vossen CY, Hoffmann MM, Hahmann H et al. Effect of Apo E genotype on lipid levels in patients with coronary heart disease during a 3-week inpatient rehabilitation program. Clin Pharmacol Ther 2008; 84(2):222-7.

Senior Medical Director review 9/2009

Policy Implementation/Update Information

10/26/09 New Evidence Based Guideline issued. Determination of the apo E genotype or phenotype may not be appropriate as a cardiovascular risk factor. Notification given 10/26/09. Effective date 2/02/10.
(adn)

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