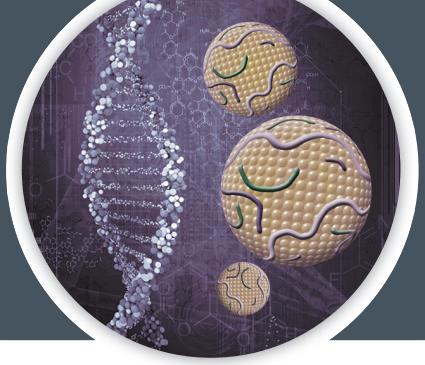
Apolipoprotein E

CPT Code 81401
Order Code C604
Sample Type EDTA Whole Blood
Tube Type Lavender Top



genetics

ApoE genotype can affect:
- Baseline levels of lipids
- Response to treatment with statins
- Response to low fat diet

ApoE functions include:
- A ligand for LDL receptors
- A contributor to lipoprotein catabolism
- A modulator of enzymes involved in lipoprotein metabolism[1]

Description

ApoE is an apolipoprotein found in blood that, in association with lipids, forms lipoproteins including very low-density lipoproteins (VLDL). ApoE plays multiple roles in the regulation of lipid and lipoprotein levels in the blood[2]. ApoE serves as a ligand for members of the low-density lipoprotein (LDL) receptor family, and is involved in the removal of lipoproteins from the circulation for excretion in the liver. ApoE is also involved in the formation of chylomicrons and VLDL, and affects the activity of other proteins and enzymes that are involved in lipid metabolism, such as hepatic lipase and lipoprotein lipase.

Polymorphisms in the ApoE gene result in three separate alleles encoding three distinct protein isoforms: e2, e3, and e4. There are 6 possible genotypes: e2/e2, e2/e3, e2/e4, e3/e3, e4/e3, and e4/e4. The allelic frequencies differ between ethnic groups, but in general the e3/e3 genotype is the most common, while e2/e4 is the least common[2].

Clinical Use

ApoE testing may be performed on individuals with premature coronary heart disease (CHD) or individuals who have high total cholesterol and triglyceride levels, but are unresponsive to treatment with medication and lifestyle changes.

Clinical Significance

- An individual's ApoE genotype may affect their lipid levels. The e2/e2 genotype is associated with increased triglycerides and reduced total cholesterol, while the e4/e3 and e4/e4 genotypes are associated with increased total cholesterol, triglycerides and LDL cholesterol[3].
- ApoE genotypes have varying impact on risk of cardiovascular disease. Carriers of an e4 allele are at 42% higher risk for CHD[4].
- The ApoE genotype can affect an individual's response to lifestyle modifications. In those with the e2/e2 or e2/e3 genotype, extremely low fat diets can increase small dense LDL levels, and therefore these individuals should have moderate fat restriction[5]. Individuals with the e4/e3 or e4/e4 genotype, on the other hand, respond well to very low fat dietary restrictions[6].
- Responsiveness to treatment with statins is also affected by the ApoE genotype. Individuals with the e2/e2 or e2/e3 genotype respond well to statins[7], while statins are less effective in individuals with the e4/e3 or e4/e4 genotype[8].

Sample Type

The ApoE test requires **one** EDTA whole blood sample. If performing other tests that require an EDTA whole blood sample, they should be collected in a separate lavender top tube.

Test Frequency

ApoE is a genetic test and therefore should only be performed **once** on an individual.

Commercial Insurance or Medicare Coverage

Coverage guidelines, also known as NCD (National Coverage Determination) or LCD (Local Coverage Determination) for reimbursement have been established and Medicare (CGS) will not reimburse for the ApoE test. Limited information has been posted by the majority of the larger Carriers (Aetna, United HealthCare, Cigna, Blues). Medical necessity and specificity of diagnosis should be provided when ordering this test.

Understanding Medical Necessity

The following ICD-9 codes for ApoE are listed as a convenience for the ordering physician. The ordering physician should report the diagnosis code that best describes the reason for performing the test and provide the 4th and 5th ICD-9 digit as appropriate.

Diagnosis	Diagnosis Code
Pure Hypercholesterolemia	272.0
Mixed Hyperlipidemia	272.2
Unspec. Hyperlipidemia	272.4
Unspec. Acquired Hypothyroidism	244.9
Benign Essential Hypertension	401.1
Unspecified Essential Hypertension	401.9
Abnormal Chemistry	790.6

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Treatment Considerations

These treatment considerations are for educational purposes only. Specific treatment plans should be provided and reviewed by the treating practitioner.

Genotype	Population Frequency	Interpretation†	Treatment
*e2/e2	1%	Approximately 5% of the people with the ApoE *e2/e2 genotype develop type III hyperlipoproteinemia, which is a rare inherited disorder characterized by increased cholesterol and triglyceride levels, the presence of beta-VLDL, xanthomas, and premature vascular disease.	• Statin therapy[7] (▼LDL-C) • Moderate alcohol intake (▼LDL-C ▲HDL-C) • Moderate (35%) fat diet if elevated triglycerides[5]
*e2/e3	10%	This genotype is associated with lower LDL-C levels and lower risk of coronary heart disease compared to those with the *e3/e3 genotype.	
*e2/e4	2%	This genotype is associated with normal lipid metabolism and low cardiovascular disease risk. However, there is some association of this genotype with type III hyperlipoproteinemia.	• Normal dietary modifications
*e3/e3	62%	This genotype is associated with normal lipid metabolism and low cardiovascular disease risk.	
*e4/e3	20%	These genotypes are associated with a predisposition to elevated total cholesterol levels and slightly elevated LDL-C levels compared to those with the *e3/e3 genotype. Additionally, these genotypes are associated with an increased risk of metabolic syndrome and atherosclerosis along with a slightly higher risk of CHD when consuming a diet high in saturated fat.	• Statin therapy[8] (Limited ▼LDL-C) • Low alcohol intake • Very low fat diet (20%) if elevated LDL-C[6] (▼LDL-C ▼Triglycerides ▼sdLDL)
*e4/e4	5%		

† *Relative risk and interpretations reported for each genotype are associated with cardiovascular risk only. The interpretations should not be used to determine the relative risk of other diseases.*

References

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3. Schaefer EJ et al. Effect of gender and menopausal status on the association of apolipoprotein E phenotype with plasma lipoprotein levels. Results from the Framingham Offspring Study. *Arterioscler Thromb Vasc Biol*. 1994; 14: 1105-1113.
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5. Moreno J et al. The effect of dietary fat on LDL size is influenced by apolipoprotein E genotype in healthy subjects. *J Nutr*. 2004; 134: 2517-2522.
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8. Nestel P et al. A comparative study of the efficacy of simvastatin and gemfibrozil in combined hyperlipoproteinemia: Prediction of response by baseline lipids, apo E genotype, lipoprotein(a) and insulin. *Atherosclerosis*. 1997; 129: 231-239.

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