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

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. 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.

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.
• ApoE genotypes have varying impact on risk of cardiovascular disease. Carriers of an e4 allele are at 42% higher risk for CHD.

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-10 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.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Diagnosis Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism, Unspecified</td>
<td>E03.9</td>
</tr>
<tr>
<td>Pure Hypercholesterolemia</td>
<td>E78.0</td>
</tr>
<tr>
<td>Mixed Hyperlipidemia</td>
<td>E78.2</td>
</tr>
<tr>
<td>Other Hyperlipidemia</td>
<td>E78.4</td>
</tr>
<tr>
<td>Hyperlipidemia, Unspecified</td>
<td>E78.5</td>
</tr>
<tr>
<td>Hyperuricemia without Signs of Inflammatory Arthritis and Tophaceous Disease</td>
<td>E79.0</td>
</tr>
<tr>
<td>Essential (primary) Hypertension</td>
<td>I10</td>
</tr>
</tbody>
</table>
### Treatment Considerations

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

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Population Frequency</th>
<th>Interpretation**</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| *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 (\(\downarrow\)LDL-C)  
• Moderate alcohol intake (\(\downarrow\)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. | • Statin therapy\(^6\) (Limited ▼ LDL-C)  
• Low alcohol intake |
| *e4/e4       | 5%                   | 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. | • Very low fat diet (20%) if elevated LDL-C\(^7\)  
\(\downarrow\)LDL-C ▲ Triglycerides ▼ sdLDL |

**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