APOE Genotyping for Alzheimer Disease

The UNCH Molecular genetics laboratory performs *APOE* Genotyping via TaqMan™ allelic discrimination assays for detection of the *APOE* e2, e3, and e4 alleles.

Biology of the disease:
Apolipoprotein E (apoE) is important for lipid metabolism in the peripheral circulation and the brain and for clearance of amyloid-beta from the brain. Variation in the *APOE* gene is associated with three major isoforms (e2, e3 and e4). The *APOE* e3 allele is the normal allele, with the e2 and e4 variant alleles encoding common isoforms that have been associated with increased risk of several conditions. The *APOE* e4 allele is associated with increased risk for the common form of Alzheimer disease, which typically has onset after age 65, and with an increase in plasma LDL cholesterol. The *APOE* e2 allele is associated with defective binding to the LDL receptor and an increase in plasma apoE, triglycerides, and total cholesterol. *APOE* e2 homozygotes are at increased risk of developing type III hyperlipidemia. In addition, the *APOE* e2 allele is associated with decreased risk of developing Alzheimer disease.

Alzheimer patients who are homozygous for the *APOE* ε4 allele are at a greater risk of developing amyloid related imaging abnormalities (ARIA) than heterozygotes and non-carriers when undergoing therapy with monoclonal antibodies against aggregated beta amyloid such as Leqembi® (lecanemab-irmb). Alzheimer patients who plan to undergo Leqembi® therapy are recommended by the FDA to be genotyped for APOE e4 status to inform the risk of developing ARIA.

Clinical Indications for Testing: Patients with Alzheimer disease being considered for treatment with monoclonal antibodies against aggregated beta amyloid such as Leqembi® (lecanemab-irmb). Testing can also be performed to predict risk of developing late-onset Alzheimer disease. Finally, testing can be performed to predict risk of developing type III hyperlipidemia or to identify familial predisposition in patients with hyperlipidemia.

Laboratory Testing for *APOE* alleles: The preferred sample is 3 mL of blood in an ACD (yellow top) or EDTA (lavender-top), which may be refrigerated up to 48 hours. *APOE* genotyping for the e2, e3 and e4 isoforms is determined by TaqMan allelic discrimination assays to detect the APOE gene single nucleotide polymorphisms rs429358 (NM_000041.4: c.388T>C, p.Cys130Arg) and rs7412 (NM_000041.4: c.526C>T, p.Arg176Cys). This assay does not detect other sequence variants within the APOE gene.

References:

1. Roberts, et al. Genetic risk assessment for adult children of people with Alzheimer's Disease: The Risk Evaluation and Education for Alzheimer's Disease (REVEAL) study. J Geriatr Psychiatry Neurol 2005; 18:250-255.
2. Yamazaki, et al. Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. Nat Rev Neurol 2019; 15:501–518.
3. Withington and Turner. Amyloid-Related Imaging Abnormalities with Anti-amyloid Antibodies for the Treatment of Dementia Due to Alzheimer's Disease. Front Neurol 2022; 13:862369.
4. Leqembi (lecanemab-irmb). FDA Package insert. Eisai Inc.; 2023.
5. Rasmussen and Frikke-Schmidt. The current state of apolipoprotein E in dyslipidemia. Current Opinion in Lipidology, Epub Ahead of Print, Dec 7, 2023.

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