Apolipoprotein E (ApoE) - A Genetic Risk Marker for Alzheimer's Disease

PrecivityAD™

What is Apolipoprotein E (ApoE)?

The Apolipoprotein E (ApoE) gene exists as three main forms – ApoE2, ApoE3 and ApoE4. An individual inherits one copy of the ApoE gene from his/her mother and second copy of the ApoE gene from his/her father. This gives rise to the common ApoE genotypes found in people: ApoE2/ApoE2, ApoE2/ApoE3, ApoE2/ApoE4, ApoE3/ApoE3, ApoE3/ApoE4, and ApoE4/ApoE4. Genetically, the ApoE4 form of the ApoE gene is the strongest risk factor for Alzheimer's disease[1-2].

Individuals with one copy of ApoE4 have a threefold higher risk, while those who inherit two copies of ApoE4 have an eight to 12-fold greater risk of developing Alzheimer's dementia compared to ApoE4 non-carriers. ApoE2 individuals have reduced risk for developing late-onset Alzheimer's[1-5].

ApoE forms differentially influence the accumulation of amyloid-β (Aβ) plaques and tau neurofibrillary tangles in the brain, the pathological hallmarks of Alzheimer's disease. ApoE4 genotype is a significant risk factor for brain amyloid accumulation[5-6]. **It is important to note that ApoE4 is neither necessary nor sufficient for the development of Alzheimer's disease so that ApoE genetic information alone cannot be used for the diagnosis of Alzheimer's disease.** A person's overall risk for developing Alzheimer's disease is dependent upon on many genetic, biochemical, epigenetic, and environmental factors.

Can the ApoE genotyping test diagnose Alzheimer's disease in an individual with cognitive impairment?

No. ApoE is a susceptibility gene, not a deterministic one. In people with symptoms, only about 60% of those with late-onset Alzheimer's disease will carry an ApoE4 gene. ApoE4 is neither necessary nor sufficient for the development of Alzheimer's disease. Thus, ApoE genetic information alone cannot be used to identify the presence of Alzheimer's disease. Further, the use of ApoE analysis alone to predict Alzheimer's disease is not currently recommended by the American College of Medical Genetics due to the poor predictive value of only measuring ApoE.

Why does the PrecivityAD™ test have ApoE proteotype (equivalent to ApoE genotype) included as a measure along with Aβ42/40 ratio to determine Alzheimer's pathology?

The PrecivityAD™ test measures the concentrations of amyloid beta 42 and 40 (Aβ42 and Aβ40), as well as the presence of apolipoprotein E (ApoE) isoforms in the blood. The test indicates if an individual is likely to have amyloid plaques in the brain, a hallmark of Alzheimer's disease. ApoE4 genotype is a significant risk factor for amyloid accumulation in the brain and Alzheimer's disease, and its incorporation into C_2N's proprietary algorithm increases the accuracy of the test. Using data from 686 patients, an algorithm based on plasma Aβ42/40 ratio, ApoE genotype, and patient age improved the accuracy of the prediction between amyloid PET positive versus amyloid PET negative patients, as compared to using the Aβ42/40 ratio alone.

What should I do before and after getting the PrecivityAD™ test or Precivity-ApoE™ test?

Only your health care provider can order the PrecivityAD™ test or Precivity-ApoE™ test. In view of the increased risk of Alzheimer's disease associated with the ApoE4 genotype, you and your family members might find it concerning if you were to receive an ApoE4 positive test result. Your physician can talk to you about genetic testing and how to obtain genetic counseling. General information and resources on genetic testing can be found at https://precivityad.com/resources. Further, C_2N recommends consultation with a medical geneticist or genetic counselor and /or a physician after the test is completed so that you understand the implications of the test results for you and your family members.

What are the limitations of the ApoE Proteotyping test?

C_2N's ApoE proteotyping test detects only peptides from ApoE2, ApoE3 and ApoE4 proteins and does not detect peptides from rare ApoE proteoforms (e.g. ApoE1, ApoE5, and ApoE7). False positive or false negative blood test results may occur. A diagnosis of Alzheimer's disease as the underlying cause for an individual's clinical presentation should always be considered in the context of that individual's medical and family history and physical, neurological examination and biomarker evaluations.

References: 1. Corder EH, Saunders AM, Strittmatter WJ, Schmechel DE, Gaskell PC, Small GW, et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science. 1993; 261:921–3. **2.** Saunders AM, Strittmatter WJ, Schmechel D, George-Hyslop PH, Pericak-Vance MA, Joo SH, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology. 1993; 43:1467–72 **3.** Verghese PB, Castellano JM, and Holtzman DM, Roles of Apolipoprotein E in Alzheimer's disease and Other Neurological Disorders. Lancet Neurol. 2011 March; 10(3): 241–252. **4.** Roses AD. Apolipoprotein E alleles as risk factors in Alzheimer's disease. Annu Rev ed. 1996; 47:387–400 **5.** Kim J, Basak JM, Holtzman DM. The role of apolipoprotein E in Alzheimer's disease. Neuron. 2009; 63:287–303 **6.** Liu CC1, Liu CC, Kanekiyo T, Xu H, Bu G.Apolipoprotein E and Alzheimer's disease: risk, mechanisms and therapy. Nat Rev Neurol. 2013 Feb;9(2):106-18. doi: 10.1038/nrneurol.2012.263. Epub 2013 Jan 8.