Amyloid Deposition Correlates With Age, Risk of Dementia, and ApoE4 Status

Risk of MCI or dementia varies with the amount of amyloid deposition:

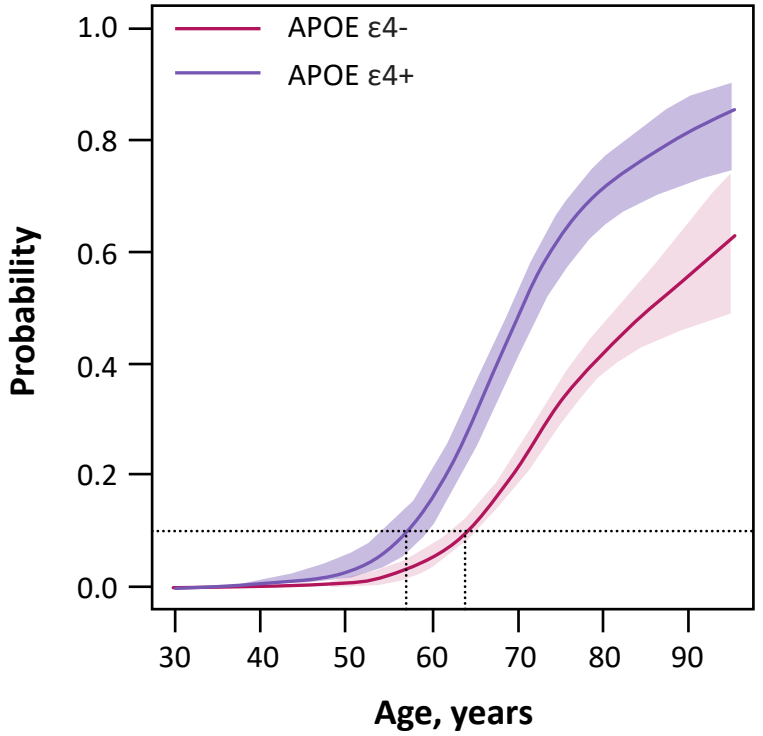
- The risk of MCI or dementia over 5 years in cognitively healthy older adults (mean age = 72): 5% if negative amyloid PET vs 25% if positive[1]
- Reaching an amyloid tipping point (SUVR 1.2) is strongly correlated ($P < 0.0001$) with the age of AD symptom onset[2]

The prevalence of amyloid positivity in people without cognitive impairment increases with age[3]

Age	Percent
50-59	2.7%
60-69	18.3%
70-79	32.1%
80-89	41.3%

ApoE4 Status

- Most people with AD and proven brain amyloidosis have 1 or 2 copies of the ApoE4 gene[4]



Probability of Amyloid Positron Emission Tomography (PET) Positivity vs Age by APOE ε4 Genotype. The data are estimated from a logistic model.[5]

MCI, mild cognitive impairment; SUVR, standardized uptake value ratio; CL, centiloid.

1. van der Kall LM et al. *Neurology.* 2021;96:e662-e670; 2. Schindler SE et al. *Neurology.* 2021;97:e1823-e1834; 3. Roberts RO et al. *JAMA Neurol.* 2018;75:970-979; 4. Cummings J et al. *J Prev Alzheimers Dis.* 2022;9:221-230; 5. Jack CR et al. *JAMA Neurol.* 2015;72:511-519.

Risk for Alzheimer's Disease (AD) Increases With Age and ApoE4 Genotype Carriage

- The lifetime risk for developing AD for a patient who is homozygotic for the ApoE4 is 91%, and the lifetime risk for a patient who is heterozygotic for ApoE4 is 47%[1,2]
- ApoE4 carrier status is highly predictive of AD; an ApoE4 carrier who is symptomatic has a 94% to 97% chance of having AD[2,3]
- In one study, the specificity of clinical diagnosis of AD improved from 55% to 84% when ApoE4 carrier status was added to the model; the sensitivity decreased[2,4]

5-Year Cumulative Incidence of Dementia, (percent [CI 95%])[5]

Age 60-64	
0 E4	0.16 (0.04, 0.62)
1 E4	0.65 (0.31, 1.36)
2 E4	2.94 (0.95, 8.89)
Age 65-69	
0 E4	0.45 (0.28, 0.72)
1 E4	1.00 (0.56, 1.76)
2 E4	**4.87** (2.45, 9.56)
Age 70-75	
0 E4	**1.44** (1.03, 2.02)
1 E4	**4.47** (2.75, 7.22)
2 E4	**11.12** (6.68, 18.20)

Bolded results are statistically significant

CI, confidence interval.

1. Corder EH et al. *Science.* 1993;261:921-923; 2. Sabbagh MN et al. *Neurol Ther.* 2017; 6:83-95; 3. Relkin NR et al. *Ann N Y Acad Sci.* 1996;802:149-176;
4. Mayeux R et al. *N Engl J Med.* 1998;338:506-511;. 5. Qian J et al. *PLOS Medicine.* 2017;14:e1002254.

Society Guidelines and Position Statements Recommend Against ApoE Predictive Testing

American College of Medical Genetics and National Society of Genetic Counselors (2011)[1]	"Genetic testing for susceptibility loci (eg, ApoE) is not clinically recommended due to limited clinical utility and poor predictive value. If a patient wishes to pursue testing despite genetic counseling and recommendations to the contrary, testing may be considered at the clinician's discretion."
American College of Medical Genetics and Genomics lists genetic testing for ApoE alleles as 1 of 5 recommendations in the Choosing Wisely initiative (2015)[2]	"Don't order ApoE genetic testing as a predictive test for Alzheimer's disease."
American Academy of Neurology (2001)[3]	"Routine use of ApoE genotyping in patients with suspected AD is not recommended at this time."

1. Goldman JS et al. *Genet Med.* 2011;13:597-605; 2. American College of Medical Genetics and Genomics. July 10, 2015. Updated July 1, 2021. Accessed March 5, 2023. https://www.choosingwisely.org/societies/american-college-of-medical-genetics-and-genomics/; 3. Knopman DS et al. *Neurology.* 2001;56:1143-1153.

Studies Indicate Minimal Psychological Distress After Receiving ApoE and Amyloid Test Results

62% of adults aged 65 to 85 understood that elevated amyloid conferred an increased but uncertain risk of developing AD[1]

Amyloid positivity disclosure (n = 105) was associated with non-clinically significant psychological changes[2]

REVEAL and SOKRATES II clinical trial results support the premise that disclosing ApoE results to cognitively unimpaired adults does not cause adverse psychological outcomes[3,4]

Disclosing ApoE results to patients with MCI did not increase anxiety or depression and may provide psychological benefits[5]

Worries about stigma were more common in people with elevated brain amyloid than among ApoE4 carriers. Amyloid indicates a pathologic change. Carrier status alone does not indicate pathology[6]

MCI, mild cognitive impairment.

1. Mozersky J et al. *JAMA Neurol.* 2018;75:44-50; 2. Caprioglio C et al. *JAMA Netw Open.* 2023;6:e2250921; 3. Largent EA et al. *J Alzheimers Dis.* 2021;84:1015-1028; 4. Christensen KD et al. *Ann Intern Med.* 2016;164:155-163; 5. Christensen KD et al. *Alzheimers Dement (N Y).* 2020;6:e12002; 6. Largent EA et al. *J Law Biosci.* 2021;8:lsab004.

Expert Insights: Liz (Asymptomatic)

- Could consider ordering the test if Liz
  - Recognizes that genetic testing is generally not covered by insurance (self-pay)
  - Truly wishes to know her ApoE genotype to better ascertain her risk of AD
- However, according to published guidelines, the **best answer is C** – no, because she is asymptomatic
- Positive amyloid PET scan confers higher risk of cognitive decline compared with a negative amyloid PET scan
- Lifestyle modifications may lower risk of impending MCI and AD
  - Diet, exercise, etc.

PET, positron emission tomography; MCI, mild cognitive impairment.