Using Biomarkers to Determine Eligibility for Amyloid-Reducing Monoclonal Antibodies

Clinical phenotype:
- 6 million people with AD
- 15 million people with MCI

If indicative of MCI or early AD

Potential candidates for amyloid-reducing monoclonal antibodies:
- 3 million people with mild AD
- 15 million people with MCI

CSF Aβ

or

Amyloid PET

Amyloid burden:
- 2 million people with mild AD likely have an amyloid burden
- 3 million people with MCI likely have an amyloid burden

If proof of amyloid burden

Meet FDA eligibility for amyloid-reducing monoclonal antibodies

AD, Alzheimer's disease; MCI, mild cognitive impairment; CSF, cerebral spinal fluid; PET, positron emission tomography; FDA, Food and Drug Administration.

Fleming WK et al. *JAMA Health Forum.* 2020;1:e201148.

ARIA Describes a Spectrum of MRI Findings Observed in Patients Receiving Anti-amyloid Monoclonal Antibodies to Treat MCI and Early AD[1]

ARIA-E

- Edema and effusion
- Factors increasing ARIA-E risk
  - Dose
  - Initial treatment period
  - ApoE4 carrier status
  - 4 or more microhemorrhages at baseline[2]

ARIA-H

- Superficial siderosis and microhemorrhages
- Factors increasing ARIA-H risk
  - Age
  - Cerebrovascular disease[2]

ARIA Symptoms:

- Headaches, loss of coordination, dizziness, visual disturbances, nausea, seizures, disorientation, vomiting, fatigue[3]
- Most ARIA events are asymptomatic (74%)[3]

ARIA Risk:

Individuals who are homozygous ApoE4 genotype are at greater risk of ARIA-E occurrence and may have a higher likelihood for ARIA-E recurrence, ARIA-E severity, and ARIA-E-related serious adverse events[4]

ARIA, amyloid-related imaging abnormalities; MCI, mild cognitive impairment.

1. Roytman M et al. *AJR Am J Roentgenol.* 2023;220:562-574; 2. Withington CG et al. *Front Neurol.* 2022;13:862369; 3. Cummings J et al. *J Prev Alzheimers Dis.* 2021;8:398-410; 4. Cummings J et al. *J Prev Alzheimers Dis.* 2022;9:221-230.

ARIA-E and ARIA-H Incidence in Anti-Aβ Clinical Trials Indicates Much Higher Frequency of ARIA in ApoE4 Carriers

	Aducanumab (10 mg/kg monthly)[1] Phase 3 results, EMERGE, ENGAGE	**Lecanemab** (10 mg/kg every 2 weeks)[2] Phase 3 results, CLARITY AD	**Donanemab** (1400 mg monthly)[3] Phase 2 results, TRAILBLAZER
ARIA-E or ARIA-H	425 (41.3%)	193 (21.5%)	51 (38.9%)
ARIA-E	362 (35.2%)	113 (12.6%)	36 (27.5%)
ApoE4 noncarrier	72/355 (20.3%)	15/278 (5.4%)	4/35 (11.4%)
ApoE3E4	185/515 (35.9%)	52/479 (10.9%)	21/68 (30.9%)
ApoE4E4	105/159 (66.0%)	46/141 (32.6%)	11/25 (44.0%)
ARIA-H	348 (33.8%)	155 (17.3%)	40 (30.5%)
ApoE4 noncarrier	66/355 (18.6%)	33/278 (11.9%)	Not reported
ApoE3E4	282/674 (41.8%) (combined)	67/479 (14%)	Not reported
ApoE4E4		55/141 (39%)	Not reported

1. Salloway S et al. *JAMA Neurology* 2022;79:13-21; 2. Van Dyck CH et al. *New Engl J Med.* 2023; 388:9-21; 3. Mintun MA et al. *N Engl J Med.* 2021; 384:1691-1704.

Expert Insights: Jack (MCI)

- Amnestic MCI by examination
  - Confirmed by neuropsychologic testing
  - Normal MRI for age (diffuse cortical atrophy and white matter changes)
- Possible CNS amyloid deposition, suggesting MCI due to AD pathology
- Recent guidelines suggest that individuals with early AD (either MCI or mild dementia) who seek an FDA-approved anti-amyloid therapy should have ApoE genotyping in order to better ascertain the risk of adverse effects (ARIA-E and ARIA-H)
- Informed consent
  - Risk of ARIA with FDA-approved anti-amyloid therapies approximately doubles with every ApoE4 allele
- A thorough discussion of the risks, benefits, and costs of treatment leads to the **best answer, B** – possibly, it depends on how many ApoE4 alleles he carries
  - ApoE4 carrier status is not a contraindication to treatment

MCI, mild cognitive impairment; MRI, magnetic resonance imaging; CNS, central nervous system; FDA, Food and Drug Administration.