Case Study: Marcie

68-year-old White female, referred to a specialty memory clinic and is accompanied by her daughter

Chief complaint: "forgetfulness"

History of present illness:

- Mild memory impairment, word-finding difficulty, and some struggles with keeping track of her daily activities (per daughter).
- Decreased interest in social activities which she blames on new-onset sleep difficulties
- Drives daily with no traffic accidents or tickets in past two years

Past medical history:

- Hypercholesterolemia treated with atorvastatin; vitamin D deficiency; hypertension managed with lisinopril
- Hospitalized only for childbirth, denies any history of trauma, seizures, or other neurologic disorders

Social history:

- Denies smoking, alcohol, or drug misuse
- 14 years of formal education
- Voluntary retirement 6 months ago after 40 years as an administrative assistant

Family history:

- Marcie's mother was diagnosed with dementia, not otherwise specified at age 77, and her older sister was diagnosed with AD at age 74

Case Study: Marcie

Neuropsychological testing:

- Deficits in memory, language, visuospatial skills, and executive function.
- Mini-Mental State Examination (MMSE) score: 23 out of 30, with points subtracted for errors in orientation, memory and calculations

Lab tests:

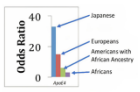
- Complete blood count, comprehensive metabolic panel, thyroid function tests, vitamin B12, and folate levels are all within normal limits

Imaging:

- MRI: mild generalized cortical atrophy, mild periventricular white matter changes, and mild-to-moderate hippocampal atrophy

Over 70 Genes or Loci Contributing to AD Have Been Identified in Non-Hispanic White Individuals, but Many Fewer in Other Ethnic Groups[1]

Cohort[2]	Genetic Ancestry	Number of haplotypes studied (gene blocks)	AD risk (ApoE4 odds ratio compared to ApoE3)
Puerto Rican	European	307	4.49
	African	67	1.26
African American	European	1341	3.05
	African	5387	2.34



ApoE4 is common in people of West African ancestry but does not meaningfully increase AD risk in this population.[4]

Most populations are admixed with genetic contributions from multiple ancestries. The ancestry of the chromosomal region around the ApoE gene impacts risk.[2]

A longitudinal prospective study following 4,606 people of African descent living in either the United States or Nigeria found that AD incidence was twice as high in Africans living in the United States compared with Nigeria.[5]

The Strong Heart Study found no evidence of neurodegenerative risk from ApoE4 in American Indians.[6]

1. Reitz C et al. *Nat Rev Neurol.* 2023;19:261–277; 2. Rajabli F et al. *PLoS Genet.* 2018;14:e1007791; 3. Rajabli F et al. *PLoS Genet.* 2022;18:e1009977 (CC by 4.0); 4. Norwitz NG et al. *Nutrients.* 2021;13:1362; 5. Hendrie HC et al. *JAMA.* 2001;285:739-747; 6. Suchy-Dicey A et al. *Alzheimer's & Dementia.* 2022;18:2518-2526.

Arguments for and Against ApoE Genotyping As Part of AD Diagnosis

Arguments For ApoE Genotyping

- Identify individuals in preclinical AD stages to facilitate earlier intervention and lifestyle modifications[1,2]
- Improve recruitment for AD prevention trials[3]
- Serve as an inclusion criteria or an enrichment strategy in AD prevention trials[4]
- Fulfill personal utility needs[5]
- Carries a low risk of psychological harm or decisional regret[2]

Arguments Against ApoE Genotyping

- Not predictive or diagnostic
- Clinical utility varies by population[4]
- Potential challenges obtaining long-term care, life and disability insurance[6]
- Not covered by most insurance companies[7]
- Potential for psychological harm[8]
- Family members may receive unwanted information about their carrier status or their potential future need to act as a caregiver[9]
- Potential for stigma and discrimination[9]

1. Sperling RA et al. *Nat Rev Neurol.* 2013;9:54-8; 2. Roberts JS et al. *Public Health Genomics.* 2017;20:36-45; 3. Langbaum JB et al. *Alzheimers Dement.* 2019;15:515-524; 4. Ryan MM et al. *Dis Assoc Disord.* 2021;35:141-147; 5. David SP et al. *Am Fam Physician.* 2018;97:600-602; 6. Joly Y et al. *Annu Rev Genomics Hum Genet.* 2020;21:491-507; 7. Arias JJ et al. *Genet Med.* 2021; 23:614-620; 8. Christensen KD et al. *Alzheimers Dement (N Y).* 2020;6:e12002; 9. Largent EA et al. *J Law Biosci.* 2021;8:lsab004.

Polling Question

Although ApoE testing is not supported by guidelines, the question of personal versus clinical utility clouds this issue. Would you order ApoE testing for your patients if they have well-reasoned arguments for requesting it?

A. No, because it is not supported by guidelines
B. No, because I do not believe patients understand the impact of genetic testing on their financial and family lives
C. Yes, I believe in shared decision making and if they have considered the risks and benefits of testing, I would order it
D. Maybe, I am not comfortable ordering the test, but would advise them to use direct-to-consumer testing and we would discuss the results

Discussion: Lifestyle Factors and AD Risk

- Suppose Marcie is an ApoE4/E4 carrier. She has a family history of AD and is symptomatic. What advice do you offer her to slow the progression of AD? (LO1, LO3)
- Since she is already symptomatic, is it too late?

Modifying 12 Risk Factors Associated With Dementia May Prevent or Delay Up to 40% Of Dementias[1]

- Minimize diabetes
- Treat hypertension
- Prevent head injury
- Stop smoking
- Reduce air pollution
- Reduce midlife obesity

→ Reduce neuropathological damage

- Exercise regularly
- Reduce depression risk
- Avoid excessive alcohol

- Treat hearing impairment
- Maintain frequent social contact
- Attain a high level of education

→ Increase and maintain cognitive reserve

→ Prevent Dementia

Middle-aged adults should aim for a systolic blood pressure of 130 mm Hg or lower[2]

1. Livingston G et al. *The Lancet.* 2020;396:413-446; 2. Abell JG et al. *Eur Heart J.* 2018;39:3119-25.

Healthy Lifestyle Practices Slow Cognitive Decline, Even in ApoE4 Carriers

- 10-year population-based, prospective study
- Nearly 30,000 adults aged 60 or older with normal cognition
- Investigated the association between 6 healthy lifestyle practices and cognitive decline
- Regardless of ApoE status, following 2 or more healthy lifestyle guidelines was associated with a slower cognitive decline
- Diet had the strongest effect, followed by cognitive activity, physical exercise, and social contact

Jia J et al. *BMJ.* 2023;380:e072691

Q1. Alzheimer's disease is multifactorial and polygenic

Which of the following statements regarding Alzheimer's disease inheritance is correct?

A. Most early-onset Alzheimer's disease is explained by autosomal dominant deterministic genes.

B. Most late-onset Alzheimer's disease is caused by dominantly inherited genetic mutations in the amyloid pathway.

C. Most cases of Alzheimer's disease occur sporadically rather than through dominant inheritance, regardless of the age of onset.

D. The heritability of late-onset Alzheimer's disease is estimated to be around 30%.

The correct answer is:
C: Most cases of Alzheimer's disease occur sporadically rather than through dominant inheritance, regardless of the age of onset.

Alzheimer's disease is a complex and multifactorial neurodegenerative disorder that affects millions of people worldwide. The exact cause of Alzheimer's disease is not yet fully understood, but genetic and environmental factors are known to play important roles in its development.[1,2]

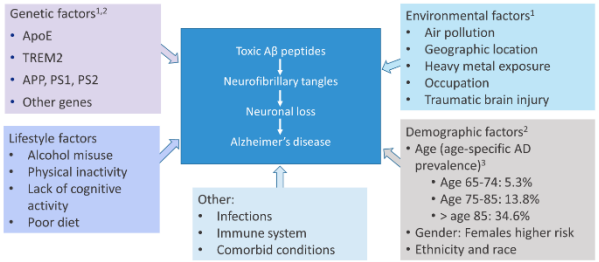
The vast majority of Alzheimer's cases are sporadic and of late-onset (after the age of 60 to 65). Dominantly inherited mutations in the amyloid pathway account for less than 1% of Alzheimer's disease cases. These cases usually present before the age of 60 to 65.[1]

Late-onset Alzheimer's disease (LOAD) heritability is high, ranging from 58 to 79%. While LOAD etiology is multifactorial and driven by a combination of genetic and environmental factors, numerous genes have been implicated in contributing to LOAD.[3]

ApoE2 (decreases risk), ApoE4 (increases risk), and ApoE3, which is frequently used as a reference, are the most common ApoE alleles.[4] Over 38 other AD-risk/protective genes have been identified.[5]

1. Armstrong R. *Folia Neuropathol.* 2019;57(2):87-105; 2. Kamboh MI. *Neurotherapeutics.* 2022 Jan;19(1):152-172; 3. Gatz M et al. *Arch Gen Psychiatry.* 2006;63(2):168-74; 4. Corder EH et al. *Science.* 1993;261(5123):921-3; 5. Uffelmann E et al. *Sci Rep.* 2023;13:4219;

Alzheimer's Disease Risk is Multifactorial



ApoE, apolipoprotein E; TREM2, Triggering receptor expressed on myeloid cells 2; APP, amyloid precursor protein; PS1, presenilin 1; PS2, presenilin 2.
1. Armstrong R. *Folia Neuropathol.* 2019;57(2):87-105; 2. Kamboh MI. *Neurotherapeutics.* 2022 Jan;19(1):152-172; 3. 2021 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2021 Mar;17(3):327-406.

Points to Consider When Communicating Genetic Risk to Patients

- Use plain language instead of medical jargon
- Use absolute risks to present data, not relative risks
- Present data using frequencies, not percentages
- Use visual aids to present quantitative risks, with the pictograph icon array as an especially valuable graphical tool
- Pay attention to time intervals when presenting risk, for example, lifetime risk vs. five-year risk
- Avoid giving unnecessary details that cloud decision-making
- Be aware that the order information is presented can affect risk perceptions
- Consider making a summary table for risks and benefits
- Recognize that comparative risk information (e.g., what the average person's risk is) is persuasive and not just informative
- Recognize that many patients lack the health literacy and numeracy skills required to fully grasp risk information
- Acknowledge that cognitive biases influence test findings interpretation

Fagerlin A et al. *J Natl Cancer Inst.* 2011;103(19):1436-43; Langlois CM et al. *Alzheimer's Dement.* 2019;5:705-716;

Learner will be asked to read the scenario and respond to the polling question before viewing the video clip of the expert presenting the following few slides

Scenario 1

Liz, 58, is a self-proclaimed anti-aging warrior who is passionate about researching anti-aging medical options. At a recent medical appointment, Liz expressed her concerns about brain fog, which she admits is most likely due to hormonal changes and environmental stressors. Seeking answers, Liz decided to participate in a clinical trial focused on investigating amyloid in the brains of cognitively healthy people.

The clinical trial was prematurely terminated due to production issues with the radiotracer. The participants were initially not informed of the results. Liz has since learned that her amyloid PET scan was positive.

Liz's maternal grandmother was diagnosed with dementia, and Liz has become increasingly concerned about her own risk of developing AD. She requests a "full workup" to assess her overall risk and explore potential preventative options. Liz has no biological children and is concerned about who will care for her if she develops AD later in life.

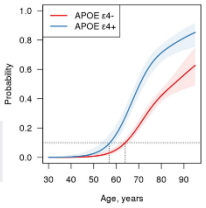
Polling Question
As part of a "full workup," would you order ApoE genotype testing in this case?

A. Yes, because her ApoE genotype would help determine her risk of developing AD in the future
B. Yes, because ApoE genotyping is recommended for people with positive amyloid-PET scans, regardless of symptoms
C. No, because Liz is asymptomatic and does not meet ApoE genotype testing guidelines
D. No, because knowing ApoE genotyping results may cause psychological harm

DRAFT – UNEDITED

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]



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

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;72:511-9.

DRAFT – UNEDITED

Graph will be recreated

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, minimal 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;164:155-63. 5. Christensen KD et al. *Alzheimers Dement (N Y).* 2020;6:e12002; 6. Largent EA et al. *J Law Biosci.* 2021;8:lsab004.

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Scenario 2

Jack, a 68-year-old lawyer, was referred to the memory disorders clinic due to concerns about his cognitive function. He reports experiencing difficulties such as missing appointments, forgetting names in conversations, and misplacing items. Initially, Jack attributed these symptoms to normal aging but realized that even with careful note-taking, he had missed several important appointments, including a meeting with a significant client. Jack lives alone and manages his household without assistance.

During a recent meeting, Jack repeatedly asked the same question to the client without recognizing his repetition. This pattern raised concerns among Jack's law partners, who informed him that he could only take on new clients once he underwent a medical evaluation.

Jack's PCP ordered an MRI and neuropsychologic testing, which revealed amnestic mild cognitive impairment (MCI). Consequently, Jack was referred to the memory disorders clinic for a comprehensive evaluation. Jack is eager to receive treatment promptly as he aims to continue working as a lawyer well into his 70s.

Polling:
Would knowing Jack's ApoE genotype affect your recommendations regarding treatment with an anti-amyloid monoclonal antibody?

A. Yes; if Jack is an ApoE4 carrier, he would not be a candidate for therapy because the risks would outweigh the potential benefits
B. Possibly; it depends on how many ApoE4 alleles he carries
C. No; I would start treatment regardless of Jack's ApoE4 carrier status, but I would monitor him closely

DRAFT – UNEDITED

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

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.
1. Roytman M et al. *AJR Am J Roentgenol.* 2021;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.

Learner will be asked to read the scenario and respond to the polling question before viewing the video clip of the expert presenting the following few slides

Scenario 3

Jan, age 72, is accompanied by her daughter Leah and son-in-law Mike for evaluation following referral by her PCP. Jan appears visibly anxious during the visit and denies having any physical or mental concerns. Leah discloses that Jan, a retired bookkeeper, has fallen victim to scams twice in the past year, resulting in substantial financial losses. This behavior is highly uncharacteristic of Jan, raising concerns about her cognitive function and vulnerability to exploitation.

Jan appears disheveled and has lost about 20 pounds. She was involved in an auto accident last month, resulting in the total loss of her car.

Leah also reveals that Jan has been having memory problems. She frequently forgets the names of her friends and distant relatives. Jan struggles to find the right words in conversations. This has had a significant impact on Jan's social life as well. She has been declining invitations to social events, stating a preference for staying home.

One particularly memorable incident occurred during a recent visit when Leah brought her two young daughters, ages 8 and 10. While Leah ran some errands, the girls were left in Jan's care. When Leah returned, she found her daughters standing outside on the front stoop. The girls claimed that their grandmother had forgotten they were there and had unintentionally locked them out.

Complete blood count, comprehensive metabolic panel, thyroid function tests, vitamin B12, and folate levels: all normal

MRI: mild generalized cortical atrophy, mild periventricular white matter changes, and mild-to-moderate hippocampal atrophy.

Neuropsychological testing: Mini-Mental State Examination (MMSE) score: 22 out of 30, with points subtracted for errors in memory, recall, construction, and calculations

CSF Amyloid beta 42 (Aβ42): 550 pg/mL

Polling:
Since Jan may be a candidate for treatment with an anti-amyloid monoclonal antibody, how would you approach ApoE genotype testing for ARIA risk stratification?
A. Assess Jan's decisional capacity to provide consent for testing
B. Seek consent for testing from Jan's daughter because Jan is cognitively impaired
C. Order ApoE genotype testing for Jan; consent is not required in the context of risk assessment prior to starting treatment

Using A Stepwise Approach to AD Diagnosis

AD Diagnosis is Typically Made 2-3 Years After Symptom Onset[1,2]

Medical History[3]	Aggregate Risk Analysis or CAIDE score[3,4]	Cognitive Testing[3]	Physical Exam and Lab Testing[3,5]	Potential Biomarkers[3,5,6]	Diagnostic Criteria[3]
• Symptoms involve 2 cognitive domains • Evidence of a longitudinal process • Informant information • Informant: IQCODE, AD8, AQ, GPCOG,	• Age • Family history • History of head injury • Education • Sex • Cardiovascular risk factors	• MMSE • MoCA • Mini-COG • SBT • SLUMS	• Evaluate comorbidities • Review medication • B12, TSH, MRI • MRI, if warranted	• Aβ or TAU CSF • Amyloid PET scan • Plasma amyloid • ApoE4 genotype testing	• IWG criteria

IQCODE, The Informant Questionnaire on Cognitive Decline in the Elderly; AQ, Alzheimer's Questionnaire; AD8, Ascertain Dementia 8-Item Informant Questionnaire; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; Mini-Cog, Mini-Cognitive Assessment Instrument; GPCOG, General Practitioner Assessment of Cognition, SBT, Short Blessed Test; SLUMS, Saint Louis University Mental Status
1. Balasa M et al. *Neurology.* 2011;76:1720–5; 2. Boise L et al. *Gerontologist.* 1999;39:457-64; 3. Sabbagh MN et al. *Neurol Ther.* 2017; 6 (Suppl 1):83-95; 4. Kivipelto M et al. *Lancet Neurol.* 2006;5:735-741; 5. Turner RS et al. *Front Neurol.* 2020;11:496; 6. Iaccarino L et al. *J Prev Alzheimers Dis* 2023.

A Clinician Has a Clinical and Ethical Responsibility to Accurately Assess the Decision-Making Capacity of a Patient[1]

Capacity[1]
- A person's ability to make a particular decision at a specific time or in a specific situation
- **Four decision-making abilities** needed for capacity: understanding, appreciation, reasoning, and expressing a choice
- Clinicians familiar with a patient can make a capacity assessment
- According to law, all adults have capacity unless there is evidence to the contrary
- Capacity is required for valid informed consent
- A durable power of attorney for healthcare designates a person (agent, proxy), to make health care decisions when a person with dementia can no longer do so[2]

Competency:[3]
- Legal capacity determined in court
- Varies by country

1. Hegde S, Ellajosyula R. *Ann Indian Acad Neurol.* 2016;19(Suppl 1):534-539; 2. Legal and Financial Planning for People with Dementia. NIH, National Institute on Aging. October 29, 2020. Accessed May 24, 2023. https://www.nia.nih.gov/health/legal-and-financial-planning-people-alzheimers Filakovic P et al. *Coll Antropol.* 2011;35:463-9.

Learner will be asked to read the scenario and respond to the polling question before viewing the video clip of the expert presenting the following few slides

Scenario 4

Mike, age 58, is considering using a direct-to-consumer (DTC) test to learn about his ApoE genotype. However, he is concerned about the potential implications for his job, life insurance, long-term care insurance, and the risk of developing AD in the future. Mike works for a local family-owned auto repair business with 10 employees.

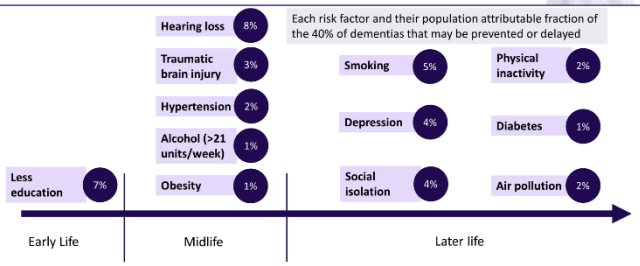
Mike is adopted and does not have access to his birth family's medical records.

Mike is athletic and cognitively and physically healthy. He is a strong advocate for making healthy lifestyle choices to prevent disease. Mike does not smoke, occasionally drinks beer, and maintains a healthy weight. His blood pressure is 135/80.

Labs: low-density lipoprotein (LDL) cholesterol: 140 mg/dL; total cholesterol: 220 mg/dL; high-density lipoprotein (HDL) cholesterol: 45 mg/dL

Polling
How would you counsel Mike regarding the implications of these genetic test results?
A. If DTC testing reveals an ApoE4 homozygous genotype, Mike would no longer be a candidate for AD prevention trials
B. Before making any major decisions regarding insurance or health care, DTC ApoE genotyping results should be confirmed by a certified lab.
C. Mike should continue to make healthy lifestyle choices, although there is no evidence they are helpful at his age.
D. Mike's job is protected through the Genetic Information Nondiscrimination ACT (GINA)

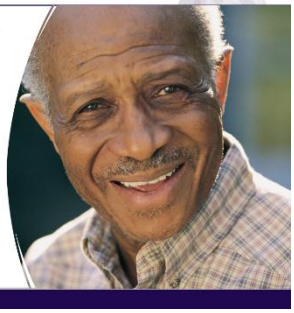
Modifying These Risk Factors May Delay or Prevent Up to 40% of Dementias



Livingston G et al. *Lancet.* 2020;396:413-446.

Counseling Patients Not Well Represented in Clinical Studies Is a Challenge

"One of the major factors limiting progress is that most genetic data have been obtained from non-Hispanic White individuals in Europe and North America, preventing the development of personalized approaches to AD in individuals of other ethnicities."



Reitz C. et al. *Nat Rev Neurol.* 2023;19:261-277.