Slowing Cognitive and Functional Decline in Early Alzheimer's Disease with

AMYLOID-BETA TARGETING THERAPIES

Considerations for Managed Care Pharmacy Professionals

Faculty

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Faculty Disclosures

- **Gary Small, MD**: Advisory Board—Acadia, Allergan, Avanir, Biogen, Cogensus, Electro Cellular Health Solutions, Handok, Herbalife, Lundbeck, Lilly, McCormick Science Institute, Merry Life Biomedical, Otsuka, Roche, Theravalues; Equity Interest—CereMark Pharma
- **Winston Wong, PharmD** has disclosed no relevant financial relationship with any ineligible company (commercial interest)

Program Information

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Learning Objectives

- Assess the economic burden, impact on patients/care partners, and unmet needs associated with AD
- Describe the value of early AD diagnosis and treatment
- Evaluate the efficacy/safety data and administration considerations of available/emerging amyloid-beta targeting therapies for early AD
- Apply evidence-based guidelines and recommendations for the timely identification, mitigation, and management of adverse events associated with amyloid-beta targeting therapies
- Implement managed care strategies to balance treatment efficacy and best practices with cost-effectiveness for optimal outcomes in patients with AD

AD = Alzheimer's disease.

AD: A Growing Global Burden

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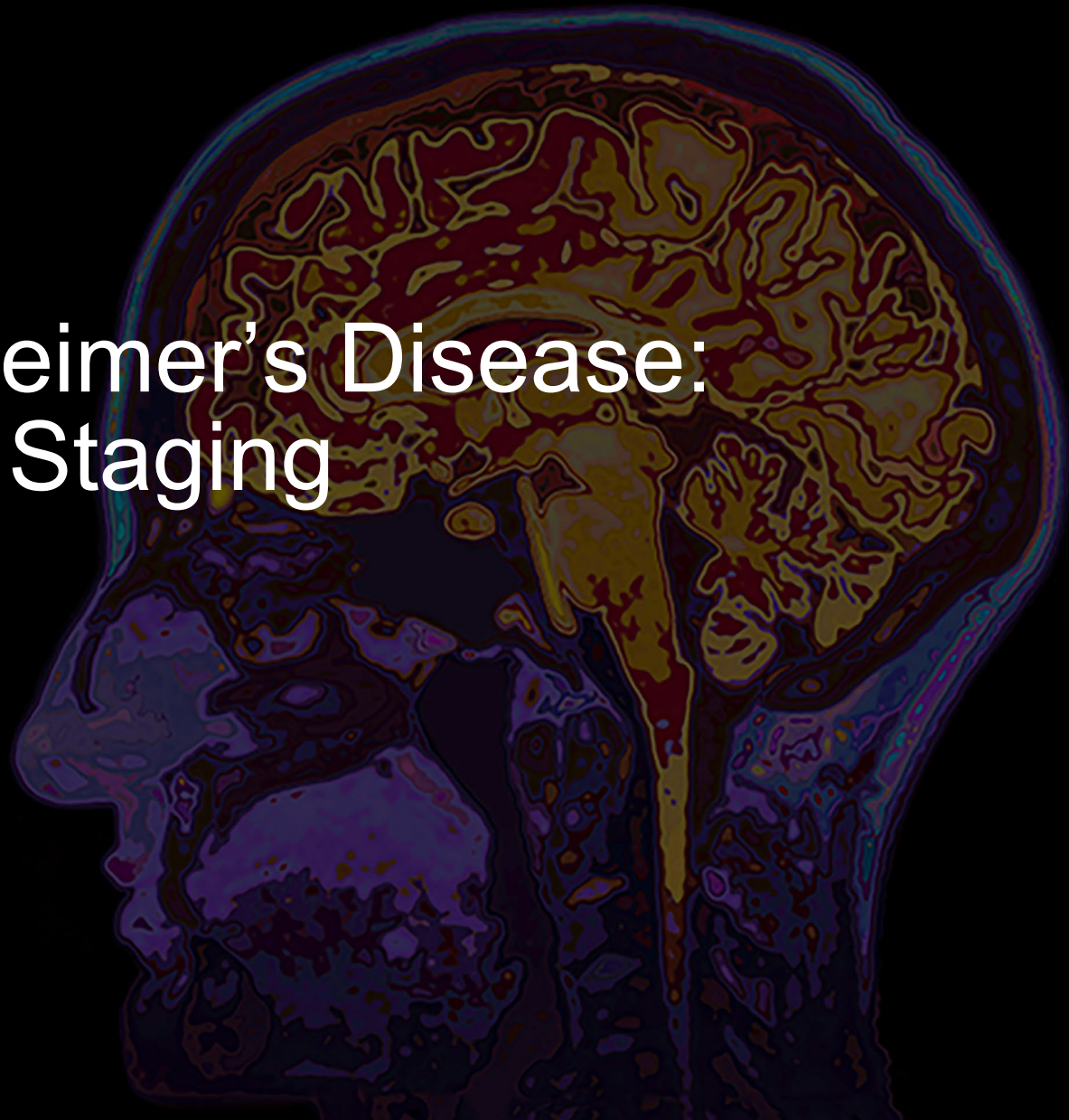
Understanding Alzheimer’s Disease: Onset and Staging

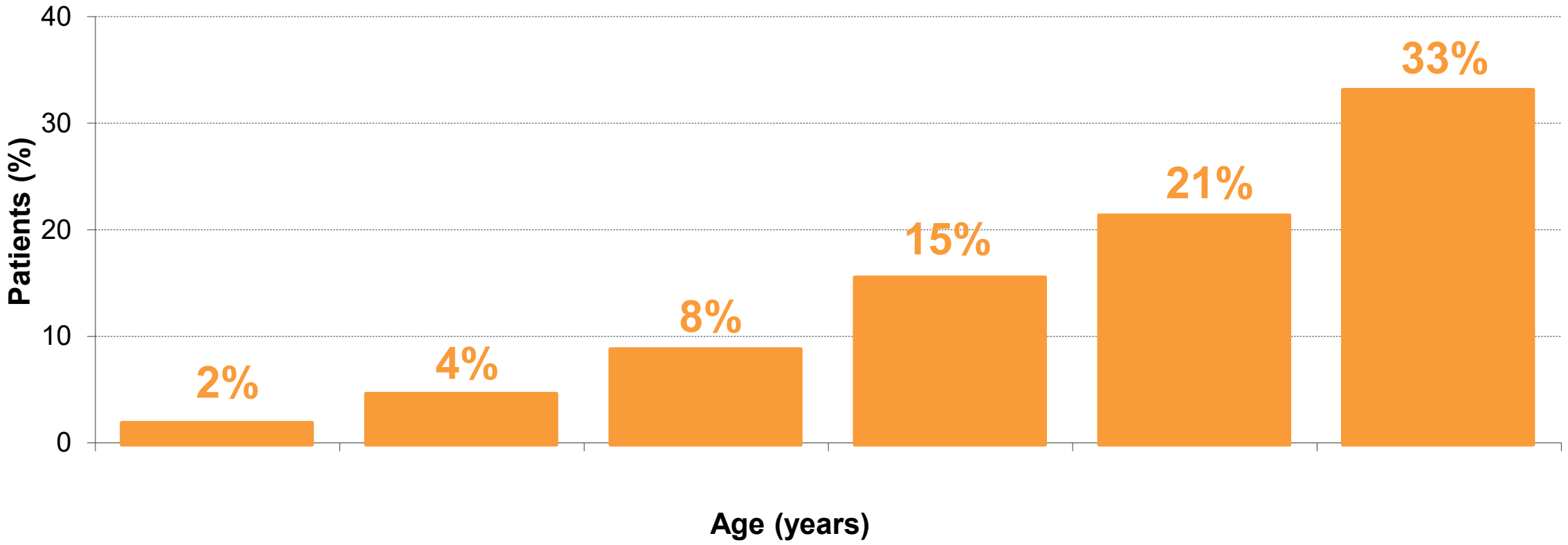


Definitions, Prevalence, and Burden of Alzheimer's Disease (AD)

- Neurodegenerative disorder with cognitive and behavioral symptoms
- Most common cause of dementia
  - In 2017, 6.08 million people in the United States had either clinical AD or mild cognitive impairment due to AD
  - That number is expected to increase to about 15 million by 2060
- Unknown cause, but multiple environmental and genetic risk factors
- Age is greatest risk: 10% of people ≥ 65 years; 40% of those ≥ 85 years
- Pathological hallmarks: amyloid plaques and tau tangles that accumulate in brain regions controlling memory and thinking

Culpepper L. Last updated July 18, 2023. Accessed December 1, 2022. https://www.medscape.com/viewarticle/994066. Rajan KB, et al. *Alzheimers Dement*. 2021;17(12):1966-1975. Alzheimer's Association. Last updated March 14, 2023. Accessed December 1, 2022. https://www.alz.org/media/documents/alzheimers-facts-and-figures.pdf.

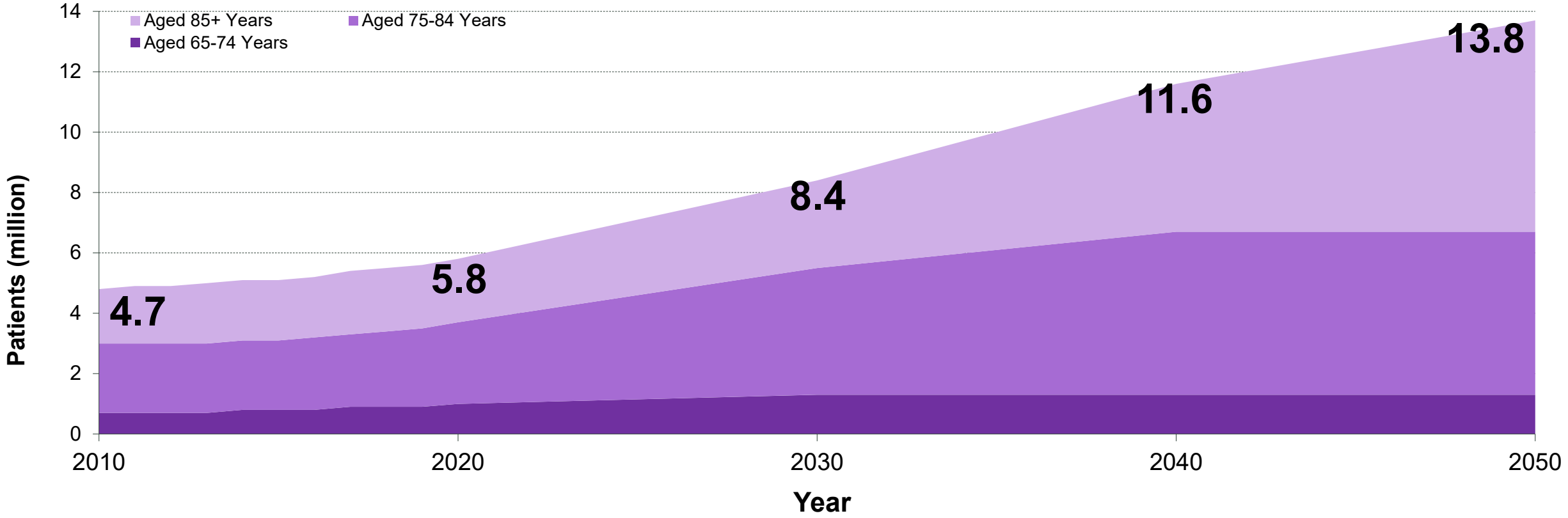
Dementia Prevalence According to Age



Chi W, et al., The Office of the Assistant Secretary for Planning and Evaluation. January 29, 2019. Accessed October 4, 2024. https://aspe.hhs.gov/reports/community-dwelling-older-adults-dementia-their-caregivers-key-indicators-national-health-aging-0.

The Aging of the US Population Is Increasing Dementia Prevalence

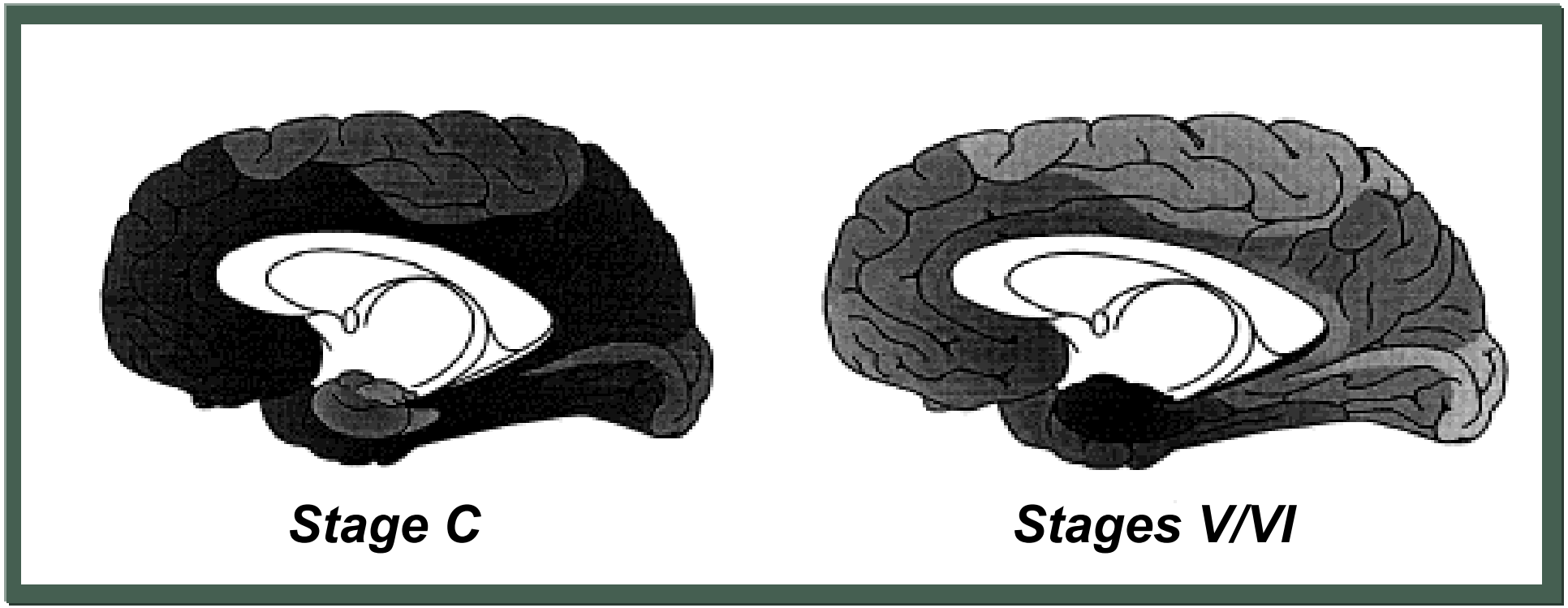
Projected Number of People Aged ≥ 65 Years With Dementia in the United States, Total and by Age



Graph adapted with permission from Alzheimer's Association as published in *Alzheimers Dement*. 2019;15(3):321-387. Hebert LE, et al. *Neurology*. 2013;80(19):1778-1783.

Progression of Alzheimer's Abnormal Proteins in Autopsy Studies

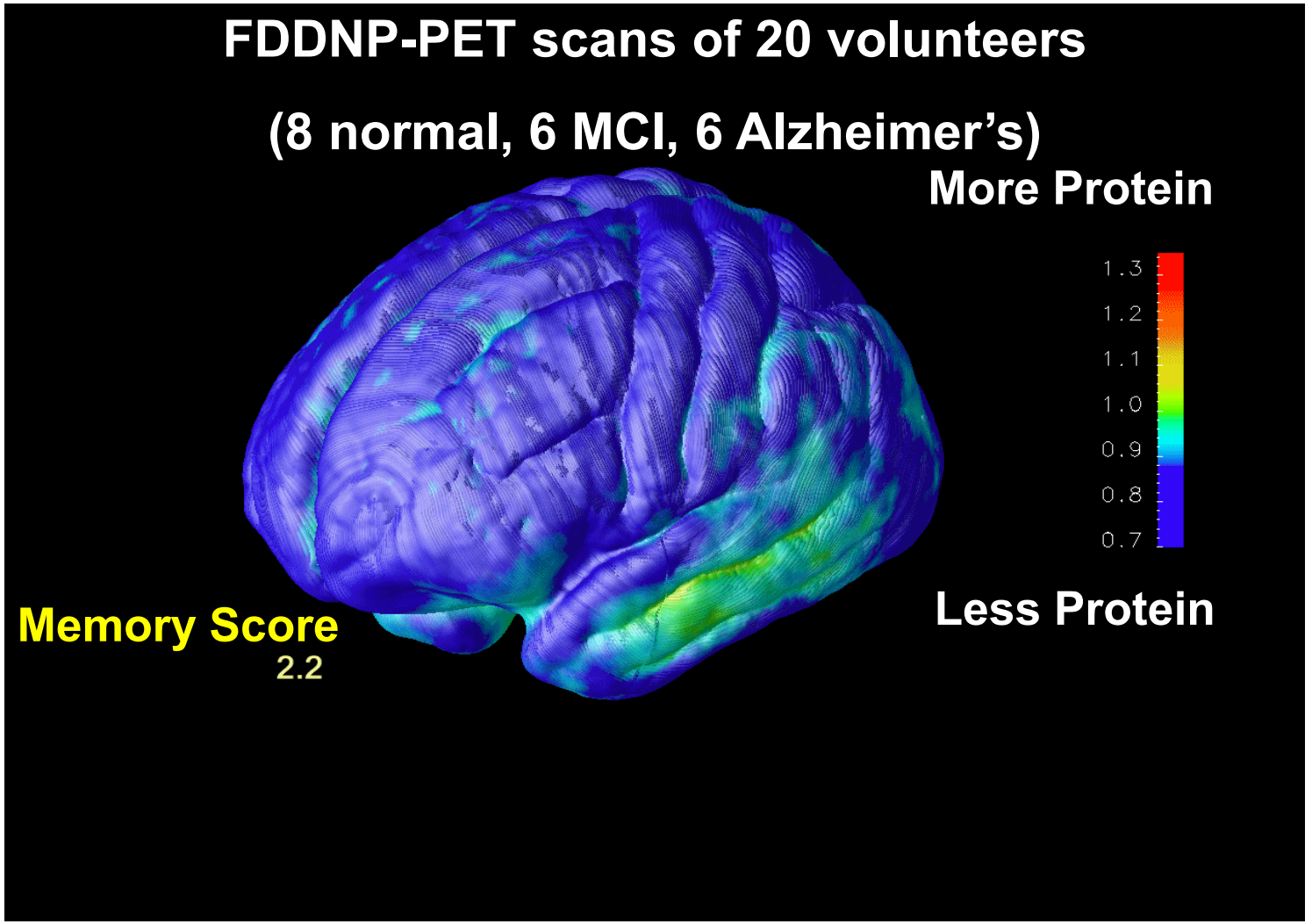
Plaques **Tangles**



Stage C ***Stages V/VI***

Braak H, et al. *Acta Neuropathol.* 1991;82(4):239-259. Price JL, et al. *Ann Neurol.* 1999;45(3):358-368.

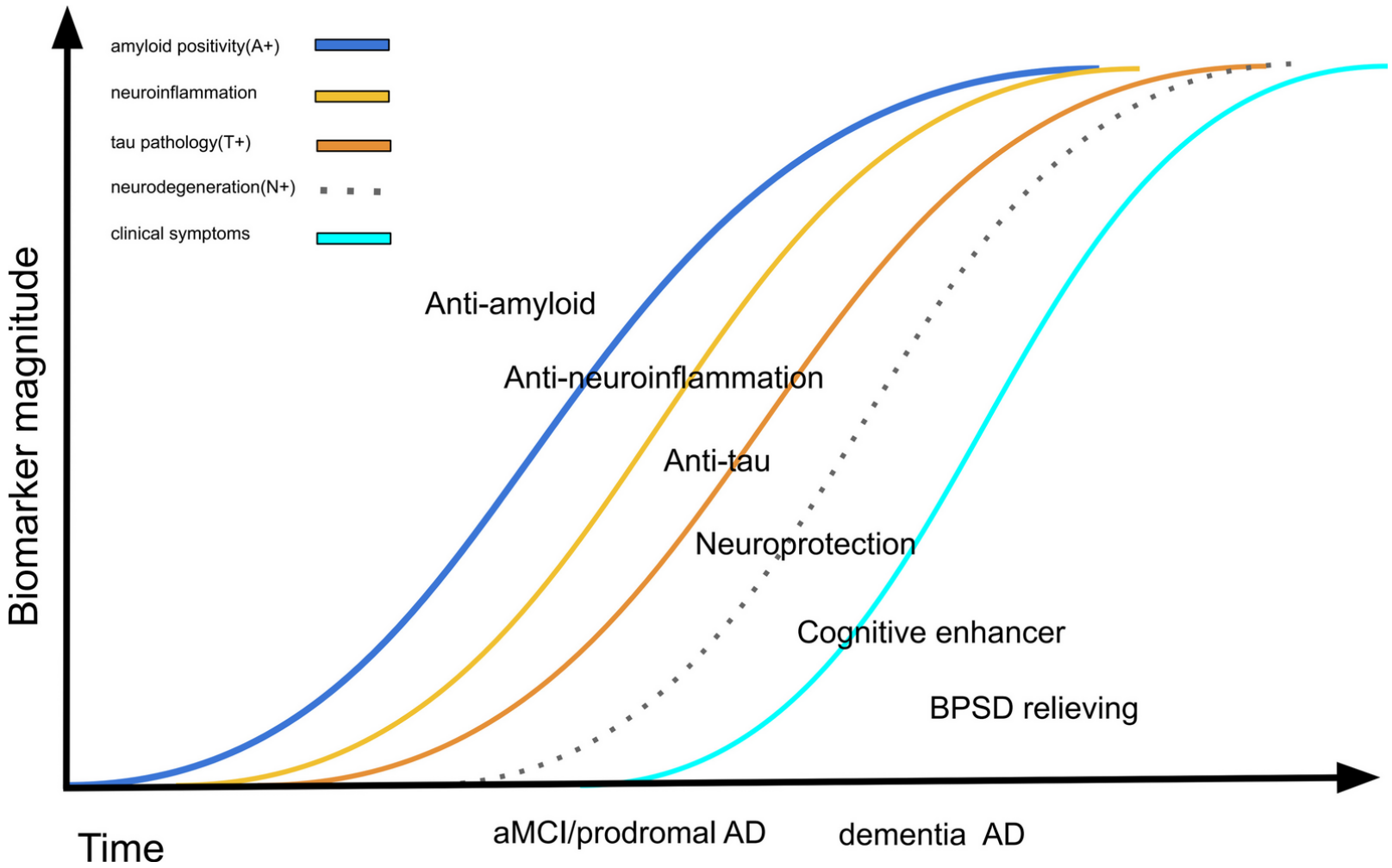
Brain Amyloid and Tau Proteins Accumulate as Memory Worsens



MCI = mild cognitive impairment; FDDNP-PET = 2-(1-{6-[(2-[fluorine-18]fluoroethyl)(methyl)amino]-2-naphthyl}-ethylidene)malononitrile positron emission tomography.

Braskie MN, et al. *Neurobiol Aging*. 2010;31(10):1669-1678. Small GW, et al. *Arch Neurol*. 2012;69(2):215-222.

Amyloid Hypothesis: Pathophysiology and Clinical Course of Alzheimer's Disease Progression

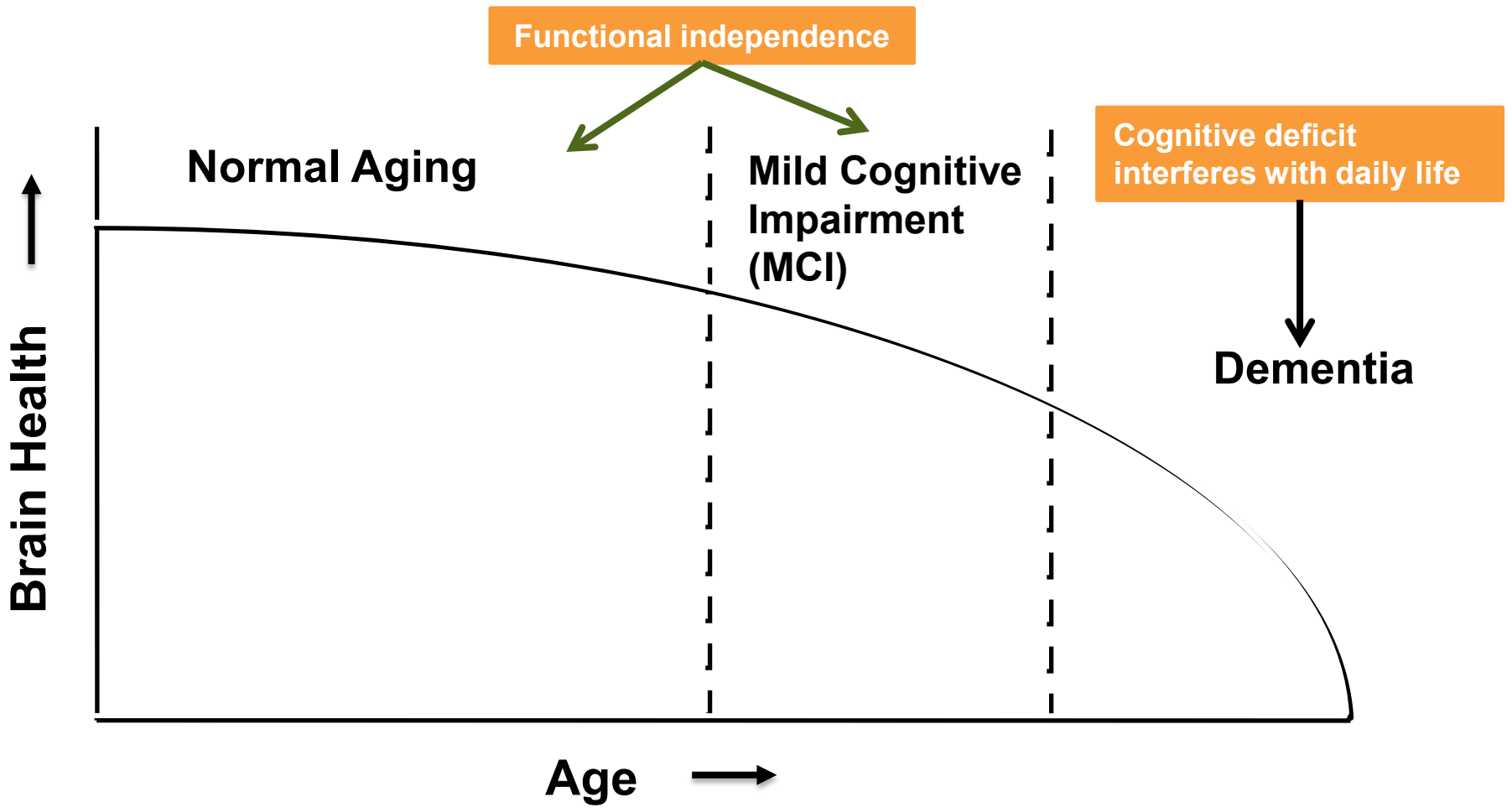


BPSD = behavioral and psychological symptoms in dementia.

Huang LK, et al. *J Biomed Sci.* 2023;30(1):83.

Alzheimer's Disease Progression

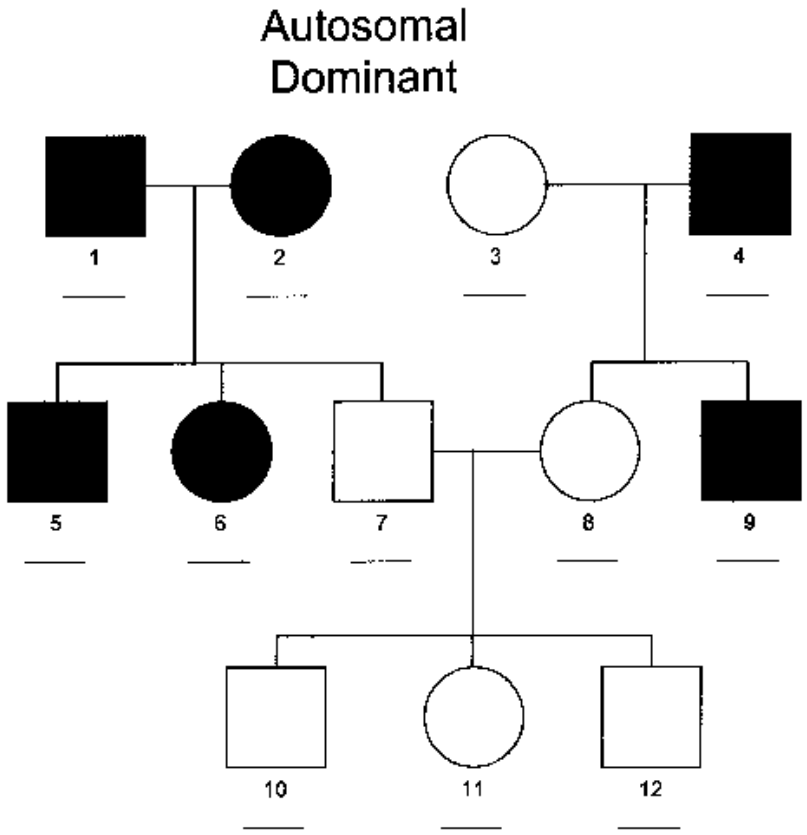
- Gradual onset and progression
- Of those with MCI, 10-15% will develop dementia each year, with ~1/3 developing dementia within 5 years



Chen ST, et al. *Am J Geriatr Psychiatry*. 2019;27(3):213-36. Porsteinsson AP, et al. *J Prev Alzheimers Dis*. 2021;8(3):371-386. Petersen RC, et al. *Neurology*. 2018;90(3):126-135. Alzheimer's Association. 2022. Accessed January 23, 2023. www.alz.org/media/Documents/alzheimers-facts-and-figures-special-report.pdf.

Alzheimer's Genetics

- Rare genetic mutations
  - Autosomal dominant inheritance
  - Presenilin, APP genes
- More common genetic risk
  - ApoE4 present in 20% of population
  - Not recommended as predictive tests
- > 30 loci implicated by linkage, GWAS, and whole-genome sequencing



APP = amyloid-beta precursor protein; apo = apolipoprotein; GWAS = genome-wide association study.

Robinson M, et al. *J Alzheimers Dis*. 2017;57(2):317-330. Small G, et al. In: Iqbal K, Winblad B (Eds). *Alzheimer's Disease and Related Disorders: Research Advances.* 2005:217-224. Pimenova AA, et al. *Biol Psychiatry*. 2018;83(4):300-310.

Importance of Timely Diagnosis of Mild Cognitive Impairment

- **An estimated 20% of people with AD are never clinically diagnosed**
- **Benefits to early diagnosis** include developing monitoring/comprehensive treatment plans, such as
  - Pharmacological treatments for symptoms
  - Clinical trials treating underlying pathophysiology

Recommendations

Evaluate for modifiable risk factors in patients with MCI

Discontinue cognitively-impairing medications

Assess for functional impairment, behavioral/neuropsychiatric symptoms

Treat behavioral/neuropsychiatric symptoms

Recommend regular exercise, consider cognitive training

Refer for multidisciplinary assessment/ management

Discuss prognosis, long-term planning

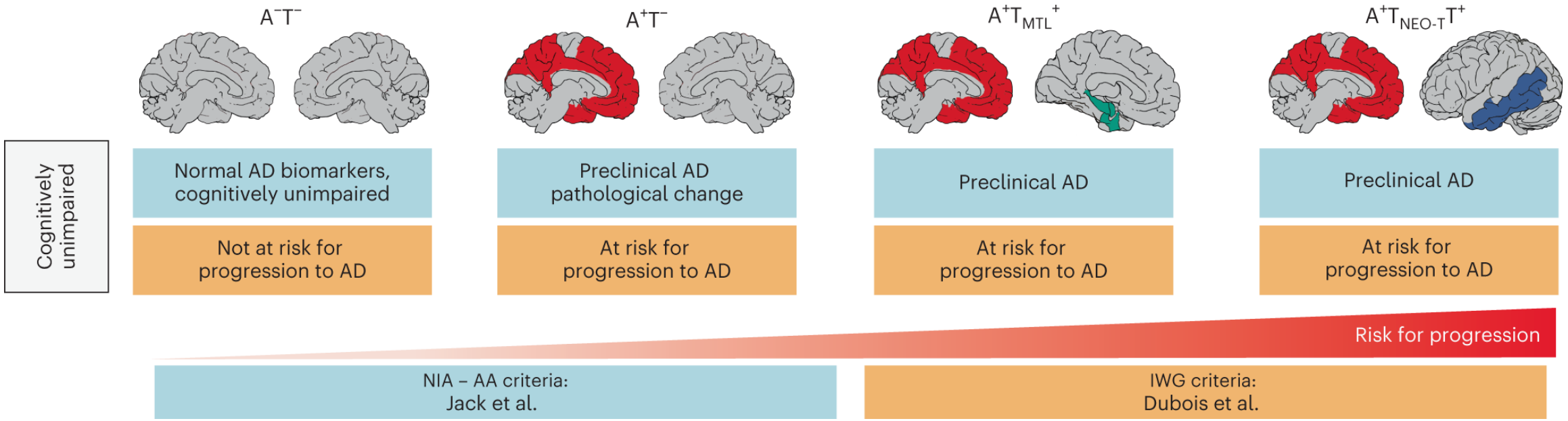
Mok W, et al. *Am J Alzheimers Dis Other Demen.* 2004;19(3):161-165. Alzheimer's Disease International. Accessed January 28, 2023. https://www.alz.co.uk/research/WorldAlzheimerReport2011ExecutiveSummary.pdf. Alzheimer's Association. 2022. Accessed January 28, 2023. https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf. Petersen RC, et al. *Neurology.* 2018;90(3):126-135.

NIA-AA 2024 Revised Diagnostic and Staging Criteria

- Defines AD as beginning with neuropathologic change while patients are still asymptomatic
- Identifies early biomarkers—amyloid PET, CSF biomarkers, and tau 217 plasma biomarkers—as sufficient to establish a diagnosis of AD
- Indicates that later stage biomarkers—biofluid and tau PET—provide prognostic information and confidence in AD diagnosis contributing to symptomatic behavior

NIA-AA = National Institute on Aging and Alzheimer's Association; CSF = cerebrospinal fluid.
Jack CR, et al. *Alzheimers Dement.* 2024;20(8):5143-5169.

NIA-AA versus IWG Criteria



Differences in the nomenclature of cognitively unimpaired individuals with ($^+$) or without ($-$) in vivo biomarker evidence of Aβ (A) and tau (T) pathology in the NIA-AA versus IWG criteria for AD. Note that for the IWG criteria, the presumed "risk for progression" level rises when both A and T biomarkers are positive.

IWG = International Working Group; MTL = medial temporal lobe; NEO-T = temporal neocortex.

Jack CR, et al. *Alzheimers Dement.* 2024;20(8):5143-5169. US FDA. Early Alzheimer's Disease: Developing Drugs Guidance for Industry 2019. Jack CR, et al. *Alzheimers Dement.* 2018;14(4):535-62. Dubois B, et al. *Lancet Neurol.* 2021;20(6):484-496.

Signs and Symptoms of AD

- Mild
  - Memory loss, confusion, trouble handling money
  - Mood and personality changes
- Moderate
  - Increasing memory loss and confusion, poor attention, problems recognizing friends/relatives, difficulty with language, organizing thoughts, inability to learn new information
  - Restlessness, agitation, anxiety, wandering, hallucinations, delusions, irritability, poor impulse control
- Severe
  - Cannot recognize family/loved ones or communicate effectively
  - Completely dependent on others for care
  - Weight loss, seizures, skin infections, difficulty swallowing, lack of bladder/bowel control

Impact of AD on Care Partners in the United States

83% of care provided to older adults comes from family, friends, or other unpaid care partners

48% of care provided to older adults is related to AD or other dementias

$13B lost by employers in 2010 due to elder care responsibilities of employees

$350B is value represented by unpaid assistance provided to patients with AD or other dementias in 2019

Alzheimers Dement. **Mar 10, 2022. Accessed September 27, 2024. https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf.**

Burden on Care Partners

Risk Factors

- Female sex
- Low educational attainment
- Residence with the care recipient
- Higher number of hours spent caregiving
- Depression, social isolation
- Financial stress
- Lack of choice in being a care partner

Psychosocial Interventions

- Support groups
- Psychoeducational interventions for care partners

Adelman RD, et al. *JAMA*. 2014;311(10):1052-1060.

Economic Burden of AD

- AD is 5th leading cause of death in adults > 65 years
- Long-term and health-related care costs for people living with AD and other dementias are projected to reach $360 billion this year
- Cost expected to increase to more than $1 trillion as the population ages
- Most direct costs of care attributed to skilled nursing care, home healthcare, and hospice care
- Indirect costs of care, including quality of life and informal caregiving, are likely underestimated and associated with significant negative societal and personal burden

Wong W. *Am J Manag Care*. 2020 Aug;26(8 Suppl):S177-S183. Alzheimer's Association. 2024. Accessed October 7, 2024. https://www.alz.org/alzheimers-dementia/facts-figures.

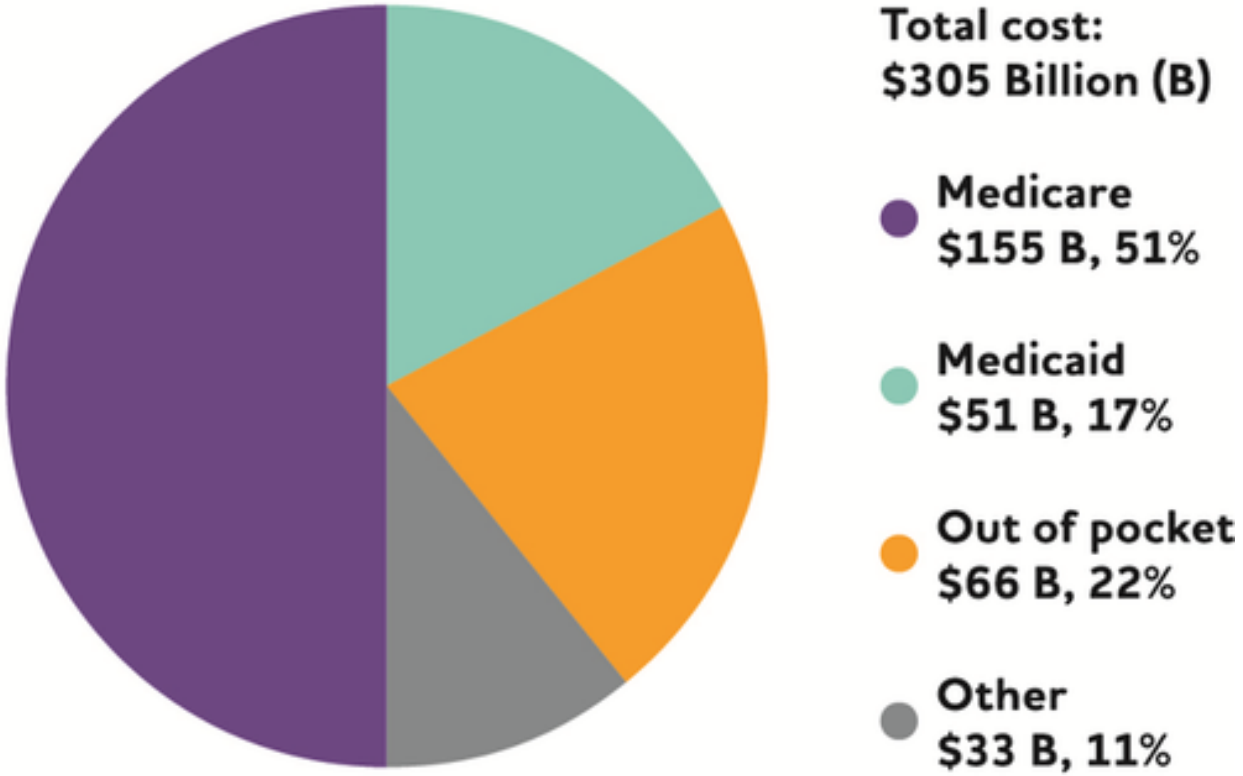
AD and the Healthcare System

Cost of care for those with AD and other dementias (US, age 65 and older)

538 Hospital stays per 1000 Medicare patients (vs 266 without AD/dementia)

25% Have at least one home health visit per year (vs 10% without AD/dementia)

$51B Total Medicaid spending projected in 2020



Alzheimers Dement. **2020 Mar 10 [Epub ahead of print].**

Impact of Early Diagnosis on Healthcare Costs

- The Alzheimer's Association conducted a study of the potential cost savings of early diagnosis
- Based on diagnosing 88% of AD patients (based on 2018 data) in the MCI phase rather than the dementia phase, the study approximated a savings of **$7 trillion dollars** in medical and long-term care costs
- Savings are based on the smaller spike in costs when diagnosed during the MCI phase and lower costs for individuals diagnosed early compared to those with unmanaged MCI and dementia

Early diagnosis may result in lower long-term costs associated with a reduction in care needs

Alzheimer's Association. *Alzheimers Dement.* 2024;20(5):3708-3821. Rasmussen J, et al. *Degener Neurol Neuromuscl Dis*. 2019;9:123-130.

Key Learning Points

- AD and related dementias afflict a growing number of older adults
- Long-term and health-related care costs for people living with AD and other dementias are projected to reach $360 billion this year
- Early diagnosis may result in lower long-term costs associated with a reduction in care needs

Challenges and New Opportunities in Early AD

Lifestyle Modification May Slow Development or Progression of Cognitive Decline

Multiple trials are currently investigating the contribution of physical activity, healthy diet, and staying cognitively active (learning and socializing)

FINGER trial: multidomain lifestyle intervention study in patients without AD at risk for cognitive decline showed cognitive benefits in older adults at risk for dementia

POINTER: lifestyle modifications targeting risk factors for protecting cognitive function

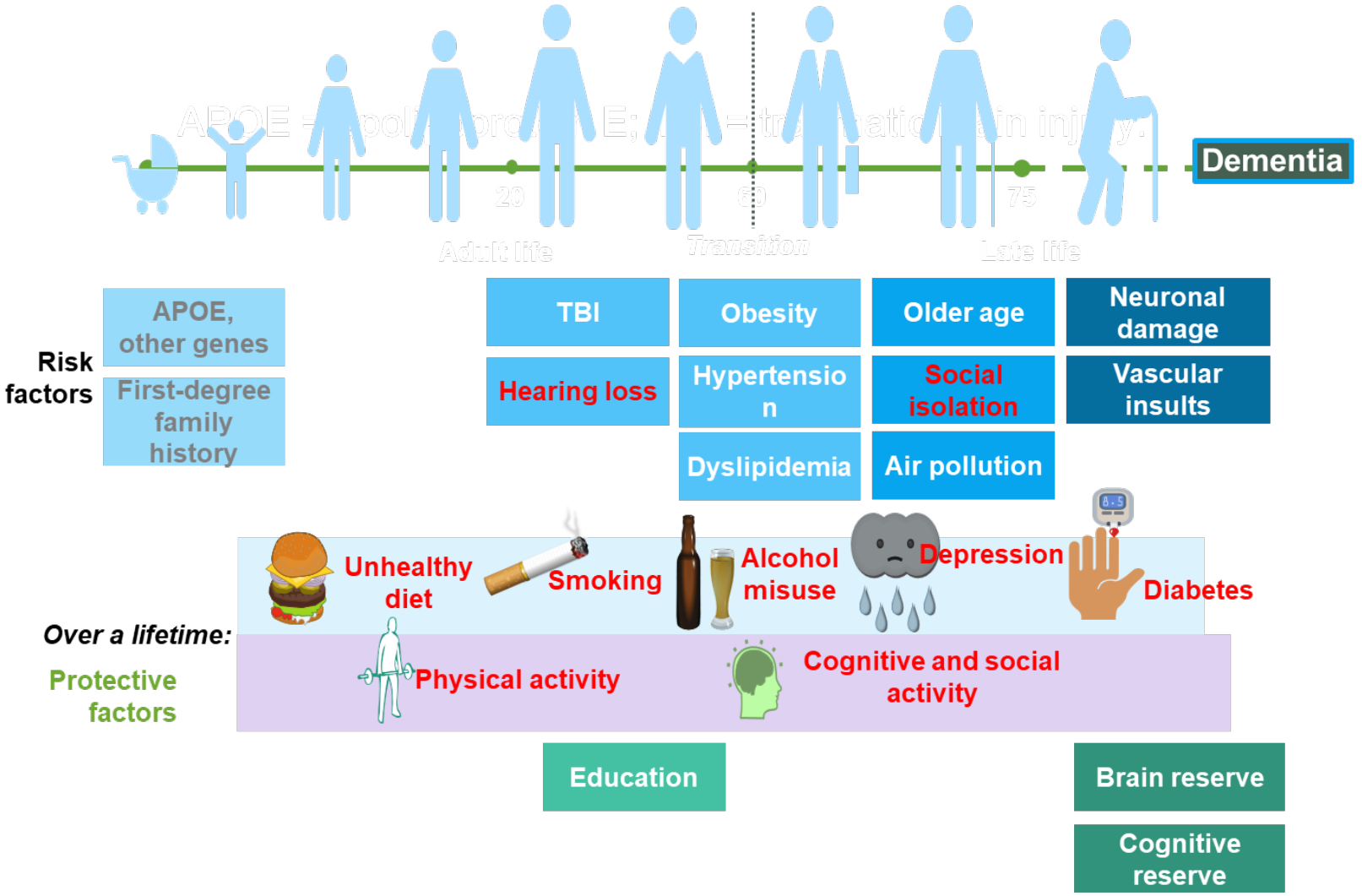
SPRINT MIND: intensive hypertension control for reducing dementia occurrence; control of systolic BP to < 120 mm Hg vs < 140 mm Hg did not significantly reduce probability

rrAD: strategies to reduce risk of AD (aerobic exercise ± intensive blood pressure and cholesterol management vs standard of care)

BP = blood pressure.

Sheng C, et al. *J Alzheimers Dis*. 2020;77(2):903-920. Rosenberg A, et al. *Alzheimers Dement*. 2018;14(3):263-270. Alzheimer's Association. Accessed January 28, 2023. https://alz.org/us-pointer/overview.asp. Williamson JD, et al. *JAMA*. 2019;321(6):553-561. Risk Reduction for Alzheimer's Disease Trial. Accessed January 28, 2023. http://rradtrial.org.

Importance of the Multi-Domain Approach



TBI = traumatic brain injury; APOE = apolipoprotein E.

Alzheimer's Association. *Alzheimer's Dement*. 2022;18(4):700-789. Livingston G, et al. *Lancet.* 2020;396(10248):413-446.

Nonpharmacological Intervention Strategies

***Target modifiable risk factors* with behavioral strategies**

***Reduce* habits that might be contributing to the problem**

- Alcohol or other substance use; use of PRN medications that have cognitive side effects
- Implement stress-reduction activities

***Increase* habits that promote resilience**

- Aerobic physical fitness (PT, OT, speech and language therapy)
- Cognitive activities and/or “training” exercises
- Healthy dietary choices
- Social or “leisure” activities

Care planning, education, and support

- Typically includes both patient and care partner
- Advance planning for medical, legal, and financial decision-making
- Safety planning/monitoring (stove, weapon, driving, poor decision-making)
- Care partner and community support resources

PRN = as needed; PT = physical therapy; OT = occupational therapy.

Atri A. *Med Clin North Am*. 2019;103(2):263-293. Livingston G, et al. *Lancet*. 2020;396(10248):413-446. Atri A. *Semin Neurol*. 2019;39(2):227-240.

Traditional AD Pharmacotherapy

- Cholinesterase inhibitors increase availability of acetylcholine, a brain neurotransmitter that supports memory function
  - Donepezil
  - Galantamine
  - Rivastigmine
- Anti-glutamatergic drug that enhances neuronal messaging needed for learning and recall
  - Memantine
- Combination therapy: adding memantine to a cholinesterase shows additional cognitive benefits

Cummings J. *J Alzheimers Dis.* 2018;64(Suppl 1):S3-S22. Cummings JL, et al. *J Alzheimers Dis.* 2019;67(3):779-794.

Symptomatic Drugs: Indications, Treatment Strategies

- Cholinesterase inhibitors: mild, moderate, or severe Alzheimer's dementia
- Memantine: moderate or severe Alzheimer's dementia
- To minimize side effects, start at low dose and increase to higher dose as tolerated, for example
  - Donepezil 5 mg QD and then 10 mg QD after one month
  - Rivastigmine 4.6 mg patch QD and then 9.5 mg QD after one month
- Avoid discontinuing medication too soon (even if no obvious cognitive improvements observed)

QD = daily.

Grossberg GT, et al. *J Alzheimers Dis*. 2019;67(4):1157-1171.

Symptomatic Drugs: Adverse Effects

- Memantine
  - Confusion
  - Constipation
  - Dizziness
  - Headache
- Cholinesterase inhibitors
  - Gastrointestinal (nausea, vomiting, diarrhea)
  - Vivid dreams
  - Bradycardia

Grossberg GT, et al. *J Alzheimers Dis.* 2019;67(4):1157-1171.

Limitations of Traditional AD Pharmacotherapy

- Cholinesterase inhibitors and anti-glutamatergic drugs impact only the symptoms of AD and do not target the cause of disease
- Administration of these treatments is less effective as disease progresses
- Permeability issues across the blood-brain barrier require increased dosing, which can increase adverse effects

Cummings J. *J Alzheimers Dis.* 2018;64(Suppl 1):S3-S22. Cummings JL, et al. *J Alzheimers Dis.* 2019;67(3):779-794.

Amyloid Plaque-Lowering Monoclonal Antibodies

- **Impact on AD biology**: amyloid plaque-lowering and downstream effects
  - Emerging evidence for moderate efficacy (*slowing of clinical decline*) when amyloid plaques are sufficiently lowered
- **Burden and safety**: infusions, costs, limited access, selected population require amyloid confirmation and serial MRI safety monitoring for amyloid-related imaging abnormalities (ARIA) detection
- **Aducanumab**: FDA accelerated approval in 2021, drug discontinued in 2024
- **Lecanemab**: FDA approved on July 6, 2023
- **Donanemab**: FDA approved on July 3, 2024

MRI = magnetic resonance imaging.

Atri A. *Semin Neurol*. 2019;39(2):227-240. Cummings J, et al. *Alzheimers Res Ther.* 2021;13(1):98. Aduhelm® PI. Drugs@FDA: FDA-Approved Drugs. Accessed October 10, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761178s011lbl.pdf. US FDA. Last updated January 6, 2023. Accessed October 10, 2024. https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-alzheimers-disease-treatment. Leqembi® PI. Drugs@FDA: FDA-Approved Drugs. Accessed October 10, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269Orig1s001lbl.pdf. Salloway S, et al. *J Prev Alzheimers Dis.* 2022;9(suppl 1):S41-S42. Abstract LB3. Doody RS, et al. *N Engl J Med.* 2014;370(4):311-321. Roche. November 14, 2022. Accessed January 28, 2023. https://www.roche.com/investors/updates/inv-update-2022-11-14c.

Aducanumab

- Aug 2015: Phase 2 efficacy trials initiated: ENGAGE and EMERGE
- Mar 2019: Trials terminated following futility analysis
- Oct 2019: Re-analysis showed cognitive improvement/Aβ reduction (highest dose: 10 mg/kg) in EMERGE but not ENGAGE
- Jul 2020: Manufacturer applies for approval application
- Nov 2020: FDA Advisory Committee votes that aducanumab not effective for AD treatment
- Jun 2020: FDA approves through accelerated pathway (for drugs that treat diseases with no known cure, even if the clinical benefit is unclear and drug needs more investigation)
- Jan 2022: Centers for Medicare & Medicaid Services (CMS) approves Medicare coverage for AD patients in clinical trials only

Dementia Care Central. Accessed February 20, 2021. https://www.dementiacarecentral.com/about dementia/treating/aducanumab. https://www.alzheimersnewstoday.com/2021/02/01/fda-extends-its-aducanumab-review-with-decision-expected-in-June. Torres A, et al. *Biomedica*. 2024;44(Suppl 1):42-46.

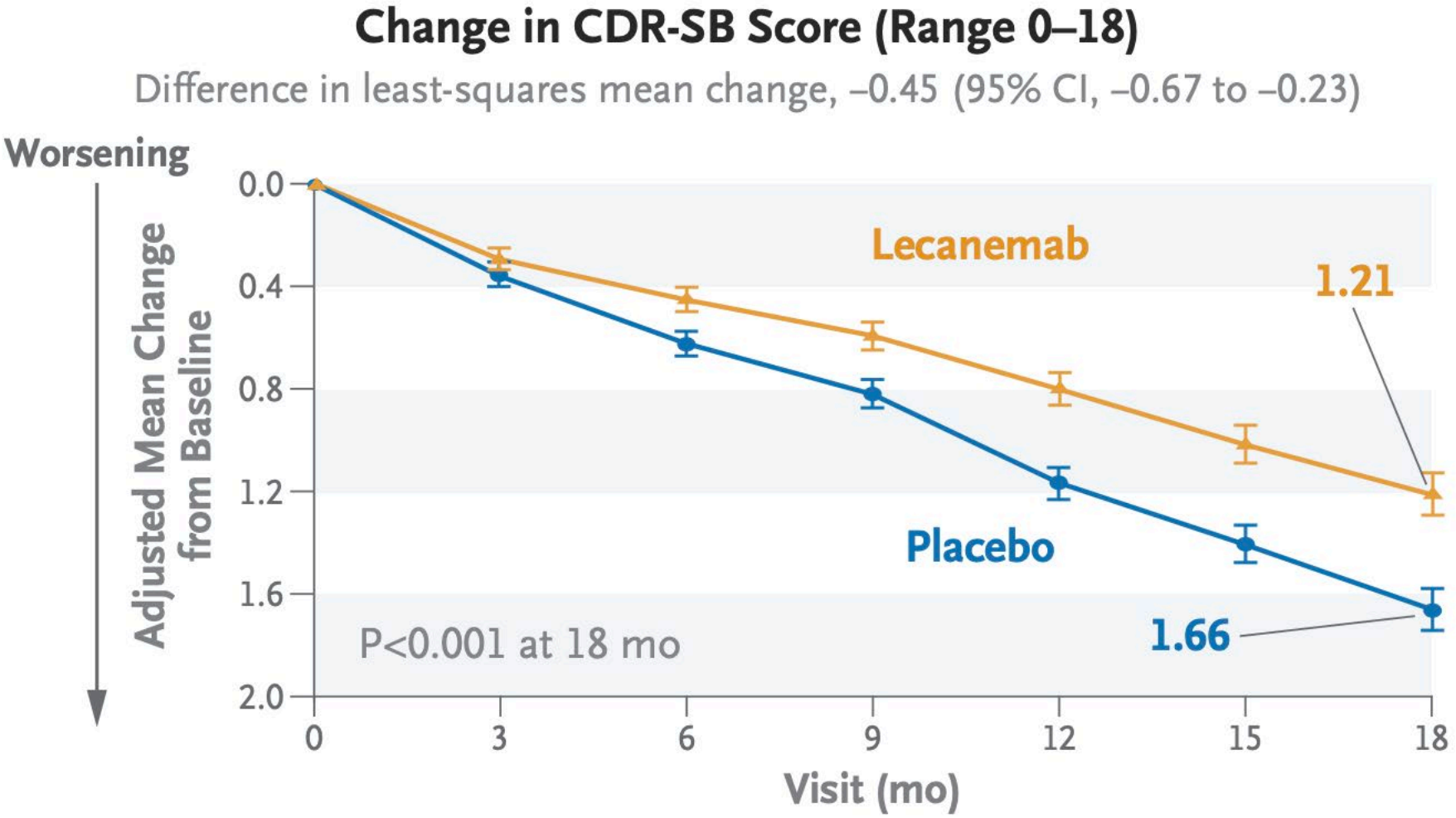
Lecanemab: Trial Design

- 18-month, multicenter, double-blind, phase 2 trial
- 1,795 patients aged 50-90 years with early AD (mild cognitive impairment or mild dementia due to AD) were randomized to lecanemab (n=898) or placebo (n=897)
- Primary endpoint: change in CDR-SB score from baseline to 18 months of treatment
- Secondary endpoints
  - Change in amyloid burden
  - Score on ADAS-Cog14, ADCOMS, and ADCS-MCI-ADL

CDR-SB = Clinical Dementia Rating—Sum of Boxes; ADAS-Cog = Alzheimer's Disease Assessment Scale—Cognitive Subscale; ADCOMS = Alzheimer's Disease Composite Score; ADCS-MCI-ADL = Alzheimer's Disease Cooperative Study—Activities of Daily Living for Mild Cognitive Impairment.

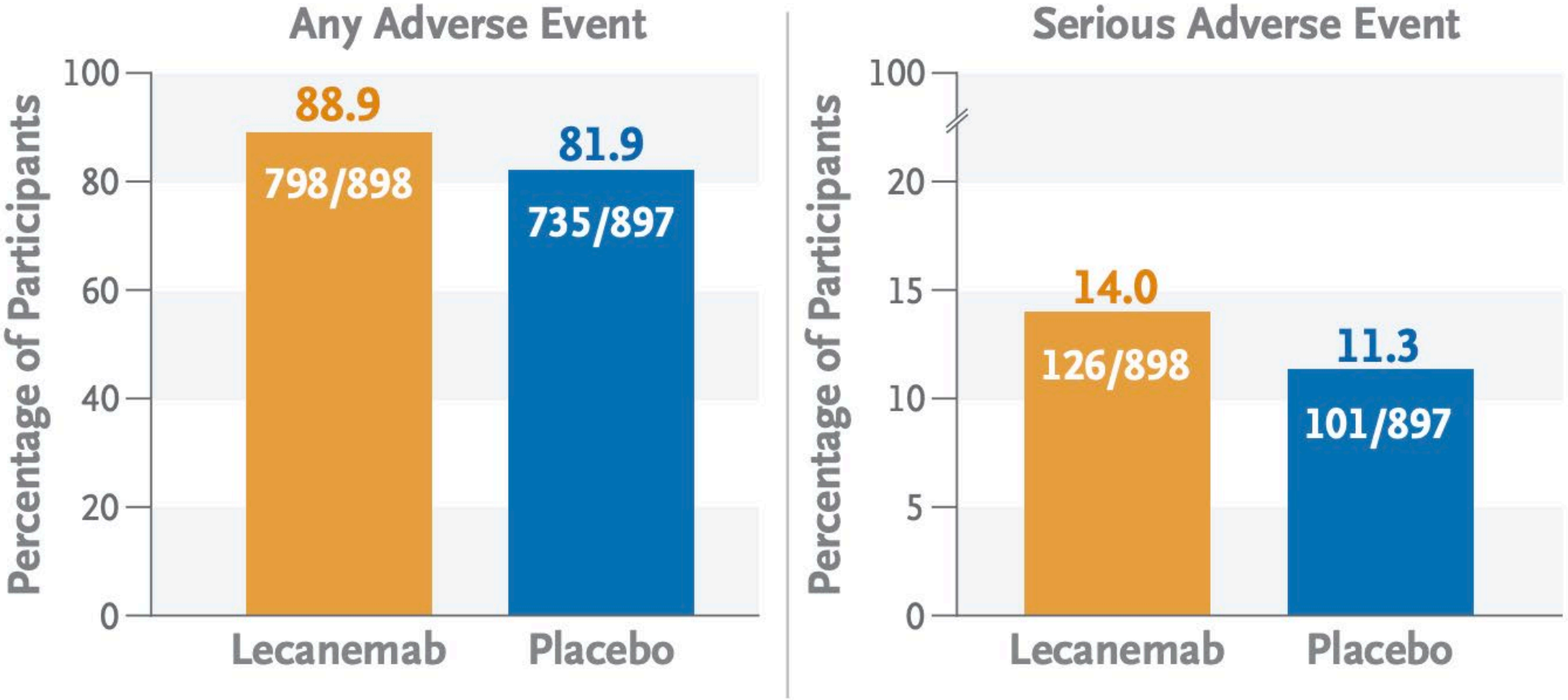
Van Dyck CH, et al. *N Engl J Med.* 2023;388(1):9-21.

Lecanemab Trial Results



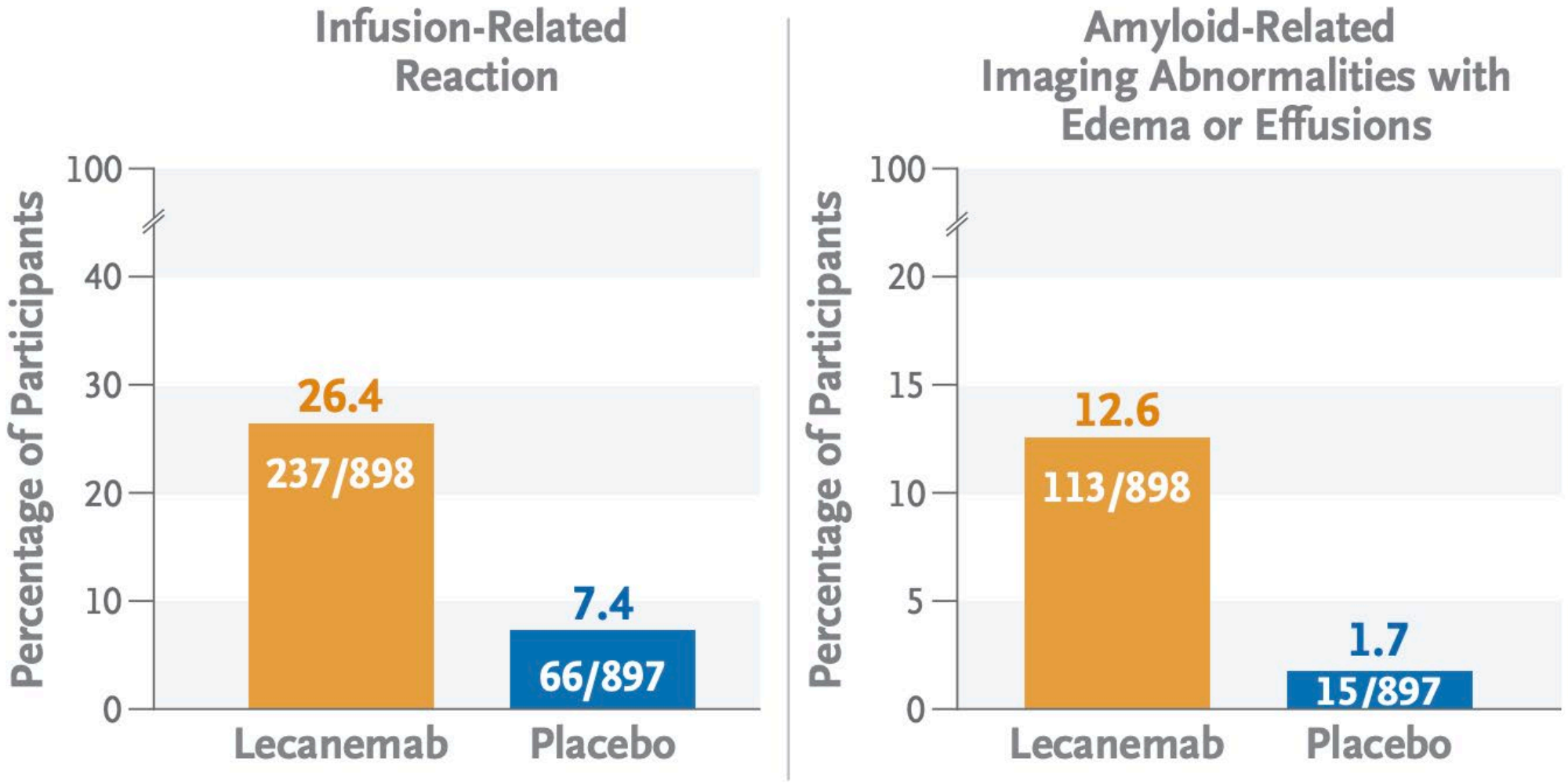
Van Dyck CH, et al. *N Engl J Med.* 2023;388(1):9-21.

Lecanemab Trial Results



Van Dyck CH, et al. *N Engl J Med.* 2023;388(1):9-21.

Lecanemab Trial Results



Van Dyck CH, et al. *N Engl J Med.* 2023;388(1):9-21.

Donanemab

Donanemab (LY3002813) is a monoclonal antibody designed to stimulate the immune system to attack and destroy a modified form of Aβ, resulting in a reduction of plaques

December 2017

TRAILBLAZER-ALZ: Phase 2 trial of donanemab alone and in combination with a BACE inhibitor LY3202626

October 2018

The BACE inhibitor arm of this trial was discontinued due to poor results of the drug in other trials

Evaluation of donanemab alone remained ongoing

October 2020

Recruitment opened for TRAILBLAZER-ALZ 2, a phase 2 safety and efficacy trial in 500 people with early AD

January 2021

Lilly announced TRAILBLAZER-ALZ met its primary end point, slowing decline on the iADRS by 32% compared with placebo at 18 months

There was improvement on all secondary end points of cognition and function, although not all were statistically significant

iADRS = Integrated Alzheimer's Disease Rating Scale; BACE = β-site amyloid precursor protein cleaving enzyme.

ALZForum. March 19, 2021. Accessed March 24, 2021. https://www.alzforum.org/news/conference-coverage/donanemab-confirms-clearing-plaques-slows-decline-bit. Mintun MA et al. *N Engl J Med.* 2021;384(18):1691-1704.

Donanemab—TRAILBLAZER-ALZ Trial

POPULATION

996 Women
740 Men

Adults aged 60-85 years with symptomatic Alzheimer disease and amyloid and tau pathology

Mean age: **73** years

LOCATIONS

277
Medical sites
in 8 countries

INTERVENTION

1736 Patients randomized
1599 Patients analyzed

860
Donanemab
Administered intravenously every 4 weeks for up to 72 weeks

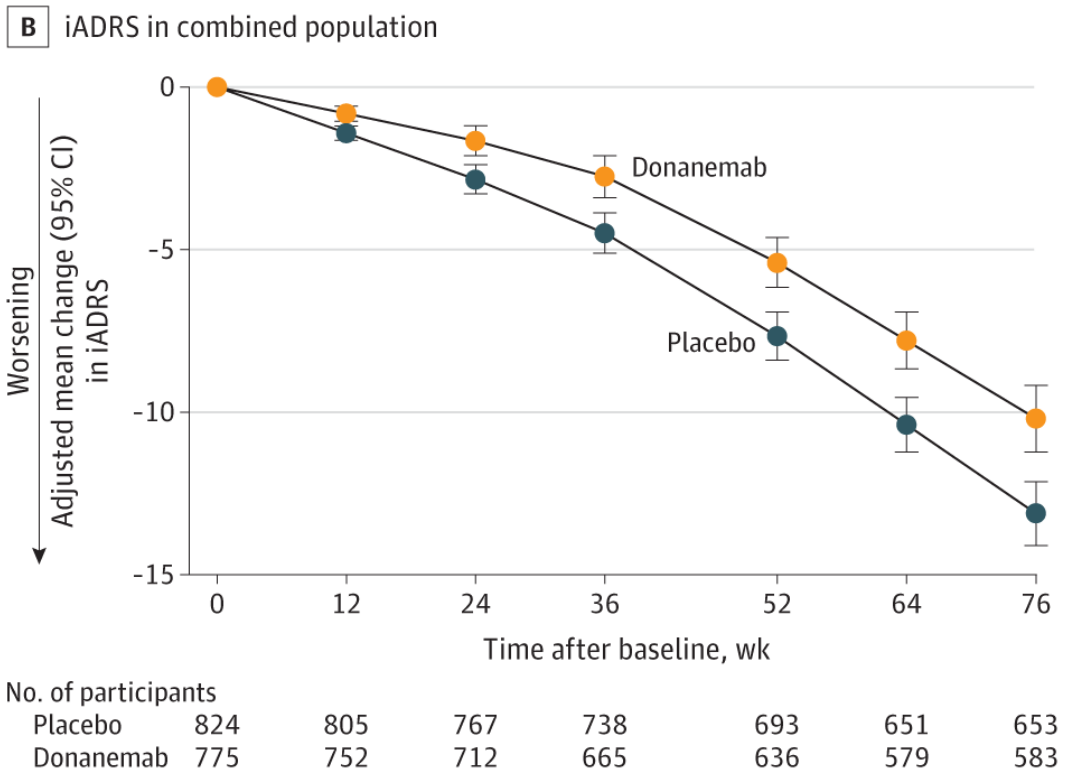
876
Placebo
Administered intravenously every 4 weeks for up to 72 weeks

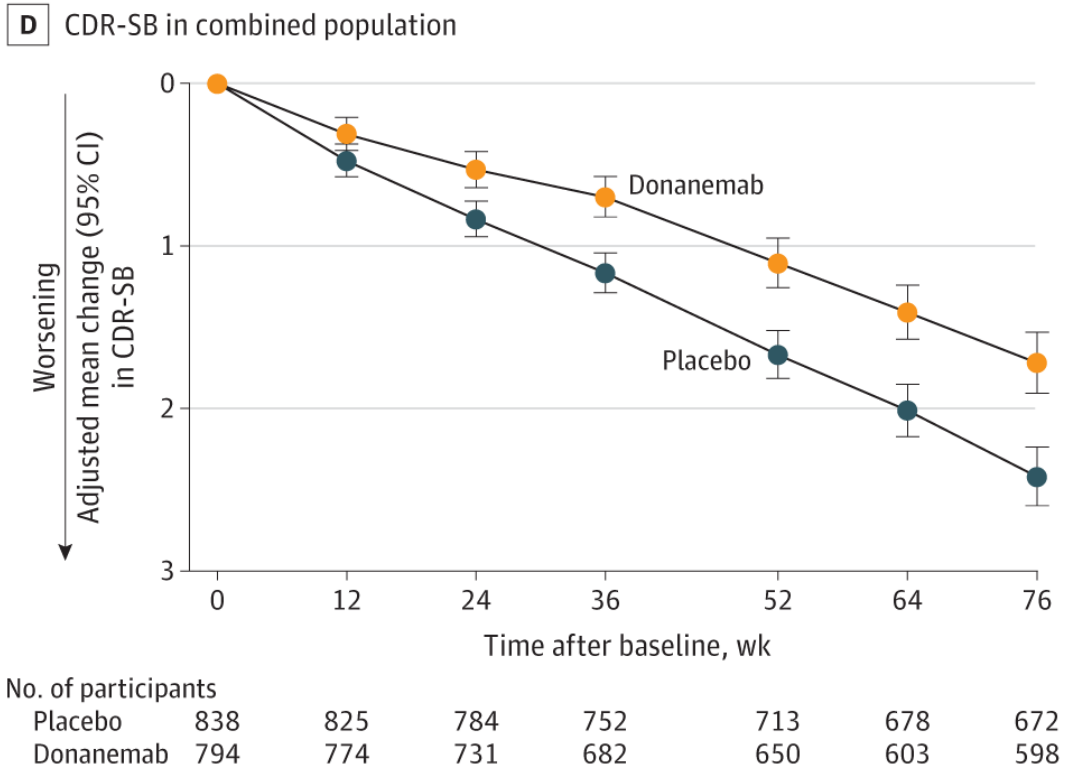
PRIMARY OUTCOME

Least-squares mean change in integrated Alzheimer Disease Rating Scale (iADRS) score (range, 0-144; lower scores indicate greater impairment) from baseline to 76 weeks

Sims JR, et al. *JAMA*. 2023;330(6):512-527.

Donanemab—TRAILBLAZER-ALZ Trial

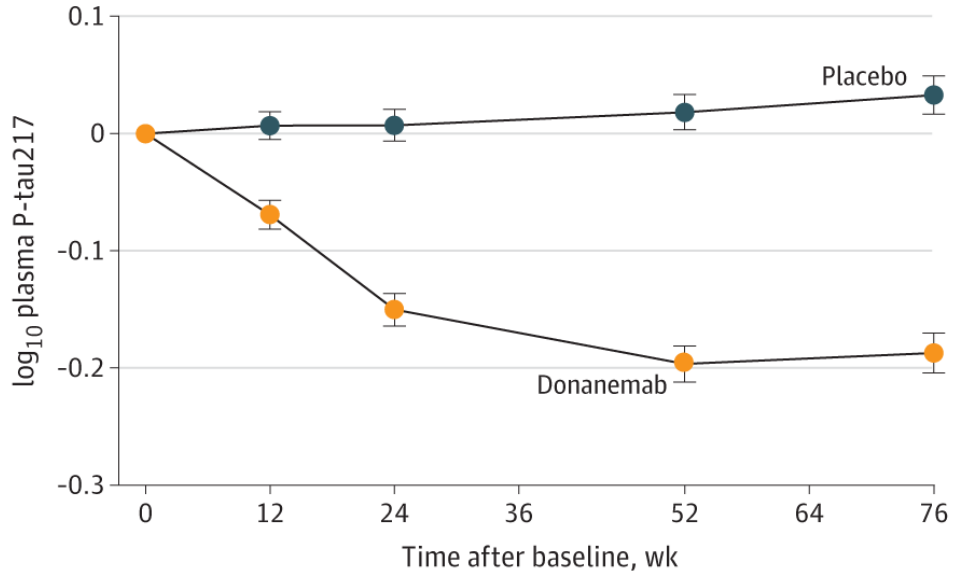




Sims JR, et al. *JAMA*. 2023;330(6):512-527.

Donanemab—TRAILBLAZER-ALZ Trial

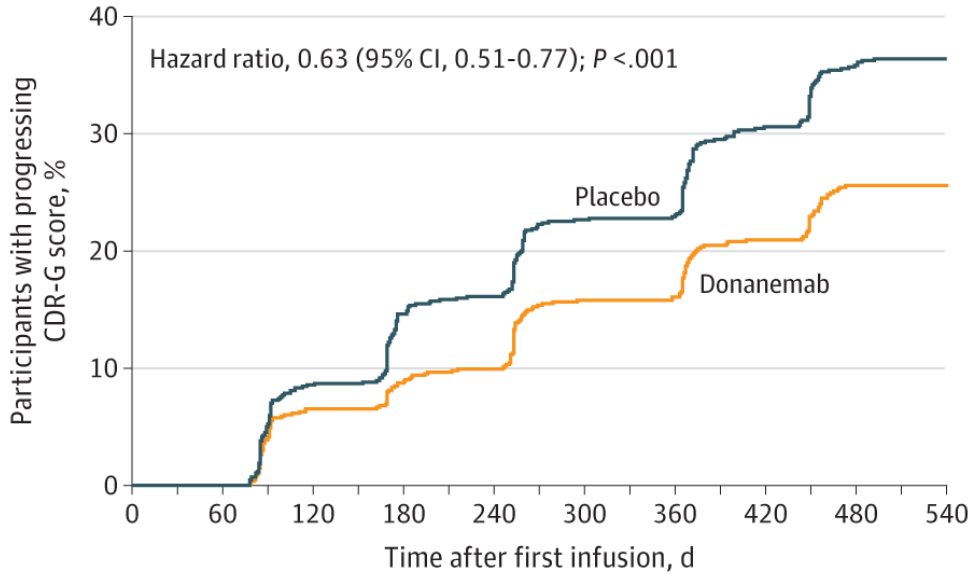
D Adjusted mean change (95% CI) of log_{10} plasma P-tau217 in combined population



No. of participants

Placebo	786	758	734	658	620
Donanemab	758	717	686	602	568

F CDR-G score in combined population



No. of participants at risk

Treatment	60 d	120 d	180 d	240 d	360 d	480 d
Placebo	840	764	700	671	587	462
Donanemab	801	737	696	696	575	474

CDR-G = global CDR.

Sims JR, et al. *JAMA*. 2023;330(6):512-527.

Donanemab—TRAILBLAZER-ALZ Adverse Effects

Event	Donanemab (n = 853)[a]	Placebo (n = 874)[a]
Overview of AEs, No. (%)		
Death[b]	16 (1.9)[c]	10 (1.1)
Death considered related to treatment[d]	3 (0.4)	1 (0.1)
Participants with ≥1 serious AE[e]	148 (17.4)	138 (15.8)
Treatment discontinuations due to AEs	112 (13.1)	38 (4.3)
Study discontinuations due to AEs	69 (8.1)	32 (3.7)
Participants with ≥1 treatment-emergent AE[f]	759 (89.0)	718 (82.2)
Treatment-emergent AEs ≥5% incidence, No. (%)		
ARIA-E	205 (24.0)	17 (1.9)
ARIA-H	168 (19.7)	65 (7.4)
COVID-19	136 (15.9)	154 (17.6)
Headache	119 (14.0)	86 (9.8)
Fall	114 (13.4)	110 (12.6)
Infusion-related reaction	74 (8.7)	4 (0.5)

Sims JR, et al. *JAMA*. 2023;330(6):512-527.

Donanemab—TRAILBLAZER-ALZ Adverse Effects

Overview of ARIA[g]		
Microhemorrhage or superficial siderosis present at baseline, No. (%)	124 (14.5)	161 (18.4)
ARIA-E by *APOE* ε4 allele status, No./total No. (%)		
Noncarrier	40/255 (15.7)	2/250 (0.8)
Heterozygous carrier	103/452 (22.8)	9/474 (1.9)
Homozygous carrier	58/143 (40.6)	5/146 (3.4)
Any ARIA, No. (%)[h]	314 (36.8)	130 (14.9)
ARIA-E, No. (%)	205 (24.0)	18 (2.1)
Asymptomatic	153 (17.9)	17 (1.9)
Symptomatic	52 (6.1)	1 (0.1)[i]
ARIA-H, No. (%)	268 (31.4)	119 (13.6)
Microhemorrhage	229 (26.8)	109 (12.5)
Superficial siderosis	134 (15.7)	26 (3.0)
Intracerebral hemorrhage >1 cm	3 (0.4)	2 (0.2)

Sims JR, et al. *JAMA*. 2023;330(6):512-527.

Adverse Events and Amyloid Plaque—Lower Monoclonal Antibodies

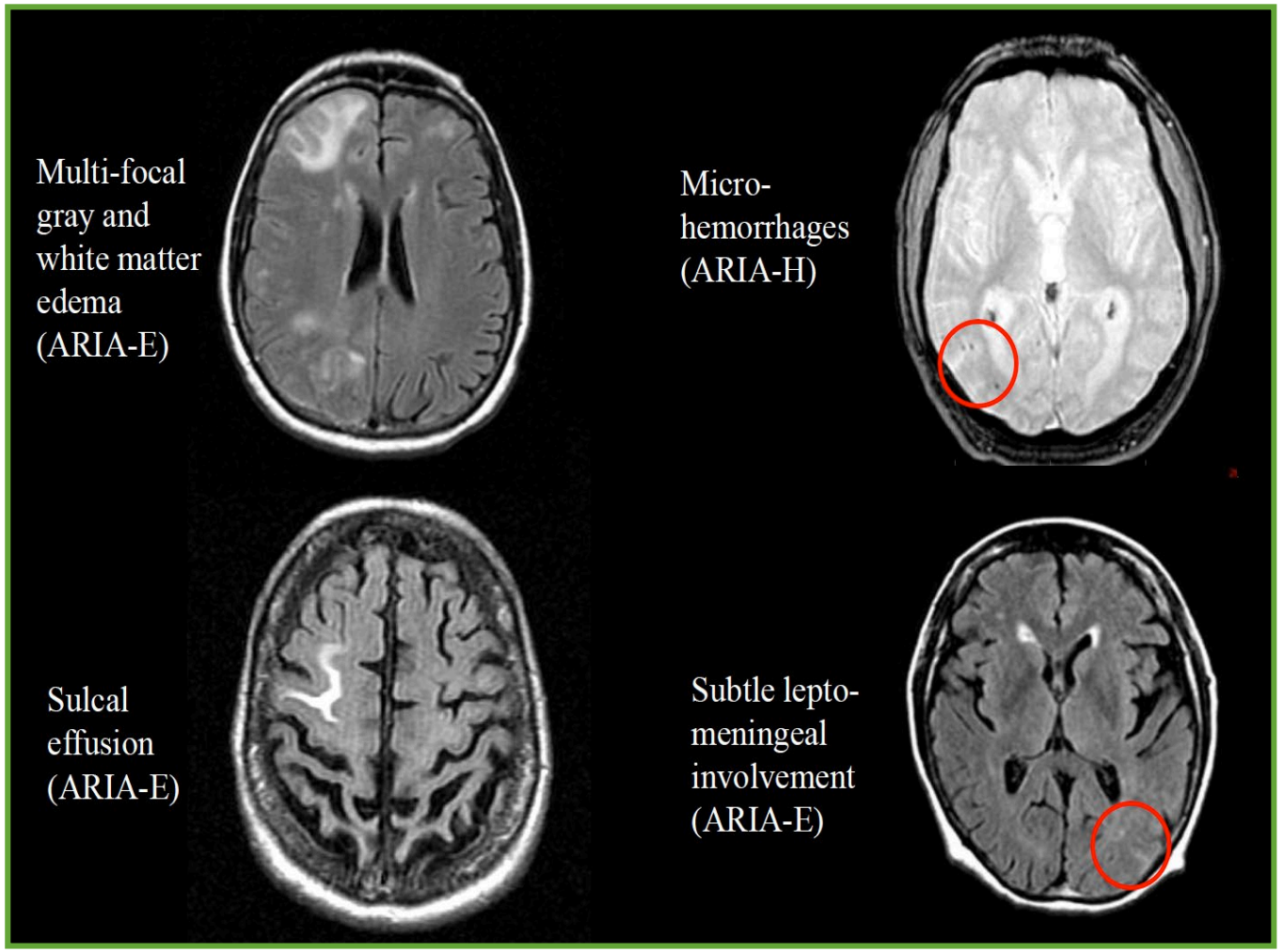
- Amyloid-related imaging abnormalities (ARIAs) are the most common side effects of amyloid-targeting therapies (ATTs)
  - Typically asymptomatic and detected only on MRI, but may lead to headache, worsening confusion, dizziness, visual disturbances, nausea, and seizures
  - ARIA risk increases with higher doses, as well as in patients with ApoE4 allele
  - MRI monitoring prior to treatment and dose escalations, and if new symptoms occur, is critical
  - Dose should balance maximum clinical efficacy alongside minimizing ARIA risk
- Infusion reactions are also common, but are typically mild to moderate

ARIAs typically occur early in the ATT treatment course and are often transient/asymptomatic

Withington CG, et al. *Front Neurol.* 2022;13:862369. Barakos J, et al. *J Prev Alzheimers Dis*. 2022;9(2):211-220.

Amyloid-Related Imaging Abnormalities

- **ARIA-E**: signal hyperintensities thought to represent "vasogenic edema" and/or sulcal effusion
- **ARIA-H**: signal hypointensities on GRE/T2-weighted MRI thought to represent hemosiderin deposits, including microhemorrhage and superficial siderosis
- Etiology is unclear, but MOA has been hypothesized



GRE = gradient recalled echo; MOA = mechanism of action.

Sperling RA, et al. *Alzheimers Dement*. 2011;7(4):367-385. Sperling R, et al. *Lancet Neurol.* 2012;11(3):241-249. Greenberg SM, et al. *Nat Rev Neurol.* 2020;16(1):30-42.

Inflammation and Brain Aging

- Normal inflammation protects the body from infection/injury
- Brain inflammation associated with aging
- Less inflammation may protect brain health
- Anti-inflammatory lifestyle strategies
  - A good night's sleep
  - Eating omega-3 fatty acids (fish oils, nuts)
  - Physical exercise

NAPDH = nicotinamide adenine dinucleotide phosphate with hydrogen source; IL = interleukin; TNF = tumor necrosis factor; iNOS = inducible nitric oxide synthase; NO = nitric oxide; O_2 = oxygen; SOD = superoxide dismutase.

Small GW. In: Berganier CD, et al (Eds). *Handbook of Nutrition and Food.* 3rd ed. CRC Press; 2013. Chen ST, Small GW. In: Aggarwal BB, et al (Eds). *Immunonutrition: Interactions of Diet, Genetics, and Inflammation*. CRC Press; 2015. Small GW. *J Fam Pract*. 2022;1771(Suppl 6):S82-S87.

Randomized, Placebo-Controlled Trials of Anti-Inflammatory Interventions in Normal Aging and MCI

- 18-month studies mean age: 59 years
- Celecoxib
  - Improved executive function (*P*=.03) and semantic memory (*P*=.02)
  - Increased prefrontal cortical metabolism by 6% (*P*=.01)
- Bioavailable curcumin
  - Improved memory and attention scores (*P*<.01)
  - Symptom benefits associated with amyloid and tau accumulations in brain regions modulating mood and memory (*P*<.05)

Small GW, et al. *Am J Geriatr Psychiatry*. 2018;26(3):266-277. Small GW, et al. *Am J Geriatr Psychiatry*. 2008;16(12):999-1009.

Key Learning Points

- Both pharmacological and non-pharmacological treatments can mitigate symptoms of AD
- Treatment with donanemab significantly slows AD clinical progression at 76 weeks in patients with early symptomatic AD and low/medium tau levels and/or combined low/medium and high tau pathology
- ARIAs typically occur early in the treatment course of amyloid-targeting therapies and are usually transient and asymptomatic

Cost Effectiveness Considerations for the Amyloid-β Targeting Therapies

Winston Wong, PharmD
President
W-Squared Group
Longboat Key, Florida

Approved Monoclonal Antibody

While aducanumab, donanemab, and lecanemab targeting beta-amyloid in the brain are of the same class of treatments, the MOAs are different

They work differently by targeting beta-amyloid at different stages of plaque formation, ultimately reducing beta-amyloid to slow progression of the disease and to reduce clinical decline

IV = intravenous; LP = lumbar puncture.

Food and Drug Administration. April 2022. Accessed September 21, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761178s005lbl.pdf. Food and Drug Administration. July 2023. Accessed September 21, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761269Orig1s001lbl.pdf. Food and Drug Administration. July 2024. Accessed September 21, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/761248s000lbl.pdf. Alzheimer's Association. Accessed September 21, 2024.

Cost Comparisons and Cost-Effective Analyses

ICER Evaluation: Lecanemab for Early Alzheimer's Disease

- Lecanemab-irmb was evaluated in a phase III randomized clinical trial—Clarity AD
- The Institute for Clinical and Economic Review (ICER) estimated the lifetime cost effectiveness of lecanemab-irmb in addition to supportive care as compared to supportive care alone from a healthcare sector perspective
- From both perspectives, lecanemab-irmb's annual price of $26,500 exceeded commonly used cost-effectiveness thresholds; ICER's Health Benefit Price Benchmark (HBPB) for lecanemab-irmb is $8,900 to $21,500, requiring a 66% to 19% discount from lecanemab-irmb's wholesale acquisition cost (WAC)

Original Investigation: Cost-Effectiveness of Donanemab for Early Alzheimer Disease in the United States

- A decision analytic model was used to estimate the lifetime health and economic outcomes of adults with early AD, from US healthcare sector and societal perspectives
- Quality-adjusted life-years (QALYs); costs, in 2020 US dollars; incremental cost-effectiveness ratios (ICERs); and value-based prices, defined as the maximum price at which a treatment would be cost-effective given a cost-effectiveness threshold of ICER of $150,000/QALY
- Relative to standard care, donanemab-azbt increased QALYs by 0.408; total healthcare sector and societal costs increased by $78,700 and $71,600, respectively
- Conclusion: donanemab-azbt is not likely to be cost-effective at their expected prices of more than $25,000/year; to become cost-effective, donanemab-azbt's price would need to decrease to less than $20,000/year

Lin GA, et al. Institute for Clinical and Economic Review. December 22, 2022. Accessed April 17, 2023. https://icer.org/wp-content/uploads/2021/12/ICER_Alzheimers-Disease_Draft-Report_12222022-1.pdf. Ross EL, et al. *JAMA Neurol*. 2022;79(5):478-487.

Considerations for a Limited-Duration Dosing Scheme

- TRAILBLAZER-ALZ 2: a 76-week, randomized, double-blind, parallel, multicenter trial
- Donanemab was switched to placebo in a blinded procedure if amyloid plaque level, assessed at weeks 24 and 52, was
  - Less than 11 Centiloids on any single PET scan, or
  - Less than 25 but greater than or equal to 11 Centiloids on 2 consecutive PET scans
    - < 24.1 Centiloids on an amyloid PET scan is consistent with a negative visual read
- Final adverse events and efficacy assessments were performed at 76 weeks
- Amyloid-related imaging abnormality monitoring occurred with scheduled MRIs at 4, 12, 24, 52, and 76 weeks and unscheduled MRIs at investigator discretion
- Clearance beyond 76 weeks and associated Alzheimer disease biomarker levels are currently being studied in the ongoing extension phase

Sims JR, et al. *JAMA*. 2023;330(6):512-527.

ICER Lecanemab Policy Recommendations

- All stakeholders have a responsibility and an important role to play in ensuring that new treatment options for patients with AD are introduced in a way that addresses the impact on health inequities
  - Payers, healthcare systems, clinicians, and policymakers should work together to ensure that the financial incentives associated with infusion delivery do not overly influence patient selection and prescribing
  - All stakeholders would benefit from a robust yet practical evidence generation system linked to payer coverage in order to learn more about the real-world risks and benefits of lecanemab
- Prior authorization criteria for lecanemab should be based on clinical evidence and input from clinical experts and patient groups; the process for authorization should also be clear, accessible, efficient, and timely for providers
  - Criteria should define age group, clinical eligibility including testing, exclusion criteria, duration of the authorization and renewal criteria, provider restrictions, and step therapy

The Bottom Line

Payers need to balance the need for better evidence with the risks to equal access for patients with fewer economic resources and those from communities with less connection to academic clinicians and institutions.

Institute for Clinical and Economic Review. April 17, 2023. https://icer.org/wp-content/uploads/2023/04/ICER_Alzheimers-Disease_Policy-Recommendations_04172023.pdf.

Managed Care Pharmacy Considerations

- MCOs should prioritize and encourage appropriate, timely testing for cognitive status earlier in the disease process utilizing the current standard evaluation tools and processes
  - Includes the timely evaluation and screening by primary care providers, eg, MMSE, MoCA, Mini-Cog
- Diagnosis of MCI or mild AD, as well as confirmation of the presence of amyloid and evaluation for comorbidities that may heighten the risk of or be contraindications to treatment are usually done by a dementia specialist
  - Use of dementia specialists within one year of diagnosis is low, particularly amongst Black and Asian Americans
- Payers need to be more open to coverage of the PET/MRI scans and ApoE genotype testing, as well as MRIs to monitor for ARIA complications
- Care planning should be encouraged and covered for all patients with AD, as it educates patients and care partners on medical and nonmedical treatments as well as assisting to coordinate care
  - This should include recognition and reimbursement of a Certified Dementia Practitioner®

MCO = managed care organization; MMSE = mini-mental state examination; MoCA = Montreal Cognitive Assessment.

Wong W. *Am J Manag Care*. 2020;26(8 Suppl):S177-S183.

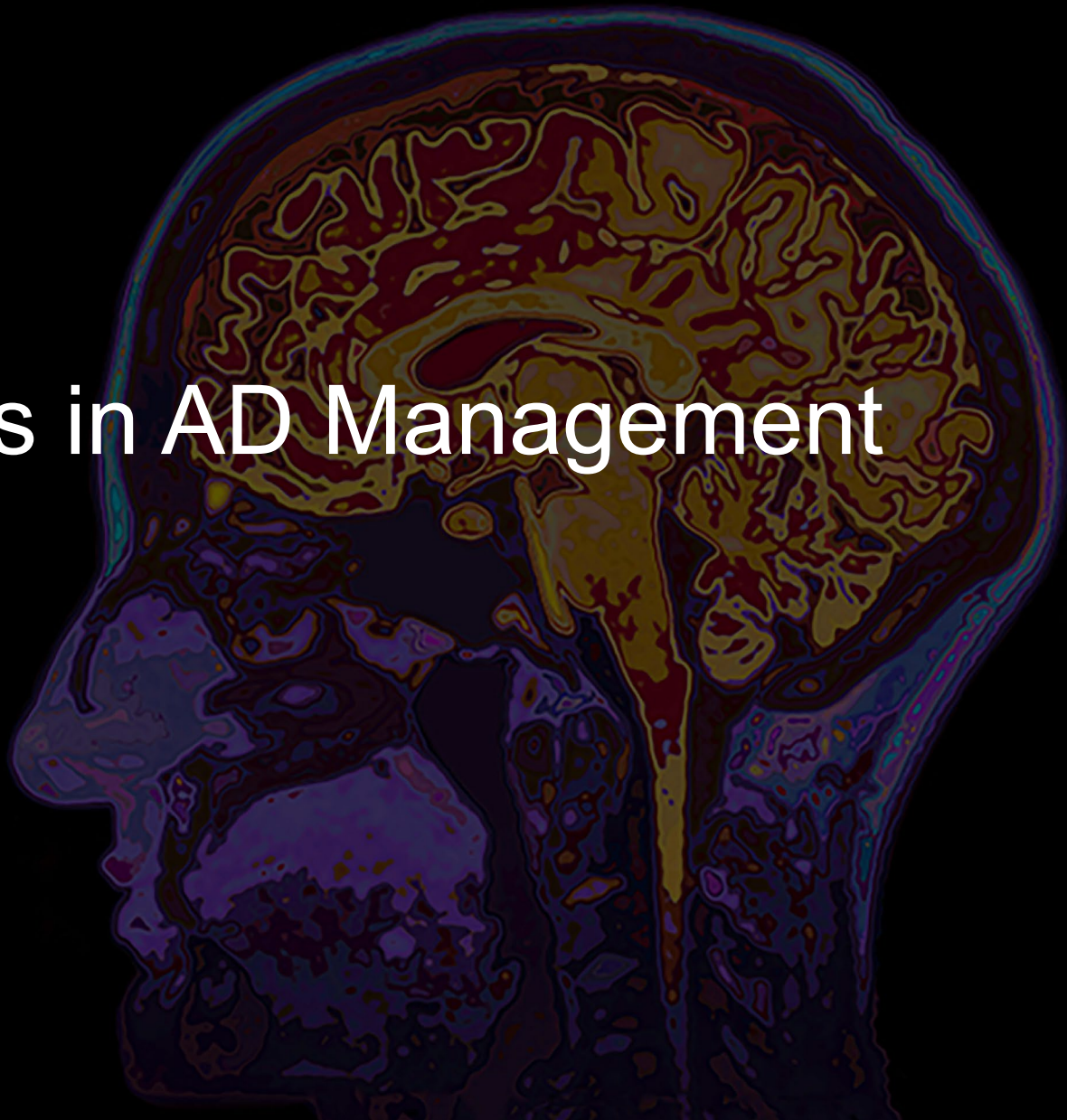
Key Learning Points

- In 2024, about 1 in 9 people (10.9%) over age 65 have Alzheimer's dementia, projecting an estimated 6.9 million Americans over age 65 are living with Alzheimer's dementia
- Total cost of care for 2024 for all individuals with Alzheimer's disease or other dementias are estimated at $360 billion, of which an estimated 64% is covered by Medicare
- Lecanemab-irmb and donanemab-azbt have full FDA approval for mild cognitive impairment (MCI) or mild dementia to slow disease progression
  - Neither medication has been shown to restore or reverse memory loss or cognitive function
  - No other medications have been shown to slow progression

- Neither medication has been shown to be cost-effective by standard cost evaluation methodologies
- Prior authorization criteria should be based on clinical evidence and input from clinical experts and patient groups; the process for authorization should also be clear, accessible, efficient, and timely for providers
- MCOs should prioritize and encourage appropriate, timely testing for cognitive status earlier in the disease process utilizing the current standard evaluation tools and processes
- Payers need to be more open to coverage of the PET/MRI scans and ApoE genotype testing, as well as MRIs to monitor for ARIA complications

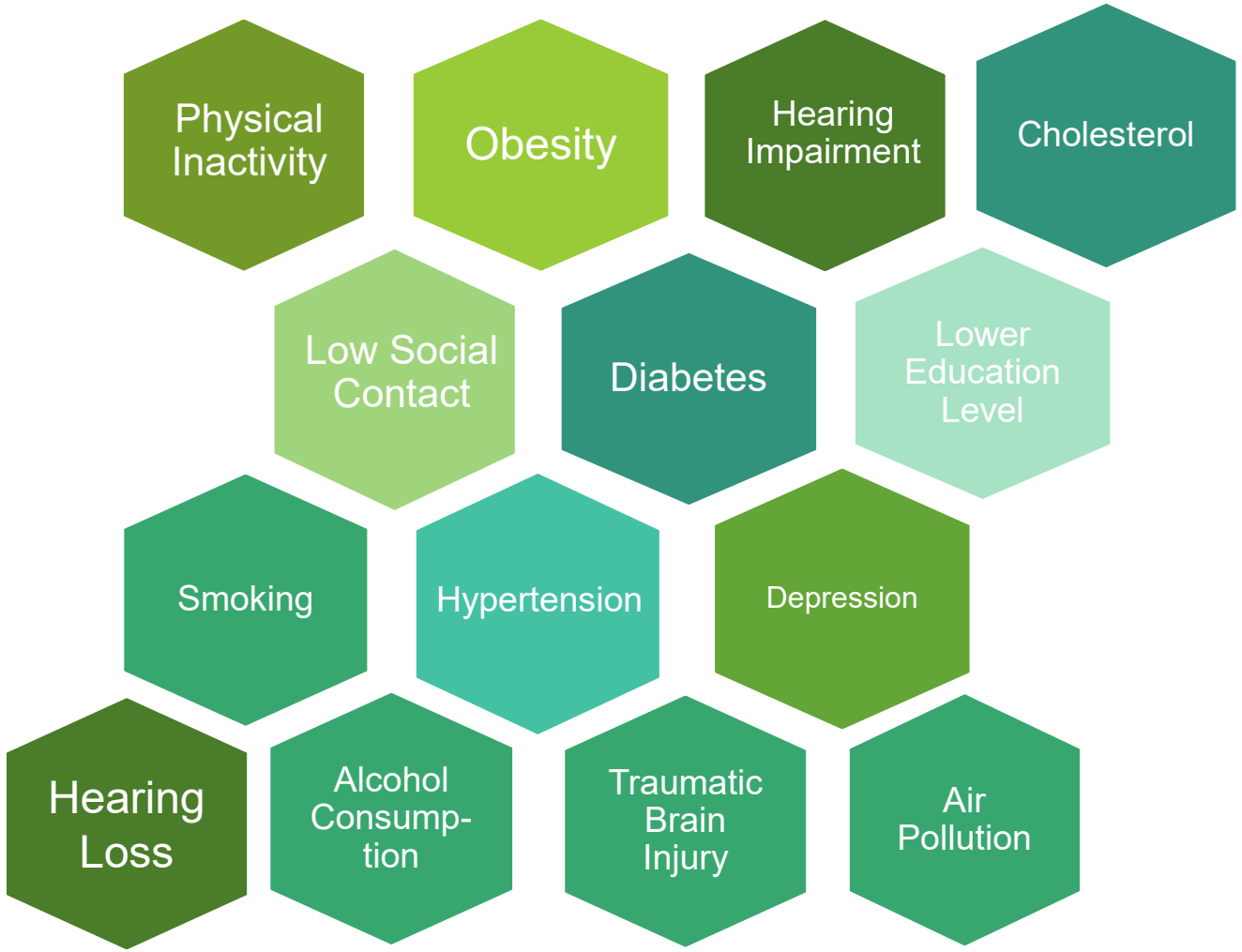
Alzheimer's Association. Accessed October 7, 2024. https://www.alz.org/alzheimers-dementia/facts-figures.

The Role of Pharmacists in AD Management



Dementia Prevention, Intervention, and Care: 2024 Report of *Lancet Standing Commission*

- Identified 14 potential modifiable risk factors for dementia →
- The potential for prevention is high and, overall, nearly half of dementias could theoretically be prevented by eliminating these 14 risk factors
- It is never too early or too late to reduce dementia risk (the earlier the better; the longer the better)
- Interventions should be individualized and consider the patient as a whole, including family care partners
- Keeping people with dementia physically healthy is important for their cognition
- It is clear that risk can be modified even in people with increased genetic risk of dementia



Livingston G, et al. *Lancet.* 2024;404(10452):572-628.

Dementia Care Practice Recommendations

Treatment Approach

- The Dementia Care Practice Recommendations were developed to better define quality care across all care settings and throughout the disease course
- The Alzheimer's Association Practice Recommendations focus care on the individual with dementia and their care partner in a person-centered care delivery model
- The focus of care is based on an individual's unique needs, personal experiences and strengths, rather than on the loss of abilities
- The guidelines for treatment of dementia-related behaviors call for nonpharmacologic psychosocial interventions to be used as first-line interventions
- Pharmacologic interventions should be used for the treatment of cognitive symptoms with the goal of improving symptoms of memory loss and confusion; however, they do not stop the progression

Fazio S, et al. *Gerontologist.* 2018;58(Suppl 1):S1-S9. Powers J, et al. *Geriatrics*. 2018;3(2):29.

Patient-Centered and Collaborative Care Strategies

- The fundamentals of patient-centered care are the foundation of the Dementia Care Practice Recommendations
  - Know the person living with dementia
  - Recognize and accept the person's reality
  - Identify and support ongoing opportunities for meaningful engagement
  - Build and nurture authentic, caring relationships
  - Create and maintain a supportive community for individuals, families, and staff
  - Evaluate care practices regularly and make appropriate changes
- Use assessment as an opportunity for information-gathering, relationship-building, education, and support, and approach the assessment and care planning with a collaborative, team approach
- Take a holistic, person-centered approach to care and embrace a positive approach to the support for persons living with dementia and their care partners that acknowledges the importance of individuals' ongoing medical care to their well-being and quality of life
- Work with the person living with dementia, the family, and the primary care physician to create and implement a person-centered plan for possible medical and social crises

Fazio S, et al. *Gerontologist.* 2018;58(Suppl 1):S1-S9.

The Role of the Pharmacist in AD Care

- The pharmacist needs to actively engage in the interdisciplinary care team, supporting the patient-centered concept
- A key priority is the identification of early management of modifiable factors that will decrease the risk, delay the onset, or slow the progression of the disease
  - Patients will most likely be asymptomatic or in the early stages of MCI
  - Care management activities would be consistent with the appropriate management of chronic diseases, eg, blood pressure, cholesterol, diabetes, depression
- Through patient interactions, pharmacists could be the point of recognition of cognitive impairment (CI), complete various screening tools for CI, and communicate the findings to the interdisciplinary team
- Once treatment is started, pharmacists can continue their MTM services to monitor for efficacy and adverse effects and provide general education pertinent to the medications to appropriately manage patient expectations
  - Most significant to targeted amyloid-β treatment are injection site reactions and the onset of ARIA
- Pharmacists represent a point of quality health information for many patients and care partners, as well as providing continuous medication monitoring and training of the interdisciplinary team

MTM = medication therapy management.

Ramos H, et al. *Int J Environ Res Public Health*. 2021;18(19):9934.

Key Learning Points

- Take a holistic, person-centered approach to care and embrace a positive approach to the support for persons living with dementia and their care partners
- Work with the person living with dementia, the family, and the primary care physician to create and implement a person-centered plan for possible medical and social crises
- MCOs should prioritize and encourage appropriate, timely testing for cognitive status earlier in the disease process utilizing the current standard evaluation tools and processes
- Interventions to reduce dementia risk should be individualized, considering the “whole” patient, including family care partners
    - Intervention to reduce risk can never start too early or too late to reduce dementia risk (the earlier, the better; the longer, the better)
- Pharmacists represent a point of quality health information for many patients and care partners, as well as providing continuous medication monitoring and training of the interdisciplinary team

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