



Alzheimer's disease and the impact of early intervention

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Topics of Discussion in Today's Presentation



Alzheimer's disease overview



Key considerations throughout the patient journey



Potential impact of early intervention

Our speaker will not be discussing or addressing questions about product-related information in this presentation.

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Alzheimer's disease overview



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AD is a chronic neurodegenerative disorder that is both progressive and irreversible¹

AD is the cause of **~60%-80%** of all dementia cases*¹

An estimated **6.5 million** people in the US aged 65 years and older are living with AD dementia in 2022; this figure is expected to increase 11% by 2025¹

In 2020, AD ranked as the **4th** leading cause of death in the US and **3rd** leading cause of death for those aged 65 years and older²

Deaths caused by AD are increasing in the US

In 2020, AD was responsible for 134,242 deaths in the US, with a 10.5% increase in cases compared with 2019¹

*Dementia refers to a group of symptoms, including difficulties with memory, language, and problem-solving, that affect a person's ability to perform daily activities.¹
AD=Alzheimer's disease.

References: 1. Alzheimer's Association. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2022;18(4):1-122. 2. CDC WONDER online database: Underlying Cause of Death, 1999-2020. Centers for Disease Control and Prevention, National Center for Health Statistics. Updated March 11, 2021. Accessed April 15, 2022. <https://wonder.cdc.gov/ucd-icd10.html>.

Multiple factors may increase the risk of AD

Fixed risk factors



Age¹

- Most individuals with AD are aged 65 and older
- After age 65, the risk of AD doubles every 10 years



Genetics¹

- *ApoE4* variant has been linked to AD
- Genetic mutations can lead to early-onset AD, the symptoms of which can start as young as age 30



Race²

- Black: 2x increased likelihood of AD
- Hispanic: 1.5x increased likelihood of AD



Sex³

- Two-thirds of people with AD are women

Modifiable risk factors



Major lifestyle factors¹

- Physical inactivity
- Smoking
- Fewer years of education
- Lack of social and cognitive engagement
- Poor sleep quality
- Excessive alcohol use
- Poor or unhealthy diet



Cardiovascular comorbidities¹

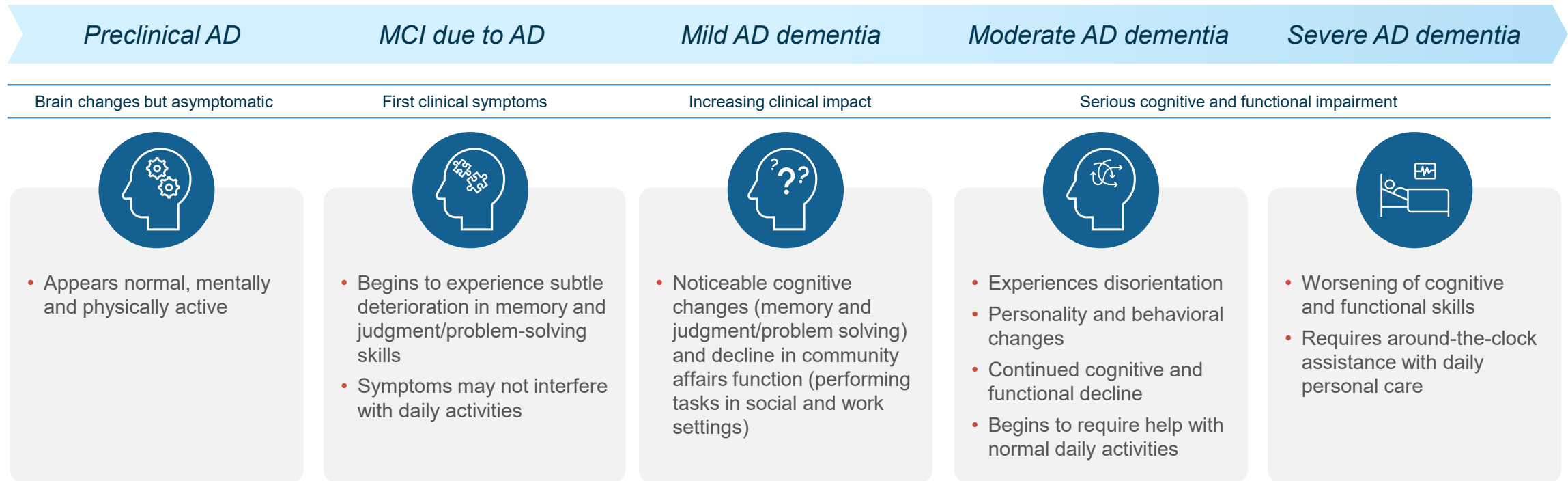
- Obesity
- High blood pressure
- High cholesterol
- Poorly controlled diabetes

AD=Alzheimer's disease; *ApoE*=apolipoprotein E.

References: 1. Alzheimer's Association. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2022;18(4):1-122. 2. Alzheimer's Association. Factsheet: race, ethnicity, and Alzheimer's. Published March 2020. Accessed May 5, 2022. https://www.alz.org/aaic/downloads2020/2020_Race_and_Ethnicity_Fact_Sheet.pdf. 3. Mielke M. *Psychiatr Times.* 2018;35(11):14-17.

Cognitive symptoms first emerge in the mild cognitive impairment stage —both cognition and function decline as AD progresses¹

AD continuum¹⁻³

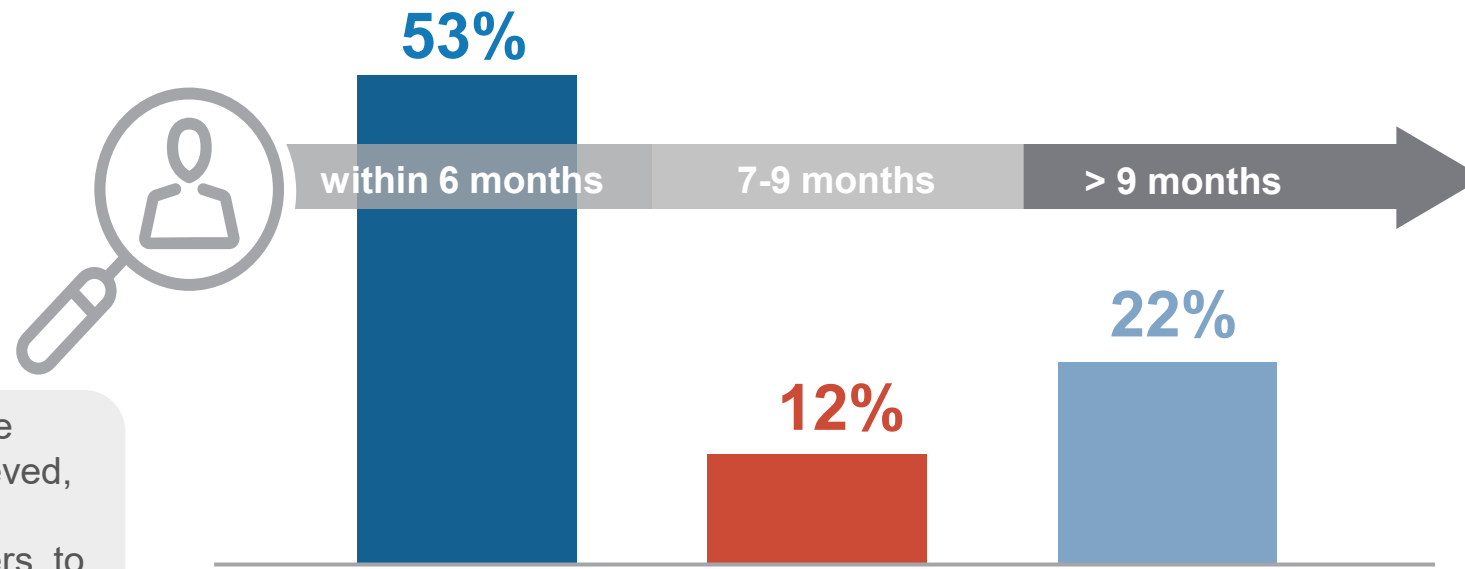


Total cost of hospitalization, nursing homes, and home care services increases as the disease progresses⁴

AD=Alzheimer's disease; MCI=mild cognitive impairment.

References: 1. Alzheimer's Association. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2022;18(4):1-122. 2. Alzheimer's Association. Stages of Alzheimer's. Accessed April 28, 2022. <https://www.alz.org/alzheimers-dementia/stages>. 3. Alzheimer's Association. Mild cognitive impairment (MCI). Accessed April 28, 2022. https://www.alz.org/alzheimers-dementia/what-is-dementia/related_conditions/mild-cognitive-impairment. 4. Ton TGN et al. *Alzheimers Dement.* 2017;13(3):217-224.

Initial symptoms may be similar to normal aging resulting in delayed diagnosis



Symptoms of cognitive decline are often believed, by some physicians, patients, and caregivers, to be part of normal aging^{1,2}

The largest portion of patients (~60%) are diagnosed in the **mild to moderate** stage of AD^{1*}

Percentage of patients and time to receiving a final AD diagnosis after presenting with first symptoms (n=868)^{1*}

? What impact could earlier diagnosis have on your care model?

*Data based on online questionnaires and patient record forms (PRFs) were created by an independent market research agency and completed by participating physicians.

AD=Alzheimer's disease.

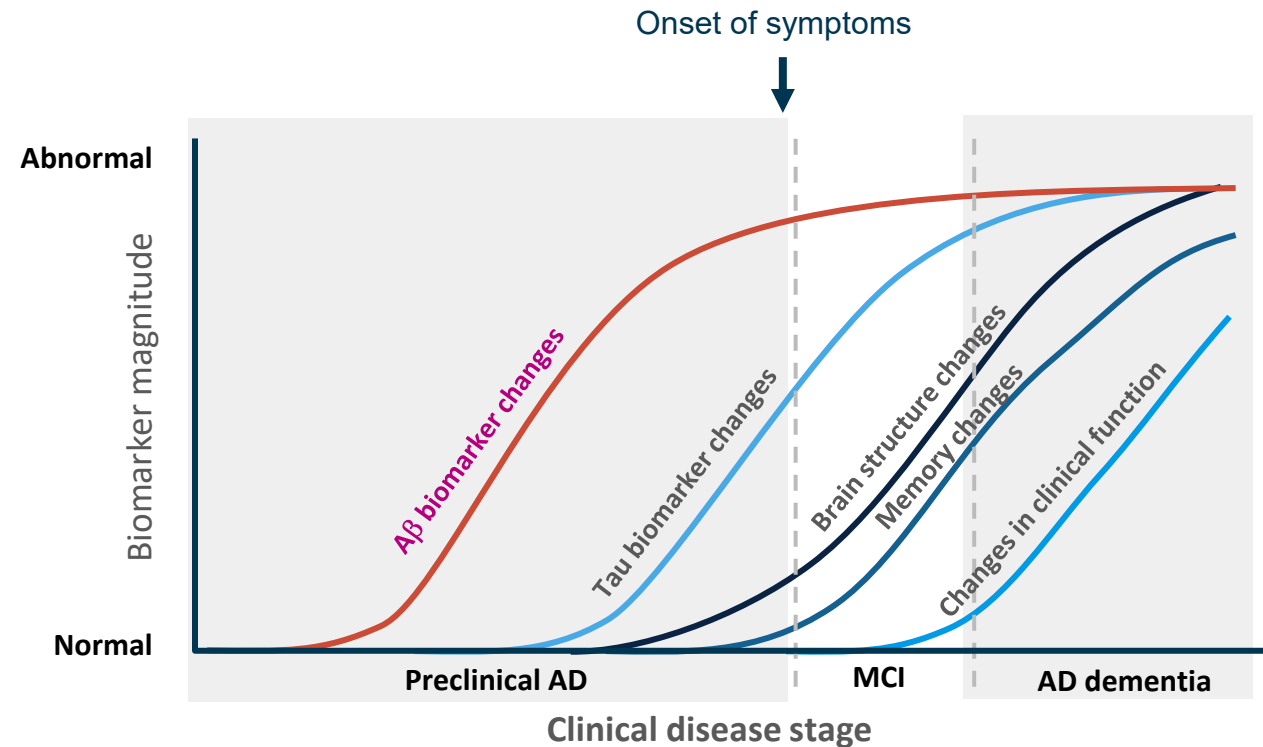
References: 1. Podhorna J et al. *Adv Ther.* 2020;37:883-893. 2. Judge D et al. *Int J Alzheimers Dis.* 2019;2019:3637954.

A β and tau accumulation occur decades before symptom onset and clinical decline^{1,2}

International Working Group Recommendation of Clinical-Biological AD Diagnosis

Evaluating both amyloid and tau biomarkers along with a patient's symptoms can help determine the likelihood of an AD diagnosis and whether additional analyses are needed³

- CSF A β 42, T-tau, and P-tau can be used to support an AD diagnosis^{1,3}
- Amyloid biomarkers are the first ones to become abnormal in the course of AD, and can be measured by CSF A β 42 or amyloid PET¹

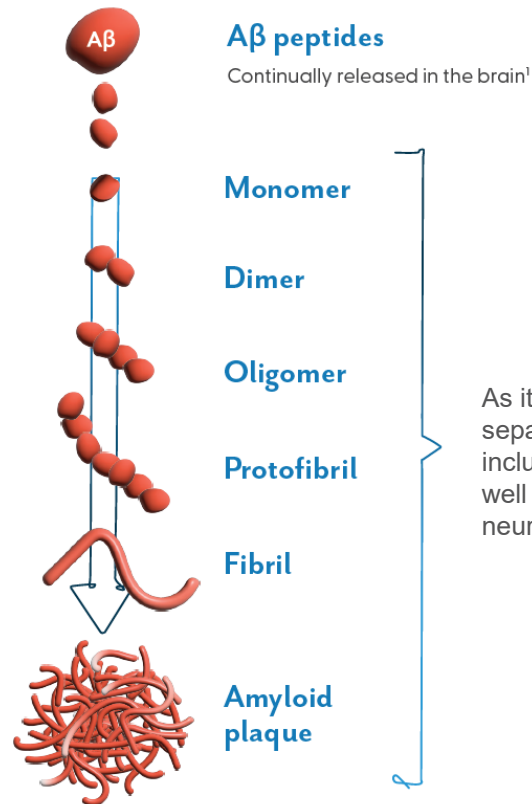


Graph adapted from Jack CR Jr, et al.

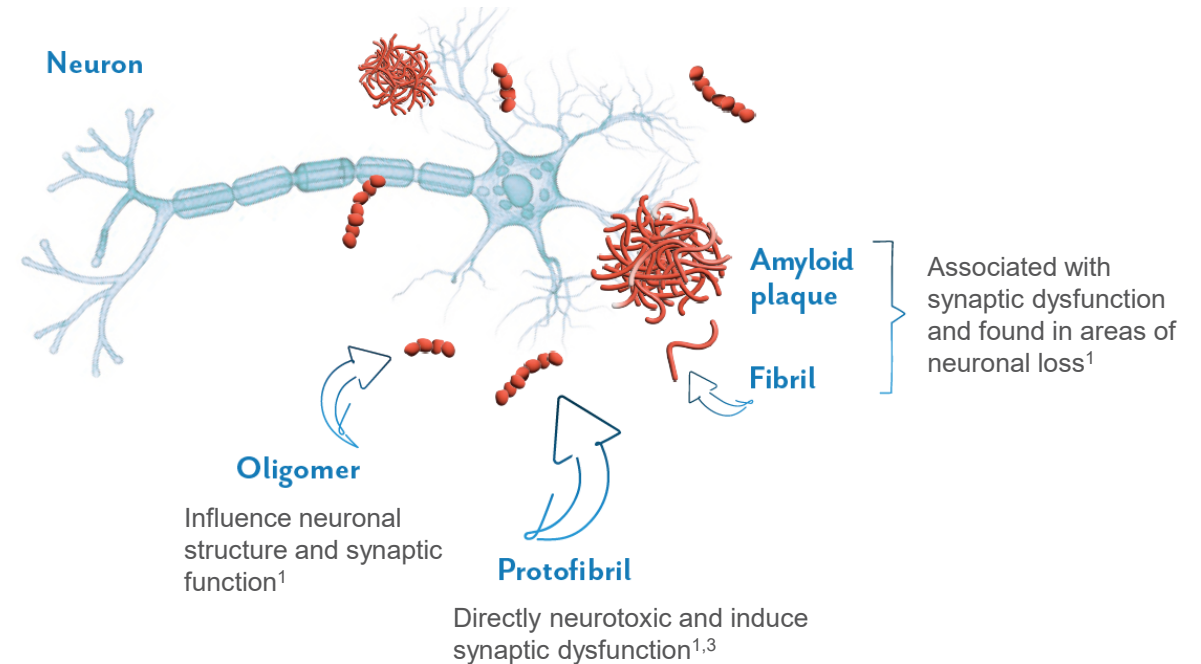
A β =amyloid beta; AD=Alzheimer's disease; CSF=cerebrospinal fluid; PET=positron emission tomography; P-tau=phosphorylated tau; T-tau=total tau.

References: 1. Jack CR Jr et al. *Lancet Neurol.* 2013;12(2):207-216. 2. Bateman RJ et al. *N Engl J Med.* 2012;367(9):795-804. 3. Dubois B et al. *Lancet Neurol.* 2021;20(6):484-496.

Ongoing accumulation of A β drives irreversible neurodegeneration*1,2



As it accumulates, A β can aggregate and separate into larger and smaller species, including oligomers and protofibrils, as well as plaque, that contribute to neurodegeneration¹



The A β cascade triggers downstream molecular pathways, including hyperphosphorylated tau, increased oxidative stress, inflammation, mitochondrial dysfunction, synaptic dysfunction, and ultimately, neuronal death^{1,4,5}

Early targeting of the accumulation of A β in MCI due to AD and mild AD phases is the most likely path to disrupting the pathological cascade^{6,7}

*Data from in vitro studies and in vivo animal models.¹

A β =amyloid beta; AD=Alzheimer's disease.

References: 1. Hampel H et al. *Mol Psychiatry*. 2021;26:5481-5503. 2. Shoji M, et al. *Science*. 1992;258(5079):126-129. 3. Walsh DM et al. *J Biol Chem*. 1999; 274(36):25945-25952. 4. Molinuevo JL et al. *Acta Neuropathol*. 2018;136(6):821-853. 5. Szabo L et al. *Int J Mol Sci*. 2020;21(17):6344. 6. Selkoe DJ, Hardy J. *EMBO Mol Med*. 2016;8(6):595-608. 7. Arbor SC et al. *Yale J Biol Med*. 2016;89(1):5-21.



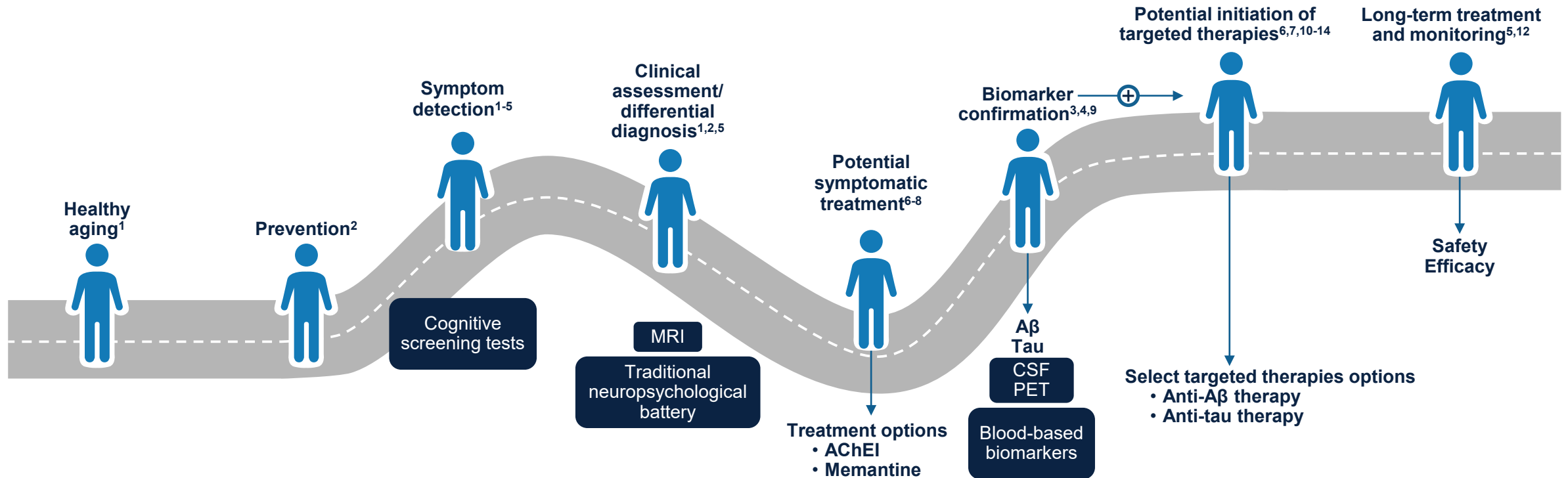
Key considerations throughout the patient journey



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Early AD patient journey involves multiple phases between symptom detection and potential treatment initiation

The average predicted wait time between the clinical diagnosis and treatment phases is 18.6 months*¹⁶



*This is the projected wait time for 2020.¹⁶

Aβ=amyloid beta; AChEI=acetylcholine esterase inhibitor; AD=Alzheimer's disease; CSF=cerebrospinal fluid; MRI=magnetic resonance imaging; PET=positron emission tomography.

References: 1. Wong-Lin K, et al. *BMC Med.* 2020;18(1):398. 2. Au R, et al. *Adv Geriatr Med Res.* 2019;1:e190003. 3. Hampel H, et al. *Nat Rev Neurol.* 2018;14(11):639-652. 4. Cummings J, et al. *Alzheimers Dement.* 2021;7:e12179. 5. Kourtis LC, et al. *NPJ Digit Med.* 2019;2(1):9. 6. Campbell NL, et al. *J Am Geriatr Soc.* 2017;65(7):1497-1504. 7. Koller D, et al. *J Am Geriatr Soc.* 2016;64(8):1540-1548. 8. Cummings J, et al. *J Alzheimers Dis.* 2019;67(3):779-794. 9. Hlavka JP, et al. *Rand Health Q.* 2019;8(3):2. 10. Cummings J. *Mol Neurodegeneration.* 2021;16(1):2. 11. Suh GH, et al. *Int Psychogeriatr.* 2009;21(6):1116-1126. 12. Brewer L, et al. *Eur J Clin Pharmacol.* 2013;69(7):1467-1475. 13. Congdon EE, et al. *Nat Rev Neurol.* 2018;14(7):399-415. 14. Yu TW, et al. *Int J Mol Sci.* 2021;22(15):1-29. 15. Van Oostveen WM, et al. *Int J Mol Sci.* 2021;22:1-34. 16. Liu JL, et al. RAND Corporation; 2017. https://www.rand.org/pubs/research_reports/RR2272.html.

Early intervention at the MCI due to AD and mild AD stages is essential for disease management

~1 in 3

people with MCI develop dementia due to AD within 5 years¹



- Begins to experience subtle deterioration in memory and judgment/problem-solving skills³
- Symptoms may not interfere with daily activities³

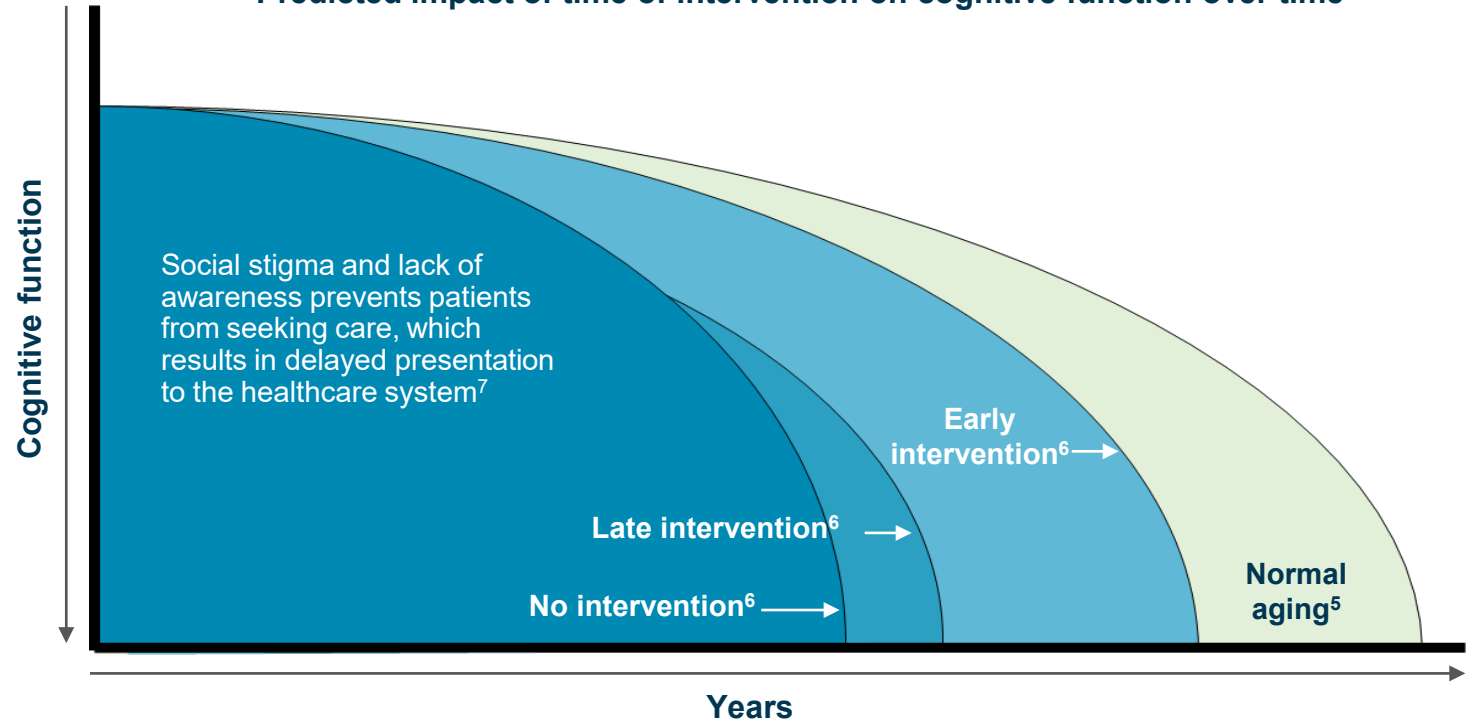
1 in 2

people with AD have mild disease²



- Noticeable cognitive changes (memory and judgment/problem solving) and decline in community affairs function (performing tasks in social and work settings)⁴

Predicted impact of time of intervention on cognitive function over time



AD=Alzheimer's disease; MCI=mild cognitive impairment.

References: 1. Alzheimer's Association. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2022;18(4):1-122. 2. Yuan J et al. *J Alzheimers Dis.* 2021;79(2):807-817. 3. Alzheimer's Association. Mild cognitive impairment (MCI). Accessed April 28, 2022. https://www.alz.org/alzheimers-dementia/what-is-dementia/related_conditions/mild-cognitive-impairment. 4. Alzheimer's Association. Stages of Alzheimer's. Accessed April 28, 2022. <https://www.alz.org/alzheimers-dementia/stages>. 5. Fuentes P. *Arch Med Res.* 2012;43(8):667-670. 6. Small GW. *Am J Geriatr Psychiatry.* 2016;24(12):1142-1150. 7. Alzheimer's Disease International. Published 2012. Accessed April 28, 2022. <https://www.alzint.org/u/WorldAlzheimerReport2012.pdf>.

To identify AD early, cognitive screening and structural imaging are key first steps

>60% of MCI patients are diagnosed with AD, although MCI may be caused by a range of processes¹



Suspected cognitive changes



Calibrated diagnostic tools are sensitive to MCI
(eg, MoCA test, Qmci screen, and CogState Brief Battery)^{2,3}



Structural imaging rules out other conditions that may cause symptoms similar to AD
(eg, MRI and CT scans)⁴

Patients screening positive on the cognitive tools may be referred to a dementia specialist for further evaluation and possible referral to testing for the presence of amyloid deposits⁵

AD=Alzheimer's disease; CT=computed tomography; MCI=mild cognitive impairment; MoCA=Montreal Cognitive Assessment; MRI=magnetic resonance imaging; Qmci=Quick Mild Cognitive Impairment.

References: 1. Knopman DS et al. *Alzheimers Dement (Amst)*. 2016;2:1-11. 2. O'Caomh R et al. *J Alzheimers Dis*. 2016;51(2):619-629. 3. Maruff P, et al. *BMC Pharmacol Toxicol*. 2013;1(1):1-11. 4. Alzheimer's Association. Medical tests for diagnosing Alzheimer's. Accessed April 8, 2022. https://www.alz.org/alzheimers-dementia/diagnosis/medical_tests. 5. Liu JL et al. RAND Corporation, 2017. Accessed April 8, 2022. https://www.rand.org/pubs/research_reports/RR2272.html.

Biomarker-confirmed AD diagnosis enables the identification of patients who would be appropriate for A β -targeting therapy



PET Scan

- Well established tool to confirm the presence of A β , 15 years before the onset of AD symptoms¹⁻⁴



CSF Assay

- Well established tool that can determine levels of A β , 20 years before the onset of MCI²⁻⁴



Blood-based biomarkers

- Attractive due to the accessible, less invasive, and relatively inexpensive nature of blood assays^{2,5}
- Once clinically validated for diagnostic use, they may help inform therapeutic decision-making^{2,5}
- Currently available tests are C₂N PrecivityADTM and Quest AD-Detect^{TM6,7}



- Cost: ~\$5,000⁸
- Limited availability and requires high-cost equipment⁹

- Cost: ~\$1,400⁸

- Cost: ~\$500-\$1,250¹⁰

Coverage limits may negatively affect diagnostic capacity and could further restrict patient access to biomarker testing⁹



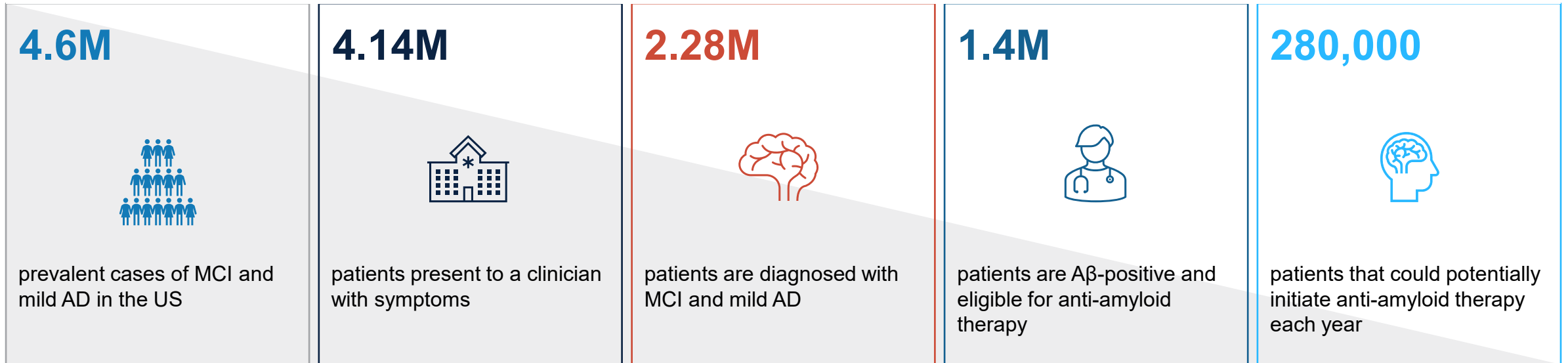
How do you plan to provide diagnostic resources for identification of A β -positive patients?

A β =amyloid beta; AD=Alzheimer's disease; CSF=cerebrospinal fluid; MCI=mild cognitive impairment; PET=positron emission tomography.


References: 1. Nakamura A et al. *Nature*. 2018;554(7691):249-254. 2. Schindler SE et al. *Neurology*. 2019;93(17):e1647-e1659. 3. Bateman RJ et al. *N Engl J Med*. 2012;367(9):795-804. 4. Jack CR et al. *Alzheimers Dement*. 2011;7(3):257-262. 5. Palmqvist S et al. *JAMA Neurol*. 2019;76(9):1060-1069. 6. PrecivityADTM. Accessed April 8, 2022. <https://precivityad.com/>. 7. Quest AD-DetectTM, Beta-Amyloid 42/40 Ratio, Plasma. Accessed April 8, 2022. <https://testdirectory.questdiagnostics.com/test/test-detail/11786/quest-ad-detect-beta-amyloid-4240-ratio-plasma>. 8. Insel PS et al. *Alzheimers Dement (Amst)*. 2016;4:76-84. 9. Liu JL et al. RAND Corporation, 2017. Accessed April 8, 2022. https://www.rand.org/pubs/research_reports/RR2272.html. 10. Scientific American. Published February 4, 2021. Accessed April 7, 2022. <https://www.scientificamerican.com/article/detecting-alzheimers-gets-easier-with-a-simple-blood-test/>.

A small subset of all patients with MCI and/or mild AD are potentially treatable with an amyloid-targeted therapy

The maximum number of treatable patients may be calculated by following the patient journey*¹



Based on a total US population of 328 million in 2019, 280,000 eligible patients equates to **854 treatable patients per 1 million²**

 How do you track patient data to determine treatment eligibility?

*Based on ICER budget impact model using an unpublished analysis based on 2019 data. A scenario begins with 4.6 million prevalent cases of MCI and mild AD in the US. From there, one could assume that 90% of prevalent cases present to a clinician with symptoms and of those, 55% are diagnosed. Of those presenting to a clinician and who are diagnosed with MCI, 61.5% were assumed to be Aβ-positive to arrive at 1.4 million patients eligible for treatment that targets Aβ. Of these 1.4 million patients, 20% were assumed to initiate treatment each year over the course of 5 years, or approximately 280,000 patients per year.

Aβ=amyloid beta; AD=Alzheimer's disease; MCI=mild cognitive impairment.

References: 1. ICER.org. Accessed April 8, 2022. https://icer.org/wp-content/uploads/2020/10/ICER_ALZ_Final_Report_080521.pdf. 2. United States Census Bureau 2019: ACS 1-Year Estimates Data Profile. Accessed March 9, 2022. <https://data.census.gov/cedsci/table?d=ACS%201-Year%20Estimates%20Data%20Profiles&tid=ACSDP1Y2019.DP05>.



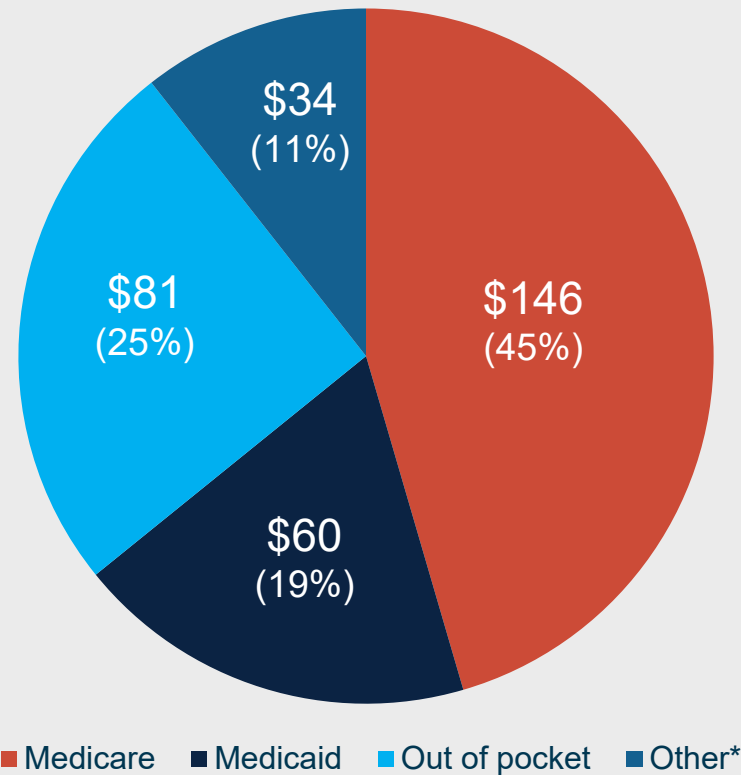
Potential impact of early intervention



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Increased costs for hospitalization and institutionalization, as well as medical, long-term, and residential care, are associated with AD and other dementia

Total direct costs for patients ≥65 years with AD or other dementia in 2022 (in billions)



\$321 billion: total estimated payments in 2022 for health care, long-term care, and hospice services for people aged 65 and older with AD or other dementia

With aging populations, in 2050, AD or other dementia are projected to cost just under **\$1 trillion**—including more than a threefold increase both in government spending under Medicare and Medicaid and in out-of-pocket spending

*Other payment sources include private insurance, health maintenance organizations, other managed care organizations, and uncompensated care.

AD=Alzheimer's disease; MCI=mild cognitive impairment.

Reference: 1. Alzheimer's Association. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2022;18(4):1-122.

The demands on care partners drive the large indirect cost of AD and other dementia

Increased health care system utilization for care partners¹

- Unpaid dementia caregiving was valued at ~\$271.6 billion in 2021¹
- Indirect costs associated with AD include family care partners' increased risk for emotional distress and negative mental and physical health outcomes*
- Caring for a patient with AD may increase household's annual health care costs



67%

of AD and other dementia caregivers are over the age of 50²



38% and 59%

of caregivers report physical and emotional stress of caregiving, respectively¹

Because individuals with MCI due to AD are still able to function independently, a treatment that slows the progression of MCI due to dementia would have a significant impact on quality of life, caregiver burden, and use and cost of care¹

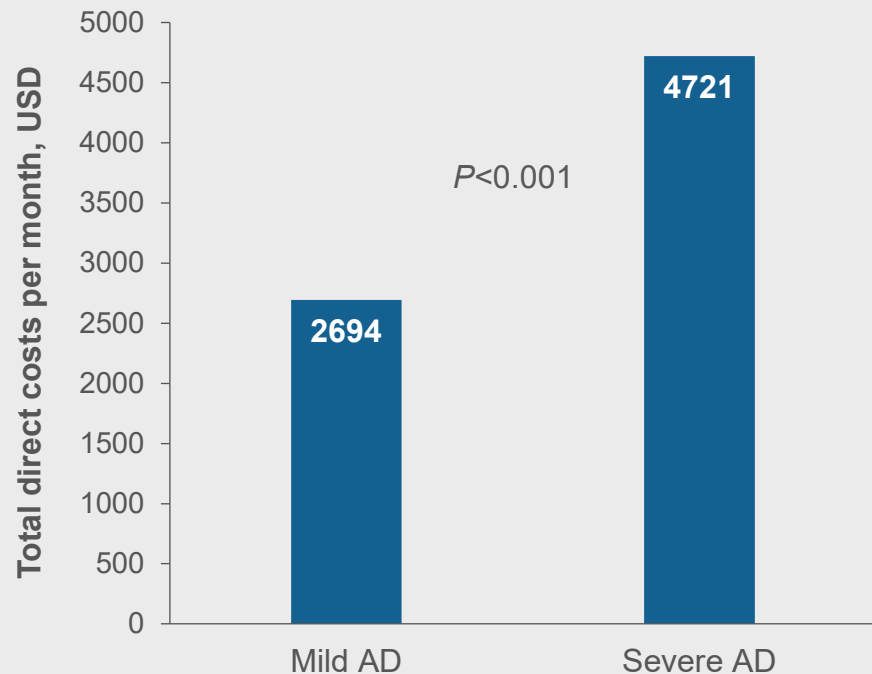
*Aggravated by COVID-19.¹

AD=Alzheimer's disease; MCI=mild cognitive impairment.

References: 1. Alzheimer's Association. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2022;18(4):1-122. 2. Alzheimer's Association Factsheet: Alzheimer's Disease Caregivers 2020.

Per patient costs may ~double as disease progresses from mild to severe AD dementia

Total direct costs per patient per month almost double from mild to severe AD*¹



Cost to Medicare/Medicaid

- Total costs for beneficiaries with AD and other dementias vs those without these conditions²
 - >2.5x higher for Medicare beneficiaries
 - >22x higher for Medicaid beneficiaries



Hospitalizations

- Medicare beneficiaries aged 65 years and older with AD or other dementia have ~2x likelihood of a hospitalization compared to those without these conditions²
 - Among Medicare beneficiaries with AD or other dementias, 22% of hospital stays are followed by a readmission within 30 days
- Medicare beneficiaries with AD or other dementias visit the emergency department an average of 1.55x per year²

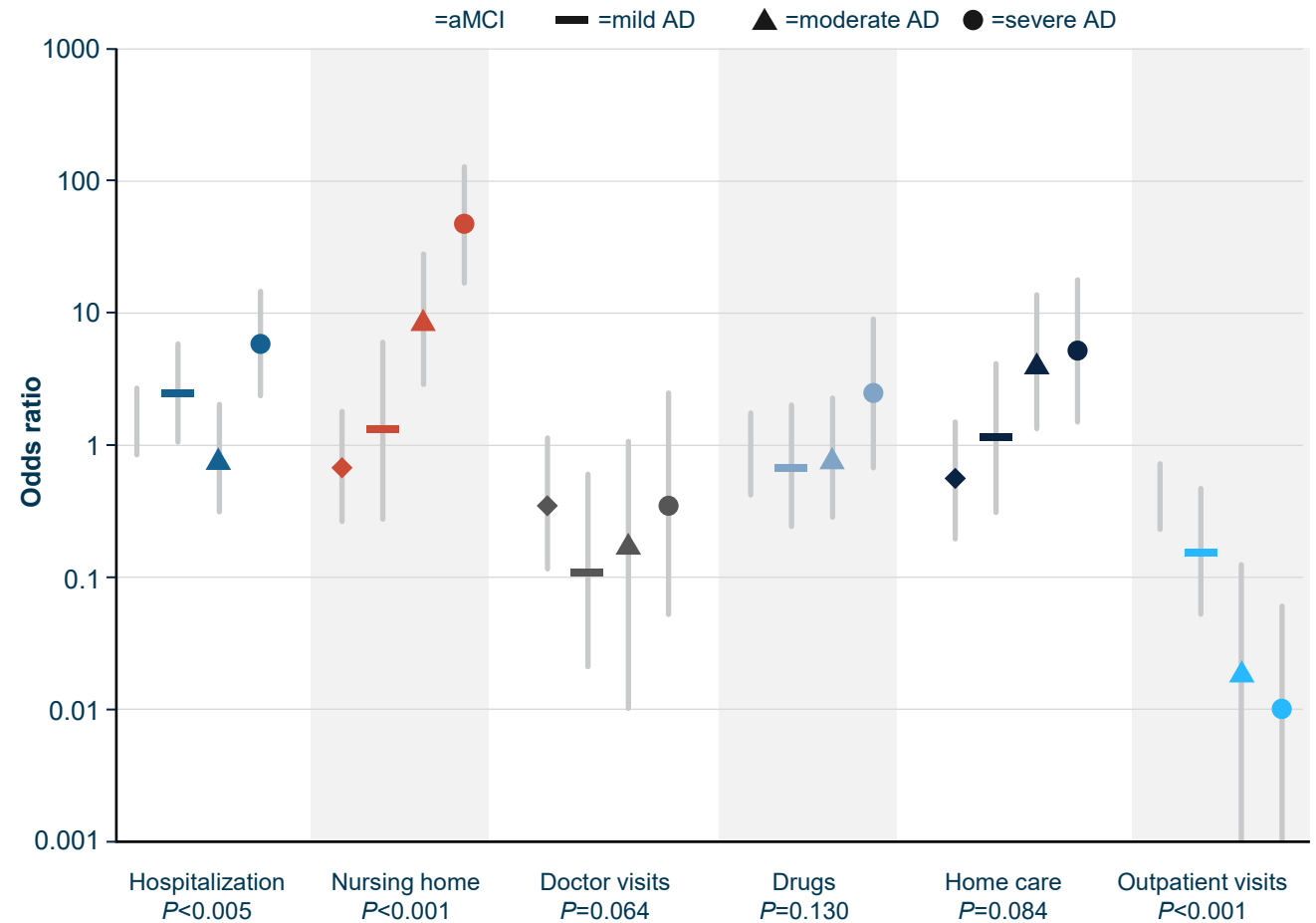
*Fully adjusted for age, gender, race, education, marital status, residential region, hypertension, diabetes, cancer, lung disease, heart disease, and stroke; *P*-values are from tests across all given cognitive states.¹
AD=Alzheimer's disease.

References: 1. Ton TGN et al. *Alzheimers Dement.* 2017;13(3):217-224. 2. Alzheimer's Association. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2022;18(4):1-122.

Total cost of hospitalization, nursing homes, and home care services increases as the disease progresses¹

- Relative to those with normal cognitive status, declining cognitive status was associated with
 - Higher likelihood of hospitalizations, use of nursing homes, and use of home care services
 - Decreased use of outpatient services
 - Similar likelihood of doctor visits or drug utilization

Early identification and intervention at the MCI stage can assist individuals with planning for the current and future financial burden associated with AD¹

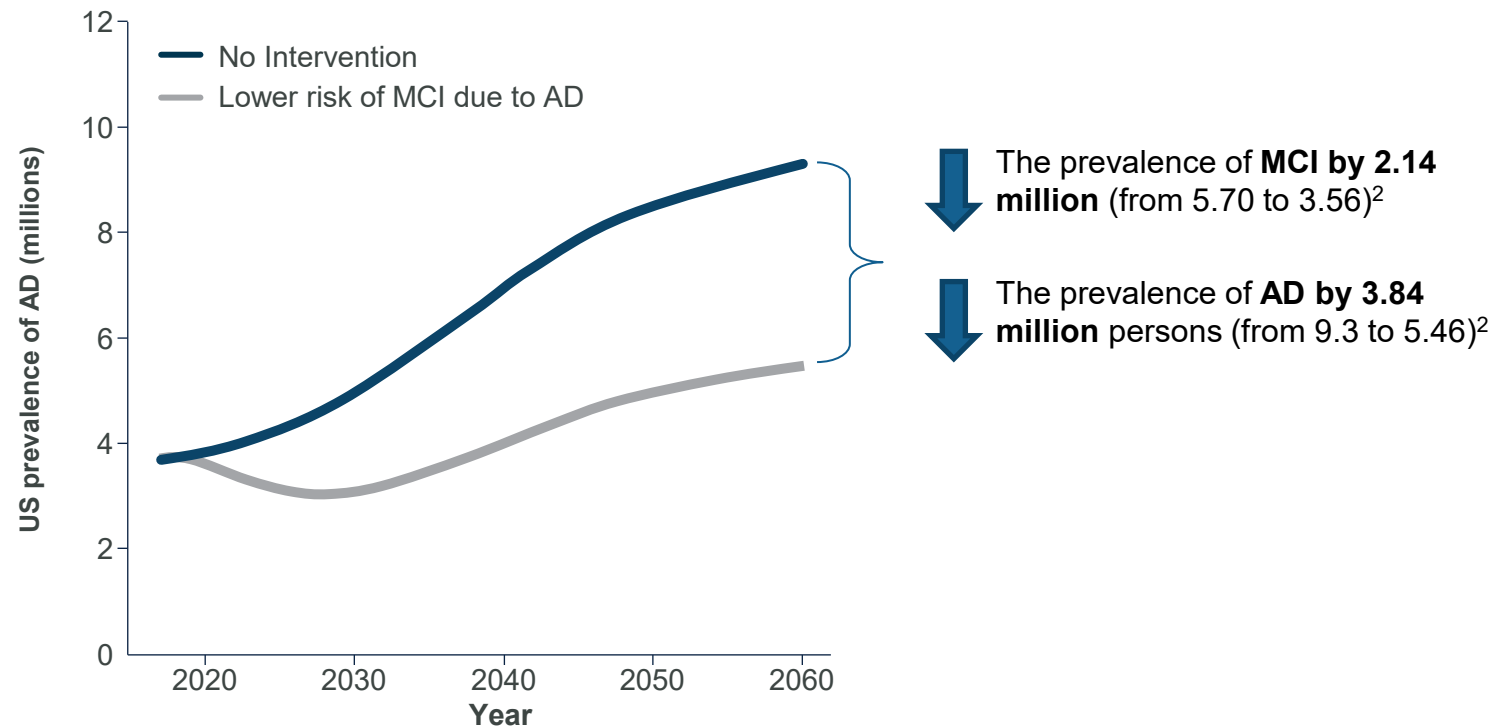


AD=Alzheimer's disease; aMCI=amnesic mild cognitive impairment.
 Reference: 1. Ton TGN et al. *Alzheimers Dement.* 2017;13(3):217-224.

The impact of early intervention on disease burden may be amplified over time

- One model created by the Alzheimer's Association predicts that diagnosis in the MCI phase rather than in the dementia phase or not at all could save approximately \$7 trillion in medical and long-term care costs¹

Anticipated impact of disease-modifying intervention on disease progression through 2060*²




*Aimed to reduce annual risk of progression of MCI due to AD by 50%.²

AD=Alzheimer's disease; MCI=mild cognitive impairment.

References: 1. Alzheimer's Association. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2022;18(4):1-122. 2. Brookmeyer R et al. *Alzheimers Dement.* 2018;14(2):121-129.

In summary, focusing on MCI due to AD and mild AD dementia enables early intervention before years of irreversible brain damage may occur



Early diagnosis

- Provide coverage for cognitive tests and/or MRI and CT scans




Early intervention at MCI due to AD and mild AD dementia

- Provide coverage for diagnostics (PET scan, CSF, BBBM) and treatment




Financial benefit

- Early intervention can reduce the long-term cost of patient care¹



Clinical benefit

- Potential future therapies impacting the underlying pathophysiology may slow disease progression¹



Familial/societal benefit

- Early intervention is associated with a less negative impact on care partners^{2,3}

AD=Alzheimer's disease; BBBM=blood-based biomarkers; CSF=cerebrospinal fluid; CT=computed tomography; MCI=mild cognitive impairment; MRI=magnetic resonance imaging; PET=positron emission tomography.

References: 1. Barnett JH et al. *BMC Neurol.* 2014;14:101. 2. Alzheimer's Disease International. Accessed April 28, 2022. <https://www.alz.co.uk/research/WorldAlzheimerReport2011.pdf>.

3. Woods B et al. *Int J Geriatr Psychiatry.* 2019;34(1):114-121.