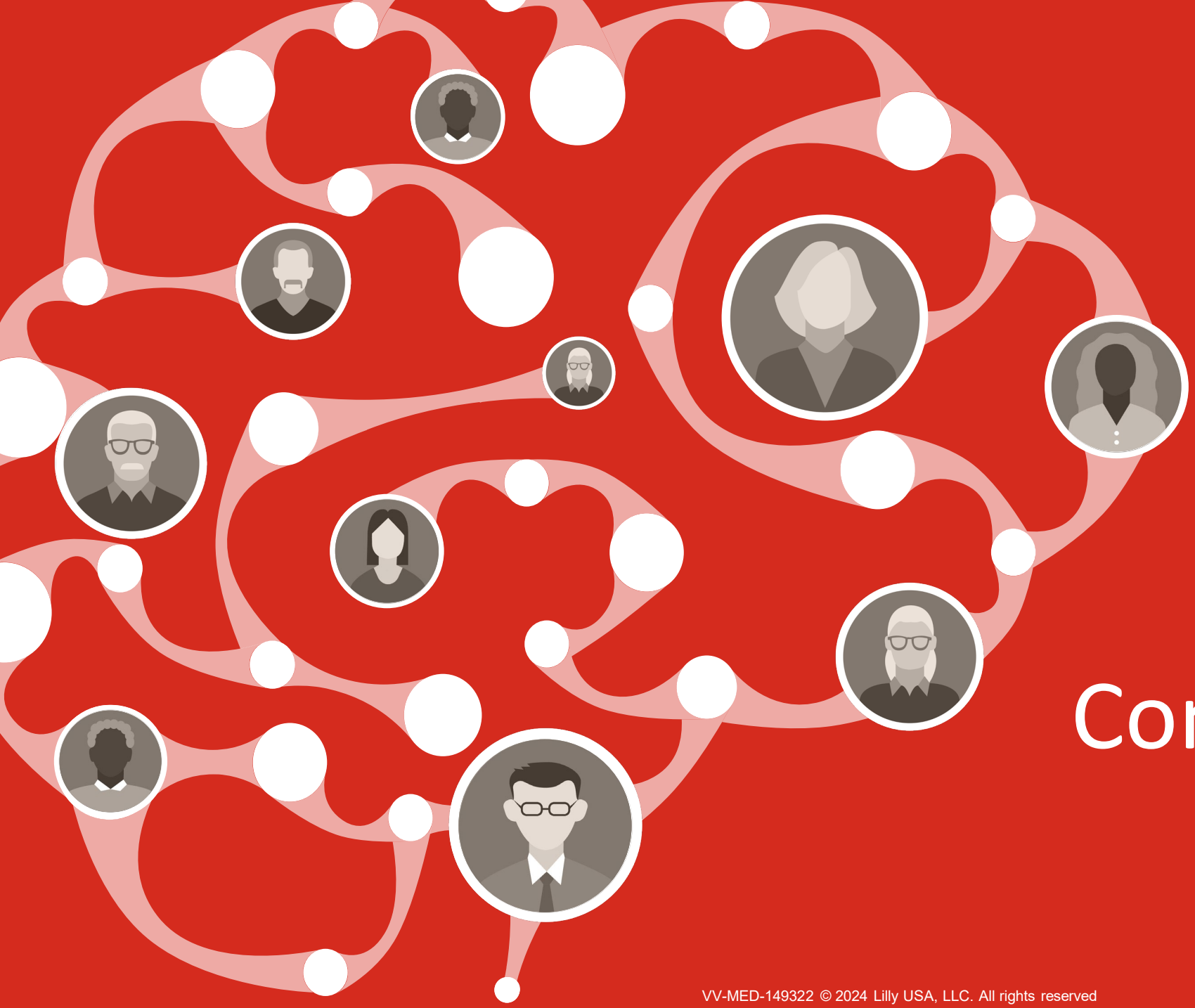


ConnectAD™

Welcome to ConnectAD™, a clinical case series created by the Eli Lilly and Company Neuroscience medical education team. This series is intended to connect healthcare professionals to resources that help them detect, diagnose, and manage Alzheimer's disease.

Disclaimer

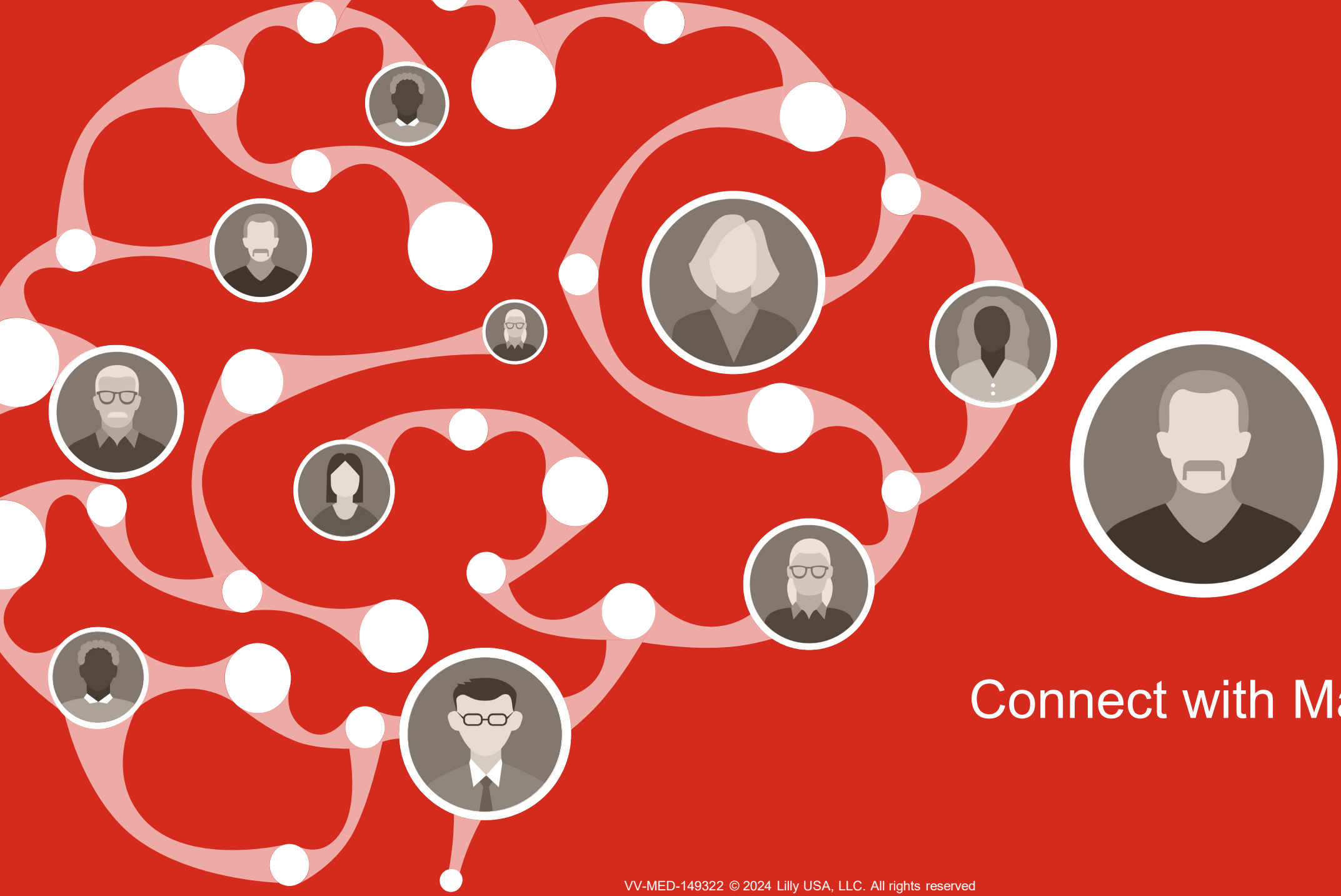
The content for this case was created by Eli Lilly and Company and is inspired by scenarios clinicians may encounter while caring for patients with Alzheimer's disease.

A variety of cognitive and diagnostic tests can reasonably be used in the detection and diagnosis of Alzheimer’s disease. Inclusion of specific cognitive and/or diagnostic tests in this case reflects the diversity of clinical preferences, and the use of particular diagnostic tools does not imply endorsement or recommendation by Lilly.

Learning Objectives

Through completing this course, you will have a deeper understanding of:

- The clinical presentation of Alzheimer's disease
- How to integrate clinical and biomarker assessments to make an accurate diagnosis of Alzheimer's disease in the earliest stages



Connect with Mateo

Our Patient

Mateo

- 73 years old
- Male
- Hispanic
- Married, 2 children, 2 grandchildren
- College degree
- High school teacher (retired)
- Family history
  - Colon cancer
  - Grandfather diagnosed with dementia (cause unknown)

Clinical Information and History

Mateo has experienced progressive worsening of the following symptoms over the past 2.5 years:

- Difficulty remembering plans, dates, and events
- Repetition of questions in conversations

In the past year, he has required assistance from his wife in handling family finances, medical appointments, and medications

General health

- Heart rate: 82 bpm
- Controlled hypertension: 124/72 mmHg
- Adenomatous colon polyps (undergoing colonoscopy surveillance)

Current medication (class)

- Angiotensin receptor blocker (ARB)

bpm=Beats Per Minute.

Initial Clinical Assessment

General neurological exam: Normal

Mental status

- Alert, diminished insight (no reports of memory concerns)
- Instrumental activities of daily living: Impaired (finances, medications, appointments)

Cognition

- MMSE: 24/30 (normal ≥25)
  - Time orientation: 3/5 (does not know date or day of the week)
  - Word recall: 0/3
  - Figure copy: Incorrect

MMSE=Mini-Mental State Examination.

Additional Findings

Blood work within normal limits, including:

- Complete blood count (CBC)
- Electrolytes
- Glucose
- Creatinine
- Thyroid stimulating hormone (TSH)
- Vitamin B12

Brain MRI

- No evidence of global or focal cortical atrophy
- No evidence of infarct, hemorrhage, or mass lesion

CSF assay

- $A\beta_{42}/A\beta_{40}$: Low
- P-tau: High
- T-tau: High

Aβ=Amyloid Beta; CSF=Cerebrospinal Fluid; MRI=Magnetic Resonance Imaging; P-tau=Phosphorylated Tau; T-tau=Total Tau.

Given the patient information presented, what is the diagnosis?

1. Mild dementia due to AD
2. MCI due to AD
3. Preclinical AD
4. Normal cognitive aging
5. Other

AD=Alzheimer's Disease; MCI=Mild Cognitive Impairment.

Given the patient information presented, what is the diagnosis?

Option 1:

Mild dementia due to AD

AD=Alzheimer's Disease.

Justification for Diagnosis

Why is Mateo diagnosed with mild dementia due to AD?

Mateo is presenting with clinical symptoms consistent with mild dementia due to AD (including functional impairment). His symptoms are corroborated by clinical assessment.

Although Mateo's MRI results showed no other potential cause for his cognitive dysfunction, the assessment of AD-specific biomarkers in CSF confirms the presence of Aβ fibrils and plaques in the brain, consistent with the pathology of AD.[1]

Evidence of functional impairment (requiring assistance for instrumental activities of daily living such as managing finances and medications) leads to the diagnosis of mild dementia due to AD.[2]

Aβ=Amyloid Beta; AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; MRI=Magnetic Resonance Imaging.

1. Hansson O, et al. *Alzheimer's Res Ther*. 2019;11(1):34. 2. Marshall GA, et al. *Neurodegener Dis Manag*. 2012;2(5):483-491.

Key Learnings in Mateo's Case (1 of 3)

AD is the most common form of dementia. Although clinical presentations with memory impairment are suggestive of AD, presence of AD biomarkers is required to formulate a neuropathology-proven diagnosis

- The diagnosis of AD has evolved; today, AD can be defined by clinical symptoms and neuropathological biomarkers of AD[1,2]
- Potential diagnostic AD biomarkers include[1]:
  - CSF Aβ and tau
  - Aβ or tau PET neuroimaging
- AD neuropathology biomarkers are important for timely and accurate diagnosis, especially in earlier clinical stages of disease[1-3]

Aβ=Amyloid Beta; AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; PET=Positron Emission Tomography.

1. Jack CR Jr, et al. *Alzheimers Dement*. 2018;14:535-562. 2. Dubois B, et al. *Lancet Neurol.* 2021;20:484-496. 3. Porsteinsson AP, et al. *J Prev Alzheimers Dis*. 2021;8(3):371-386.

Key Learnings in Mateo's Case (2 of 3)

MRI can be a useful assessment to[1]:

- **Rule out non-AD conditions that can cause cognitive decline**
- **Provide information suggestive of AD; for example, observed hippocampal atrophy**

MRI does not provide information on Aβ and tau pathology, and therefore cannot be used as a standalone test for the diagnosis of AD[2]

Structural neuroimaging (MRI)

- Is useful in evaluation of cognitive impairment by:
  - Ruling out several causes (eg, vascular lesions, mass lesions)[1]
  - Detecting atrophy (especially in the hippocampus/medial temporal lobe), which correlates with cognitive status and is a marker of neurodegeneration[2]
- MRI has limited sensitivity (~80%) for neuropathology-proven AD diagnosis and should therefore not be considered a stand-alone test to diagnose AD[1,2]
  - Patients with no notable MRI abnormalities could still potentially be positive for Aβ and tau pathology and thus be on the AD continuum[3]

Aβ=Amyloid Beta; AD=Alzheimer's Disease; MRI=Magnetic Resonance Imaging.

1. Park M, et al. *Korean J Radiol*. 2016;17(6):827-845. 2. Aramadaka S, et al. *Cureus*. 2023;15(5):e38544. 3. Jack CR Jr, et al. *Alzheimers Dement*. 2018;14:535-562.

Key Learnings in Mateo's Case (3 of 3)

The CSF biomarker assay can be used to confirm the presence of pathology consistent with AD[1]

CSF assays

- Quantitatively measure the levels of Aβ and tau protein within the fluid of the lumbar sac[2]
- Reflect the rates of Aβ and tau protein production and clearance[2]
- Advantages include:
  - Less expensive than PET by 10-15-fold[3]
  - Simultaneous information on Aβ and tau biomarkers[4]
- Limitations include:
  - CSF is obtained via lumbar puncture; this is invasive and can be uncomfortable for patients[5]
  - Limited availability outside of specialized clinics[6]
  - Do not detect regional Aβ or tau deposition[2,3]

Aβ=Amyloid Beta; AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; PET=Positron Emission Tomography.

1. https://alz.org/media/Documents/scientific-conferences/Figures-and-Tables-Clinical-Criteria-for-Staging-and-Diagnosis-for-Public-Comment-Draft-2.pdf (Accessed January 2024). 2. Jack CR Jr, et al. *Alzheimers Dement*. 2018;14:535-562. 3. Hansson O, et al. *Alzheimer's Res Ther*. 2019;11(1):34. 4. Dubois B, et al. *Lancet Neurol*. 2021;20(6):484-496. 5. Lee JC, et al. *Exp Mol Med*. 2019;51(5):1-10. 6. Zetterberg H, et al. *Alzheimer's Dement (Amst)*. 2019;784-786.

Thank you for connecting with Mateo