ConnectAD™

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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.

Lilly

Disclaimer

The content for this clinical case was developed in collaboration between a group of global clinicians who care for patients with Alzheimer's disease and Eli Lilly and Company.

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
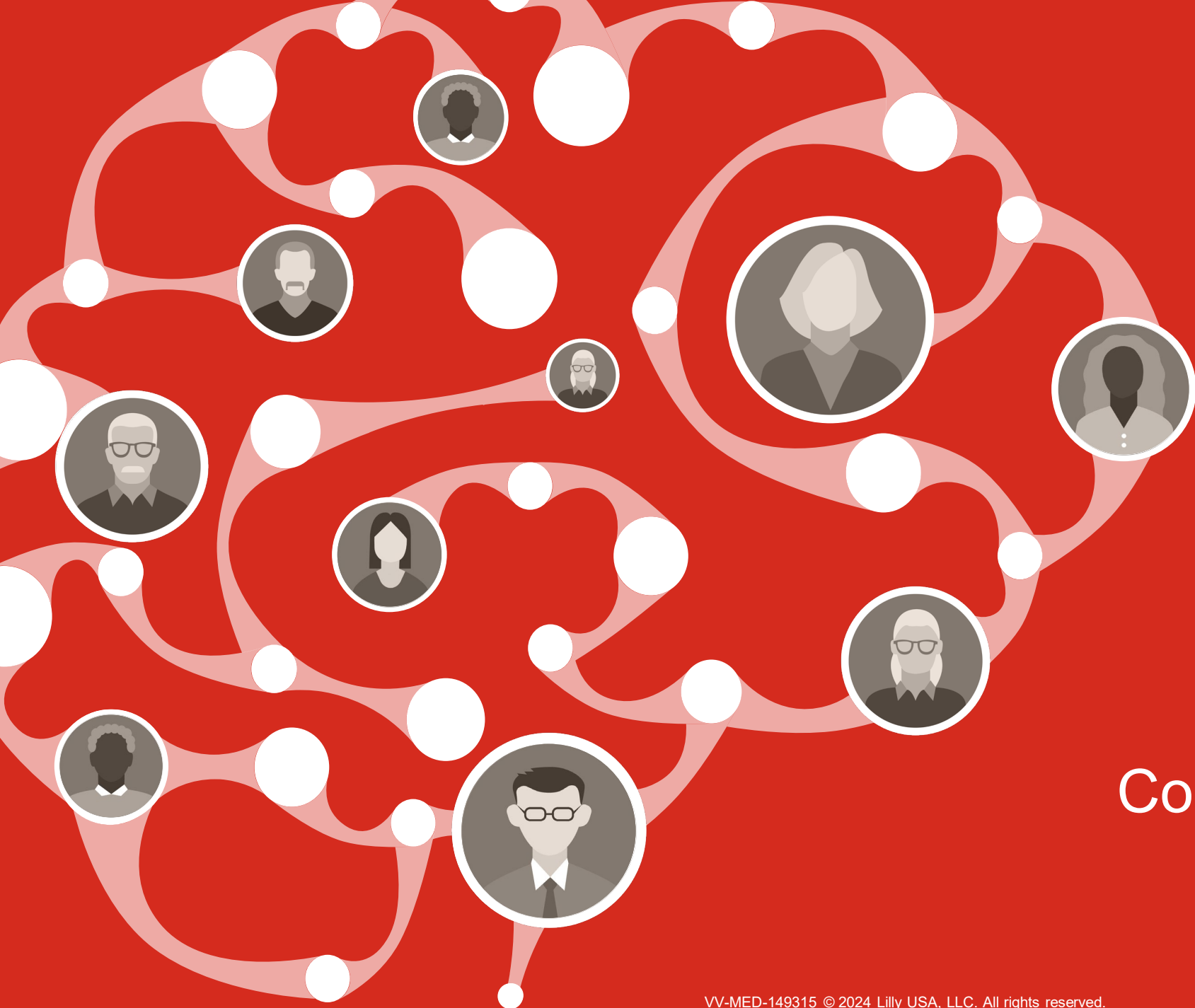
Connect with John

Our Patient

John

- 61 years old
- Male
- White
- Married, 1 child
- College degree
- Graphic designer
- Family history
  - Mother and grandmother diagnosed with dementia in their 60s (cause unknown)

John

Clinical Information and History

Over the past few years, John has manifested progressive behavioral changes and difficulties in language.

- John reports feeling angrier and more irritable, mistreating colleagues at work

- He can no longer:

  - Organize or plan projects

  - Work without an assistant

  - Communicate effectively – speaks in abbreviated sentences and chooses the incorrect words

- His work supervisor has encouraged him to pursue evaluation to address these issues

General health

- Heart rate: 67 bpm

- Blood pressure: 124/77 mmHg

Current medication

- None

John

bpm=Beats Per Minute.

Initial Clinical Assessment

General neurological exam: Normal

Mental status

- Alert, aloof, limited insight, mildly argumentative, anomic, reduced speech initiation
- John reports:
  - He can perform activities of daily living independently
  - He can commute to work without issue
  - Issues at work are mostly due to changes in software
- John's wife reports:
  - He is at risk of losing his job or being forced to retire

Cognition

- MMSE: 20/30
- NPI-Q severity: 7/36
  - Apathy; irritability; disinhibition

John

MMSE=Mini Mental State Examination; NPI-Q=Neuropsychiatric Inventory-Questionnaire.
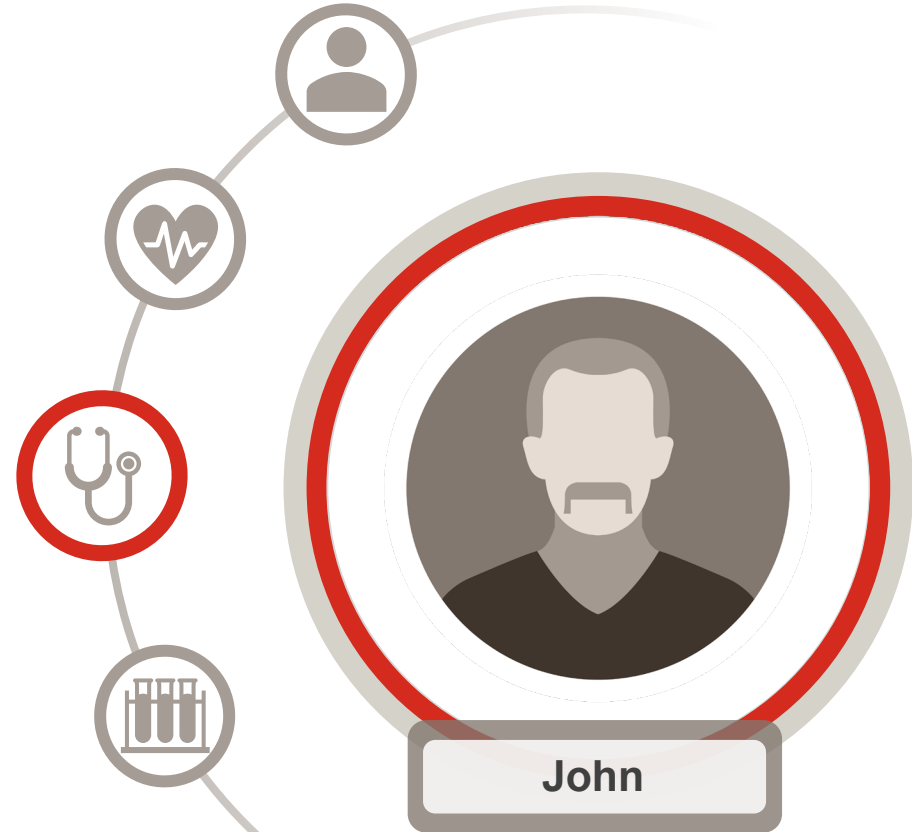
Additional Findings

Blood work within normal limits, including:

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

Brain MRI

- Moderate atrophy with left frontoparietal predilection

Amyloid PET

- Negative for significant neocortical accumulation

John

MRI=Magnetic Resonance Imaging; PET=Positron Emission Tomography.

Given the patient information presented, what is the diagnosis?

1. Vascular dementia
2. MCI due to AD
3. Frontotemporal dementia (FTD)
4. Corticobasal degeneration
5. Other

Given the patient information presented, what is the diagnosis?

Option 2:

Frontotemporal dementia (FTD)

Justification for Diagnosis

Why is John diagnosed with frontotemporal dementia?

John's clinical profile is consistent with FTD
- Symptom presentation:
  - Predominantly behavioral and emotional dysfunction
  - Early onset
  - Quick progression
- Strong family history of early-onset dementia

Additionally, biomarker assessment is not consistent with a diagnosis of AD
- Amyloid PET imaging: No detection of amyloid plaques in the brain

Brain FDG PET could be considered for additional biomarker testing to support the diagnosis of FTD.

AD=Alzheimer's Disease; FDG=Fluorodeoxyglucose; FTD=Frontotemporal Dementia; PET=Positron Emission Tomography.

What is frontotemporal dementia (FTD)?

- FTD is a neurodegenerative disorder characterized by changes in behavior and/or language due to selective atrophy of the frontal and temporal lobes[1,2]

- FTD is often misdiagnosed as AD[3] and is the second leading cause of early-onset dementia after AD[2]

FTD

Onset	• Typically early-onset (<65 years old)[1]
% familial cases	• 30-50%[1]
Typical early symptoms	• Changes in behavior and/or language[3]
Heritability	• Varies across subtypes; 48% for bvFTD[1]
Genetics	• Causative genes: *MAPT, GRN, C9orf72, TBK1*[1]
	• Key risk genes: *TMEM106B, RAB8, HLA, GFRA2*[1]
Biomarkers	• CSF/plasma biomarkers: Vary according to underlying disease mechanism, but include elevated p-Tau, reduced $A\beta_{42}/A\beta_{40}$ ratio, and presence of GFAP[1]
	• Neuroimaging biomarkers: MRI, FDG-PET[1]

Aβ=Amyloid Beta; AD=Alzheimer's Disease; bvFTD=Behavioral Variant Frontotemporal Dementia; C9orf72=Chromosome 9 Open Reading Frame 72; CSF=Cerebrospinal Fluid; FDG=Fluorodeoxyglucose; FTD=Frontotemporal Dementia; GFAP=Glial Fibrillary Acidic Protein; GFRA2=Glial Cell-derived Neurotrophic Factor Family Receptor Alpha 2; GRN=Progranulin; HLA= Human Leucocyte Antigen; MAPT=Microtubule-Associated Protein Tau; MRI=Magnetic Resonance Imaging; PET=Positron Emission Tomography; p-Tau=Phosphorylated Tau; RAB8=Ras-Associated Binding Protein 8; TBK1=TANK Binding Kinase 1; TMEM106B=Transmembrane protein 106B.

1. Antonioni A, et al. *Int J Mol Sci.* 2023;24(14):11732. 2. Leroy M, et al. *Alzheimers Res Ther.* 2021;13(1):19. 3. https://altoida.com/blog/frontotemporal-dementia-different-from-alzheimers/ (Accessed January 2024).

In John's case, age of onset and family history suggest early AD or FTD. Genetic testing could have been used to support diagnosis

Family history and genetic risk factors alone do not confirm diagnosis for AD nor FTD.[1,2] Enough information was available to diagnose FTD without genetic testing in John's case.

	FTD	AD
Onset	Typically early-onset (<65 years old)[1]	Typically late-onset (>65 years old)[3,4]
% familial cases	30-50%[1]	<1%[5]
Typical early symptoms	Changes in behavior and/or language[3]	Memory impairment[3]
Heritability	Varies across subtypes; 48% for bvFTD[1]	Estimates vary between 38 and 84%[6]
Genetics	Causative genes: *MAPT, GRN, C9orf72, TBK1*[1]	Causative genes: *APP, PSEN1, PSEN2*[4]
	Key risk genes: *TMEM106B, RAB8, HLA, GFRA2*[1]	Key risk gene: *APOE*[4]
Biomarkers	CSF/plasma biomarkers: Vary according to underlying disease mechanism[1]	Hallmark biomarkers are Aβ and tau in CSF/neuroimaging[1]
	Neuroimaging biomarkers: MRI, FDG-PET[1]	

Aβ=Amyloid Beta; AD=Alzheimer's Disease; APOE=Apolipoprotein E; APP=Amyloid Precursor Protein; bvFTD=Behavioral Variant Frontotemporal Dementia; C9orf72=Chromosome 9 Open Reading Frame 72; CSF=Cerebrospinal Fluid; FDG=Fluorodeoxyglucose; FTD=Frontotemporal Dementia; GFAP=Glial Fibrillary Acidic Protein; GFRA2=Glial Cell-derived Neurotrophic Factor Family Receptor Alpha 2; GRN=Progranulin; HLA= Human Leucocyte Antigen; MAPT=Microtubule-Associated Protein Tau; MRI=Magnetic Resonance Imaging; PET=Positron Emission Tomography; PSEN=Presenilin; p-Tau=Phosphorylated Tau; RAB8=Ras-Associated Binding Protein 8; TBK1=TANK Binding Kinase 1; TMEM106B=Transmembrane protein 106B.

1. Antonioni A, et al. *Int J Mol Sci.* 2023;24(14):11732. 2. 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). 3. https://altoida.com/blog/frontotemporal-dementia-different-from-alzheimers/ (Accessed January 2024). 4. Hoogmartens J, et al. *Alzheimers Dement (Amst).* 2021;13(1):e12155. 5. https://www.raredementiasupport.org/familial-alzheimers-disease/understanding-fad/ (Accessed January 2024). 6. Baker E, et al. *PLoS ONE.* 2023;18(4):e0281440.

John's case is challenging, but assessment of biomarkers helps to confirm or reject a diagnosis of AD. In this case, an amyloid PET scan was utilized to define the level of amyloid plaque present in the brain

Amyloid PET is a diagnostic imaging procedure in which a radioactive agent binds to Aβ in the brain[a] allowing clinicians to estimate Aβ neuritic plaque density[1-3]

- Advantages[4]:
  - Aβ plaques are one of the earliest known neuropathological hallmarks of AD
  - Radiotracer retention time matches the spreading pattern of Aβ plaques

- Limitations[4]:
  - No standard method for quantifying Aβ plaques
  - Weak correlation between Aβ deposition and AD clinical severity
 - Aβ accumulation stabilizes in late-stage AD

[a]Florbetapir F 18 binds to Aβ aggregates; florbetaben F 18 and flutemetamol F 18 bind to Aβ plaques.[1-3]
Aβ=Amyloid Beta; AD=Alzheimer's Disease; PET=Positron Emission Tomography.
1. Amyvid (florbetapir F 18) [US Prescribing Information]. Indianapolis, IN: Eli Lilly and Company, 2019. 2. Vizamyl (flutemetamol F 18) [US Prescribing Information].
3. Neuraceq (florbetaben F 18) [US Prescribing Information]. Warwick, UK: Life Molecular Imaging Ltd., 2021. 4. van Oostveen WM, de Lange ECM. *Int J Mol Sci.* 2021;22(4):2110.
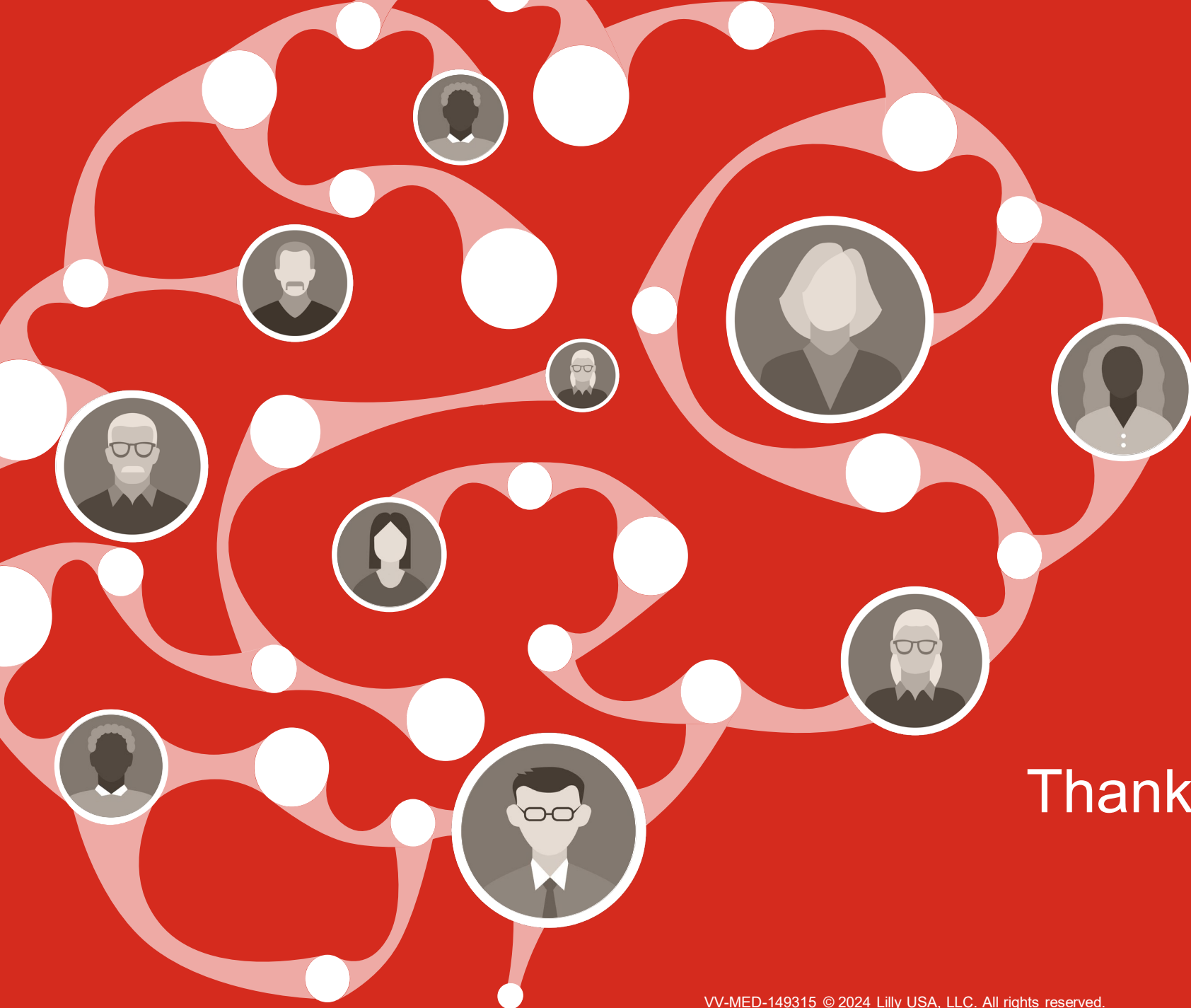
Thank you for connecting with John