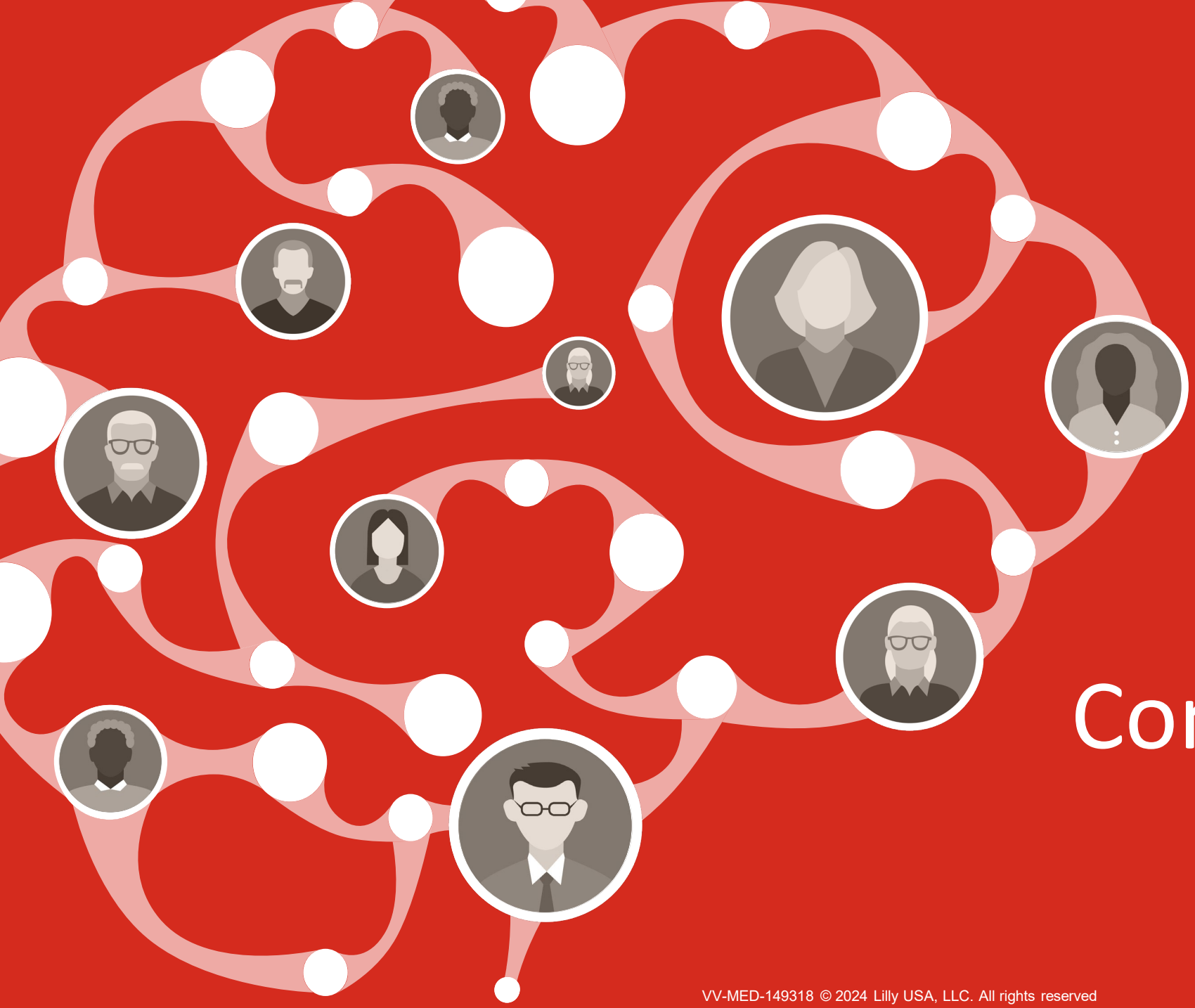


ConnectAD™

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

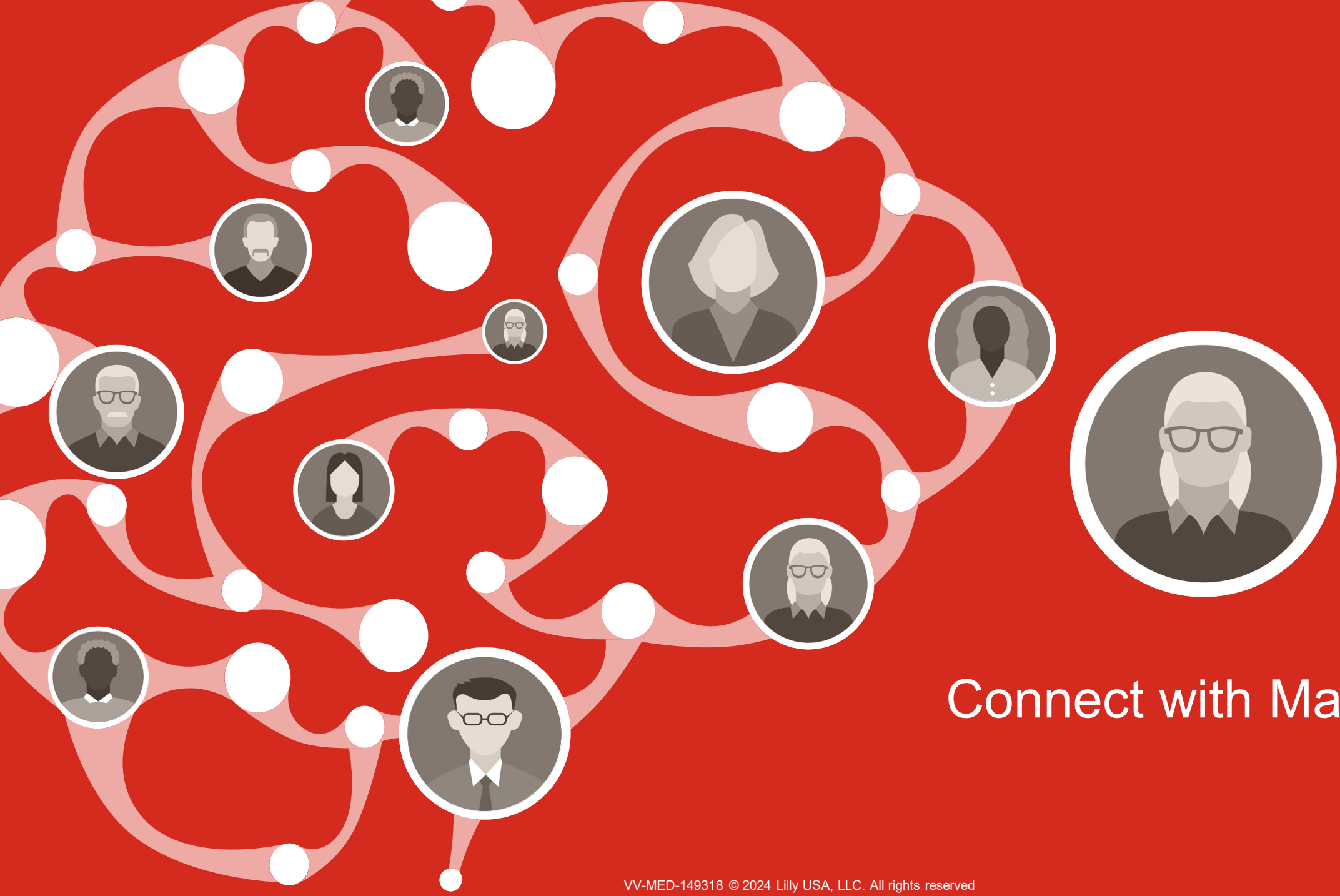
The content for this clinical case was developed in collaboration between a group of global clinicians who care for patients with Alzheimer's disease and Eli Lilly and Company.

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 Marlene

Our Patient

Marlene

- 72 years old
- Female
- White
- Married, 1 child, 3 grandchildren
- College degree
- Retired interpreter (fluent in German, French, and Italian)

Clinical Information and History

Marlene noted the following symptoms:

- Difficulty in shifting from one language to another
- Impairment in word finding

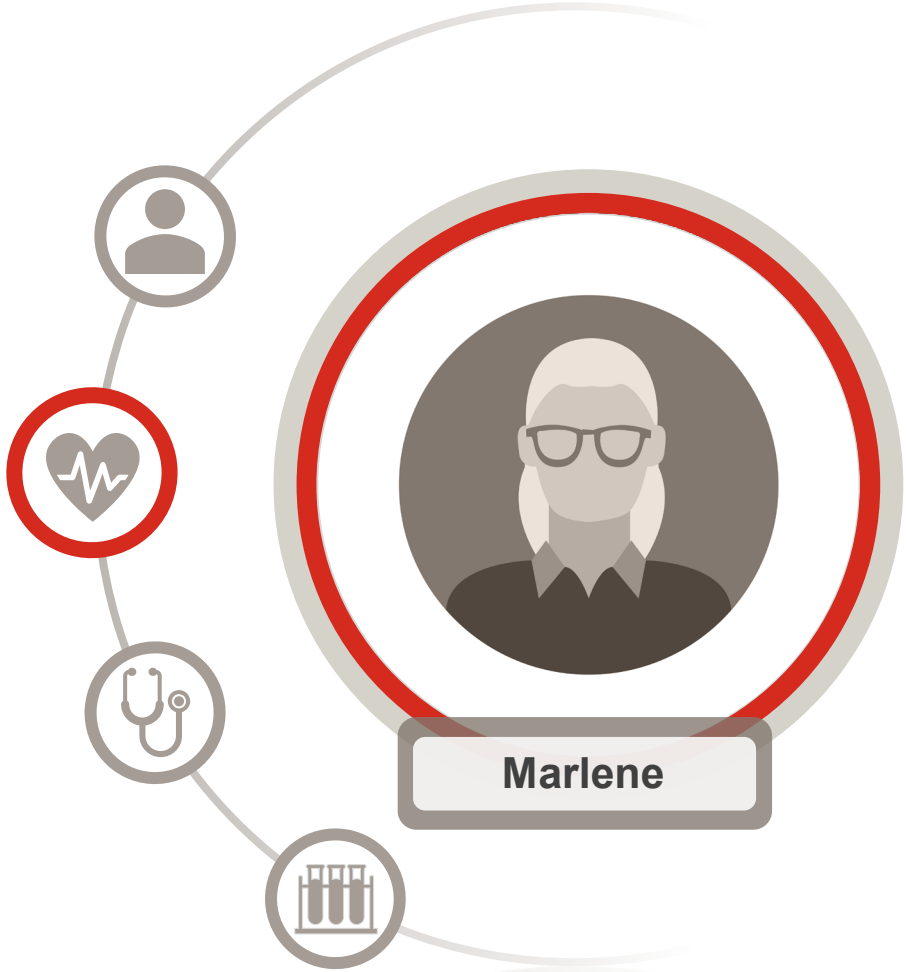
Clinical history

- **40 years old: Diagnosed with MS**
  - Episode of optic neuritis
  - Brain MRI showed white matter lesions
  - CSF analysis: IgG OCB were present
- History of occasional, short-duration episodes of paresthesia since diagnosis

General health

- Heart rate: 70 bpm
- Blood pressure: 121/83 mmHg

Current medication: None



bpm=Beats Per Minute; CSF=Cerebrospinal Fluid; IgG=Immunoglobulin G; MRI=Magnetic Resonance Imaging; MS=Multiple Sclerosis; OCB=Oligoclonal Bands.

Initial Clinical Assessment

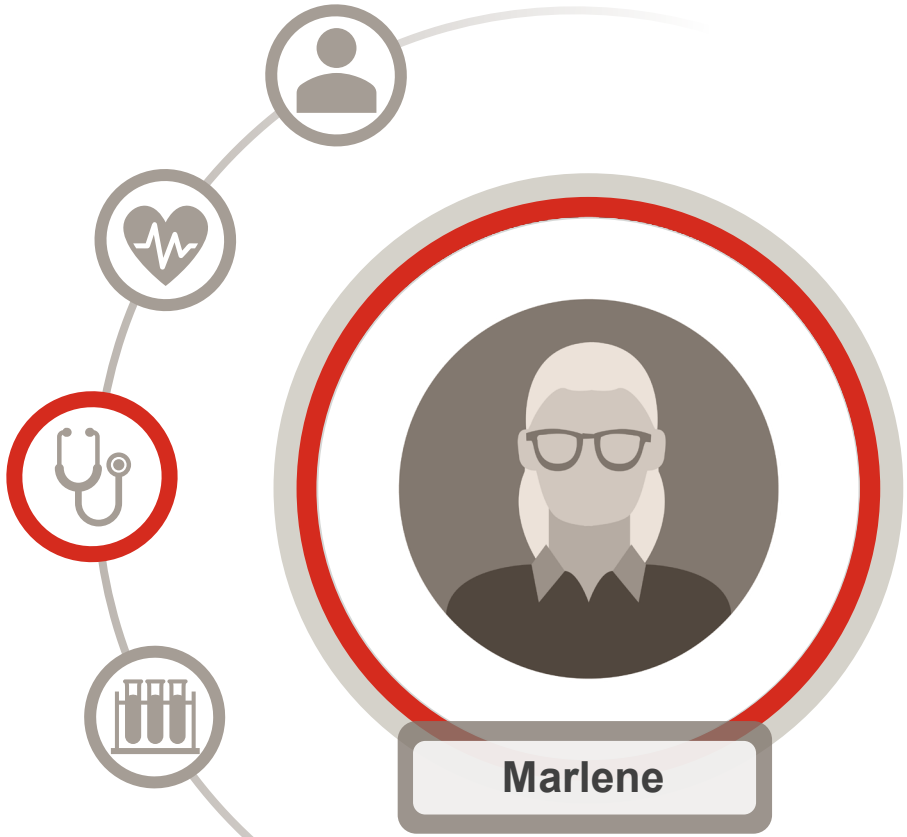
General neurological exam: Normal

Mental status

- Alert and responsive. Slight impairment in verbal fluency noted
- Independent in performing activities of daily living

Cognition

- Neuropsychological evaluation was consistent with new onset of impairment in verbal fluency
- No other significant change in cognition was apparent
- Assessment was that symptoms were related to MS and the patient would follow up in 12 months, or sooner if symptoms worsened



MS=Multiple Sclerosis.

Follow-up Clinical Assessment (12 Months Later)

Marlene and her husband returned for her next annual neurology visit. They reported Marlene's cognitive and functional decline.

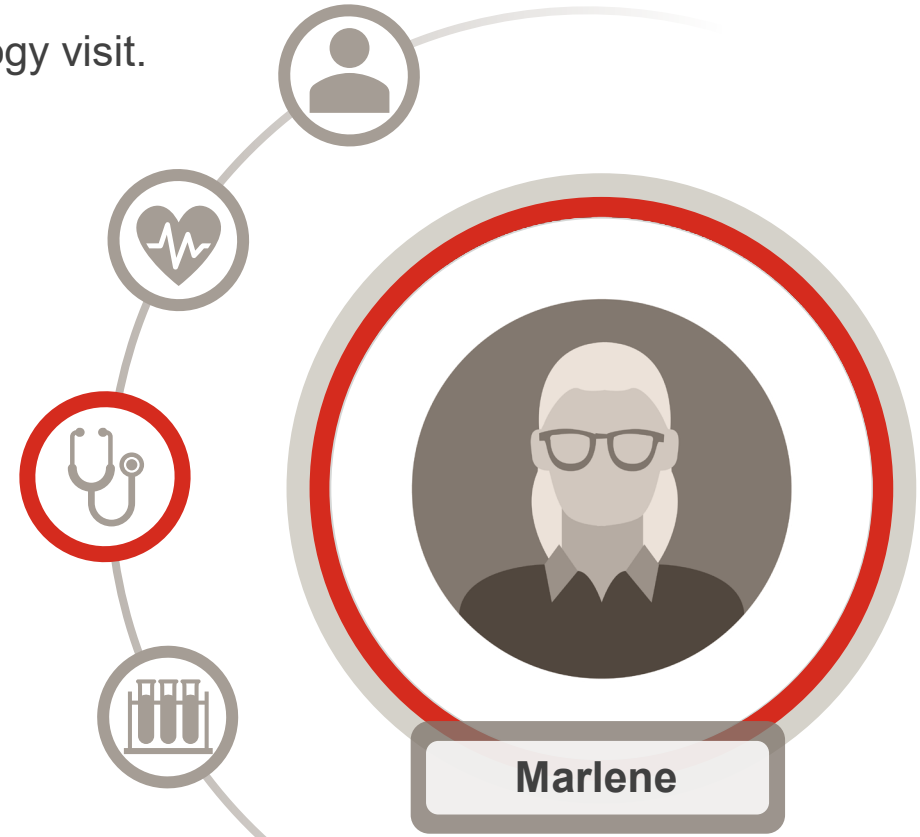
General neurological exam: Unchanged

Mental status

- Worsening of verbal fluency:
  - Occasionally repeats herself
- Worsening memory and cognition:
  - Has trouble remembering appointments and tasks
  - Repeats questions that have been answered recently
  - Defers to husband to answer some questions
- Activities of daily living: Needs more help completing household tasks and preparing food

Cognition

- Neuropsychological evaluation: Confirmed worsening of verbal fluency issues with additional mild memory impairment noted



Additional Findings

Blood work within normal limits, including:

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

Brain MRI

- White matter lesions, unchanged from previous MRI

Plasma assay (screening offered via clinical trial)

- $A\beta_{42}$ and $A\beta_{42}/A\beta_{40}$: Low
- P-tau: Elevated

} Consistent with AD pathology

CSF assay (initiated after positive screening using plasma assay)

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

} Consistent with AD pathology

Aβ=Amyloid Beta; AD=Alzheimer's Disease; 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. Depression
2. Worsening MS
3. MCI due to AD
4. Mild dementia due to AD
5. Other

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

Given the patient information presented, what is the diagnosis?

Option 4:

Mild dementia due to AD

AD=Alzheimer's Disease.

Justification for Diagnosis

Why is Marlene diagnosed with mild dementia due to AD?

- Marlene's initial concerns were issues with verbal fluency
- Due to her comorbidity and the lack of typical early AD symptoms (ie, memory impairment) her HCP suspected she was suffering from a worsening of MS
- Within 12 months, Marlene started demonstrating worsening cognition and functional ability:
  - Issues with memory
  - Difficulty in ability to perform activities of daily living
- After initial testing indicated no other explanation for cognitive and functional decline, Marlene was referred to a clinical trial for an experimental blood-based AD biomarker, which indicated the presence of AD pathology. This was confirmed by follow-up CSF analysis
- Marlene's case is consistent with atypical AD – specifically the logopenic variant, of which the most prominent feature is language impairment
- Due to this atypical presentation, biomarker assessment was crucial to establish an AD diagnosis

AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; HCP=Healthcare Provider; MS=Multiple Sclerosis.

Key Learnings in Marlene's Case (1 of 5)

Marlene's diagnosis of AD was complicated by its atypical presentation involving prominent language impairment

Atypical AD (logopenic variant) usually presents with[1]:

- Single word retrieval problems
- Difficulty repeating sentences
- Spared word comprehension and object knowledge
- Spared motor speech

This is different from the more common presentation of AD, which may involve[2]:

- Memory complaints
- Difficulties with planning, judgment, or problem-solving
- Changes in mood, personality, or behavior
- Confusion with time or place

AD=Alzheimer's Disease.

1. Shea YF, et al. *Psychogeriatrics.* 2021;21(3):396-406. 2. https://altoida.com/blog/frontotemporal-dementia-different-from-alzheimers/ (Accessed February 2024).

Key Learnings in Marlene's Case (2 of 5)

Marlene's care team was focused on her prior diagnosis of MS, and the reasonable expectation that her symptoms were related to that. It was only when her symptoms progressed that they became concerned about other potential causes, such as AD

The use of AD biomarkers helps to confirm the diagnosis of AD even in the case of atypical presentations and/or concomitant neurodegenerative conditions

When distinguishing between AD and **non-AD pathologies**, combining CSF $A\beta_{42}$ and CSF P-tau181 gives a sensitivity and specificity of ~90%

- CSF $A\beta_{42}$ levels and the $A\beta_{42}/A\beta_{40}$ ratio inversely correlate with cerebral Aβ
- CSF T-tau and P-tau concentrations directly correlate with cerebral neurofibrillary-tangle pathology

Aβ=Amyloid Beta; AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; MS=Multiple Sclerosis; P-tau=Phosphorylated Tau; T-tau=Total Tau.

Graff-Radford J, et al. *Lancet Neurol*. 2021;20(3):222-234.

Key Learnings in Marlene's Case (3 of 5)

Having undergone many assessments to diagnose and monitor her MS, Marlene was reluctant to have a lumbar puncture to assess her CSF. However, she decided to take part in a clinical trial in which her blood was assessed to identify biomarkers of AD pathology

Several blood-based biomarkers have shown sufficient accuracy in the diagnosis of AD, and may be available for clinical use in the future[1]:

Pathology	A Amyloid	T Tau	N Neurodegeneration
Plasma biomarkers	$A\beta_{42}/A\beta_{40}$ ratio[2-4,6]	P-tau[2-5] (P-tau181,[2-6] P-tau217,[2-5] and P-tau231[2-5]) P-tau217/nP-tau217 ratio[1]	NfL[2-4,6] GFAP[2-4,6]

Aβ=Amyloid Beta; AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; GFAP=Glial Fibrillary Acidic Protein; MS=Multiple Sclerosis; nP-tau=Non-phosphorylated Tau; NfL=Neurofilament Light; P-tau=Phosphorylated Tau.

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. Teunissen CE, et al. *Lancet Neurol*. 2022;21(1):66-77. 3. Zetterberg H. *Alzheimers Dement*. 2022;18(9):1687-1693. 4. Angioni D, et al. *J Prev Alzheimers Dis*. 2022;9(4):569-579.
5. Therriault J, et al. *JAMA Neurol*. 2023;80(2):188-199. 6. Simrén J, et al. *Alzheimers Dement*. 2021;17(7):1145-1156.

Key Learnings in Marlene's Case (4 of 5)

Referral to clinical trials can help patients get screened for health disorders, and/or access newer diagnostic procedures and treatments

- A US survey registered that two thirds of geriatricians and neurologists reported being familiar with clinical trials related to AD[1]
- A good relationship and strong connection between HCP/researcher and patient can facilitate participation and retention in clinical trials[2]
- Participation in a clinical trial may offer a higher quality of care (ie, screening, monitoring, and treatment) to patients, allowing access to leading healthcare facilities, cutting-edge treatments and expert medical care[3,4]

AD=Alzheimer's Disease; HCP=Healthcare Provider; US=United States of America.

1. https://www.alz.org/media/Documents/alzheimers-facts-and-figures.pdf (Accessed February 2024). 2. https://orwh.od.nih.gov/sites/orwh/files/docs/orwh_outreach_toolkit_litreview.pdf (Accessed February 2024).
3. https://www.alz.org/alzheimers-dementia/research_progress/clinical-trials/why-participate (Accessed February 2024). 4. Schwarz K, et al. *Clin Med (Lond).* 2021;21(6):e645-e647.

Key Learnings in Marlene's Case (5 of 5)

Since Marlene is already receiving care at a specialty neurology clinic for MS, she has had prior neuropsychological assessment. When available, historical neuropsychological test results can help in assessment and diagnosis of AD

Referral for neuropsychological testing may introduce significant delays to diagnosis.

- In a survey conducted by the Alzheimer's Association, most PCPs reported that the number of dementia specialists in their area is insufficient to meet patient demand[1]
- Additionally, in the face of increasing demand, memory assessment services may struggle to find resource capacity to be able to keep waiting times within national recommendations[2]

Yet, it is helpful to request past medical records or inquire about any potential past assessments as part of the diagnostic workup.

- A prior neuropsychological assessment can be useful for diagnosis by providing a baseline against which comparisons with longitudinal follow-up examinations can be made, in order to track progression[3]

AD=Alzheimer's Disease; MS=Multiple Sclerosis; PCP=Primary Care Physician.

1. Alzheimer's Association. *Alzheimers Dement.* 2022;18(4):700-78. 2. Donovan H, et al. *BMJ Open Qual.* 2020;9(3):e000767. 3. Weintraub S. *Continuum (Minneap Minn).* 2022;28(3):781-799.

Thank you for connecting with Marlene