Diagnose

Lilly 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 understand biomarkers and biomarker testing for 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 some of the options available to clinicians, but the use of particular diagnostic tools does not imply endorsement or recommendation by Lilly.

Learning Objectives

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

1. The clinical presentation of Alzheimer’s disease

2. The role clinical and biomarker assessments can play in diagnosing early symptomatic Alzheimer’s disease

Lilly ConnectAD™

Connect *with Annie*

Diagnose

The clinical case presented here is entirely fictional and is not based on any real patient.

Our Patient Annie

- 69 years old
- Female
- White
- Married, lives with husband
- High school diploma
- Grocery store clerk (retired)
- Family history
  - No family history of dementia

Clinical Information and History

Annie reports the onset of impaired cognitive symptoms and memory difficulties over the past 6 months. She reports difficulty with mentally stimulating tasks that she used to enjoy, such as puzzles and other activities requiring reasoning or word recall.

Annie’s husband confirms her account.

Clinical Information and History

Clinical history

- Anxiety
- Hypertension
- Hypercholesterolemia

Current medication (class)

- Benzodiazepine PRN
- Beta-blocker
- Statin

Vital signs

- Heart rate: 76 bpm
- Blood pressure: 125/75 mmHg

Physical exam

- Normal (no tremors or gait dysfunction)

bpm=Beats Per Minute; mmHg=Millimeters of Mercury; PRN=Pro Re Nata (As Needed).

Initial Clinical Assessment

General neurological exam

- Normal

Mental status

- Alert and responsive
- Oriented to person, time, and place
- Independent in all activities of daily living

Cognition

- MoCA: 23/30 (normal ≥26)

MoCA=Montreal Cognitive Assessment.

Additional Findings: Routine Labs and Further Assessments

Blood work within normal limits, including:

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

Based on the differential diagnosis, the following were also ordered:

Brain MRI

- Age-related involutional changes

Blood biomarker assay

- P-tau217 test **indeterminant/intermediate**

MRI=Magnetic Resonance Imaging; P-tau217=Phosphorylated Tau at Position 217.

Given the Patient Information Presented, What Are Possible Diagnoses the HCP Could Consider?

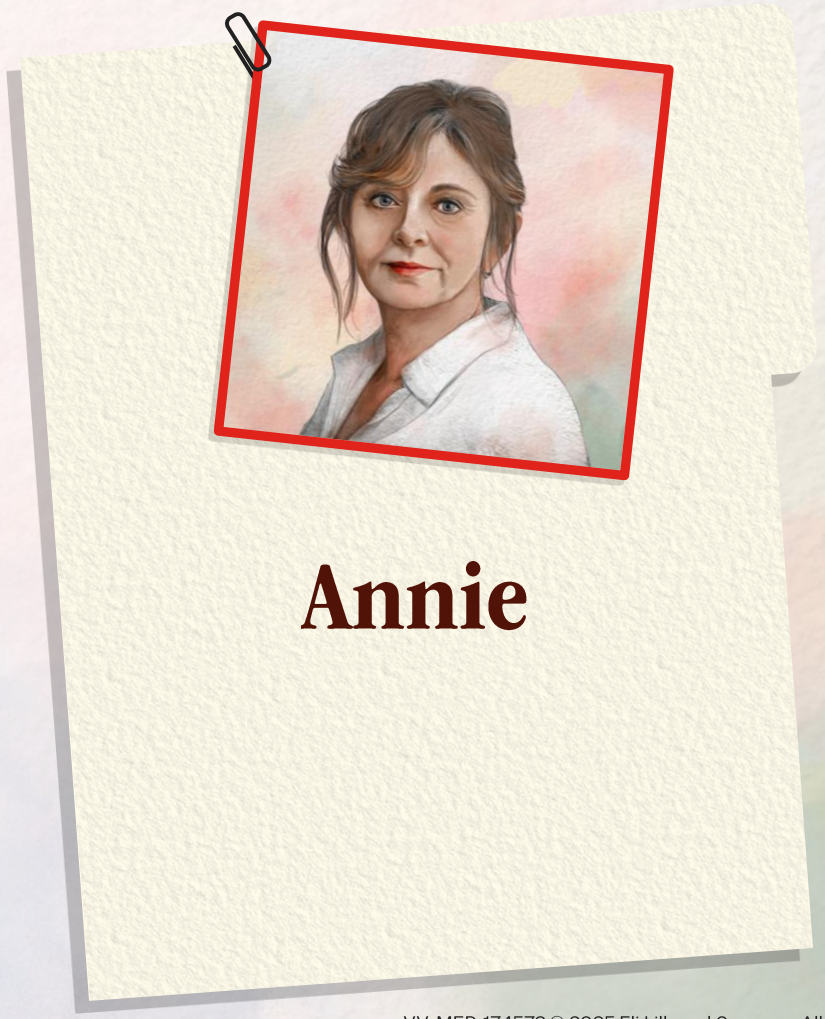
1. Generalized anxiety
2. MCI due to AD
3. Preclinical AD
4. MCI of uncertain etiology
5. Other

Annie

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

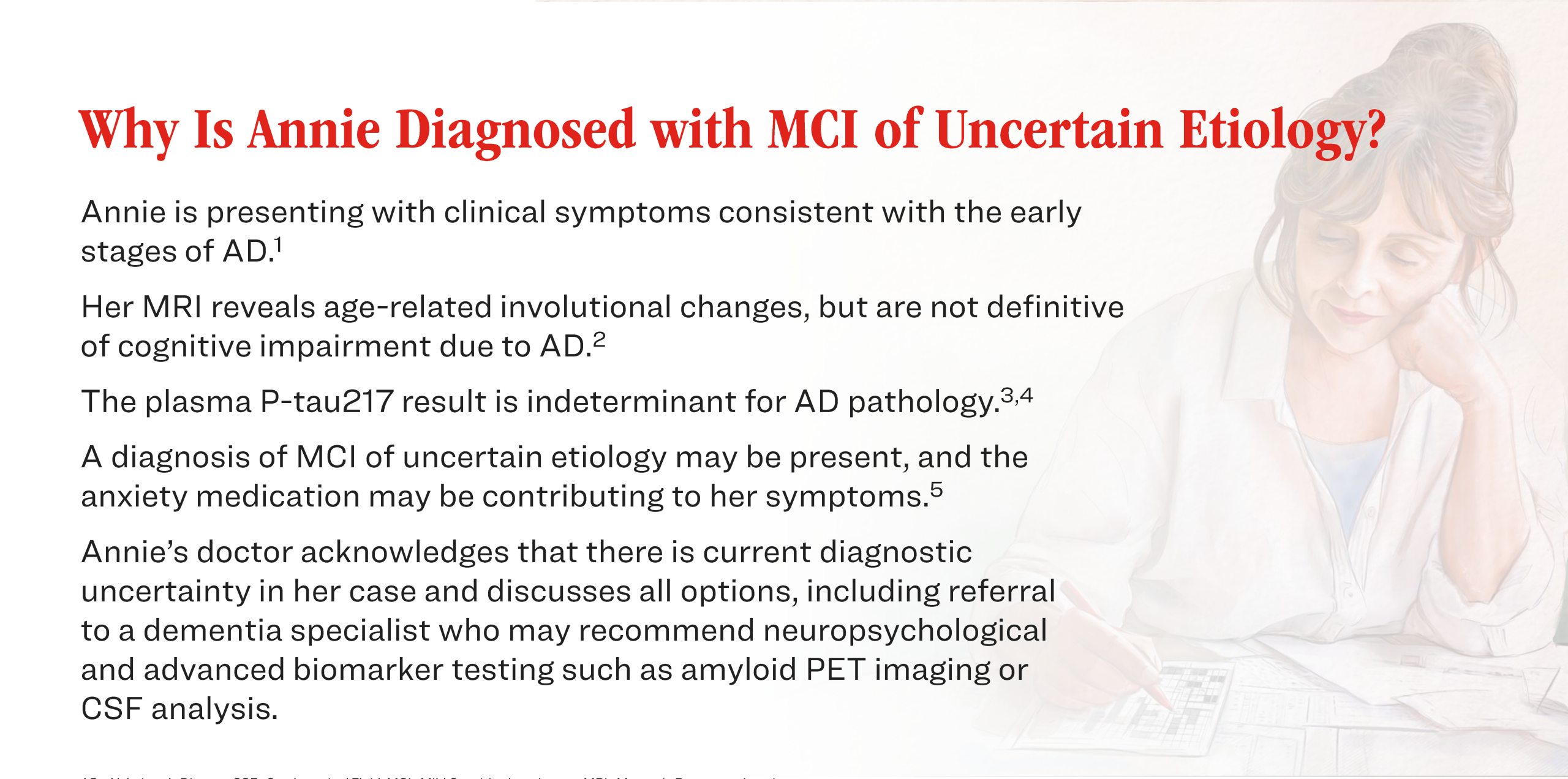
Given the Patient Information Presented, What Is the HCP's Diagnosis?

1. Generalized anxiety
2. MCI due to AD
3. Preclinical AD
4. **MCI of uncertain etiology**
5. Other



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

Why Is Annie Diagnosed with MCI of Uncertain Etiology?



Annie is presenting with clinical symptoms consistent with the early stages of AD.[1]

Her MRI reveals age-related involutional changes, but are not definitive of cognitive impairment due to AD.[2]

The plasma P-tau217 result is indeterminant for AD pathology.[3,4]

A diagnosis of MCI of uncertain etiology may be present, and the anxiety medication may be contributing to her symptoms.[5]

Annie's doctor acknowledges that there is current diagnostic uncertainty in her case and discusses all options, including referral to a dementia specialist who may recommend neuropsychological and advanced biomarker testing such as amyloid PET imaging or CSF analysis.

AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; MCI=Mild Cognitive Impairment; MRI=Magnetic Resonance Imaging; P-tau217=Phosphorylated Tau at Position 217; PET=Positron Emission Tomography.

1. https://www.merckmanuals.com/professional/neurologic-disorders/delirium-and-dementia/alzheimer-disease? (Accessed November 6, 2025). 2. LeMay M. Review. *AJNR Am J Neuroradiol*. 1984;5(3):269-275. 3. Hazan J, et al. *Alzheimers Dement*. 2025;21(3):e70113. 4. Hu S, et al. *Drug Discov Ther*. 2025;19(3):208-209. 5. Stewart SA. *J Clin Psychiatry*. 2005;66[suppl 2]:9-13.

Key Learnings in Annie's Case (1 of 4)

The two hallmark pathological features of AD are[1]:

- Extracellular β-amyloid plaques
- Intracellular neurofibrillary tangles, which are composed of abnormally hyperphosphorylated tau protein, like P-tau217

Soluble $A\beta_{42}$ and P-tau217 appear at roughly the same time early in the disease process.[2]

- As AD progresses, $A\beta_{42}$ levels decline in CSF and blood (reflecting plaque formation), while P-tau markers rise in CSF and blood[3-6]

$A\beta_{42}$=42-Amino-Acid Version of Amyloid Beta; AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; P-tau=Phosphorylated Tau; P-tau217=Phosphorylated Tau at Position 217.

1. Palmqvist S, et al. *Alzheimers Dement*. 2025;21(7):e70535. 2. Arnsten AFT, et al. *Alzheimers Dement*. 2025;21(8):e70404. 3. Sunderland T, et al. *JAMA*. 2003;289(16):2094-2103. 4. Padala SP, Newhouse PA. *Metab Brain Dis*. 2023;38(1):185-193. 5. Graff-Radford NR, et al. *Arch Neurol*. 2007;64(3):354-362. 6. Teunissen CE, et al. *Alzheimers Dement*. 2025;21(1):e14397.

Key Learnings in Annie's Case (2 of 4)

Blood biomarker tests, including those that measure P-tau217, can provide evidence of amyloid pathology as a potential cause of symptoms. However, even highly accurate blood biomarker tests can return intermediate/indeterminant results.[a,1]

The two cut-off approach, used by the BBM Workgroup, defines three categories of results[1]:

1

POSITIVE

Values above the upper cut-off indicate a high likelihood of brain amyloid pathology.[1,2]

2

INTERMEDIATE/INDETERMINANT

Values in between the two cut-offs warrant further evaluation with amyloid PET imaging or amyloid CSF assays.[1,2]

3

NEGATIVE

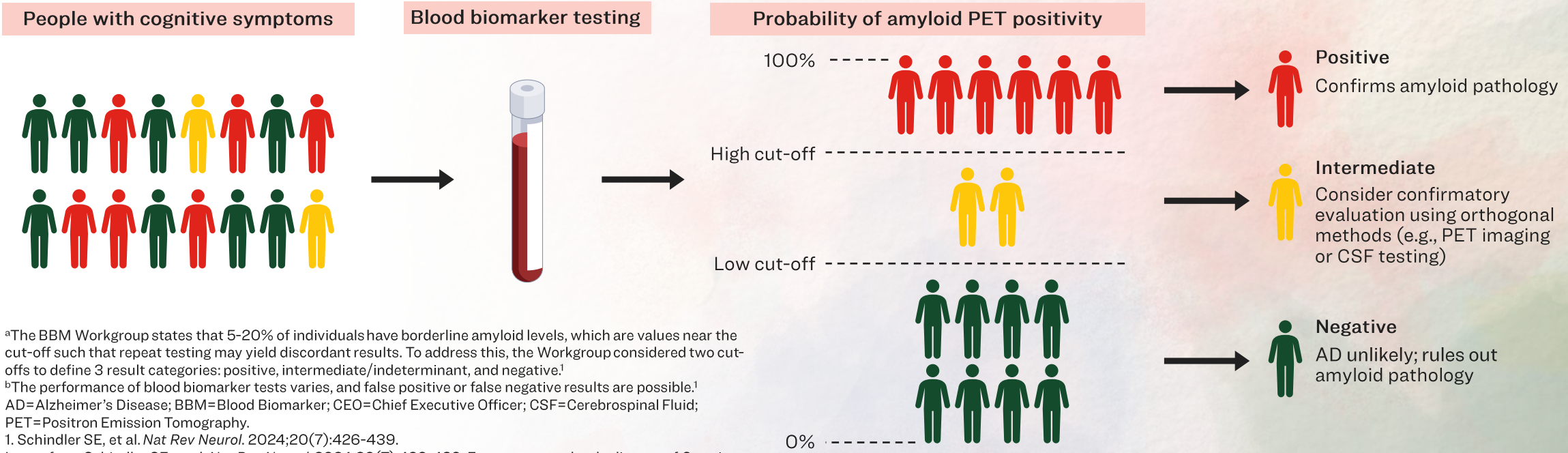
Values below the lower cut-off suggest brain amyloid pathology is unlikely.[1,2]

[a]The BBM Workgroup states that 5-20% of individuals have borderline amyloid levels, which are values near the cut-off such that repeat testing may yield discordant results. To address this, the Workgroup considered two cut-offs to define 3 result categories: positive, intermediate/indeterminant, and negative.[1]
BBM=Blood Biomarker; CSF=Cerebrospinal Fluid; P-tau217=Phosphorylated Tau at Position 217; PET=Positron Emission Tomography.

1. Schindler SE, et al. *Nat Rev Neurol.* 2024;20(7):426-439. 2. Palmqvist S, et al. *Alzheimers Dement.* 2025;21(7):e70535.

Key Learnings in Annie's Case (3 of 4)

The BBM Workgroup, convened by the Global CEO Initiative on Alzheimer's Disease, recommends that no more than 15-20% of individuals in a typical clinical population would have intermediate/indeterminant BBM test results[a,b,1]



[a]The BBM Workgroup states that 5-20% of individuals have borderline amyloid levels, which are values near the cut-off such that repeat testing may yield discordant results. To address this, the Workgroup considered two cut-offs to define 3 result categories: positive, intermediate/indeterminant, and negative.[1]
[b]The performance of blood biomarker tests varies, and false positive or false negative results are possible.[1]
AD=Alzheimer's Disease; BBM=Blood Biomarker; CEO=Chief Executive Officer; CSF=Cerebrospinal Fluid; PET=Positron Emission Tomography.

1. Schindler SE, et al. *Nat Rev Neurol.* 2024;20(7):426-439.

Key Learnings in Annie's Case (4 of 4)

Comprehensive assessment involves: Medical evaluation, neurological exam, cognitive testing, laboratory assessment of potentially reversible etiologies of cognitive impairment, and structural neuroimaging.[1]

- Cognitive symptoms often have multiple causes, and misdiagnosis may result in delayed care, inappropriate treatment, and inaccurate prognoses[1]
- Many conditions other than AD can cause or exacerbate cognitive impairment; therefore, a comprehensive assessment should be used to identify the potential alternative etiologies[1]

AD biomarker testing is not intended as a standalone diagnostic test for symptomatic AD; it should always be used in the context of a comprehensive assessment.[1]

AD=Alzheimer's Disease.

1. Schindler SE, et al. *Nat Rev Neurol*. 2024;20(7):426-439.

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Thank you for Connecting *with Annie*

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