




# Blood-based Biomarkers in the Clinical Diagnosis of Alzheimer's Disease

**October 7, 2026**

Washington University in St. Louis
School of Medicine

**Suzanne E. Schindler, MD, PhD**
**Professor of Neurology**

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

# Disclosures: Suzanne Schindler, MD, PhD

- Research support/grants: Salary and research support is primarily from R01AG070941 (PI Schindler); P30AG066444, P01AG003991 and P01AG026276 (PI Morris).
- Dr. Schindler has previously analyzed biomarker data provided to Washington University by C2N Diagnostics and Roche Diagnostics; no financial incentives or research funding were provided to Dr. Schindler in return.
- Stock/Equity: None.
- Consulting/Employment: **SES has not received any personal compensation from ineligible companies for over 2 years.** She has recently received honoraria for educational presentations from Medscape, PeerView, the Academy for Continued Healthcare Learning, Med Learning Group, and the Global Learning Collaborative. **She has provided unpaid advising to Acumen, Biogen, Cognito Therapeutics, Danaher, Eisai, Eli Lilly, Johnson and Johnson Innovative Medicine, Roche, Sanofi, and Siemens.**
- Speakers Bureau/Honoraria: Dr. Schindler receives honoraria as a member of the biorepository review committee for the non-profit National Centralized Repository for Alzheimer's Disease (NCRAD); she has received honoraria for participating in expert panels and reviewing grants from non-profit organizations.
- Other: Dr. Schindler previously served as a sub-PI for the A4, DIAN-TU, and ENGAGE trials. Dr. Schindler participated in the IDEAS trial.

# Is cognitive impairment due to Alzheimer's disease?

**Clinical assessment to determine potential causes of cognitive impairment:**

- **Clinical history-** Was there an insidious onset, slow progression, and early impairment of memory?
- **Medical history-** Does the patient have medical conditions that can cause cognitive impairment?
- **Medication history-** Is the patient taking medications that impair cognition?
- **Family history-** Did family members have dementia symptoms at approximately the patient's age?
- **Cognitive testing-** Are there impairments on tasks of memory, orientation, attention/concentration, language, executive function, visuospatial function, etc.?
- **Neurological exam-** Are there signs of language dysfunction, visuospatial dysfunction, stroke or parkinsonism?
- **Routine blood work-** Are there metabolic issues that could cause cognitive impairment (blood chemistries, blood cell counts, thyroid function tests and vitamin B12 levels)
- **Structural brain imaging**- Is there evidence of strokes or brain atrophy?

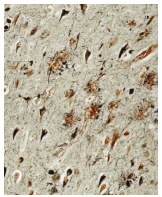
**Even after completing a comprehensive clinical evaluation, the cause(s) of cognitive impairment is often uncertain or incorrect!**

# Biomarkers are required for an accurate Alzheimer's diagnosis

- Alzheimer's disease is mis-diagnosed (or not diagnosed) in ~30-40% of patients![1-3]

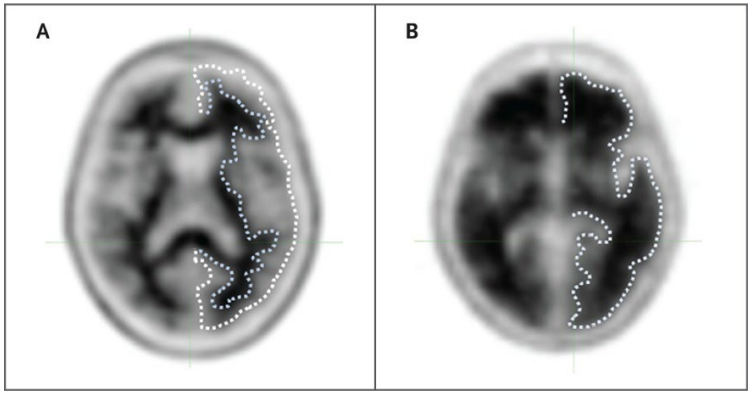



- **Biomarkers can determine whether Alzheimer's disease pathology is present and may be causing or contributing to cognitive impairment**

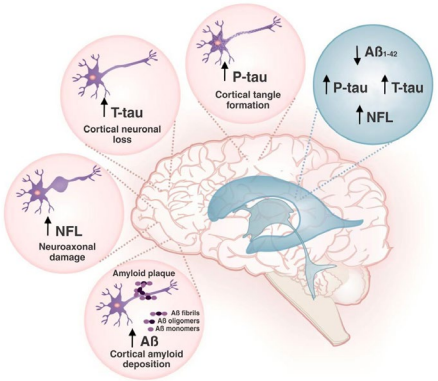


[1]Rabinovici *et al. JAMA* 2019 [2]Karran *et al. NEJM* 2014 [3]Palmqvist *et al. JAMA* 2024

# Clinically available Alzheimer's disease biomarker tests




Amyloid PET




CSF tests



Blood tests

# Current indications for clinical AD biomarker testing

**Patients who are undergoing an evaluation who have objective evidence of cognitive impairment**

1) In whom Alzheimer's disease is a potential cause of cognitive impairment

2) AND biomarker testing is expected to affect diagnosis and/or management by

a) improving the accuracy of dementia diagnosis[1-3]

b) and/or determining whether patients may be candidates for Alzheimer's-specific treatments, such as amyloid-targeting treatments (ATTs)[4,5]

[1]Johnson *et al. Alzheimer's & Dementia* 2013 [2]Shaw *et al. Alzheimer's & Dementia* 2018
[3]Palmqvist *et al. Alzheimer's & Dementia* 2025 [4]Cummings *et al. JPAD* 2023 [5]Rabinovici *et al. JPAD* 2025

# All biomarker results must interpreted in the context of clinical symptoms

| | Pre-test probability of amyloid pathology | Positive biomarker result | Negative biomarker result |
|---|---|---|---|
| 75-year-old patient with a typical AD dementia syndrome | 85% | 98% of patients have a true positive result (have amyloid pathology) | 61% of patients have a true negative result (do not have amyloid pathology) |
| | | 2% of patients have a false positive result (do not have amyloid pathology) | 39% of patients have a false negative result (have amyloid pathology) |
| 60-year-old patient with subjective cognitive decline | 20% | 69% of patients have a true positive result (have amyloid pathology) | 97% of patients have a true negative result (do not have amyloid pathology) |
| | | 31% of patients have a false positive result (do not have amyloid pathology) | 3% of patients have a false negative result (have amyloid pathology) |

The biomarker test is assumed to have 90% sensitivity and specificity for amyloid pathology.

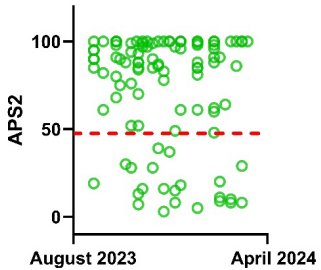
**Treat the patient, not the test!**

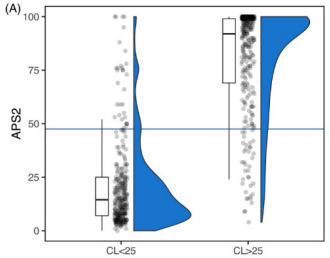
**VandeVrede and Schindler, *Alzheimer's & Dementia 2024***

# Blood biomarkers

- **Procedure:**
  - Patient undergoes a blood draw
  - Concentrations of certain proteins in the plasma/serum (e.g., **p-tau217**, Aβ42, Aβ40,) are measured
- **Interpretation:** Positive or negative (or intermediate) based on the cut-off value; continuous values provided
- **Advantages:** More acceptable, more accessible, less burdensome, and less expensive than other modalities
- **Drawbacks (potentially modifiable/addressable):**
  - Reimbursement issues
  - Some tests may not perform consistently in all groups or in patients with certain comorbidities (e.g., kidney disease)
  - Current tests do not reflect amyloid clearance on an individual level
  - Variability in the accuracy of various AD blood tests





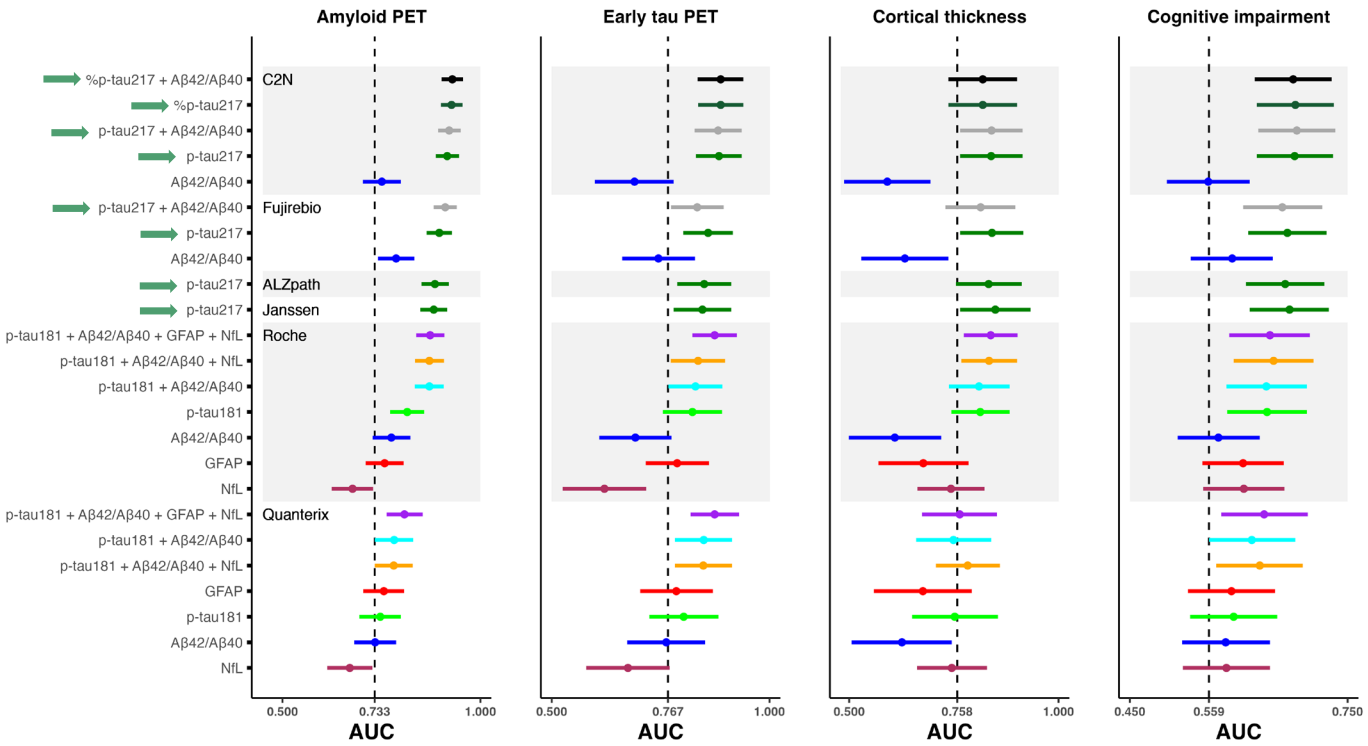



# Some clinically available AD blood tests in the US

| Company | Assay type | Biomarkers | Reference |
|---|---|---|---|
| **ARUP** | Immunoassay | p-tau217 | https://ltd.aruplab.com/Tests/Pub/3019017 |
| **C2N Diagnostics** | IP-MS | **Aβ42/40 + %p-tau217** | https://precivityad.com |
| **Labcorp** | Immunoassay | **p-tau217**, Aβ42/40, NfL, GFAP, **p-tau181, p-tau217/Aβ42** | https://www.labcorp.com/treatment-areas/neurology/conditions/neurodegenerative |
| **Quanterix** | Simoa | p-tau217, Aβ42/40, NfL, GFAP | https://alzpath.bio/healthcare-providers<br>https://www.lucentdiagnostics.com/about-lucentad-providers |
| **Quest Diagnostics** | IP-MS for Aβ42/40; immunoassay for p-tau217 and p-tau181 | Aβ42/40, **p-tau217**, p-tau181, NfL, **p-tau181, p-tau217/Aβ42** | https://www.questdiagnostics.com/healthcare-professionals/about-our-tests/neurological-disorders/campaigns/alzheimers-risk-assessment |
| **Mayo Clinic Laboratories** | Immunoassay | p-tau217 | https://www.mayocliniclabs.com/test-catalog/overview/621635 |
| **Neurocode Labs** | Immunoassay | GFAP, NfL, p-tau217 | https://neurocode.com/ |

***FDA cleared**

# All roads lead to plasma p-tau217




FNIH
Foundation for the National Institutes of Health

BIOMARKERS CONSORTIUM
IMPROVING HEALTH THROUGH MEANINGFUL MEASUREMENTS

ADNI
Alzheimer's Disease Neuroimaging Initiative

Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Schindler *et al., Alzheimer's & Dementia 2024*

# Some plasma p-tau217-based tests are highly accurate

nature medicine

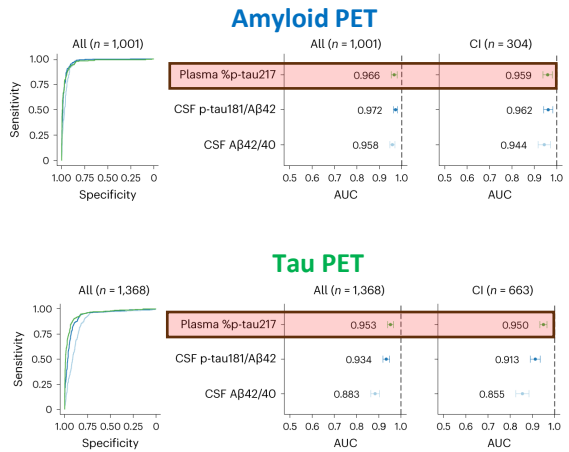
Explore content · About the journal · Publish with us

nature › nature medicine › articles › article

Article | Open access | Published: 21 February 2024

## Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests

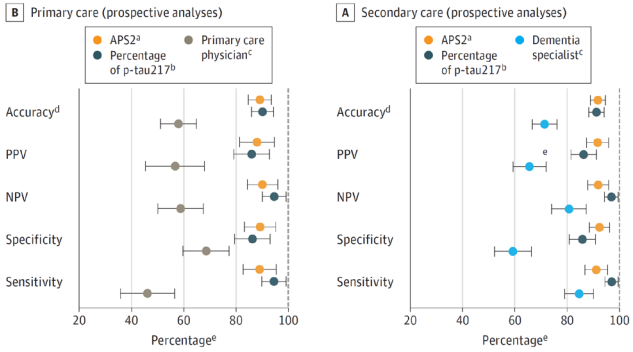
Nicolas R. Barthélemy, Gemma Salvadó, Suzanne E. Schindler, Yingxin He, Shorena Janelidze, Lyduine E. Collij, Benjamin Saef, Rachel L. Henson, Charles D. Chen, Brian A. Gordon, Yan Li, Renaud La Joie, Tammie L. S. Benzinger, John C. Morris, Niklas Mattsson-Carlgren, Sebastian Palmqvist, Rik Ossenkoppele, Gil D. Rabinovici, Erik Stomrud, Randall J. Bateman & Oskar Hansson




JAMA | Original Investigation

## Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary Care

Sebastian Palmqvist, MD, PhD; Pontus Tideman, MSc; Niklas Mattsson-Carlgren, MD, PhD; Suzanne E. Schindler, MD, PhD; Ruben Smith, MD, PhD; Rik Ossenkoppele, PhD; Susanna Calling, MD, PhD; Tim West, PhD; Mark Monane, MD, MBA; Philip B. Verghese, PhD; Joel B. Braunstein, MD, MBA; Kaj Blennow, MD, PhD; Shorena Janelidze, PhD; Erik Stomrud, MD, PhD; Gemma Salvadó, PhD; Oskar Hansson, MD, PhD




| | Primary care | Secondary care |
|---|---|---|
| Medical history, No./total (%) | | |
| Cardiovascular disease | 355/511 (69.5) | 337/692 (48.7) |
| Hyperlipidemia | 269/512 (52.5) | 230/692 (33.2) |
| Chronic kidney disease | 134/511 (26.2) | 117/691 (16.9) |
| Diabetes | 113/512 (22.1) | 103/691 (14.9) |

# Memory Diagnostic Center at Washington University

- The Washington University (WashU) Memory Diagnostic Center (MDC), the dementia specialty practice associated with Washington University and the Knight Alzheimer's Disease Research Center, includes 16 clinicians (12 physicians and 4 advanced practice providers)
- ~4,000 unique patients with memory complaints seen over the past year
- Washington University has participated in many clinical trials of amyloid-lowering treatments, including the DIAN-TU, CLARITY, ENGAGE, and AHEAD 3-45
- Extensive experience using clinical biomarker testing for AD, including amyloid PET, blood tests, and CSF tests

# Our experience with ATTs at the WashU MDC

- As of 10/1/2026, we have initiated lecanemab in ~536 patients and donanemab in ~178 patients (donanemab was approved later)
- We detailed our experience with our first 234 patients treated with lecanemab in a paper published in *JAMA Neurology* in May 2025
- We treated some *APOE* ε4 homozygotes and some patients on anticoagulants (but did have discussion of increased risks)
- Biomarker modality used to confirm amyloid pathology:
  - CSF test: 139 (59%)
  - Amyloid PET: 55 (24%)
  - High accuracy blood test: **40 patients (17%);** in 37 patients the blood test was the only AD biomarker performed



Research

JAMA Neurology | Original Investigation

Lecanemab Treatment in a Specialty Memory Clinic

Madeline Paczynski, PA, MCMSc; Anna Hofmann, MD; Zachary Posey, MA; Maren Gregersen, MD; Michelle Rudman, MD, PhD; Dawn Ellington, RN; Melissa Aldinger, BS; Erik S. Musiek, MD, PhD; David M. Holtzman, MD; Randall J. Bateman, MD; Justin M. Long, MD, PhD; Nupur Ghoshal, MD, PhD; David B. Carr, MD; Alan Dow, MSHA, MBA; Sheyda Namazie-Kummer, MD, MBA; Najvid Jana, BA; Chengjie Xiong, PhD; John C. Morris, MD; Tammie L. S. Benzinger, MD, PhD; Suzanne E. Schindler, MD, PhD; B. Joy Snider, MD, PhD

Supplemental content

**IMPORTANCE** Two monoclonal antibodies targeting amyloid plaques, lecanemab and donanemab, have received traditional US Food and Drug Administration (FDA) approval for the treatment of early symptomatic Alzheimer disease (AD). The most significant adverse events associated with these therapies are infusion-related reactions and amyloid-related imaging abnormalities (ARIA) with edema/effusion (ARIA-E) and/or hemorrhage/hemosiderin deposition (ARIA-H). The feasibility and safety of providing these treatments in clinical practice is unclear.

**OBJECTIVE** To examine the feasibility and safety of treating patients in specialty memory clinics with lecanemab.

**DESIGN, SETTING, AND PARTICIPANTS** This retrospective analysis of consecutive patients in whom lecanemab was initiated between August 1, 2023, and October 1, 2024, at Washington University Memory Diagnostic Center, an outpatient specialty memory clinic. Lecanemab was initiated in 234 patients with early symptomatic AD. Eligibility was based on the FDA label and appropriate use recommendations with occasional exceptions.

**EXPOSURE** Patients were treated with lecanemab, 10 mg/kg, intravenously every 2 weeks.

**MAIN OUTCOMES AND MEASURES** Infusion-related reactions, ARIA, and withdrawal from treatment were assessed.

**RESULTS** The 234 patients treated with lecanemab had a mean age of 74.4 (SD, 6.7) years, 117 were female (50%), and 117 were male. (50%) Infusion-related reactions occurred in 87 patients (37%) and were typically mild. Of the 194 patients at risk for ARIA during the study period, 44 had at least 1 microhemorrhage and/or superficial siderosis before initiation of lecanemab (23%). Over an average treatment period of 6.5 months, 42 total patients (22%) developed ARIA; 29 developed ARIA-E with or without ARIA-H (15%) and 13 developed isolated ARIA-H (6.7%). Eleven patients (5.7%) developed symptomatic ARIA, 2 of those patients (1.0%) with clinically severe symptoms. No patients developed a macrohemorrhage or died. Patients with mild dementia had a 27% rate of symptomatic ARIA; those with mild cognitive impairment or very mild dementia had a 1.8% rate. Overall, 23 of 234 patients (9.8%) withdrew from treatment for various reasons, 10 for ARIA (4.3%).

**CONCLUSIONS AND RELEVANCE** A single-specialty memory clinic initiated lecanemab treatment in 234 patients over 14 months. The frequency of significant adverse events, including ARIA, was manageable. These results may inform discussions about the risks of anti-amyloid treatments.

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Authors: Suzanne E. Schindler, MD, PhD, and B. Joy Snider, MD, PhD, Washington University School of Medicine in St Louis, 660 S Euclid Ave, Campus Box 8111, St Louis, MO 63110 (schindler.s.e@wustl.edu; snider@wustl.edu).

JAMA Neurol. doi:10.1001/jamaneurol.2025.1232
Published online May 12, 2025.

E1

rom jamanetwork.com by Washington University - St Louis user on 05/12/2025

**Paczynski *et al. JAMA Neurol 2025***

# Should multiple biomarker tests be performed “just to be sure?”

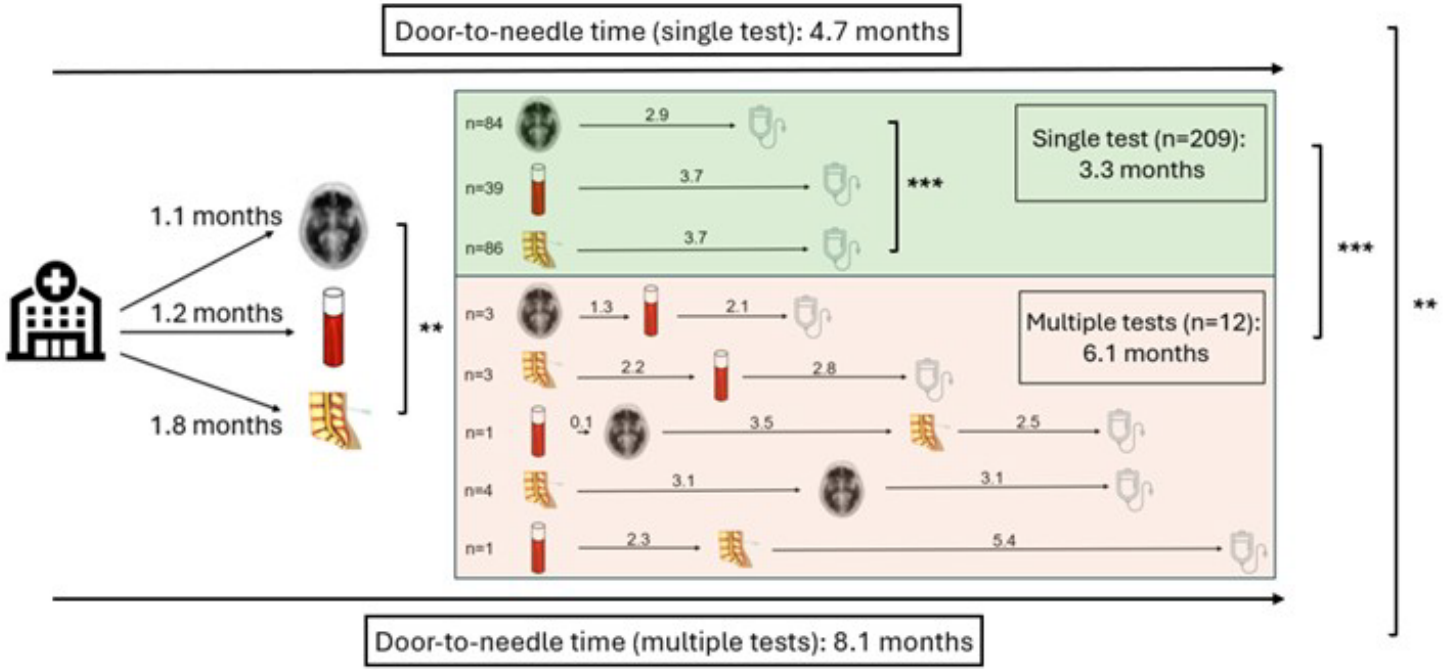
- **For a patient who is younger (<65 years), who has a more complex clinical syndrome, intermediate biomarker results, or concern about biomarker test accuracy[1-3]: Yes**
  - A second test may be **necessary** to diagnose symptomatic Alzheimer’s disease with high certainty
  - Biomarker testing with a **different modality** may be reasonable

- **For a patient with a typical Alzheimer’s clinical syndrome and a high accuracy biomarker test that is clearly positive (e.g., above 95% specificity) [1-3]: Probably not**
  - The likelihood of amyloid pathology is **over 95%**
  - Performing a second test (e.g., CSF test and amyloid PET scan with 90% sensitivity/specificity) could actually **decrease overall diagnostic accuracy** due to a significant number of false negatives
    - **Nearly all patients will have a positive second test**
    - The few patients who test negative have a high likelihood of being false negative may need a **third test** as a “tie-breaker,” potentially prolonging the time until treatment

[1]Schindler *et al. Nature Rev Neurol* 2024 [2]Therriault *et al. Nature Aging* 2024 [3]Palmqvist *et al. Alzheimer’s & Dementia* 2025

# Performing multiple biomarker tests may delay treatment

- Performing **a second (or third) biomarker** test is associated with nearly **double the time** from clinical assessment to initial infusion compared to a single test (4.7 to 8.1 months)

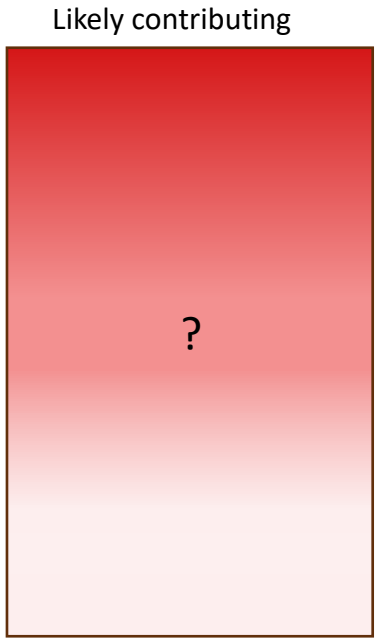



Hofmann *et al., Alzheimer's & Dementia 2026: DADM*

# Man in early 70s

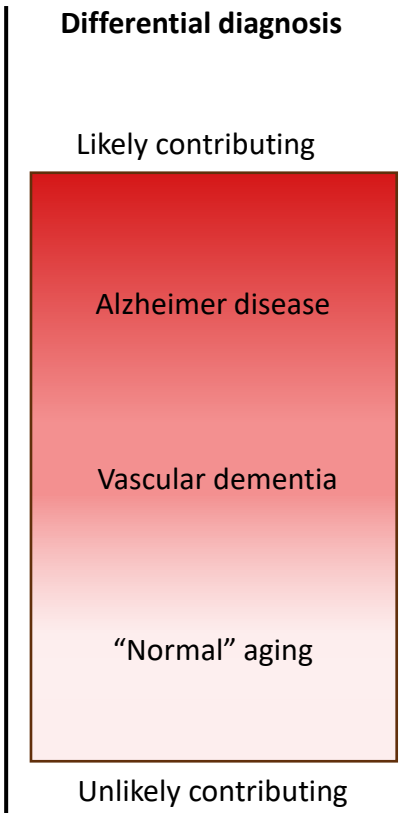
- **Brief history:** Busy professional in his early 70s has a strong family history of Alzheimer's disease (father died of AD in early 80s, brother and sister developed symptomatic AD in early 70s). He and his wife report progressive forgetfulness over the past three years with repetition of questions about the schedule, misplacing items, and having more difficulty using his phone for texting. His function at home and in the community is otherwise normal.
- **Exam:** Normal general and neurological exam, 26 on the MMSE (2/3 word recall), 6 on the Short Blessed (2/5 word recall), borderline impairment on word list recall and paragraph recall
- **Labs:** TSH, B12, blood counts and blood chemistries were normal
- **Brain MRI:** "mild cerebral atrophy and cerebral microangiopathy"

**Differential diagnosis**



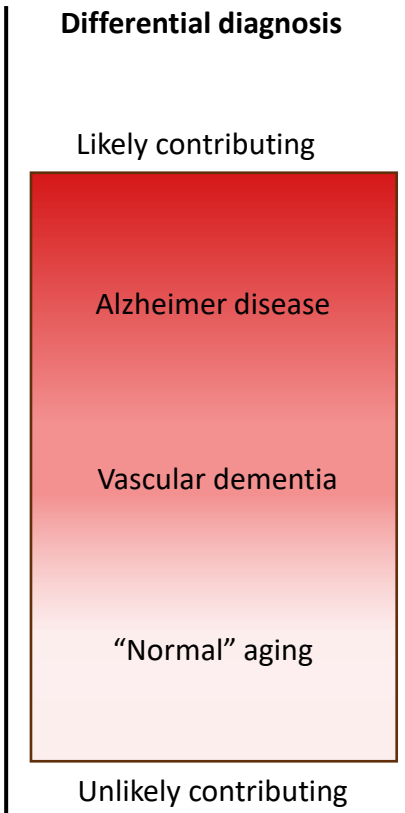
# Man in early 70s

- **Brief history:** Busy professional in his early 70s has a strong family history of Alzheimer's disease (father died of AD in early 80s, brother and sister developed symptomatic AD in early 70s). He and his wife report progressive forgetfulness over the past three years with repetition of questions about the schedule, misplacing items, and having more difficulty using his phone for texting. His function at home and in the community is otherwise normal.
- **Exam:** Normal general and neurological exam, 26 on the MMSE (2/3 word recall), 6 on the Short Blessed (2/5 word recall), borderline impairment on word list recall and paragraph recall
- **Labs:** TSH, B12, blood counts and blood chemistries were normal
- **Brain MRI:** "mild cerebral atrophy and cerebral microangiopathy"



# Man in early 70s

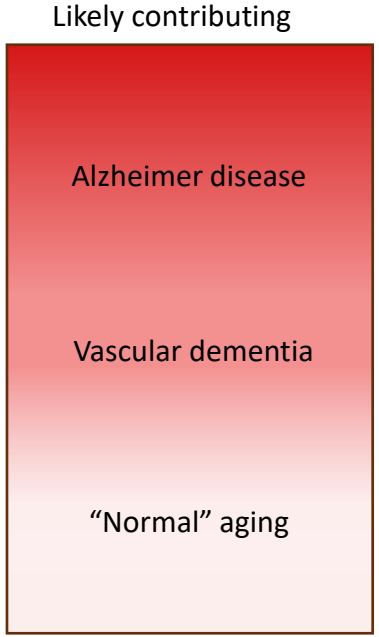
- **Brief history:** Busy professional in his early 70s has a strong family history of Alzheimer's disease (father died of AD in early 80s, brother and sister developed symptomatic AD in early 70s). He and his wife report progressive forgetfulness over the past three years with repetition of questions about the schedule, misplacing items, and having more difficulty using his phone for texting. His function at home and in the community is otherwise normal.
- **Exam:** Normal general and neurological exam, 26 on the MMSE (2/3 word recall), 6 on the Short Blessed (2/5 word recall), borderline impairment on word list recall and paragraph recall
- **Labs:** TSH, B12, blood counts and blood chemistries were normal
- **Brain MRI:** "mild cerebral atrophy and cerebral microangiopathy"



# Man in early 70s

- **AD blood test:**
  - Plasma Aβ42/40 0.148 (normal >0.170)
  - Plasma p-tau217 0.19 (normal <0.15)

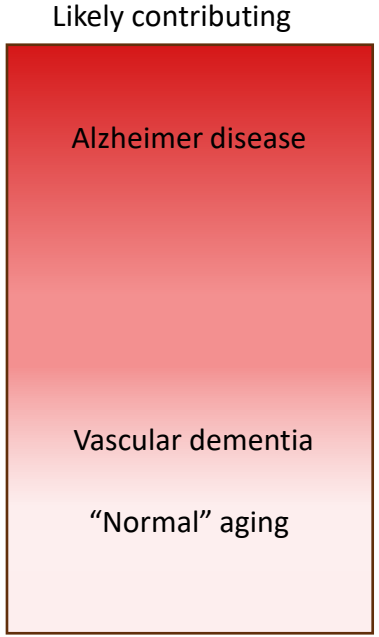
**Differential diagnosis**



# Man in early 70s

- **AD blood test:**
  - Plasma Aβ42/40 0.148 (normal >0.170)
  - Plasma p-tau217 0.19 (normal <0.15)

**Differential diagnosis**

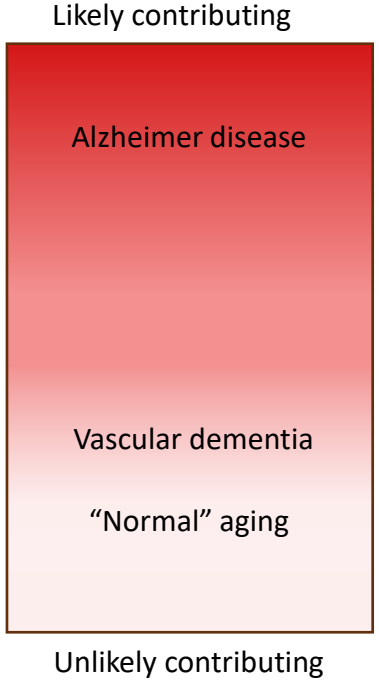


# Man in early 70s

- **AD blood test:**
  - Plasma Aβ42/40 0.148 (normal >0.170)
  - Plasma p-tau217 0.19 (normal <0.15)

- **CSF test:**
  - CSF p-tau181/Aβ42 0.034 (normal <0.023)

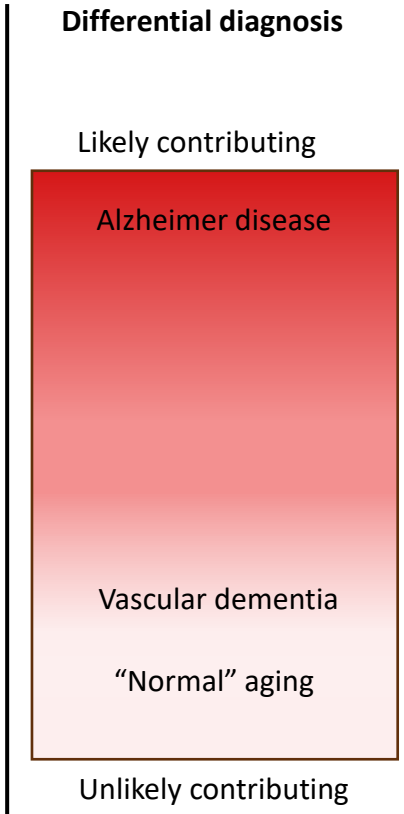
**Differential diagnosis**



# Man in early 70s

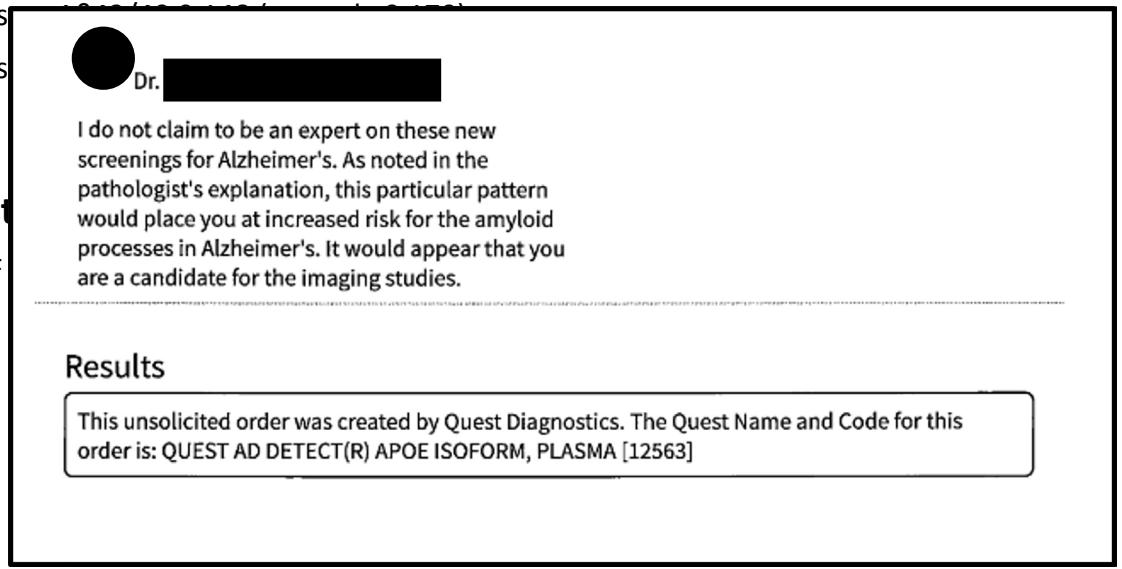
- **AD blood test:**
  - Plasma Aβ42/40 0.148 (normal >0.170)
  - Plasma p-tau217 0.19 (normal <0.15)

- **CSF test:**
  - CSF p-tau181/Aβ42 0.034 (normal <0.023)



# Man in early 70s

- **AD blood test:**
  - Plas
  - Plas
- **CSF test**
  - CSF



Dr. [redacted]

I do not claim to be an expert on these new screenings for Alzheimer's. As noted in the pathologist's explanation, this particular pattern would place you at increased risk for the amyloid processes in Alzheimer's. It would appear that you are a candidate for the imaging studies.

Results

This unsolicited order was created by Quest Diagnostics. The Quest Name and Code for this order is: QUEST AD DETECT(R) APOE ISOFORM, PLASMA [12563]

**Differential diagnosis**

Likely contributing

Alzheimer disease

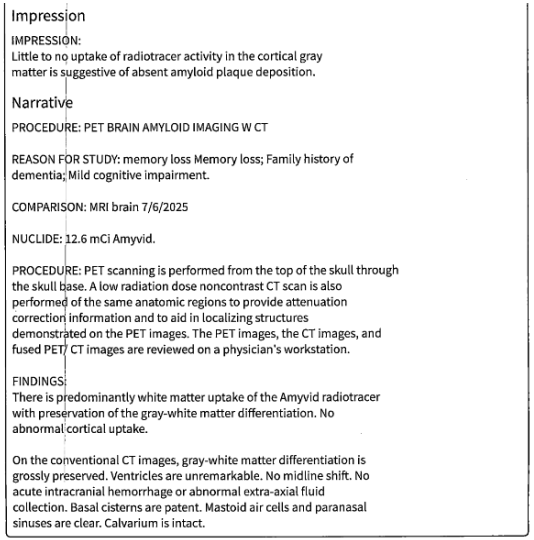
Vascular dementia

"Normal" aging

Unlikely contributing

# Man in early 70s

- **AD blood test:**
  - Plasma Aβ42/40 0.148 (normal >0.170)
  - Plasma p-tau217 0.19 (normal <0.15)
- **CSF test:**
  - CSF p-tau181/Aβ42 0.034 (normal <0.023)
- **Amyloid PET:**
  - **Negative?!**



Impression

IMPRESSION:
Little to no uptake of radiotracer activity in the cortical gray matter is suggestive of absent amyloid plaque deposition.

Narrative

PROCEDURE: PET BRAIN AMYLOID IMAGING W CT

REASON FOR STUDY: memory loss Memory loss; Family history of dementia; Mild cognitive impairment.

COMPARISON: MRI brain 7/6/2025

NUCLIDE: 12.6 mCi Amyvid.

PROCEDURE: PET scanning is performed from the top of the skull through the skull base. A low radiation dose noncontrast CT scan is also performed of the same anatomic regions to provide attenuation correction information and to aid in localizing structures demonstrated on the PET images. The PET images, the CT images, and fused PET/CT images are reviewed on a physician's workstation.

FINDINGS:
There is predominantly white matter uptake of the Amyvid radiotracer with preservation of the gray-white matter differentiation. No abnormal cortical uptake.

On the conventional CT images, gray-white matter differentiation is grossly preserved. Ventricles are unremarkable. No midline shift. No acute intracranial hemorrhage or abnormal extra-axial fluid collection. Basal cisterns are patent. Mastoid air cells and paranasal sinuses are clear. Calvarium is intact.

**Differential diagnosis**

Likely contributing

Alzheimer disease

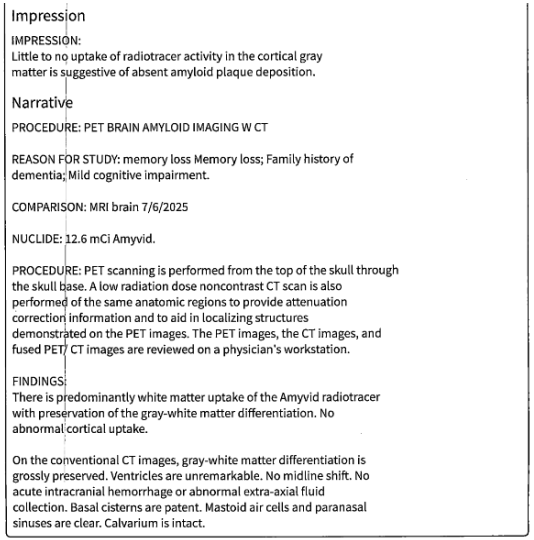
Vascular dementia

“Normal” aging

Unlikely contributing

# Man in early 70s

- **AD blood test:**
  - Plasma Aβ42/40 0.148 (normal >0.170)
  - Plasma p-tau217 0.19 (normal <0.15)
- **CSF test:**
  - CSF p-tau181/Aβ42 0.034 (normal <0.023)
- **Amyloid PET:**
  - **Negative?!**



Impression

IMPRESSION:
Little to no uptake of radiotracer activity in the cortical gray matter is suggestive of absent amyloid plaque deposition.

Narrative

PROCEDURE: PET BRAIN AMYLOID IMAGING W CT

REASON FOR STUDY: memory loss Memory loss; Family history of dementia; Mild cognitive impairment.

COMPARISON: MRI brain 7/6/2025

NUCLIDE: 12.6 mCi Amyvid.

PROCEDURE: PET scanning is performed from the top of the skull through the skull base. A low radiation dose noncontrast CT scan is also performed of the same anatomic regions to provide attenuation correction information and to aid in localizing structures demonstrated on the PET images. The PET images, the CT images, and fused PET/CT images are reviewed on a physician's workstation.

FINDINGS:
There is predominantly white matter uptake of the Amyvid radiotracer with preservation of the gray-white matter differentiation. No abnormal cortical uptake.

On the conventional CT images, gray-white matter differentiation is grossly preserved. Ventricles are unremarkable. No midline shift. No acute intracranial hemorrhage or abnormal extra-axial fluid collection. Basal cisterns are patent. Mastoid air cells and paranasal sinuses are clear. Calvarium is intact.

**Differential diagnosis**

Likely contributing

Alzheimer disease

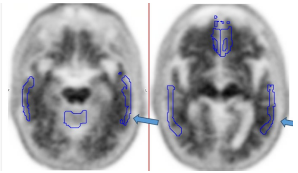
Vascular dementia

“Normal” aging

Unlikely contributing

# Man in early 70s

- “The scans are quite challenging to interpret visually. My first impression was that they were visually negative. However, after quantification and closer inspection of the regions that appear positive, there does seem to be cortical amyloid binding, particularly in the left lateral temporal cortex and precuneus, with a Centiloid (CL) value of 32.8.”
- “I also imported and reviewed the prior PET from the outside hospital (also a difficult visual read), which yielded a CL of 45.4. Of course, differences in technique and acquisition may account for some of this number discrepancy.”
- “Overall, my opinion is that this case is best characterized as borderline positive (more positive than negative) and may represent early amyloid deposition.”



**Differential diagnosis**

Likely contributing

Alzheimer disease

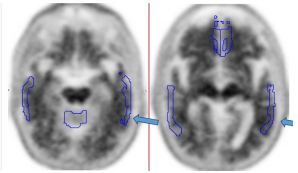
Vascular dementia

“Normal” aging

Unlikely contributing

# Man in early 70s

- “The scans are quite challenging to interpret visually. My first impression was that they were visually negative. However, after quantification and closer inspection of the regions that appear positive, there does seem to be cortical amyloid binding, particularly in the left lateral temporal cortex and precuneus, with a Centiloid (CL) value of 32.8.”
- “I also imported and reviewed the prior PET from the outside hospital (also a difficult visual read), which yielded a CL of 45.4. Of course, differences in technique and acquisition may account for some of this number discrepancy.”
- “Overall, my opinion is that this case is best characterized as borderline positive (more positive than negative) and may represent early amyloid deposition.”



**Differential diagnosis**

Likely contributing

Alzheimer disease

Vascular dementia

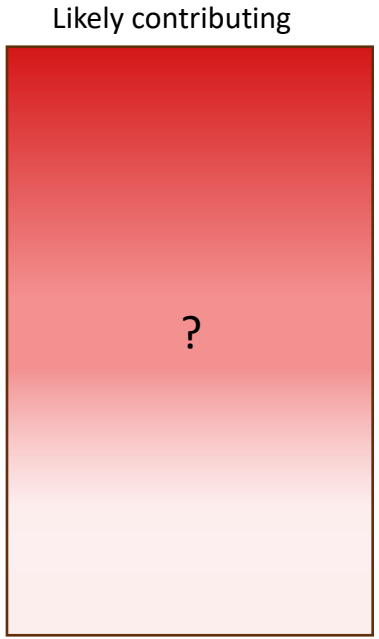
“Normal” aging

Unlikely contributing

# Woman in early 80s

- **Brief history:** Woman in her early 80s is accompanied by family members who report that the patient developed word-finding difficulties, increased misplacing of personal items, and difficulty managing her schedule over the past year. She is having more difficulty cooking but she is able to do laundry and dishes and she has a variety of hobbies. Her hygiene or grooming are unchanged.
- **Exam:** Normal general and neurological exam except some pauses with word finding, 23 on the MMSE, 13 on Boston Naming, mild impairment on episodic memory tasks
- **Labs:** TSH, B12, blood counts and blood chemistries were normal
- **Brain MRI: "**Volume loss more pronounced at left temporal and parietal regions on visual assessment"

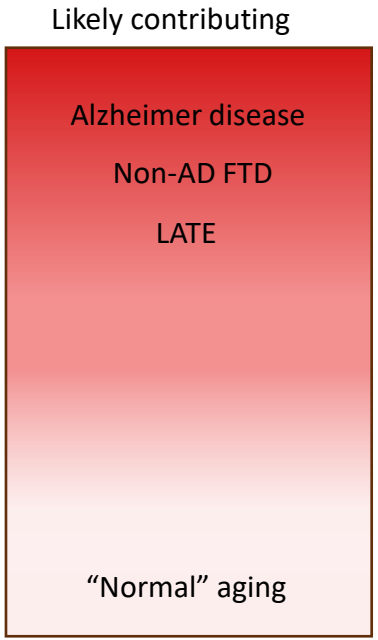
**Differential diagnosis**



# Woman in early 80s

- **Brief history:** Woman in her early 80s is accompanied by family members who report that the patient developed word-finding difficulties, increased misplacing of personal items, and difficulty managing her schedule over the past year. She is having more difficulty cooking but she is able to do laundry and dishes and she has a variety of hobbies. Her hygiene or grooming are unchanged.
- **Exam:** Normal general and neurological exam except some pauses with word finding, 23 on the MMSE, 13 on Boston Naming, mild impairment on episodic memory tasks
- **Labs:** TSH, B12, blood counts and blood chemistries were normal
- **Brain MRI: "**Volume loss more pronounced at left temporal and parietal regions on visual assessment"

**Differential diagnosis**

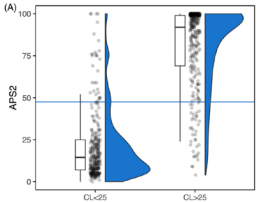


# Woman in early 80s

**Amyloid Probability Score 2 (APS2)** **100** **POSITIVE**

***Interpretation:*** *This patient has a* ***positive*** *APS2 value. A positive APS2 (48-100) is consistent with a* ***positive*** *amyloid PET scan; it reflects a* ***high likelihood*** *of brain amyloid plaques, one of the neuropathological findings of Alzheimer's disease (AD). The presence of amyloid plaques alone does not establish a clinical diagnosis of AD; the APS2 result should be interpreted in conjunction with other patient information. Clinical correlation is recommended.*

| Results Table | Value | Reference Interval |
|---|---|---|
| APS2 | 100 | 0-47 consistent with absence of brain amyloid plaques |
| p-tau217 Ratio | 15.8% | < 4.2% consistent with absence of brain amyloid plaques |
| Aβ42/40 Ratio | 0.080 | > 0.089 consistent with absence of brain amyloid plaques |




Meyer *Alzheimer's and Dementia* 2024

- eGFR > 70 (normal)
- APS2 was positive at 100 (≤47 is normal)
- If the pre-test probability of amyloid pathology is 50%, >97% of individuals with an APS2 90-100 have a positive amyloid PET
  - %p-tau217 was positive at 15.8% (<4.2% is normal)
  - Aβ42/40 was negative at 0.080 (>0.089 is normal)

- On the basis of these results (without CSF testing or amyloid PET), the patient was started on lecanemab

**Differential diagnosis**

Likely contributing

Alzheimer disease

Non-AD FTD

LATE

"Normal" aging

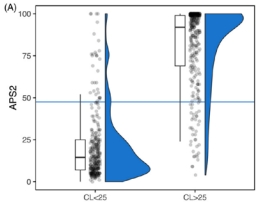
Unlikely contributing

# Woman in early 80s

**Amyloid Probability Score 2 (APS2)** **100** **POSITIVE**

***Interpretation:*** *This patient has a* ***positive*** *APS2 value. A positive APS2 (48-100) is consistent with a* ***positive*** *amyloid PET scan; it reflects a* ***high likelihood*** *of brain amyloid plaques, one of the neuropathological findings of Alzheimer's disease (AD). The presence of amyloid plaques alone does not establish a clinical diagnosis of AD; the APS2 result should be interpreted in conjunction with other patient information. Clinical correlation is recommended.*

| Results Table | Value | Reference Interval |
|---|---|---|
| APS2 | 100 | 0-47 consistent with absence of brain amyloid plaques |
| p-tau217 Ratio | 15.8% | < 4.2% consistent with absence of brain amyloid plaques |
| Aβ42/40 Ratio | 0.080 | > 0.089 consistent with absence of brain amyloid plaques |




Meyer *Alzheimer's and Dementia* 2024

- eGFR > 70 (normal)
- APS2 was positive at 100 (≤47 is normal)
- If the pre-test probability of amyloid pathology is 50%, >97% of individuals with an APS2 90-100 have a positive amyloid PET
  - %p-tau217 was positive at 15.8% (<4.2% is normal)
  - Aβ42/40 was negative at 0.080 (>0.089 is normal)

- On the basis of these results (without CSF testing or amyloid PET), the patient was started on lecanemab

**Differential diagnosis**

Likely contributing

Alzheimer disease

Non-AD FTD

LATE

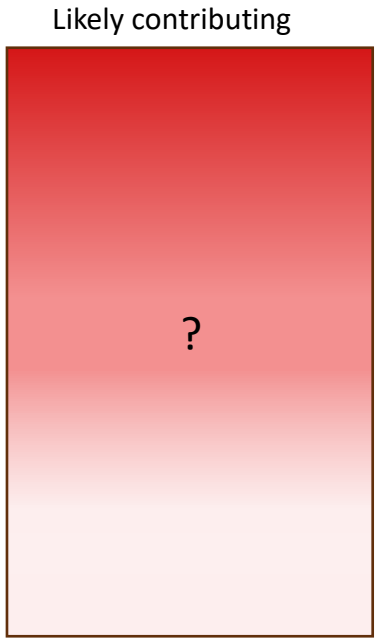
"Normal" aging

Unlikely contributing

# Man in late 50s

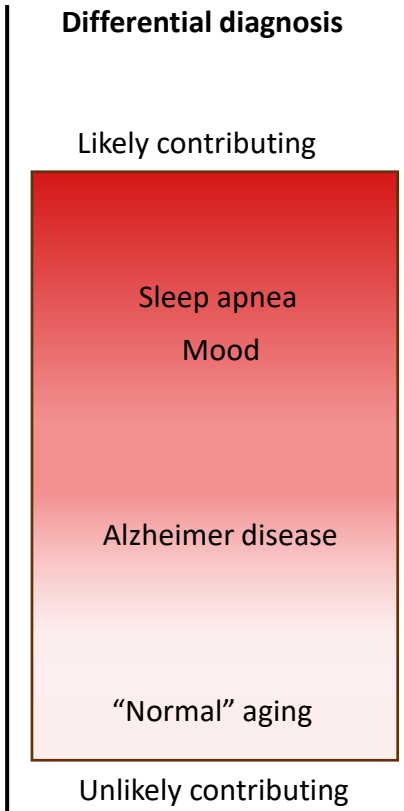
- **Brief history:** Professor in his late 50s with a history of hypertension, depression, and sleep apnea (partially compliant with CPAP). His wife and sister are concerned about changes in his memory. He has occasionally repeated questions for the past five years, which is worse when he doesn't use his CPAP. Recently he has had several episodes of confusion and forgetting personal events. He has no decline in his activities of daily living.
- **Exam:** Normal general and neurological exam. He had inconsistent performance on episodic memory tasks, scoring a 25/30 on the MMSE (0/3 word recall) but a perfect score on the Short Blessed (5/5 word recall).
- **Labs:** TSH, B12, blood counts and blood chemistries were normal

**Differential diagnosis**



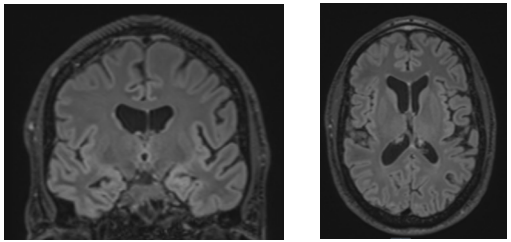
# Man in late 50s

- **Brief history:** Professor in his late 50s with a history of hypertension, depression, and sleep apnea (partially compliant with CPAP). His wife and sister are concerned about changes in his memory. He has occasionally repeated questions for the past five years, which is worse when he doesn't use his CPAP. Recently he has had several episodes of confusion and forgetting personal events. He has no decline in his activities of daily living.
- **Exam:** Normal general and neurological exam. He had inconsistent performance on episodic memory tasks, scoring a 25/30 on the MMSE (0/3 word recall) but a perfect score on the Short Blessed (5/5 word recall).
- **Labs:** TSH, B12, blood counts and blood chemistries were normal



# Man in late 50s

- **Brief history:** Professor in his late 50s with a history of hypertension, depression, and sleep apnea (partially compliant with CPAP). His wife and sister are concerned about changes in his memory. He has occasionally repeated questions for the past five years, which is worse when he doesn't use his CPAP. Recently he has had several episodes of confusion and forgetting personal events. He has no decline in his activities of daily living.
- **Exam:** Normal general and neurological exam. He had inconsistent performance on episodic memory tasks, scoring a 25/30 on the MMSE (0/3 word recall) but a perfect score on the Short Blessed (5/5 word recall).
- **Labs:** TSH, B12, blood counts and blood chemistries were normal
- **Brain MRI:** Somewhat greater atrophy than expected for his age



**Differential diagnosis**

Likely contributing

Sleep apnea

Mood

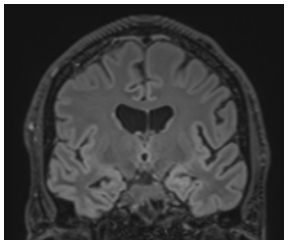
Alzheimer disease

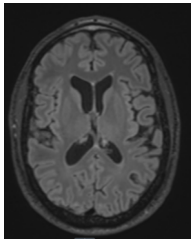
"Normal" aging

Unlikely contributing

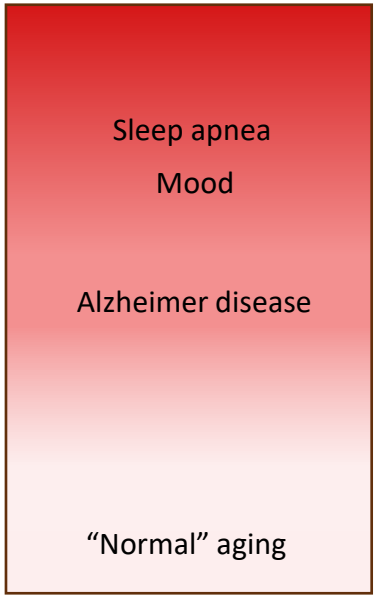
# Man in late 50s

- **Brief history:** Professor in his late 50s with a history of hypertension, depression, and sleep apnea (partially compliant with CPAP). His wife and sister are concerned about changes in his memory. He has occasionally repeated questions for the past five years, which is worse when he doesn't use his CPAP. Recently he has had several episodes of confusion and forgetting personal events. He has no decline in his activities of daily living.
- **Exam:** Normal general and neurological exam. He had inconsistent performance on episodic memory tasks, scoring a 25/30 on the MMSE (0/3 word recall) but a perfect score on the Short Blessed (5/5 word recall).
- **Labs:** TSH, B12, blood counts and blood chemistries were normal
- **Brain MRI:** Somewhat greater atrophy than expected for his age





**Differential diagnosis**



# Man in late 50s

- **Blood test result:**
  - Borderline positive based on APS2
  - Positive based on %p-tau217
  - Negative based on Aβ42/40

**PrecivityAD2™ Blood Test Result Summary**

| Amyloid Probability Score 2 (APS2) | 68 | POSITIVE |
|---|---|---|

**Interpretation:** This patient has a positive APS2 value. A positive APS2 (48-100) is consistent with a positive amyloid PET scan; it reflects a high likelihood of brain amyloid plaques and is therefore consistent with a neuropathological diagnosis of Alzheimer's disease (AD). The APS2 result should be interpreted in conjunction with other patient information. Clinical correlation is recommended.

| RESULTS TABLE | VALUE | REFERENCE INTERVAL |
|---|---|---|
| %p-tau217 | 7.2 % | < 4.2% consistent with absence of brain amyloid plaques |
| Aß42/40 Ratio | 0.096 | > 0.095 consistent with absence of brain amyloid plaques |
| APS2 | 68 | 0-47 consistent with absence of brain amyloid plaques |

*%p-tau217 (p-tau217/np-tau217) - concentration of phosphorylated tau at threonine 217 (p-tau217) divided by nonphosphorylated tau at threonine 217 (np-tau217), multiplied by 100; Aß42/40 Ratio - concentration of amyloid beta(Aß)42 divided by Aß40.*

**Differential diagnosis**

Likely contributing

Sleep apnea

Mood

Alzheimer disease

“Normal” aging

Unlikely contributing

# Man in late 50s

- **Blood test result:**
  - Borderline positive based on APS2
  - Positive based on %p-tau217
  - Negative based on Aβ42/40

**PrecivityAD2™ Blood Test Result Summary**

| Amyloid Probability Score 2 (APS2) | 68 | POSITIVE |
|---|---|---|

**Interpretation:** This patient has a positive APS2 value. A positive APS2 (48-100) is consistent with a positive amyloid PET scan; it reflects a high likelihood of brain amyloid plaques and is therefore consistent with a neuropathological diagnosis of Alzheimer's disease (AD). The APS2 result should be interpreted in conjunction with other patient information. Clinical correlation is recommended.

| RESULTS TABLE | VALUE | REFERENCE INTERVAL |
|---|---|---|
| %p-tau217 | 7.2 % | < 4.2% consistent with absence of brain amyloid plaques |
| Aß42/40 Ratio | 0.096 | > 0.095 consistent with absence of brain amyloid plaques |
| APS2 | 68 | 0-47 consistent with absence of brain amyloid plaques |

*%p-tau217 (p-tau217/np-tau217) - concentration of phosphorylated tau at threonine 217 (p-tau217) divided by nonphosphorylated tau at threonine 217 (np-tau217), multiplied by 100; Aß42/40 Ratio - concentration of amyloid beta(Aß)42 divided by Aß40.*

**Differential diagnosis**

Likely contributing

Alzheimer disease

Sleep apnea

Mood

"Normal" aging

Unlikely contributing

# Man in late 50s

- **Blood test result:**
  - Borderline positive based on APS2
  - Positive based on %p-tau217
  - Negative based on Aβ42/40

- **Amyloid PET result:**
  - Positive visual read
  - Centiloid 144.4

**PrecivityAD2™ Blood Test Result Summary**

| Amyloid Probability Score 2 (APS2) | 68 | POSITIVE |
|---|---|---|

**Interpretation:** This patient has a positive APS2 value. A positive APS2 (48-100) is consistent with a positive amyloid PET scan; it reflects a high likelihood of brain amyloid plaques and is therefore consistent with a neuropathological diagnosis of Alzheimer's disease (AD). The APS2 result should be interpreted in conjunction with other patient information. Clinical correlation is recommended.

| RESULTS TABLE | VALUE | REFERENCE INTERVAL |
|---|---|---|
| %p-tau217 | 7.2 % | < 4.2% consistent with absence of brain amyloid plaques |
| Aß42/40 Ratio | 0.096 | > 0.095 consistent with absence of brain amyloid plaques |
| APS2 | 68 | 0-47 consistent with absence of brain amyloid plaques |

*%p-tau217 (p-tau217/np-tau217) - concentration of phosphorylated tau at threonine 217 (p-tau217) divided by nonphosphorylated tau at threonine 217 (np-tau217), multiplied by 100; Aß42/40 Ratio - concentration of amyloid beta(Aß)42 divided by Aß40.*

FINDINGS:

There is normal cortical-white matter contrast in the cerebellum.

There is absent cortical-white matter contrast involving the frontal, temporal, parietal, occipital, cingulate, and precuneus.

Hermes software was used for centiloid quantification of the current study.
The calculated centiloid value (CL) is 144.4.

Incidental CT findings: No acute intracranial abnormality.

IMPRESSION:

1. Positive amyloid-PET study, indicating moderate to frequent beta-amyloid neuritic plaques.

2. The centiloid score falls in the Positive range (see below for discussion of this score).

**Differential diagnosis**

Likely contributing

Alzheimer disease

Sleep apnea

Mood

"Normal" aging

Unlikely contributing

# Man in late 50s

- **Blood test result:**
  - Borderline positive based on APS2
  - Positive based on %p-tau217
  - Negative based on Aβ42/40

- **Amyloid PET result:**
  - Positive visual read
  - Centiloid 144.4

**PrecivityAD2™ Blood Test Result Summary**

| Amyloid Probability Score 2 (APS2) | 68 | POSITIVE |
|---|---|---|

**Interpretation:** This patient has a positive APS2 value. A positive APS2 (48-100) is consistent with a positive amyloid PET scan; it reflects a high likelihood of brain amyloid plaques and is therefore consistent with a neuropathological diagnosis of Alzheimer's disease (AD). The APS2 result should be interpreted in conjunction with other patient information. Clinical correlation is recommended.

| RESULTS TABLE | VALUE | REFERENCE INTERVAL |
|---|---|---|
| %p-tau217 | 7.2 % | < 4.2% consistent with absence of brain amyloid plaques |
| Aß42/40 Ratio | 0.096 | > 0.095 consistent with absence of brain amyloid plaques |
| APS2 | 68 | 0-47 consistent with absence of brain amyloid plaques |

*%p-tau217 (p-tau217/np-tau217) - concentration of phosphorylated tau at threonine 217 (p-tau217) divided by nonphosphorylated tau at threonine 217 (np-tau217), multiplied by 100; Aß42/40 Ratio - concentration of amyloid beta(Aß)42 divided by Aß40.*

FINDINGS:

There is normal cortical-white matter contrast in the cerebellum.

There is absent cortical-white matter contrast involving the frontal, temporal, parietal, occipital, cingulate, and precuneus.

Hermes software was used for centiloid quantification of the current study.
The calculated centiloid value (CL) is 144.4.

Incidental CT findings: No acute intracranial abnormality.

IMPRESSION:

1. Positive amyloid-PET study, indicating moderate to frequent beta-amyloid neuritic plaques.

2. The centiloid score falls in the Positive range (see below for discussion of this score).

**Differential diagnosis**

Likely contributing

Alzheimer disease

Sleep apnea

Mood

"Normal" aging

Unlikely contributing

# Man in late 50s

- **Blood test result:**
  - Borderline positive based on APS2
  - Positive based on %p-tau217
  - Negative based on Aβ42/40

**PrecivityAD2™ Blood Test Result Summary**

| Amyloid Probability Score 2 (APS2) | 68 | POSITIVE |
|---|---|---|

**Interpretation:** This patient has a positive APS2 value. A positive APS2 (48-100) is consistent with a positive amyloid PET scan; it reflects a high likelihood of brain amyloid plaques and is therefore consistent with a neuropathological diagnosis of Alzheimer's disease (AD). The APS2 result should be interpreted in conjunction with other patient information. Clinical correlation is recommended.

| RESULTS TABLE | VALUE | REFERENCE INTERVAL |
|---|---|---|
| %p-tau217 | 7.2 % | < 4.2% consistent with absence of brain amyloid plaques |
| Aß42/40 Ratio | 0.096 | > 0.095 consistent with absence of brain amyloid plaques |
| APS2 | 68 | 0-47 consistent with absence of brain amyloid plaques |

*%p-tau217 (p-tau217/np-tau217) - concentration of phosphorylated tau at threonine 217 (p-tau217) divided by nonphosphorylated tau at threonine 217 (np-tau217), multiplied by 100; Aß42/40 Ratio - concentration of amyloid beta(Aß)42 divided by Aß40.*

- **Amyloid PET result:**
  - Positive visual read
  - Centiloid 144.4

FINDINGS:

There is normal cortical-white matter contrast in the cerebellum.

There is absent cortical-white matter contrast involving the frontal, temporal, parietal, occipital, cingulate, and precuneus.

Hermes software was used for centiloid quantification of the current study.
The calculated centiloid value (CL) is 144.4.

Incidental CT findings: No acute intracranial abnormality.

IMPRESSION:

1. Positive amyloid-PET study, indicating moderate to frequent beta-amyloid neuritic plaques.

2. The centiloid score falls in the Positive range (see below for discussion of this score).

- **Patient started on donanemab**

**Differential diagnosis**

Likely contributing

Alzheimer disease

Sleep apnea

Mood

“Normal” aging

Unlikely contributing

# Man in late 50s

- **Blood test result:**
  - Borderline positive based on APS2
  - Positive based on %p-tau217
  - Negative based on Aβ42/40

**PrecivityAD2™ Blood Test Result Summary**

| Amyloid Probability Score 2 (APS2) | 68 | POSITIVE |
|---|---|---|

**Interpretation:** This patient has a positive APS2 value. A positive APS2 (48-100) is consistent with a positive amyloid PET scan; it reflects a high likelihood of brain amyloid plaques and is therefore consistent with a neuropathological diagnosis of Alzheimer's disease (AD). The APS2 result should be interpreted in conjunction with other patient information. Clinical correlation is recommended.

| RESULTS TABLE | VALUE | REFERENCE INTERVAL |
|---|---|---|
| %p-tau217 | 7.2 % | < 4.2% consistent with absence of brain amyloid plaques |
| Aß42/40 Ratio | 0.096 | > 0.095 consistent with absence of brain amyloid plaques |
| APS2 | 68 | 0-47 consistent with absence of brain amyloid plaques |

*%p-tau217 (p-tau217/np-tau217) - concentration of phosphorylated tau at threonine 217 (p-tau217) divided by nonphosphorylated tau at threonine 217 (np-tau217), multiplied by 100; Aß42/40 Ratio - concentration of amyloid beta(Aß)42 divided by Aß40.*

- **Amyloid PET result:**
  - Positive visual read
  - Centiloid 144.4

FINDINGS:

There is normal cortical-white matter contrast in the cerebellum.

There is absent cortical-white matter contrast involving the frontal, temporal, parietal, occipital, cingulate, and precuneus.

Hermes software was used for centiloid quantification of the current study.
The calculated centiloid value (CL) is 144.4.

Incidental CT findings: No acute intracranial abnormality.

IMPRESSION:

1. Positive amyloid-PET study, indicating moderate to frequent beta-amyloid neuritic plaques.

2. The centiloid score falls in the Positive range (see below for discussion of this score).

- **Patient started on donanemab**

**Differential diagnosis**

Likely contributing

Alzheimer disease

Sleep apnea

Mood

“Normal” aging

Unlikely contributing

# Conclusions

- Accurate blood tests for Alzheimer's disease pathology are here now and are increasingly being used in the clinic
- Alzheimer's disease blood tests may be appropriately used in patients with cognitive impairment to determine the cause of their symptoms
- Blood biomarkers have major practical advantages compared to CSF or PET
- Plasma p-tau217 is an outstanding biomarker of amyloid pathology and is superior to Aβ42/40 and p-tau181
- Accurate diagnosis of symptomatic Alzheimer's disease requires integrating the clinical assessment and biomarker results
- Patients with a high likelihood of symptomatic Alzheimer's based on the clinical assessment and a clear-cut positive biomarker result indicating Alzheimer's disease pathology may not need a second test; those with complicating factors or intermediate results need a second test for a high certainty diagnosis

# Acknowledgements


- **Our clinic patients and their supportive families**
- Compilation and analysis of clinical biomarker and demographics data: Anna Hofmann, Madeline Paczynski, Melissa Aldinger, Sade Agboola, Will Powell, Abigail Lewis, Aditi Gupta, Inez Oh
- **Washington University Memory Diagnostic Center:**
  - Clinicians: Joy Snider (Director), Madeline Paczynski (treatment clinic and LP clinic PA), John Morris, Erik Musiek, David Holtzman, Suzanne Schindler, Jee-Young Han, Cassandra Ward, Alexandra Venuto, Joo Lim, David Carr, Nupur Ghoshal, Justin Long, Kyle Womack, Randall Bateman, Eric McDade, Michele Rudman, Maren Gregersen
  - Nursing staff: Dawn Ellington, Zachary Posey, Maria Carroll, Erica Woolfolk, Leslie Green
  - Wash U Neuroimaging: Tammie Benzinger, Maria Rosana Ponisio, Cyrus Raji, Manu Goyal


Knight ADRC
Alzheimer's Disease Research Center
WASHINGTON UNIVERSITY ST. LOUIS

Washington University in St. Louis
SCHOOL OF MEDICINE