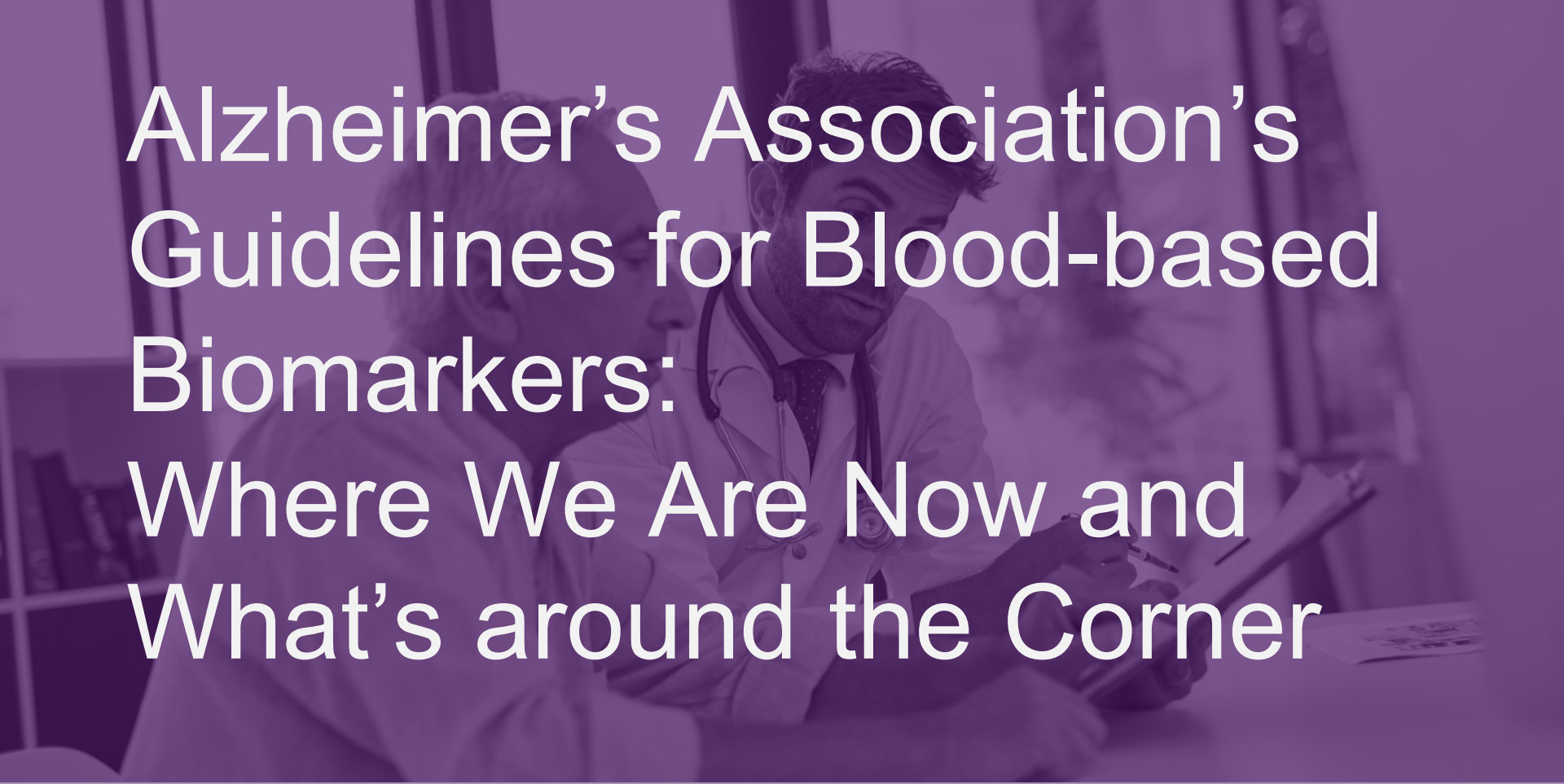

Alzheimer's Association's Guidelines for Blood-based Biomarkers: Where We Are Now and What's around the Corner

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Learning Objectives



Describe the clinical questions addressed thus far and the recommendations of the Alzheimer's Association's Clinical Practice Guidelines (CPG) related to blood-based biomarkers for diagnosis of Alzheimer's disease



Describe updates that will differentiate the next iteration of the Alzheimer's Association's CPG for blood-based biomarkers from the 2025 CPG, including focus on commercially available tests and attention to the two-cut off approach for ruling in or ruling out brain amyloid.



Apply the concept of pre-test probability and describe how it relates to interpretation of negative and positive test results and the CPG recommendations.

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Disclosures

I have research funding from the National Institute on Aging.

I co-Chair the Alzheimer's Association BBM Clinical Practice Guideline Panel.

I am on the American Geriatrics Society Board of Directors.

I have no relevant financial disclosures.

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Dr. Heather Whitson, MD

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Dr. Rebeca Edelmayer, PhD
Ms. Sarah Pahlke, MS
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Dr. Sheena Aurora, MD



A global, multidisciplinary team of leading clinicians and scientists in AD biomarkers.

All panel members have adhered to rigorous COI management policies.

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Amyloid Cascade Hypothesis

Alzheimer's disease is an amyloid-mediated tauopathy

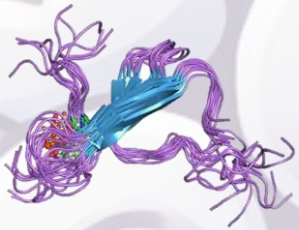
Amyloid-Dependent

Amyloid-Independent

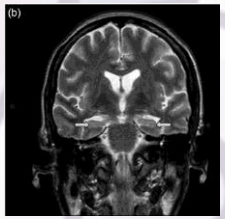
Amyloid β



Tau



CaTAUstrophe



Dementia

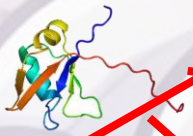
- Trisomy 21 (Down Syndrome)
- Familial AD (APP, PSEN1, PSEN2)
- APOE-ε4

Spread of tau tangles into the neocortex, i.e., "CaTAUstrophe"

Other Contributors

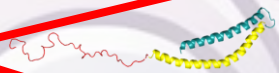
Endolysosomal Dysfunction (SORL1)

TDP-43



Vascular Contributions (VCID)

α Synuclein

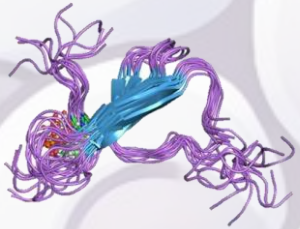


Microglial Dysfunction (TREM2)

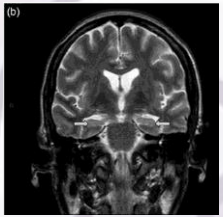
Amyloid β



Tau



CaTAUstrophe



Dementia

- Trisomy 21 (Down Syndrome)
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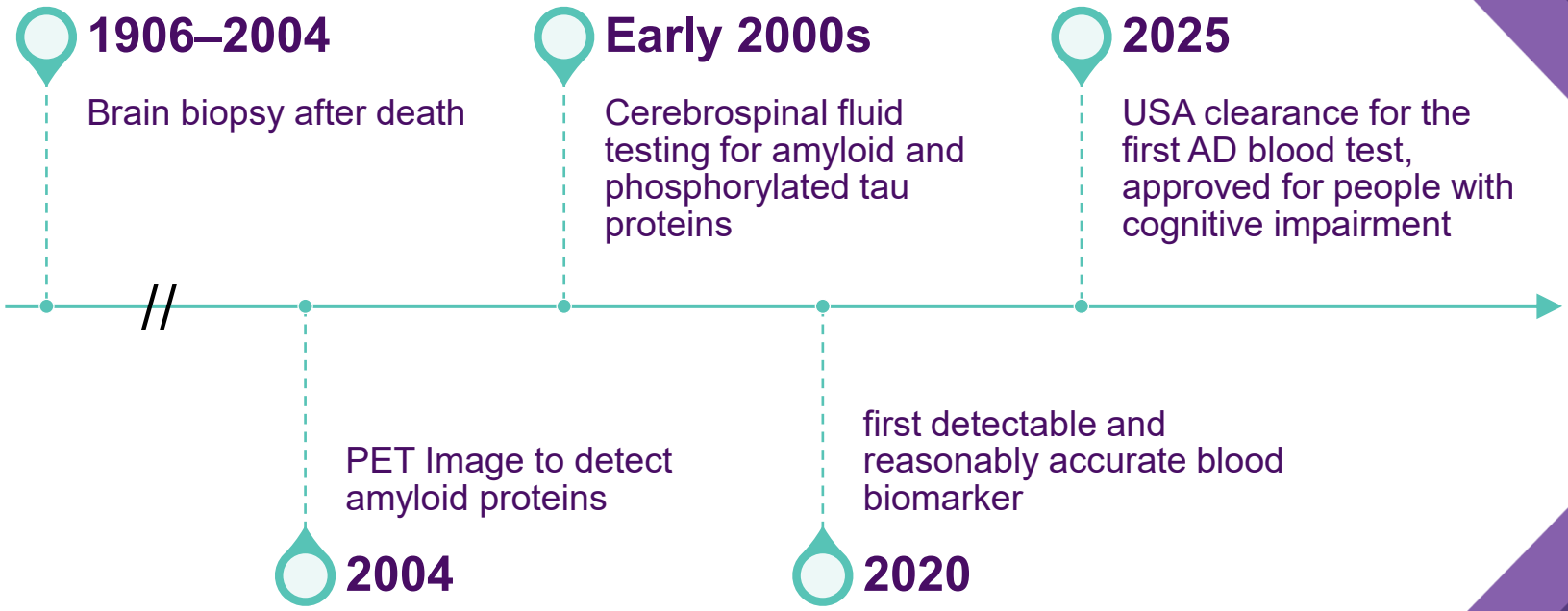
- APOE-ε4

Spread of tau tangles into the neocortex, i.e., “CaTAUstrophe”

Timeline of options to detect AD-specific proteins



ALZHEIMER'S ASSOCIATION | AAIC 26

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Advantages of blood-based biomarkers

Compared to lumbar puncture and PET imaging, blood biomarkers are:

- Safer, less invasive
- Less expensive
- Do not require access to specialists
- Have the potential to democratize access to biomarker-based diagnosis of cognitive disorders
- Preferred by patients and care partners

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Common Misconception:

"I hear there is a new blood test for Alzheimer's disease."

Truth: There are many blood tests for AD.

Several are already commercially available.
They use different methods to test for different protein species (amyloid, phosphorylated tau, etc).
Performance characteristics vary.

A New Frontier:
Blood-Based Biomarkers



Problem

Traditional AD biomarkers have significant access, cost and invasiveness barriers.

Goal

Provide guidance on using BBMs to improve diagnostic process.

Population

Patients with objective cognitive impairment in specialized care settings.

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Where We Started:
2025 Question and Evidence

QUESTION

Can BBMs serve as **triaging** or **confirmatory tests** for AD in specialized care?

Population

Patients with MCI or dementia in specialized care.

Evidence Base

49 studies | **31** tests | **Low** certainty of evidence

Two clinical roles examined: triaging (rule out AD, determine need for PET/CSF) and confirmatory (rule in or out AD, replace PET/CSF).

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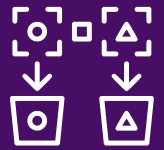
Where We Started:
2025 Recommendations

Conditional recommendations (low certainty of evidence) for BBM use as:

TRIAGING TEST



≥ 90% sensitivity
≥ 75% specificity

CONFIRMATORY TEST



≥ 90% sensitivity
≥ 90% specificity

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The Panel Weighed a Range of Factors

CRITICAL CAVEAT:

BBM testing should not occur before comprehensive clinical evaluation. Avoid or interpret with caution when modifiable causes, limited life expectancy, interfering conditions, or patient refusal are present.

- Balance of effects
- Patient values and preferences
- Resources required
- Equity
- Acceptability
- Feasibility

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Strengthening the Evidence Base
Alzheimer's Association Reporting Guidance

ALZHEIMER'S ASSOCIATION REPORTING GUIDANCE FOR RESEARCHERS:

- Clearly state population studied
- Report cutoff and how it was determined
- Report TP, TN, FP, FN frequencies
- Use consistent reference tests within studies



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2026 UPDATES

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Updated Systematic Review and Recommendations

- Patients with cognitive impairment in specialty care
- **UPDATE** Commercially available tests only
- **UPDATE** One and two cutoff approach
- **UPDATE** Ratios/combination tests (e.g., p-tau217/AB42, %p-tau217+AB42/40)
- Brand agnostic recommendations
  - **UPDATE** based on pre-test probabilities/risk groups and thresholds for allowable FP and FN
- Link to SR results
  - **UPDATE** modeled for different pre-test probabilities

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CLINICAL QUESTION

Can a BBM test be used to **rule-in and/or rule-out AD pathology** in the diagnostic work-up of patients with objective cognitive impairment in specialized care?

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The PICO Question for BBM CPG

Population	Patients with MCI or dementia in specialized care; insufficient data in subjective cognitive dysfunction
Intervention (index test)	Commercially available plasma biomarker tests measuring p-tau217, %p-tau 217, p-tau181, p-tau231, p-tau181/Aβ42, p-tau217/Aβ42, or Aβ42/40; using a one or two cut-off approach
Comparison (reference test)	"Gold standard" tests (amyloid PET, CSF, neuropath)
Outcome	Diagnostic accuracy for detecting AD pathology

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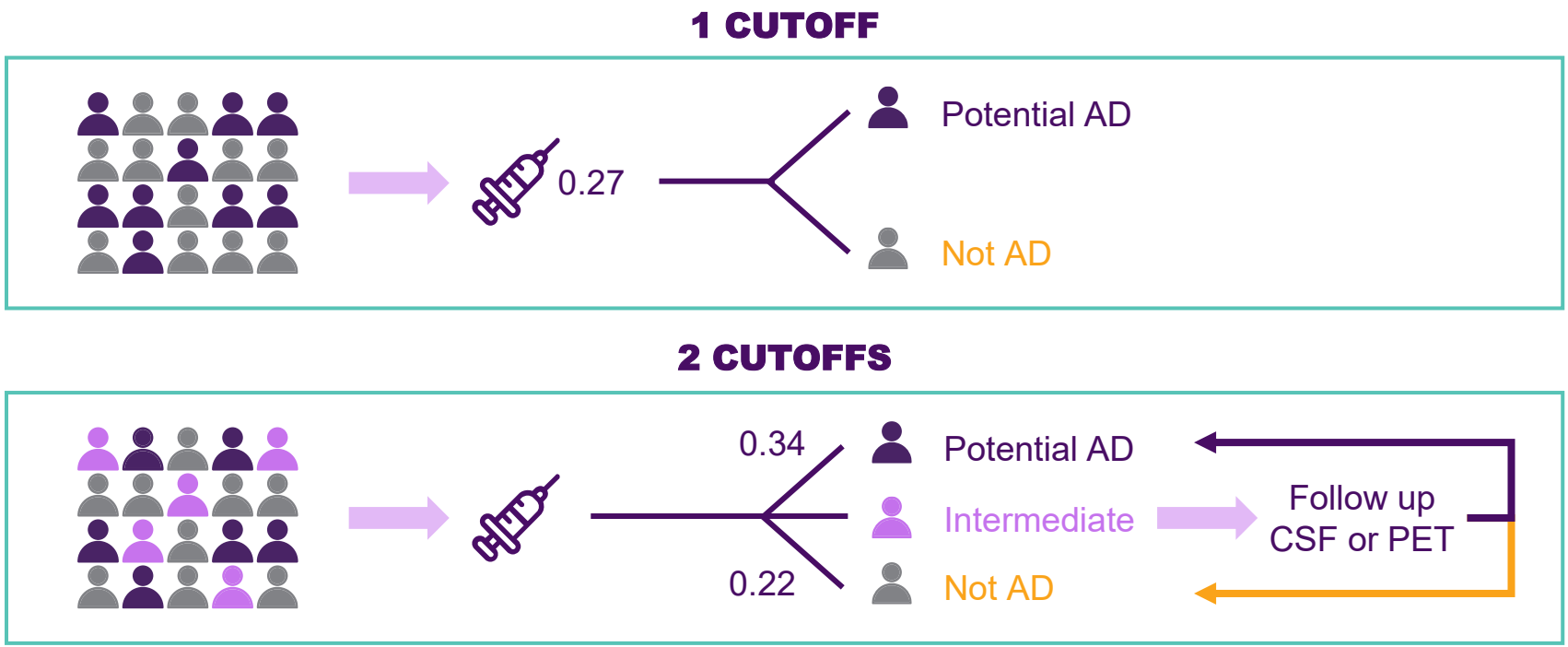
One vs. Two Cut-off Approach



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Two Clinical Roles:
Ruling-in Vs. Ruling-out Ad Pathology

RULE-IN

Goal:
Rule in AD, positive test confirms presence of disease pathology

Requires:
High positive predictive value (PPV); low number of false positives (FP)

Panel Decision Threshold:
No more than **5 false positives** per 100 determinant results

RULE-OUT

Goal:
Rule-out AD, negative test confirms absence of disease pathology

Requires:
High negative predictive value (NPV); low number of false negatives (FN)

Panel Decision Threshold:
No more than **5 false negatives** per 100 determinant results

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Likelihood of False Negatives and False Positives is Influenced by Pre-Test Probability

35%	Low baseline risk for AD pathology	• Goal is often to rule-out disease • Most tests will result in a high number of false positives • Positive results often require additional confirmatory testing
50%	Moderate baseline risk for AD pathology	• Depending on sensitivity and specificity of test and clinical scenario, it is possible to rule-in and/or rule-out disease
75%	High baseline risk for AD pathology	• Goal is often to rule-in disease • Most tests will result in a high number of false negatives • Negative results often require additional confirmatory testing

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What Will Recommendations Look Like?

RECOMMENDATION

In patients with objective cognitive impairment presenting for specialized memory-care, the panel suggests the use of blood-based biomarker (BBM) tests that minimize false positives to rule-in and minimize false negative results to rule-out disease in the diagnostic workup of AD.

(Conditional recommendation, Low certainty evidence)

REMARKS / IMPLEMENTATION CONSIDERATIONS

Selection of a BBM should be guided by the intended use of the test (i.e., ruling in or ruling out Alzheimer's disease pathology) and the test's diagnostic accuracy characteristics.

For tests using a two cut-off approach, the panel considered an intermediate zone affecting ≤20% of tested individuals to be preferable.

Depending on its diagnostic accuracy, a given test may be sufficiently accurate to support ruling in and ruling out AD pathology across multiple pretest probability ranges.
Please refer to MAGICapp for the most current accuracy data for commercially available tests.

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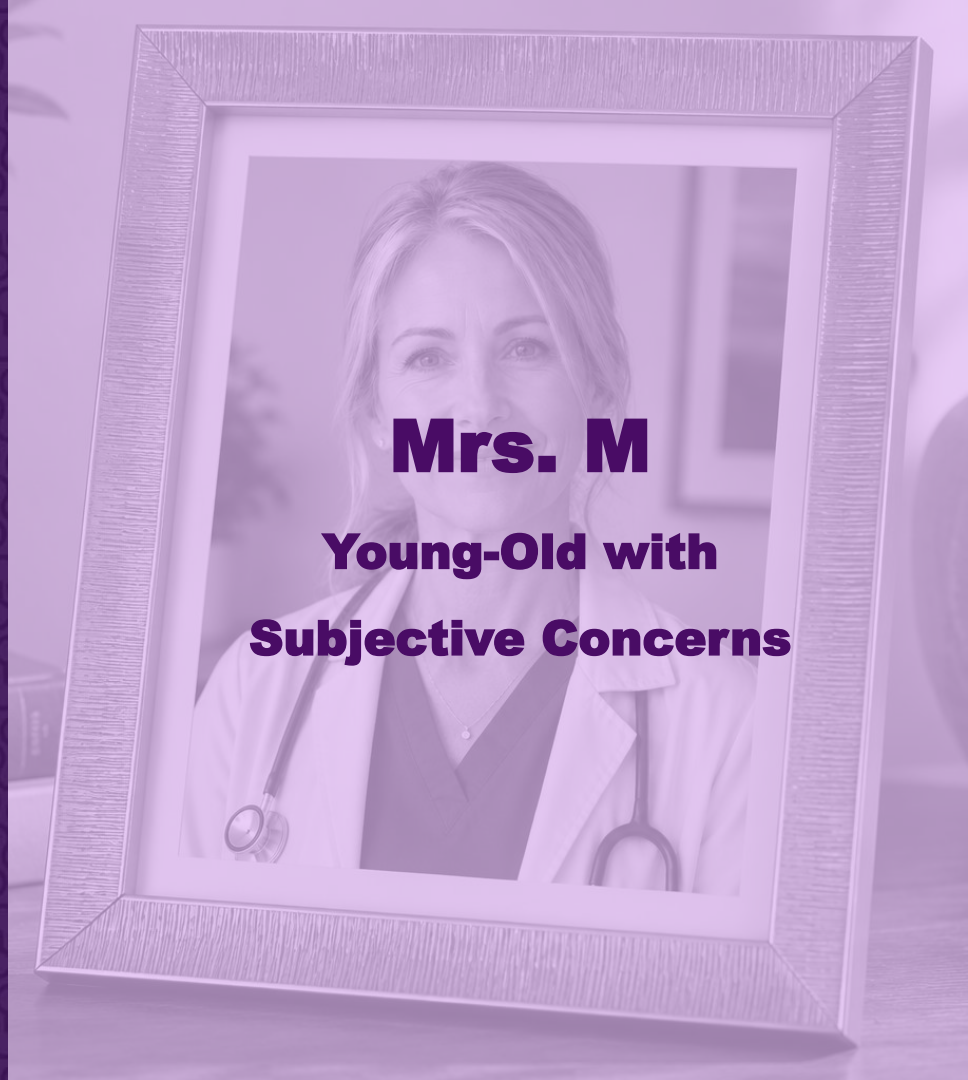
Clinical Scenario



Mrs. M Clinical Scenario:

Young-Old with Subjective Concerns



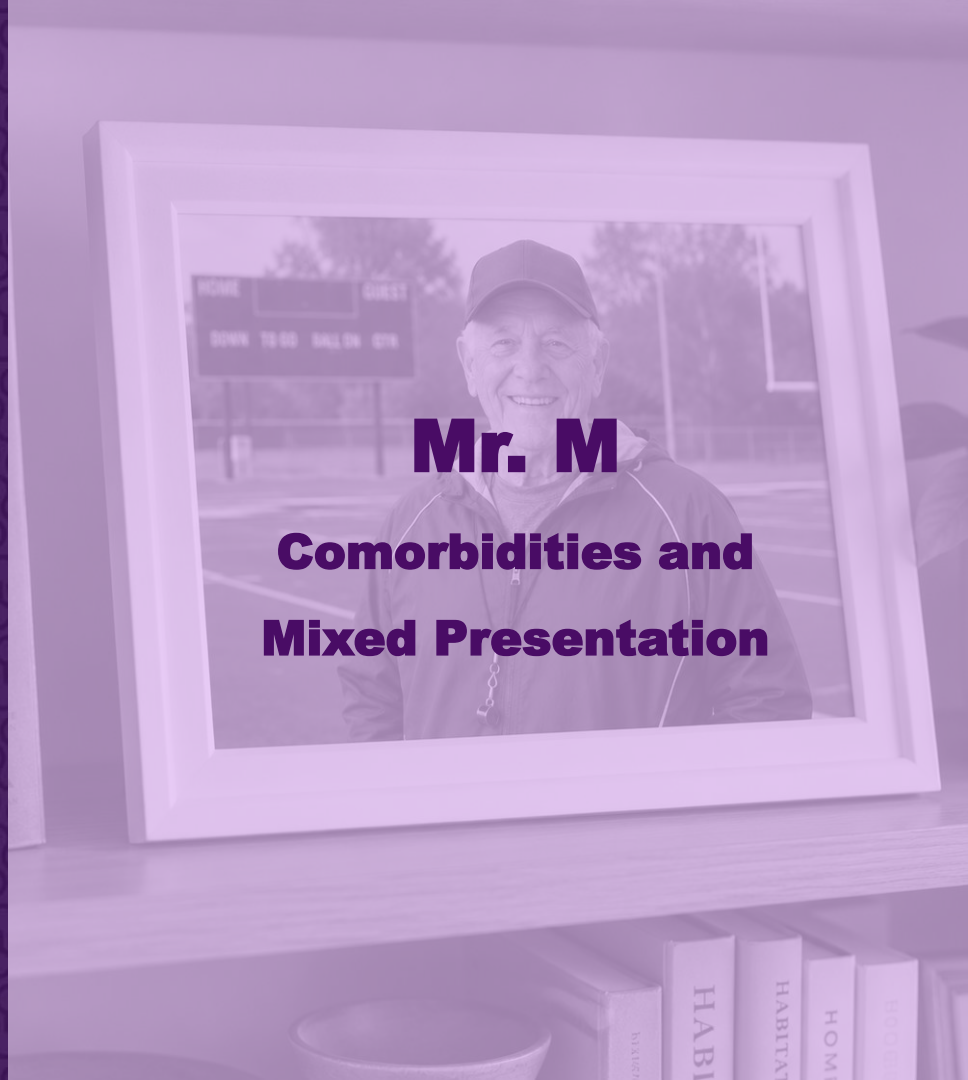
Patient Profile:
58 year-old nurse practitioner with family history of dementia

Key History:
Feels more forgetful, not as “quick” to learn new technology

Key Findings:
MoCA: 27/30 (misses 2 on recall)

Pretest probability for brain amyloid: 35%

Clinical Scenario



Mr. M

Comorbidities and Mixed Presentation

Mr. M Clinical Scenario:

Patient with Comorbidities and Mixed Presentation



Patient Profile:
76-year-old retired PE teacher/coach

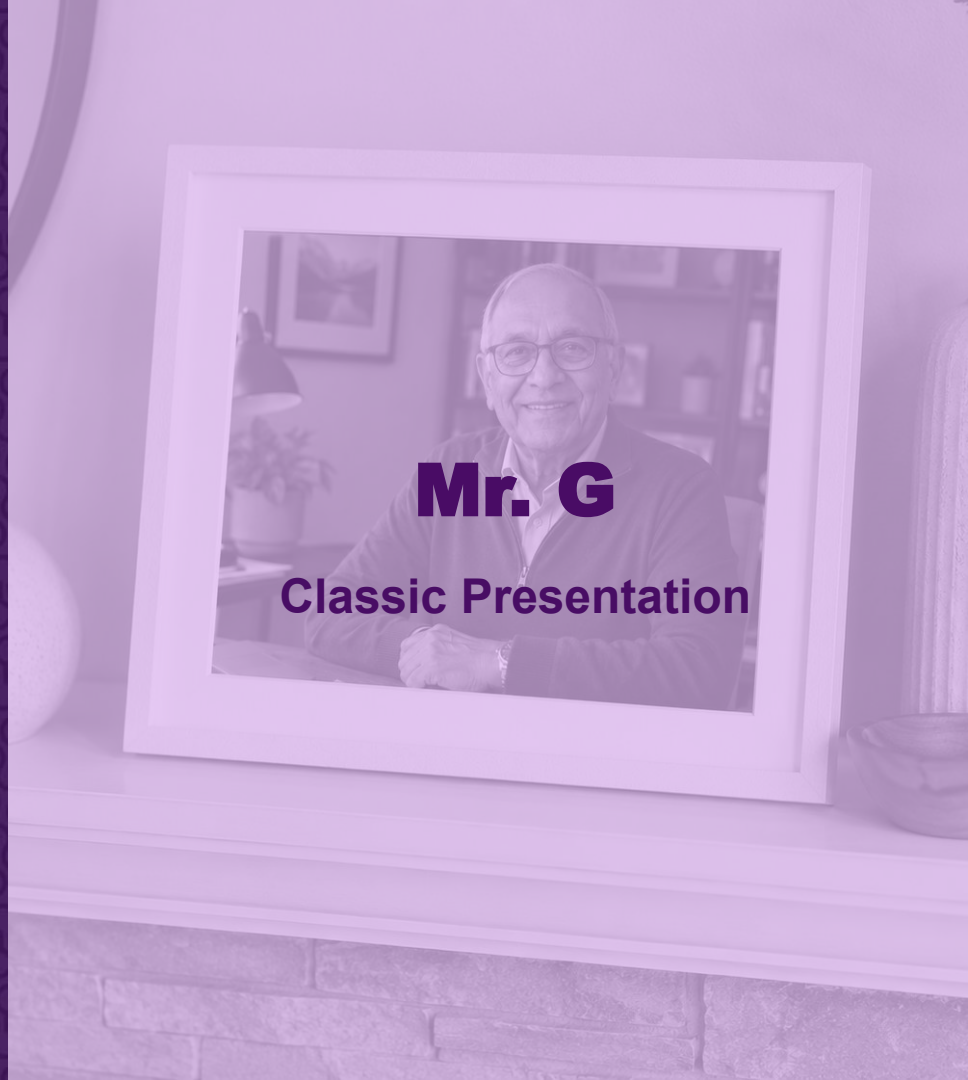
Key History:
Diabetes, chronic kidney disease (creatinine 3.2), chronic pain, obstructive sleep apnea, h/o concussions

Medications:
Gabapentin, duloxetine, oxycodone, lorazepam

Key Findings:
Wife reports cognitive decline, sleep disruptions.
You note a right hand tremor. MoCA 21/30

Pretest probability for brain amyloid: 50%

Clinical Scenario



Mr. G Clinical Scenario:

Classic Presentation



Patient Profile:
74-year-old retired accountant with a family history of AD

Key History:
2+ years gradual memory/executive decline

Key Findings:
MoCA: 22/30. Misses 4 of 5 on recall

Pretest probability for brain amyloid: 75%

Additional BBM Resources

Blood Sample Handling for Alzheimer's Biomarkers: A Recommended Workflow



Preferred Methodological Reporting for Blood-based Biomarker Research for The Alzheimer's Disease and Related Dementias Research Community



Blood-Based Biomarker CPG Summary
Note: Intended for specialty care settings.



Coming soon!
BBM Conversation Framework
BBM Patient FAQ

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THANK YOU

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