2025 Alzheimer's Disease Diagnosis and Hope

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TENNESSEE MEMORY DISORDERS FOUNDATION AND CLINIC

Disclosures

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- Biogen, Novonordisk, American College of Radiology and Alzheimer's Association, Roche, Amylx, Eli Lilly
- Community Collaborations: University of Tennessee-Knoxville, Alzheimer's Tennessee, Center for Biomedical Research

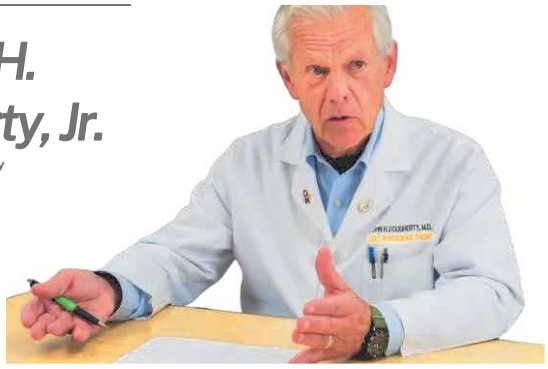
I will not include discussion of investigational treatments. Pharmaceutical clinical trial research funds are paid to the foundation.

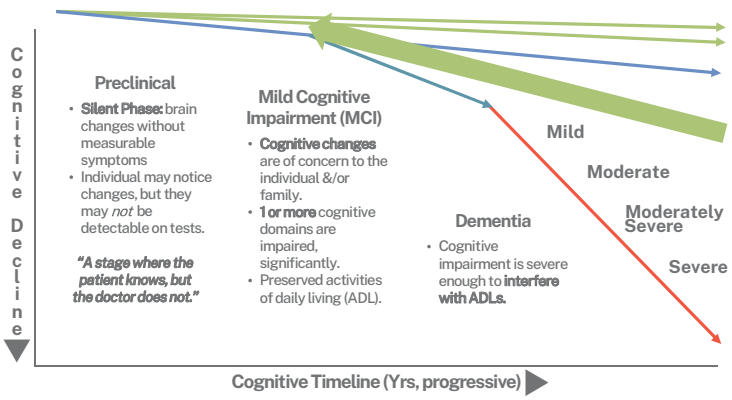
I have no actual or potential conflicts of interest in relation to the contents of this presentation.

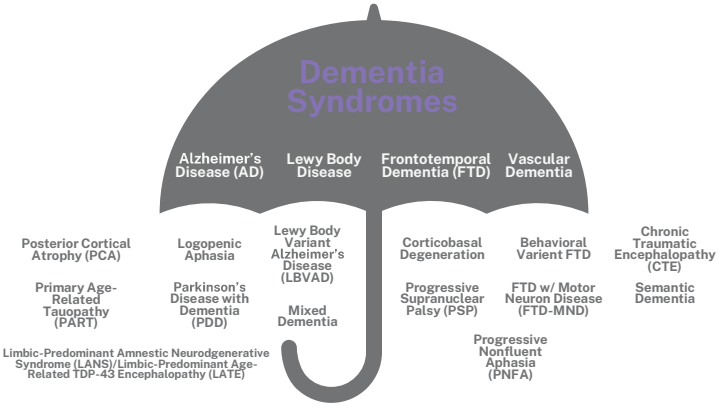
In Memory & Honor of:

Dr. John H. Dougherty, Jr.

A Leading Force in Neurology







Over

70%

of dementia cases are MIXED PATHOLOGY.

Alzheimer's disease (AD) is the most common.

AD (40-60%)

Early onset, late onset	Frontal Variant AD (Nonamnestic)
Logopenic PPA	AD with CBS
Posterior Cortical Atrophy (PCA)	

Lewy Body (15-25%)

Lewy Body Varient AD (LBVAD)	Multiple System Atrophy (MSA)
Diffuse LB Disease (DLB)	Parkinson's Disease Dementia (PDD)

LATE/LANS (PART)

FTD (5-10%)

Behavioral Variant FTD (bvFTD)	Progressive Supranuclear Palsy (PSP)
Semantic Dementia	Corticobasal Degeneration (CBD)
Progressive Nonfluent Aphasia (PNFA)	FTD/ALS

Vascular (5-20%)

Mixed AD & Vascular	Multi-infarct Dementia
Subcortical Vascular Dementia	CADSIL

2024 NIA-AA and International Work Group (IWG) Definitions

AD is a Clinical-Biological Disease.
AD exists on a *continuum.*
AD is first evident with *disease-specific biomarkers* in asymptomatic people. **
The same AD biology may result in different phenotypic presentations.
It is *more than* just "memory loss".
Clinical symptoms *overlap* with diseases other than AD.

**NIA-AA only

Dubois B, Villain N, Schneider L, et al. Alzheimer Disease as a Clinical-Biological Construct—An International Working Group Recommendation. JAMA Neurol. 2024;81(12):1304–1311. jamanetwork.com/journals/jamaneurology/article-abstract/2825806

Jack Jr. et al. Alzheimer's & Dementia. 2024;20(8):5143-5169. alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.13859

2024 NIA-AA Criteria: Integrated biological (letters) and clinical (numbers staging)

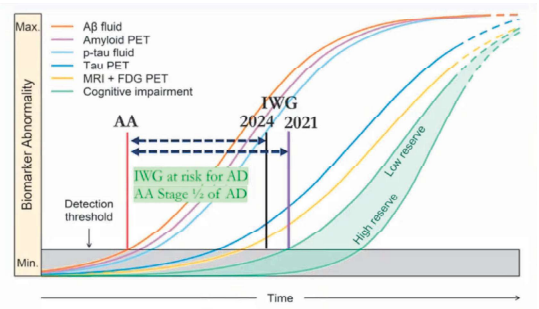
	Stage 0	Clinical Stage 1	Clinical Stage 2	Clinical Stage 3	Clinical Stages 4–6
Initial biological stage (A)	X	1A	2A	3A	4-6A
Early biological stage (B)	X	1B	2B	3B	4-6B
Intermediate biological stage (C)	X	1C	2C	3C	4-6C
Advanced biological stage (D)	X	1D	2D	3D	4-6D

Note: The typical expected progression trajectory is along the diagonal shaded cells, from 1A to 4–6D. However, considerable individual variability exists in the population. Individuals who lie above the diagonal (i.e., worse clinical stage than expected for biological stage) often have greater than average comorbid pathology. Individuals who lie below the diagonal (i.e., better clinical stage than expected for biological stage) may have exceptional cognitive reserve or resilience.

Why an orthogonal staging? Because clinical stage and biological stage do not always track.

. 2024 Aug;20(8):5143-5169. doi: 10.1002/alz.13859. Epub 2024 Jun 27.

Biological definition (NIA-AA) versus Clinical Definition (IWG)



- Lancet Neurology 2010, 2013, 2022

A Double Standard?

- With the NIA-AA definition it is true that some of the cognitively unimpaired individuals with positive markers will not develop AD symptoms within their lifetime.
- Risk of cognitive impairment with elevated amyloid is much higher than the risk of a cardiovascular event with elevated cholesterol.
  - The number needed to treat with simvastatin to prevent one MI/stroke was 23 over 5 years (Lancet 2002)
  - The number needed to treat based with high positive biomarkers to prevent MCI/dementia is 7 over 5 years (Mayo Clinic (Research from Graff Radford J et al Mayo Clinic presented at AAIC)

Clinical Checklist for Cognitive Disorders

1. **Detailed clinical history/physical exam**
2. **Neuropsychological/cognitive testing**
3. **B12, thyroid testing, CBC, BMP, LFTs**
   - Neurosyphilis testing only with high clinical suspicion*
4. **Genetic testing**
5. **Biomarkers**
   - *Imaging:* structural MRI or CT with coronal and sagittal reconstruction views; FDG PET; amyloid PET
   - CSF biomarkers
   - Blood-based biomarkers

MoCA©

Montreal Cognitive Assessment (MoCA)

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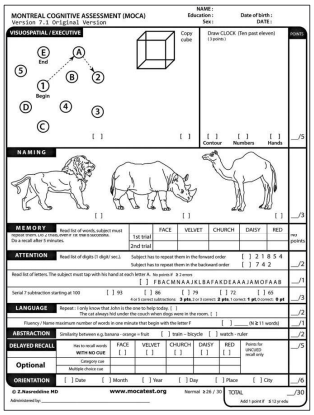
mocacognition.com/permission



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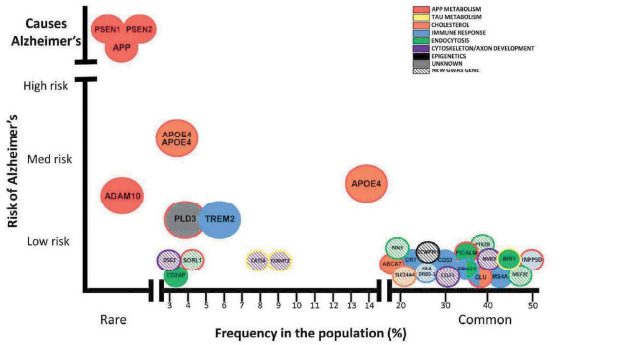
Genetic Causative/Risk Factors for AD

Karch CM, Goate AM. Alzheimer's disease risk genes and mechanisms of disease pathogenesis. Biol Psychiatry. 2015 Jan 1; 77(1):43–51. [PubMed: 24951455]

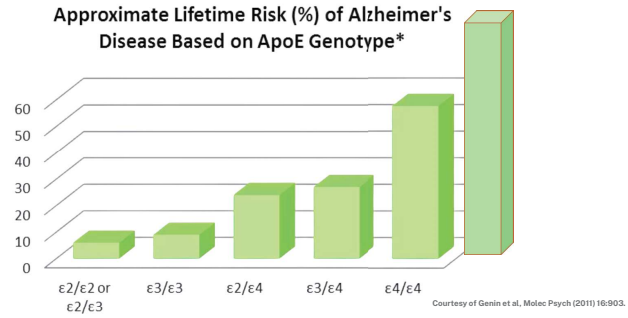


ApoE4/4 (Apolipoprotein ε4/ε4)

- With pooled data on more than 10,000 people of European descent, 95% of APOE4/4 (homozygotes) had amyloid plaques in the blood, cerebrospinal fluid (CSF), amyloid PET, or autopsy by age 55.
- On average, symptoms in APOE4 homozygotes emerge at age 65, a *decade earlier than in noncarriers.*

pubmed.ncbi.nlm.nih.gov/38710950/
Fortea J et al. APOE4 homozygozity represents a distinct genetic form of Alzheimer's disease. *Nat Med*. 2024 May;30(5):1284-1291.

ApoE 4 (Apolipoprotein ε4) Increases Risk of AD



Courtesy of Genin et al, Molec Psych (2011) 16:903.

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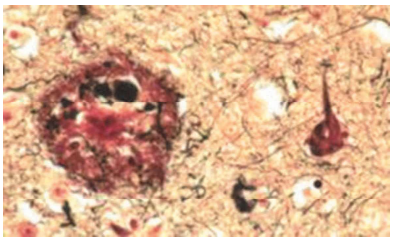
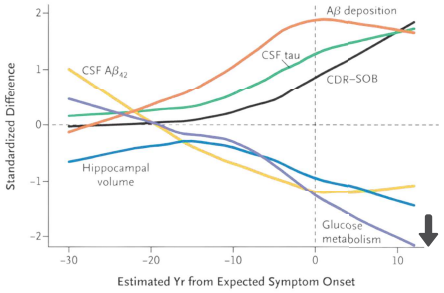
Old Way: Post-Mortem



Serrano-Pozo CSHPM 2011 Reproduced for Educational Use Only

AD Biomarker Timeline: Autopsy



Courtesy of N Engl J Med 2012; 367:795-804 DOI: 10.1056/NEJMoa1202753

ATNIVS Classification of AD

A = Amyloid-β (Aβ) Biomarkers: Detects amyloid plaques, a hallmark of Alzheimer's. *Tests:* Amyloid PET scan or CSF Aβ42 (low Aβ42 indicates plaque buildup).

- **AND T_1:** p-tau217 (preferred) – indicates early tau changes due to amyloid buildup.
  - Less specific alternatives: p-tau181 and p-tau231.

T_2 = Tau Pathology Biomarkers: Detect neurofibrillary tangles (tau aggregates) and monitor disease progression. *Tests:* CSF phosphorylated tau (p-tau) or Tau PET scan. MTBR-tau243: A more specific marker for disease progression.

N = Neuronal Injury Biomarker: Detects damage or loss of neurons. *Test:* Neurofilament light chain (NfL) – elevated levels suggest axonal injury.

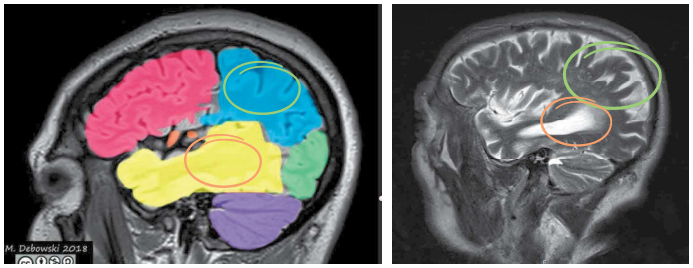
I = Inflammation Biomarker: Measure brain inflammation, often due to astrocyte activation. *Test:* GFAP (glial fibrillary acidic protein) – elevated in astrocyte response to injury.

V = Vascular Damage: Identify structural damage in brain blood vessels, which can worsen cognitive decline. *Tests:* MRI or CT scans – look for white matter lesions, microbleeds, strokes, etc.

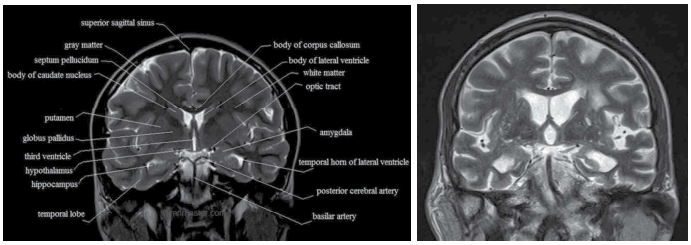
S = Alpha-Synuclein Biomarker: Detect abnormal α-synuclein protein, important in Lewy body dementia and Parkinson's disease. *Test:* αSyn-SAA (seeding aggregation assay) – detects misfolded α-synuclein.

Alzheimer's & Dementia, Clifford R Jack Jr, et al, Volume 20, Issue 8: 5143-5169. doi.org/10.1002/alz.13859

AD Pattern of Atrophy: Brain MRI Sagittal Image

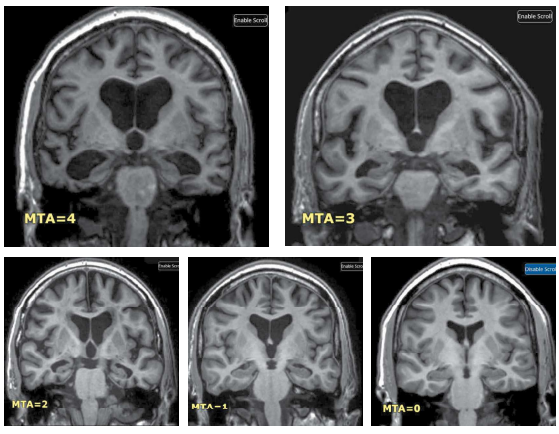


AD Pattern of Atrophy: Brain MRI Image



MRI high resolution, T2 coronal thin slices.

Medial Temporal Atrophy (MTA) Scale 0 - 4



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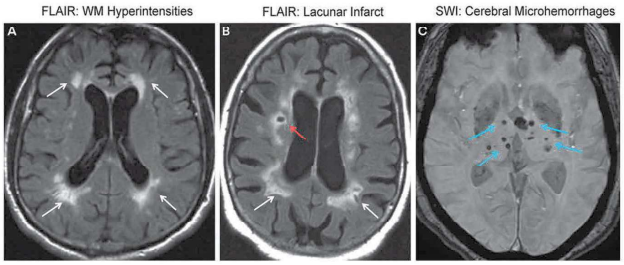
Axial MRI Scans of Vascular Cognitive Impairment



Courtesy of Continuum 2023;2 9(1 , Neuroimaging):219–254 and Razek and Elsebaie, Clinical Imaging 2021 Elsevier Inc.

Dementia Protocol: MRI Without Contrast

Required Sequences

- **T1-weighted:**
  - Axial, Coronal, Sagittal
  - Include high-resolution coronal thin slices for hippocampal evaluation
- **T2-weighted:**
  - Axial, Coronal, Sagittal
- **FLAIR (T2 FLAIR):**
  - Axial, Coronal, Sagittal
- **Diffusion Weighted Imaging (DWI) & Apparent Diffusion Coefficient (ADC)**
- **Susceptibility Imaging:** T2* SWI or GRE

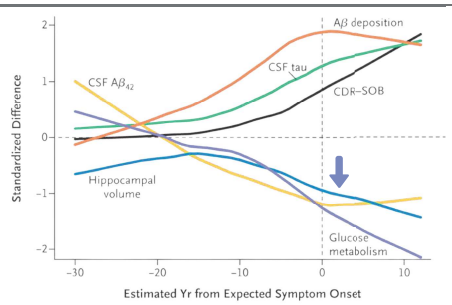
Qualitative Visual Rating Scales *(Include in Radiology Report)*

- **Global Cortical Atrophy (GCA): 0–3**
- **Medial Temporal Atrophy (MTA): 0–4**
- **Parietal Lobe Atrophy (Koedam Score): 0–3**
- **White Matter Disease (Fazekas Scale): 0–3**

If MRI is not available and CT is the only option: *Request thin-slice (≤1 mm) acquisition with coronal and sagittal reconstructions.*

(Standard CT uses 5 mm slices, which may limit evaluation of cortical and medial temporal atrophy.)

AD Biomarker Timeline: MRI Changes



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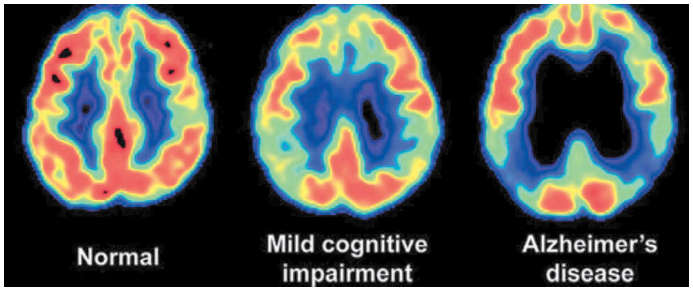
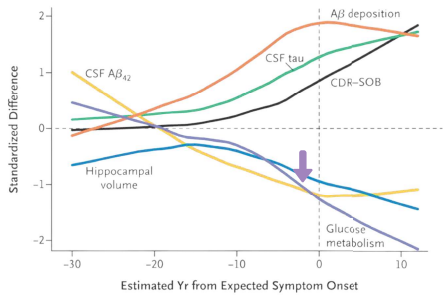
Glucose Metabolism Using 18F-FDG PET



AD Biomarker Timeline: Glucose PET



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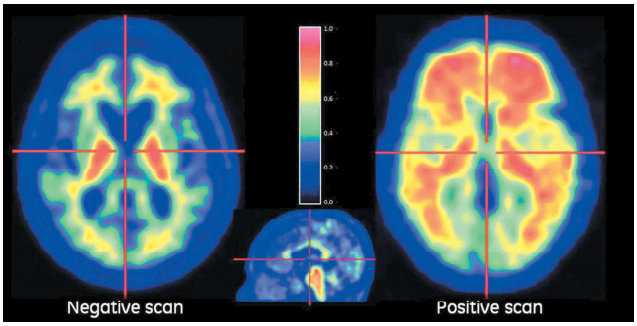
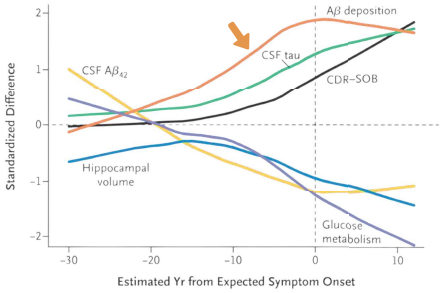
   - CSF biomarkers
   - Blood-based biomarkers

Amyvid (Amyloid Scan) = Virtual Biopsy



AD Biomarker Timeline: Amyloid Scan



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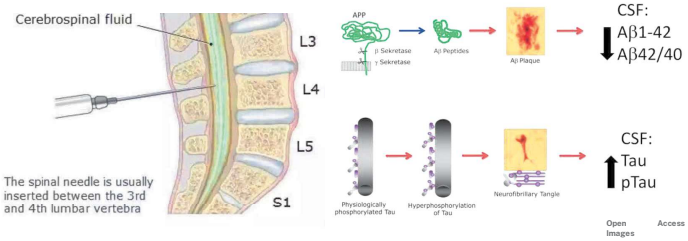
Cerebrospinal Fluid (CSF) Biomarkers

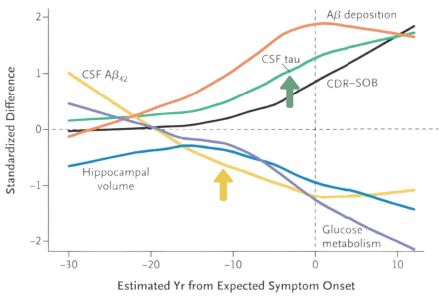
Highly Specific and Sensitive Indicators:

- Aβ42/Aβ40 Ratio – decreased in AD
- Total Tau – elevated with neurodegeneration
- Phosphorylated Tau (p-Tau) – reflects tau pathology



Open Access Images

AD Biomarker Timeline: CSF



Courtesy of N Engl J Med 2012; 367:795-804 DOI: 10.1056/NEJMoa1202753

Landmark changes for Current Practice: Blood Based Biomarkers (BBMs)

Neurodegenerative Dementia Test: BBM

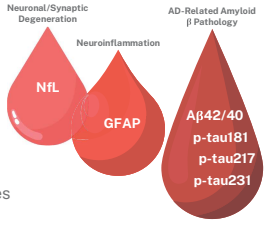
Key biomarkers detectable in blood include:

- Plasma Aβ42/40 ratio
- Phosphorylated tau (p-tau181, p-tau217, p-tau231)
- Serum neurofilament light chain (NfL)
- Glial fibrillary acidic protein (GFAP)

Emerging areas:

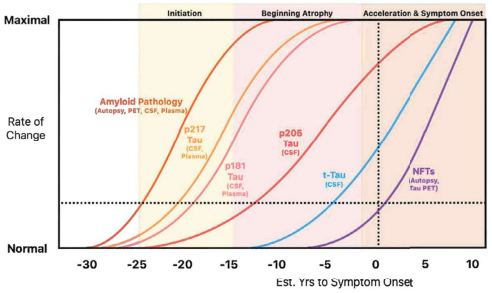
- α-Synuclein
- TDP-43

Note: p-tau217 levels remain low in non-AD tauopathies (diseases with a *different* form of tau).



Mielke, M.M., Fowler, N.R. Alzheimer disease blood biomarkers: considerations for population-level use. Nat Rev Neurol 20, 495–504 (2024). doi.org/10.1038/s41582-024-00989-1

p-tau217: Diagnose Symptomatic AD without the Need for CSF (requiring a lumbar puncture) or a PET Scan



A Primary Care Blood-Based Biomarker (BBM)?

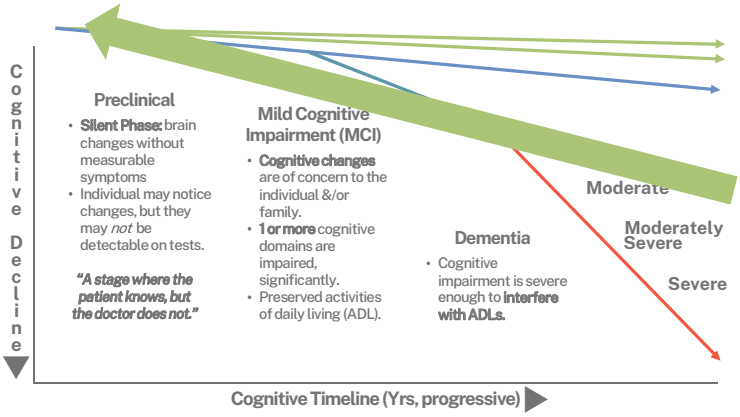
Primary care providers can make a biomarker-confirmed diagnosis of AD. Among available tests, plasma *p-tau217* currently offers the *highest accuracy* for detecting Alzheimer's pathology (comparable to CSF).

DMielke, M.M., Fowler, N.R. Alzheimer disease blood biomarkers: considerations for population-level use. Nat Rev Neurol 20, 495–504 (2024). https://doi.org/10.1038/s41582-024-00989-1

AA Workgroup 2025 BBM Guidelines

- **Rec 1**: Patients w/ objective cognitive impairment presenting for ~~specialized memory care~~ - a **high-specificity BBM test** as a **triaging test** in the diagnostic workup of Alzheimer's disease
- **Rec 2:** Patients w/ objective cognitive impairment presenting for ~~specialized memory care~~ - a **high-sensitivity and high-specificity BBM test** as a **confirmatory test** in the diagnostic workup of Alzheimer's disease.

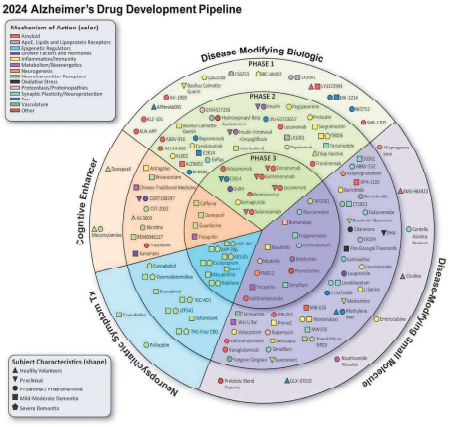
The majority of dementias are diagnosed and treated in primary care. Therefore we support the use of BBM as a triaging test as well as management tool especially in patients that are not eligible for disease modifying therapies



HOPE

- AD is a biological disease. It begins years, often decades, before symptoms appear, *progressing silently* in the brain.
- AD is defined by its *pathology*. The presence of amyloid plaques and tau tangles confirms a diagnosis at the biological level.
- *BBM* offers a breakthrough, especially p-tau217, which enables earlier and less invasive detection of amyloid and tau pathology.

There is HOPE.



TN Dementia ECHO: 12 Weeks to Stronger Dementia Care

Enroll today, to:

Lead with Clinical Excellence
Learn evidence-based strategies for early diagnosis, care planning, medication use, & behavior management, enhancing the quality & impact of your clinical care.

Strengthen Care Coordination
Build stronger connections across primary care, specialists, public health, & social services. Improve referrals, reduce duplication, & streamline care for complex patients.

Improved Patient & Caregiver Experience
Deliver person-centered, compassionate care that supports both patients & caregivers. Increase satisfaction, trust, & outcomes, while reducing crises & burnout.

TENNESSEE DEMENTIA ECHO

Thank You Alzheimer's Tennessee

TDAC
TN Dementia Action Collaborative

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Tennessee Memory Disorders Foundation and Clinic

TN Department of Health

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Knox County Tennessee Health Department

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