Future of Dementia Care in Rural North Dakota: How Blood Biomarkers Can Lead the Way

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Disclosure

I have no conflicts of interest with the presented content;
For educational purposes, not intended as a clinical advice.

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Learning Objectives

At the end of this presentation the attendee will be able to:

1. Highlight updated diagnostic criteria for Alzheimer's disease
2. Recognize the clinical utility of fluid biomarkers (blood and CSF)
3. Evaluate the analytical performance of currently available blood-based biomarkers

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Outline

- Alzheimer's Disease Pathophysiology
- Diagnostic Criteria & Clinical Practice Guidelines
- CSF and Blood - Biomarkers
- Analytical & Clinical Performance – Plasma pTau217
- Implementation & Outlook

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Case Study

51-year-old male presents with a progressive two-year history of short-term memory impairment

Symptoms: increasing forgetfulness, misplacing items, episodes of absent-mindedness, associated anxiety, depression and apathy

Neuropsycological evaluation: Montreal cognitive assessment score of 22

Pathways Case Study, Mayo Clinic Laboratories, Feb 2025

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Case Study

Lab workup: CSF(2 mL) collected in a 2.5 mL polypropylene low-binding tube was sent for AD biomarker analysis

	Alzheimer's Disease Evaluation, CSF	Result	Reference Interval	Result Flag
	Aβ42	616 pg/mL	> 834 pg/mL	Abnormal Low
	Total Tau	219 pg/mL	≤ 238 pg/mL	Normal
	Phospho Tau 181	25.7 pg/mL	≥ 21.6 pg/mL	Abnormal High
★	p-Tau/ Aβ42	0.042	≤ 0.028	Abnormal High

MAYO CLINIC LABORATORIES

Pathways Case Study, Mayo Clinic Laboratories, Feb 2025

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Case Study

What is the most likely interpretation of these findings?

- ❑ Results consistent with Alzheimer's disease pathological changes
- ❑ Results indicate Alzheimer's disease, PET scan is necessary for further confirmation
- ❑ Normal total tau suggests disorders of CSF dynamics such as normal pressure hydrocephalus
- ❑ p-Tau/Aβ42 ratio was falsely elevated due to improper collection

Pathways Case Study, Mayo Clinic Laboratories, Feb 2025

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The Alzheimer's Crew

Yang HD *et al.*, Dement Neurocogn Disord., 2016

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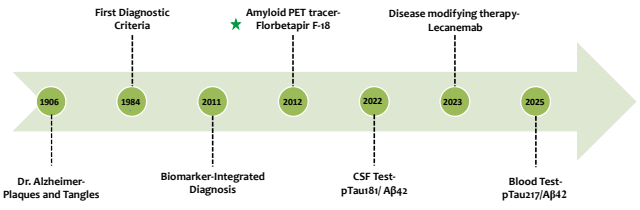
From Plaques to Plasma: A Century of Progress



Mohd Sajad *et al.*, IBRO Neuroscience Reports, 2022

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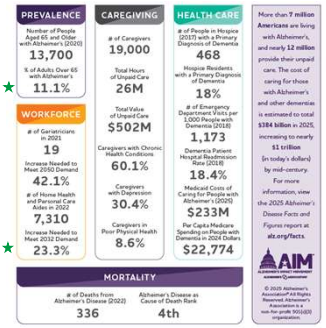
2025 North Dakota AD Statistics



Provided by Joan Danks, ND Program Director, Alzheimer's Association

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Limited Access to Amyloid PET in North Dakota

Accessed from Society of Nuclear Medicine and Molecular Imaging Page

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Amyloid Plaques and Neurofibrillary Tangles are Pathological Hallmarks of Alzheimer's Disease

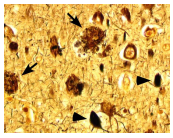
Amyloid Cascade:

1. Accumulation of the aggregation-prone amyloid β peptide 1-42 (Aβ42) in extracellular diffuse plaques drives neurodegeneration
2. Inhibits hippocampal long-term potentiation and impairs synaptic function

Tau Pathology:

1. Intracellular tau tangles contributes to cognitive symptoms
2. Downstream event after Aβ accumulation

Bielschowsky Stain



Molinuevo JL *et al.*, Acta Neuropathologica, 2018

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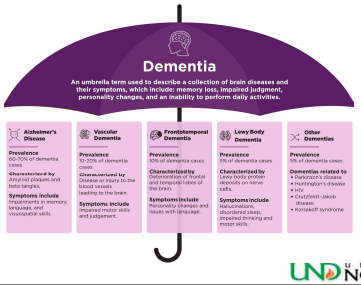
Dementia ≠ Alzheimer's Disease



O.Grari *et al.*, eJIFCC, 2023

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Patho-etiology of Alzheimer's Disease

Genetic (5-10%)

- Early Onset: APP, PSEN1/2, Trisomy 21
- Late Onset: APOE-ε4
- Family History: >40 variants

★ **Sporadic (90-95%)**

- Age: 65-85 years
- **Lifestyle** (diet, smoking, physical inactivity), **Chronic Disease** (High BP, hyperlipidemia, cerebrovascular disease), **Environmental** (Head Trauma, stress, depression)

Molinuevo, JL *et al.*, Acta Neuropathologica, 2018

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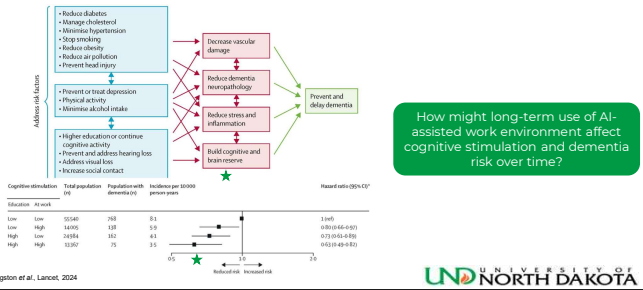
Building Cognitive Reserve Reduces Alzheimer's Disease Risk



How might long-term use of AI-assisted work environment affect cognitive stimulation and dementia risk over time?

Livingston *et al.*, Lancet, 2024

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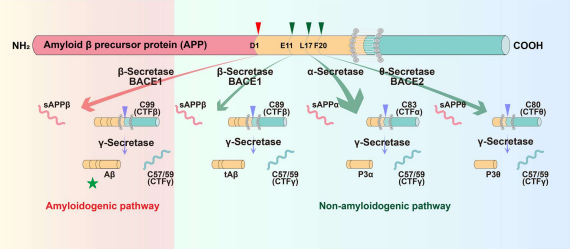
Amyloid β peptides are formed by proteolytic cleavage of APP at neuronal synapses



Zhang Y *et al.*, Signal Transduction and Therapy, 2023

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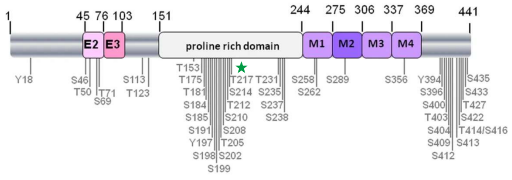
Tau stabilizes neuronal microtubules and possess ~80 phosphorylation sites



Noble W *et al.*, Frontiers in Neurology, 2013

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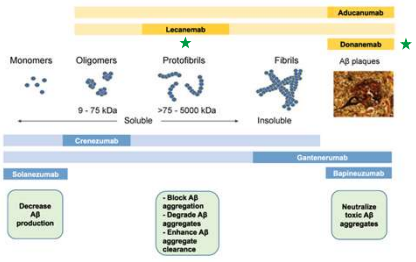
Two FDA-Approved Anti-Amyloid Therapies



Park KW *et al.*, Nuclear Medicine and Molecular Imaging, 2024

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Eligibility Criteria for Anti-Amyloid Therapies

Cognitive Assessment
Structural Imaging
Amyloid Biomarker
APOE Testing

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Clinical Practice Guidelines for Alzheimer's Diagnosis Continue to Evolve

2018: Biological Definition
AT(N) Framework

2011: Clinical Syndrome
Preclinical->MCI->Dementia

2024: Biomarkers
Core 1 and Core 2

NIA-AA Clinical Practice Guidelines, Alzheimer's and Dementia, 2011, 2018 and 2024

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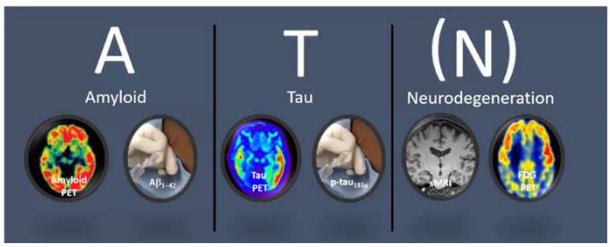
2018 AD Diagnostic Criteria: AT(N) Framework



Jack CR et al., Alzheimer's and Dementia, 2018

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2018 AD Diagnostic Criteria: AT(N) Framework

AT(N) profiles	Biomarker category	
A-/T-/(N)-	Normal AD biomarkers	
A+/T-/(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+/T+/(N)-	Alzheimer's disease	Alzheimer's continuum
A+/T+/(N)+	Alzheimer's disease	Alzheimer's continuum
A+/T-/(N)+	Alzheimer's change and concomitant suspected non-AD pathologic change	Alzheimer's continuum
A-/T+/(N)-	Non-AD pathologic change	
A-/T-(N)+	Non-AD pathologic change	
A-/T+/(N)+	Non-AD pathologic change	

Kang JH *et al.*, Clinical Chemistry, 2023

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2024 Revised Criteria: Core 1 and Core 2 Biomarkers

Detection of AD neuropathologic changes by **biomarkers is equivalent** to diagnosing the disease

Core 1 biomarkers establishes AD diagnosis, utilized for symptomatic and asymptomatic individuals

Core 2 biomarkers are linked to onset of symptoms, utilized for disease severity

Jack CR *et al.*, Alzheimer's and Dementia, 2024

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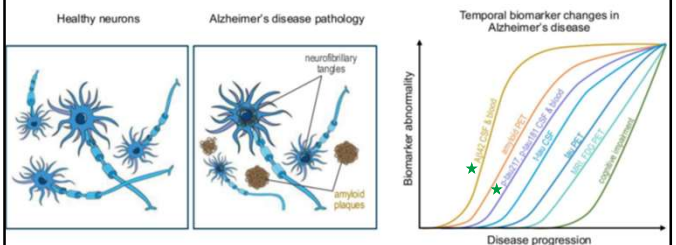
Temporal Sequence of AD Biomarker Changes



Algeciras-Schimnich A *et al.*, ADLM Guidance Document, 2026

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2024 Revised Criteria: Core 1 and Core 2 Biomarkers

Biomarker category	CSF or plasma analytes	Imaging
Core biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ42/40 or P-tau/AB42	Amyloid PET
T_1: (phosphorylated and secreted AD tau)	P-tau 217, p-tau 181, p-tau 231	
Core 2		
T_2 (AD tau proteinopathy)	pT205, MTBR-243, non-phosphorylated tau fragments	Tau PET
Biomarkers of non-specific processes involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MR or CT, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD co-pathology		
V vascular brain injury		Anatomic infarction, WMH
S α-synuclein	αSyn-SAA*	

Jack CR *et al.*, Alzheimer's and Dementia, 2024

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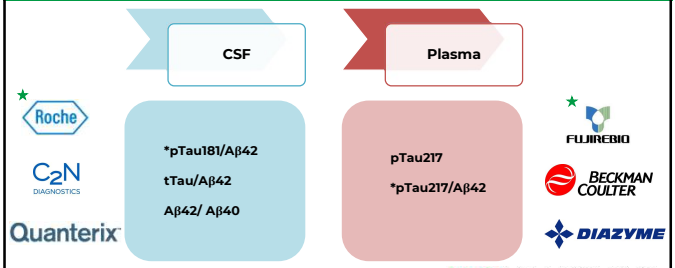
ADLM Recommendations for AD Fluid Biomarkers



Algeciras-Schimnich A *et al.*, ADLM Guidance Document, 2026

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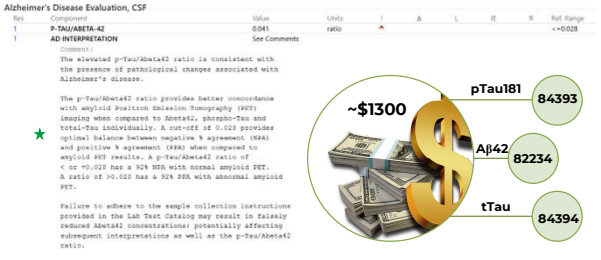
Interpret CSF pTau181/Aβ42 in the context of disease probability


Alzheimer's Disease Evaluation, CSF

Res	Component	Value	Units	Ref. Range
1	P-TAU/ABETA-42	0.041	ratio	<=0.028
1	AD INTERPRETATION	See Comments		

Comment:

The elevated p-Tau/Abeta42 ratio is consistent with the presence of pathological changes associated with Alzheimer's disease.

The p-Tau/Abeta42 ratio provides better concordance with amyloid Positron Emission Tomography (PET) imaging when compared to Abeta42, phospho-Tau and total-Tau individually. A cut-off of 0.028 provides optimal balance between negative % agreement (NPA) and positive % agreement (PPA) when compared to amyloid PET results. A p-Tau/Abeta42 ratio of < or =0.028 has a 92% NPA with normal amyloid PET. A ratio of >0.028 has a 92% PPA with abnormal amyloid PET.

Failure to adhere to the sample collection instructions provided in the Lab Test Catalog may result in falsely reduced Abeta42 concentrations, potentially affecting subsequent interpretations as well as the p-Tau/Abeta42 ratio.

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Clinical Indications for AD CSF Biomarker Testing

SCI at increased risk for AD	Cognitively unimpaired (screening)
Clinical diagnosis of MCI that is persistent and progressing	Cognitively unimpaired and an APOE ε4 carrier
Symptoms that suggest possible AD	SCI but cognitively unimpaired based on objective testing
MCI or dementia with an onset < 65 yers	Suspected autosomal dominant AD
Meets clinical criteria for probable AD with typical age of onset	Known autosomal dominant AD with or without symptoms
Dominant symptom is a change in behavior* and where AD is a diagno-stic consideration	

Algeciras-Schimnich A *et al.*, ADLM Guidance Document, 2026

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Preanalytical Considerations for AD CSF Biomarkers




Phase	Pre-analytical consideration	Reason
Lumbar puncture	Morning collection	Diurnal variation
	Collection of 2nd or later fraction	Avoidance of cellular debris and blood contamination
	Collection by gravity drip direct into a polypropylene tube with a low propensity to bind proteins	Minimize loss of Aβ peptides to adsorption to surfaces
	Polypropylene collection tube optimized for CSF volume to tube surface area (e.g., required fill-line noted)	Minimize loss of Aβ peptides
Sample processing	Minimal to no intervention (e.g., no aliquoting, only centrifuge if debris present)	Minimize loss of Aβ peptides
Shipment	Ship via temperature- and protocol-validated method	Avoidance of freeze/thaw cycles
Storage prior to analysis	If properly collected, sample can be stored frozen for prolonged periods	Enables shipment to analysis site & "add-on" testing

Kumar P *et al.*, Clinical Biochemistry, 2025

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Paradigm Shift with AD Plasma Biomarkers



Imaging	CSF Biomarkers	Plasma Biomarkers
Limited scanner access	Mildly invasive	Longitudinal follow-up
Expensive	Patient discomfort	Faster Triage
Radiation exposure	Physician time	Better access to care

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Analytical Performance of Plasma pTau217

Manufacturer	Fujirebio	Beckman Coulter
Assay	Lumipulse G pTau217	Access pTau217
Instrument	Lumipulse G1200	Dxl 9000
Regulatory Approval	FDA-Cleared	FDA Breakthrough Device Designation
Method	Two-step, Sandwich Immunoassay	Two-step, Sandwich Immunoassay
Antibodies	Proprietary, Mouse Monoclonal	ALZpath, Sheep/Rabbit Monoclonal
Readout	Enzymatic-Chemiluminescent	Enzymatic-Chemiluminescent
Assay Time	30 mins	38 mins
Specimen Type	EDTA Plasma	EDTA Plasma
Minimum Volume	250 µL	360 µL
Calibrator	5 point	5 point
AMR	0.05-10 pg/mL	0.03-8 pg/mL
Precision	<10%	<10%

Lumipulse G pTau217 and Access pTau217 Assay IFU

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Improved Diagnostic Accuracy with Dual Cut-off Strategy for Plasma pTau217/Aβ42

In patients aged ≥50 years presenting at a specialized care setting with signs and symptoms of cognitive decline, results should be interpreted as follows:

RESULT	RATIO INTERPRETATION*		PREDICTIVE VALUE (95% CI)
≥0.00738	POSITIVE	Consistent with patients **LIKELY** to have amyloid pathology. Result does not establish a diagnosis of AD or other cognitive disorders.	PPV 91.8% (87.8%-94.6%)
0.00371 - 0.00737	INDETERMINATE**	Consistent with patients **UNCERTAIN** to have amyloid pathology. Consider further testing.	
≤0.00370	NEGATIVE	Consistent with patients **UNLIKELY** to have amyloid pathology. Should investigate for other causes of cognitive decline.	NPV 97.3% (93.9%-98.8%)

*Test results must be interpreted in conjunction with other patient clinical information. This test is not intended as a screening or stand-alone diagnostic assessment.
**19.6% of patients had an indeterminate result in the clinical study that supported the FDA clearance.
PPV, positive predictive value; NPV, negative predictive value

Lumipulse G pTau217/Aβ42 Assay IFU

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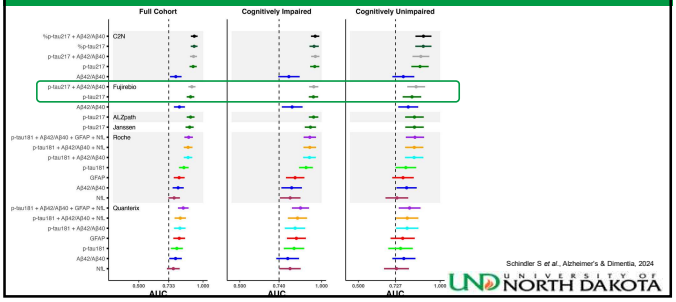
Clinical Performance of Plasma pTau217



Schindler S *et al.*, Alzheimer's & Dimentia, 2024

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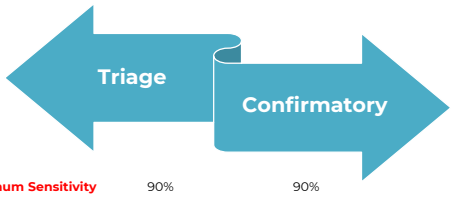
Clinical Performance Targets for pTau217 Assays



Minimum Sensitivity	90%	90%
Minimum Specificity	75%	90%

Palmqvist S *et al.*, Alzheimer's and Dementia, 2025

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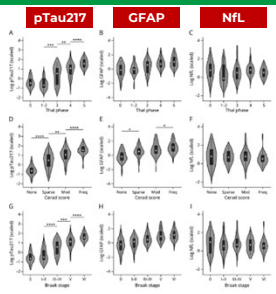
Plasma pTau217 shows robust association with postmortem AD pathology



Kivisakk P *et al.*, Neurology, 2026

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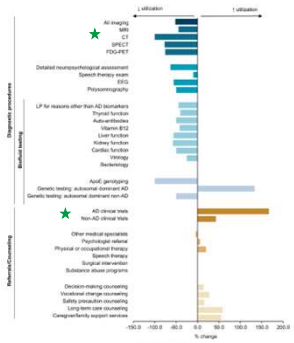
IMPACT-AD BC Clinical Trial



Patel KJ *et al.*, Alzheimer's Dement., 2024

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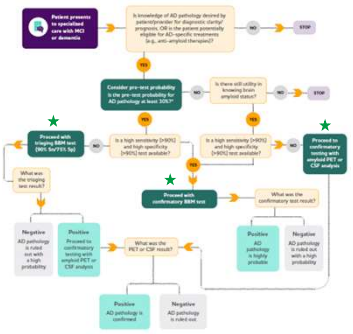
AD Diagnostic Algorithm



Palmqvist S et al., Alzheimers Dement., 2025

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Implementation and Outlook

- Lack of proficiency testing material, depend on alternate proficiency assessment
- None of the AD biomarkers except CSF Aβ42 are standardized
- Limited availability of linearity and QC material from third party vendors
- Patients with CKD may show basal high pTau217 levels
- Not recommended for serial monitoring of patients undergoing anti-amyloid therapy
- Limited guidance on the integration of plasma biomarkers into clinical pathway at the primary care setting

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Key Takeaways

1. Prioritize implementation of plasma pTau217 assays due to superior diagnostic accuracy
2. Classify plasma pTau217 assays as triage or confirmatory tests based on diagnostic performance
3. Limit plasma pTau217 testing to patients with objective cognitive decline presenting to specialty care clinic

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