NAPA Advisory Council: Biomarkers

UCSF Weill Institute for Neurosciences

Lawren VandeVrede, MD/PhD
Assistant Professor of Neurology
Department of Neurology, UCSF

Fein Memory and Aging Center

August 3, 2026

Disclosures

Research grants or travel reimbursement from the NIH (NIA), Alzheimer's Association, Part the Cloud, Tau Consortium, American Academy of Neurology, American Brain Foundation, and Shenandoah Foundation.

Research collaborations with C2N, Labcorp, and Quanterix.

Clinical trial investigator for Biogen, Denali, and Merck, and Novartis-sponsored clinical trials.

Consulting and speaking fees from Biogen, Lilly, Novartis, Roche, and Siemens.

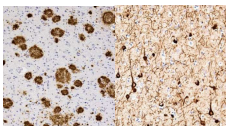
Dementia vs. Alzheimer's Disease: Biomarkers Needed

Dementia: Umbrella term for thinking and memory problems that impair day-to-day function. There are many causes of cognitive symptoms, many stages of cognitive symptoms, and many syndromes that present with cognitive symptoms.

Alzheimer's disease (AD): Specific brain disease defined by specific brain proteins (amyloid plaques and tau tangles). AD has many stages of severity, AD has typical and atypical syndromes, and different proteins can mimic the typical syndrome.

"Alzheimer's Disease"

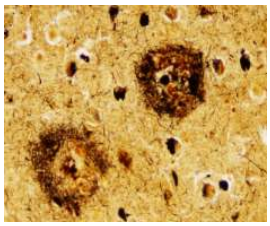
Thinking & Memory Problems



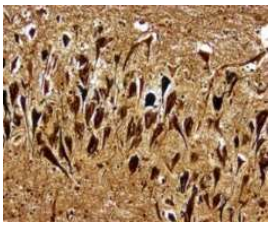
Amyloid Plaques **Tau Tangles**

Modified with Permission, Suzanne Schindler

1906: Dr. Alzheimer Discovers Plaques & Tangles



"Distributed all over the cortex, but especially numerous in the upper layers, there are minute miliary foci which are caused by the deposition of a special substance in the cortex."

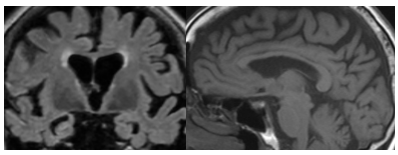


"Bielschowsky's silver method show very striking changes of the neurofibrils…[t]he cell itself disintegrate and only a tangle of fibrils indicates the place where a neuron was previously located."

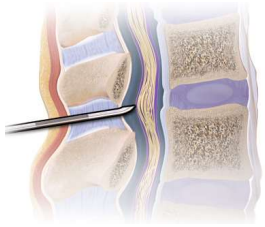
"The post-mortem showed an evenly atrophic brain…[t]he larger vascular tissues show arteriosclerotic change."

Alzheimer *Neurol Central* 1906

2026: Biomarkers in AD, An Embarrassment of Riches

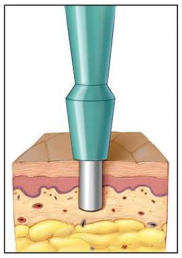


MRI

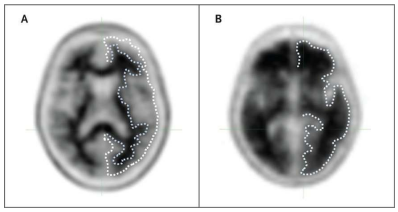


CSF

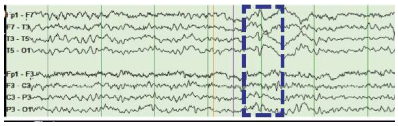
Blood



Biopsy



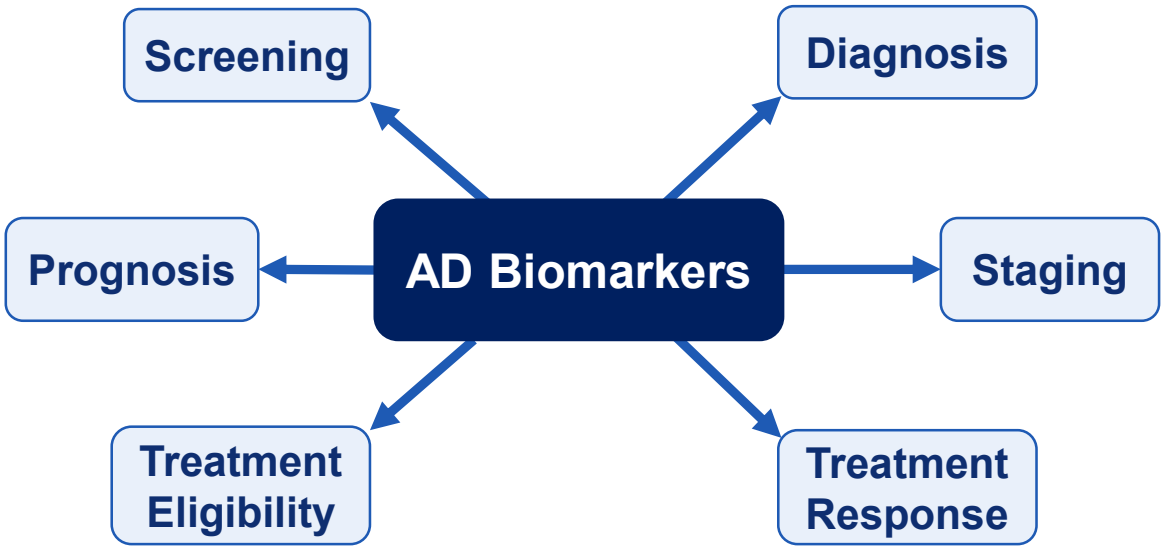
PET



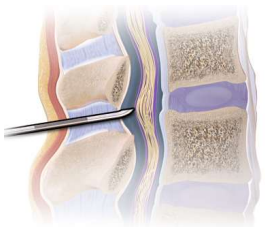
EEG/MEG

Genetics

Biomarker Roles in the Clinic and Trials



Cerebrospinal Fluid



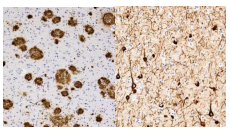
Description: CSF is drawn via lumbar puncture (spinal tap), and results are interpreted on a numeric scale as either positive, negative, or uncertain.

Advantages:

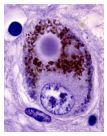
- Decades of clinical experience
- Testing for non-AD causes can be performed
- Covered by most insurances

Drawbacks:

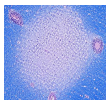
- Negative stigma around lumbar puncture
- Patient may have contraindications
- Time-consuming and expensive to set up
- Frequently poorly reimbursed
- Occasionally unsuccessful, may cause side effects



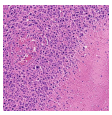
Amyloid Plaques **Tau Tangles**



α-Synuclein



Multiple Sclerosis



Certain Cancers

VandeVrede *Alzheimer's and Dementia* 2024

Amyloid PET

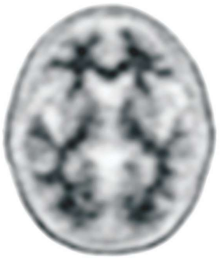
Description: Radiotracer binds plaques and PET scanner detects binding. Read as positive or negative, but a numeric scale is available (centiloids).

Advantages:

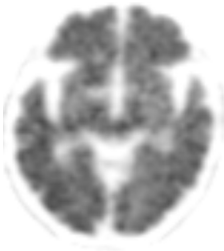
- Can see the amount and location of plaques
- Tracks plaque removal by amyloid-targeting treatments
- Covered by most insurances for AD diagnosis

Drawbacks:

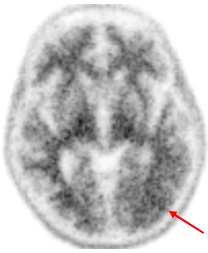
- Requires expensive, specialized equipment
- Experts not available at every center
- Requires a small amount of radioactivity
- Cost is typically high (~$5,000/scan)



Negative



Diffusely Positive



Focally Positive

VandeVrede *Alzheimer's and Dementia* 2024

Tau PET

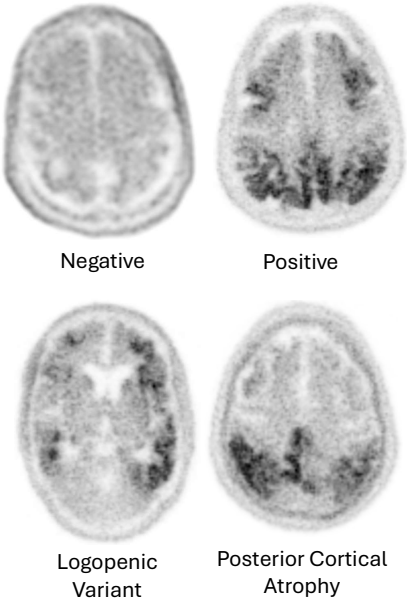
Description: Radiotracer binds tangles and PET scanner detects binding. Read as positive or negative, but numeric scales are being developed.

Advantages:

- Can see the amount and location of tangles
- Amount of tau tells you about stage of disease
- Location predicts what symptoms a patient has

Drawbacks:

- Requires expensive, specialized equipment
- Experts not available at every center
- Requires a small amount of radioactivity
- Cost is typically high (~$10,000/scan) and insurance coverage is less clear



Negative Positive

Logopenic Variant Posterior Cortical Atrophy

VandeVrede *Alzheimer's and Dementia* 2024

Blood Biomarkers

Description: Blood is drawn from vein, and results are interpreted on a numeric scale as either positive, negative, or uncertain.

Advantages:

- Blood labwork is part of routine medical care
- Acceptable to patients (less burdensome/invasive)
- Less expensive (with similar accuracies)
- Easier to scale up to meet demands

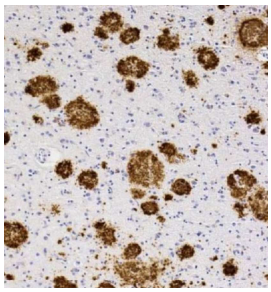
Drawbacks:

- Accuracy varies between tests (difficult for non-experts)
- Certain factors impact results (e.g., kidney disease)
- Unclear reimbursement/lack of insurance coverage

VandeVrede *Alzheimer's and Dementia* 2024

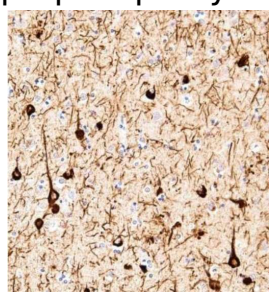
Alzheimer's Disease Pathology

$A\beta_{42}$



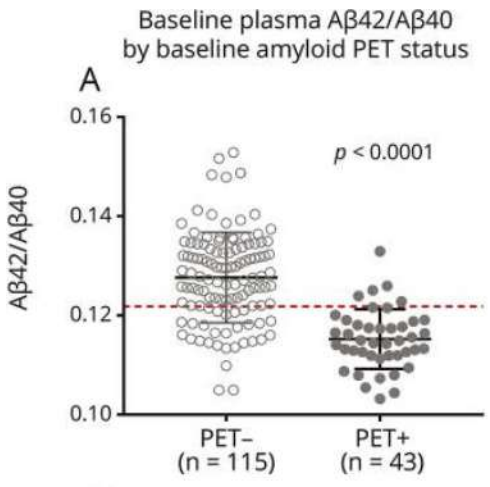
Amyloid Plaques

Tau (Hyperphosphorylated)



Neurofibrillary Tangles

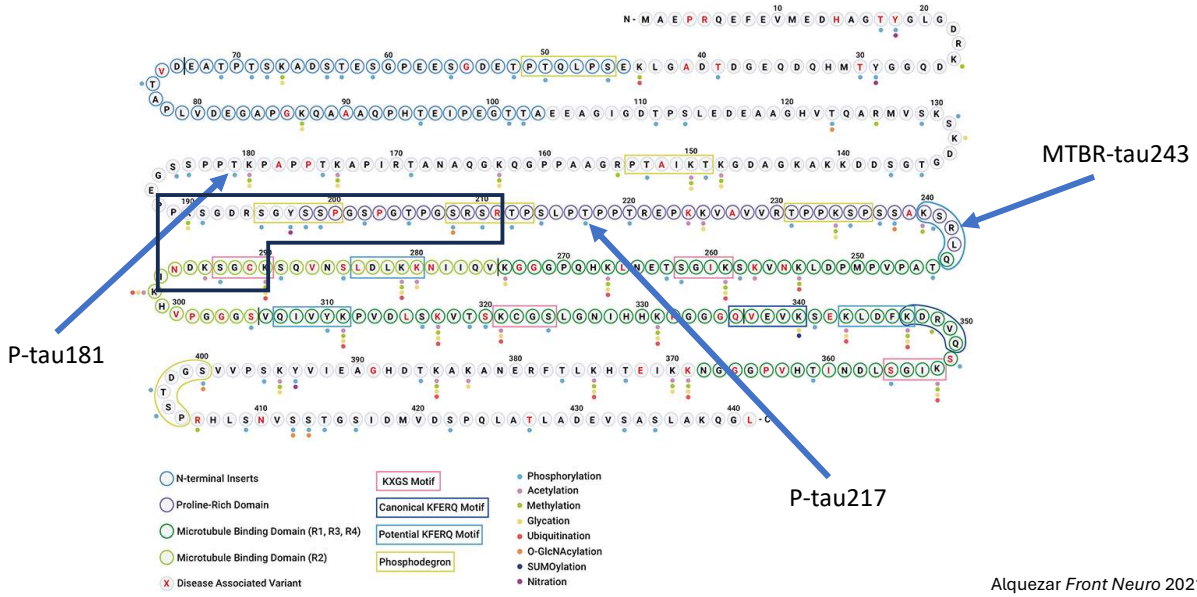
First Blood Biomarker: $A\beta_{42/40}$



- Sensitive to early plaque accumulation
- Specific to AD but limited amount of change
- Limited uptake in clinic as standalone test

Schindler *Neurology* 2019

Tau Biomarkers are Changes Seen in AD



Alquezar *Front Neuro* 2021

Two FDA-Cleared Tests for AD (so far)

FDA NEWS RELEASE

FDA Clears First Blood Test Used in Diagnosing Alzheimer's Disease

New Test Provides Less Invasive Option, Reduces Reliance on PET Scans and Increases Diagnosis Accessibility

Fujirebio Lumipulse G p-tau217/Aβ$_{42}$

- First blood test for aid in diagnosing AD
- Symptomatic patients age 55 and older
- Intended as confirmatory diagnostic test

Roche Elecsys p-tau181

- Second test cleared, first for primary care
- Symptomatic patients age 55 and older
- Intended as triage or "rule out" test

www.fda.gov

P-tau217 is Gold Standard Blood Biomarker for AD

Plasma phosphorylated tau 217 and phosphorylated tau 181 as biomarkers in Alzheimer's disease and frontotemporal lobar degeneration: a retrospective diagnostic performance study

Elisabeth H Thijssen, Renaud La Joie*, Amelia Strom, Corrina Fonseca, Leonardo Iaccarino, Amy Wolf, Salvatore Spina, Isabel E Allen, Yann Cobigo, Hilary Heuer, Lawren VandeVrede, Nicholas K Proctor, Argentina Lario Lago, Suzanne Baker, Rajeev Sivasankaran, Agnieszka Kieloch, Arvind Kinhikar, Lili Yu, Marie-Anne Valentin, Andreas Jeromin, Henrik Zetterberg, Oskar Hansson, Niklas Mattsson-Carlgren, Danielle Graham, Kaj Blennow, Joel H Kramer, Lea T Grinberg, William W Seeley, Howard Rosen, Bradley F Boeve, Bruce L Miller, Charlotte E Teunissen, Gil D Rabinovici, Julio C Rojas, Jeffrey L Dage, Adam L Boxer, on behalf of the Advancing Research and Treatment for Frontotemporal Lobar Degeneration investigators†*

nature medicine

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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 Neurology | Original Investigation

Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology

Nicholas J. Ashton, PhD; Wagner S. Brum; Guglielmo Di Molfetta, MSc; Andrea L. Benedet, PhD; Burak Arslan, MD; Erin Jonaitis, PhD; Rebecca E. Langhough, PhD; Karly Cody, PhD; Rachael Wilson, PhD; Cynthia M. Carlsson, PhD; Eugeen Vanmechelen, PhD; Laia Montoliu-Gaya, PhD; Juan Lantero-Rodriguez, PhD; Nesrine Rahmouni, MSc; Cecile Tissot, PhD; Jenna Stevenson, PhD; Stijn Servaes, PhD; Joseph Therriault, PhD; Tharick Pascoal, MD, PhD; Alberto Lleó, MD, PhD; Daniel Alcolea, MD, PhD; Juan Fortea, MD, PhD; Pedro Rosa-Neto, MD, PhD; Sterling Johnson, MD, PhD; Andreas Jeromin, PhD; Kaj Blennow, MD, PhD; Henrik Zetterberg, MD, PhD

JAMA Neurology | Original Investigation

Detection of Alzheimer Neuropathology in Alzheimer and Non-Alzheimer Clinical Syndromes With Blood-Based Biomarkers

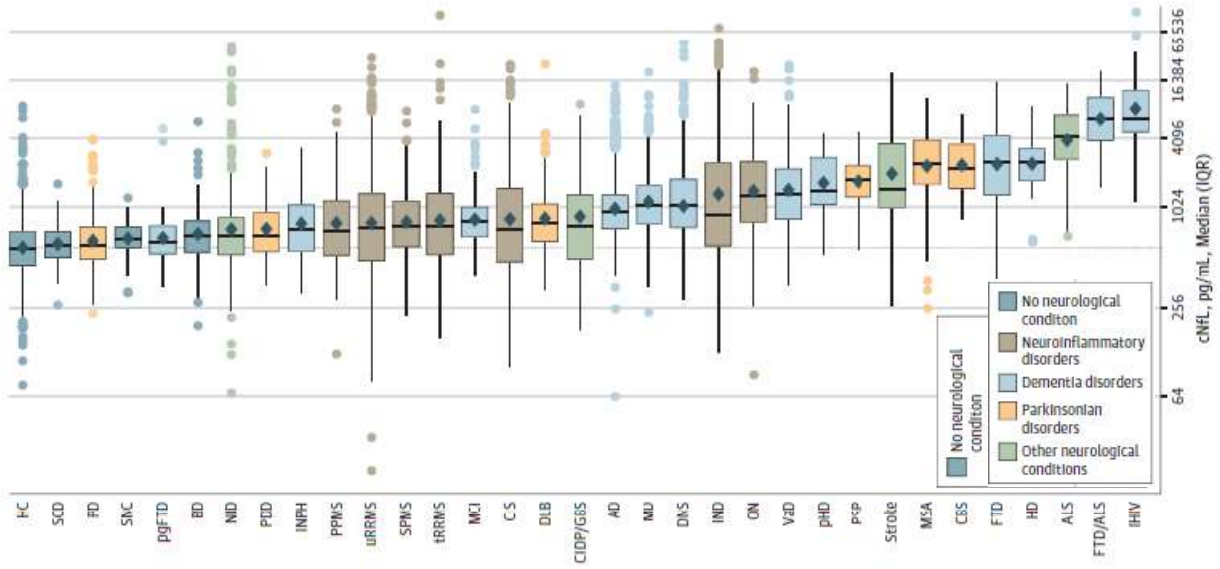
Lawren VandeVrede, MD, PhD; Hanna Cho, MD, PhD; Mark Sanderson-Cimino, PhD; Fattin Welkselman, BS; Yann Cobigo, PhD; Maria Luisa Gorno-Tempini, MD; Hilary W. Heuer, PhD; Joel H. Kramer, PhD; Argentina Lario Lago, PhD; Dana Leichter, BS; Peter Ljubenkov, MD; Bruce L. Miller, MD; David C. Perry, MD; Gil D. Rabinovici, MD; Julio C. Rojas, MD, PhD; Howard J. Rosen, MD; Rowan Saloner, PhD; Adam Staffaroni, PhD; Gallen Triana-Baltzer, PhD; Salvatore Spina, MD, PhD; William W. Seeley, MD; Lea T. Grinberg, MD, PhD; Hartmuth C. Kolb, PhD; Renaud La Joie, PhD; Adam L. Boxer, MD, PhD

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

NfL is Elevated when Brain is Injured



Bridel *JAMA Neurology* 2019

Synuclein Biomarkers are in CSF/Skin

Result

Detected-1: Misfolded α-Synuclein protein aggregates detected.

Interpretation:

Amplification profile consistent with that found predominantly in patients with primary or secondary neuronal synuclein disease (e.g., Parkinson's disease, dementia with Lewy bodies, Alzheimer's disease with Lewy body pathology (AD-LB)).

Result

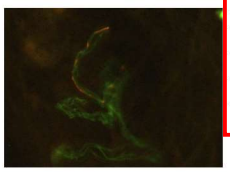
Not Detected

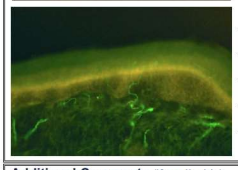
Interpretation:

Misfolded α-Synuclein protein aggregates not detected.

SAAmplify-αSyn
Amprion

Pathology Results





Phosphorylated Alpha-Synuclein (P-SYN)

Bx Site	P-SYN Deposition	Description
Posterior Cervical (Left)	Abnormal	One colocalized fiber seen across all stained sections.
Distal Thigh (Left)	Abnormal	One colocalized fiber seen across all stained sections.
Distal Leg (Left)	Abnormal	One colocalized fiber seen across all stained sections.

The green regions indicate PGP 9.5 immunostained nerve fibers. The regions in red/orange are immunostained regions of phosphorylated alpha-synuclein within nerve fibers. This region displays evidence of phosphorylated alpha-synuclein deposition.

Intraepidermal Nerve Fiber Density

Bx Site	Observed Measurement (fibers/mm)	Normal Range (fibers/mm)
Posterior Cervical (Left)	15	≥17.5
Distal Thigh (Left)	5.5	≥8.4
Distal Leg (Left)	0.6	≥5.1

The image on the left is not of the patient's own specimen but is included as an example only. The linear green structures indicate PGP 9.5 immunostained nerve fibers. This region displays reduced intraepidermal nerve fiber density. Patient-specific images are available upon request.

Additional Comments (if applicable)

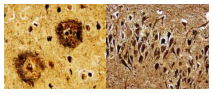
*Posterior cervical: clinically significant histologic abnormalities: Edge of squamous cell carcinoma in situ. Follow- up with dermatology is warranted.
Distal thigh: no significant histologic abnormalities
Distal leg: no significant histologic abnormalities

Signed: Todd Levine, MD
Medical Director, CMO

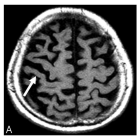
Syn-One
CND Life Sciences

Biomarkers for Related Diseases are Still Needed

Simple Model of AD:



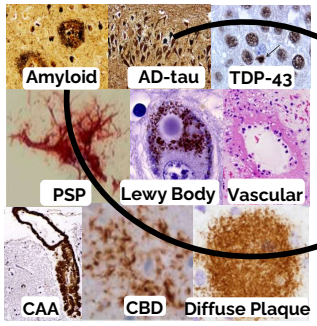
Amyloid/Tau

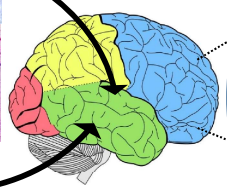


Neurodegeneration

Dementia

Pathologic Changes | **Location** | **Individual Factors** | **Syndromes**





Genetics
Education
Age
Environment

AD-Related Syndromes	Syn-Related Syndromes
Late-Onset Amnestic	Parkinson's Disease
Early-Onset Amnestic	Dementia w/ Lewy Bodies
Corticobasal Syndrome	Multiple System Atrophy
Frontal/Dysexecutive	Pure Autonomic Failure
Logopenic Aphasia	
Posterior Cortical Atrophy	

Tau-Related Syndromes	TDP-Related Syndromes
Corticobasal Syndrome	Behavioral Variant of FTD
Richardson's Syndrome	Semantic Variant of PPA
Non-fluent Aphasia	Non-fluent Aphasia Variant
Behavioral Variant of FTD	LATE

Appropriate Use of AD Tests in the Clinic

Patients being evaluated for thinking and memory problems as part of a comprehensive workup, and

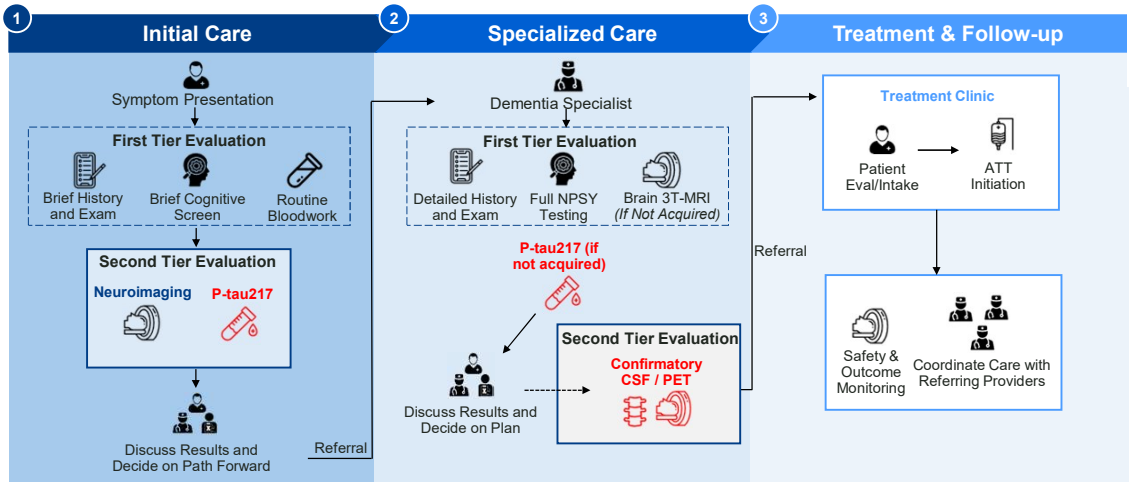
1) AD is considered a potential cause, and
2) Testing will increase certainty of diagnosis or determine eligibility for treatments.

Alzheimer's Association Clinical Practice Guideline:

1) Triage test: ≥90% sensitivity & ≥75% specificity
2) Confirmatory test: ≥90% sensitivity & specificity

Palmqvist *A&D* 2025
Hazan *A&D* 2025

Biomarkers Inform Every Step of Patient Journey



Modified with Permission

What do we call someone with positive AD biomarkers but no symptoms?

DOI: 10.1002/alz.13859

RESEARCH ARTICLE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup

Clifford R. Jack Jr.[1] | J. Scott Andrews[2] | Thomas G. Beach[3] | Teresa Buracchio[4] | Billy Dunn[5] | Ana Graf[6] | Oskar Hansson[7,8] | Carole Ho[9] | William Jagust[10] | Eric McDade[11] | Jose Luis Molinuevo[12] | Ozioma C. Okonkwo[13] | Luca Pani[14] | Michael S. Rafii[15] | Philip Scheltens[16] | Eric Siemers[17] | Heather M. Snyder[18] | Reisa Sperling[19] | Charlotte E. Teunissen[20] | Maria C. Carrillo[18]

JAMA Neurology | Special Communication

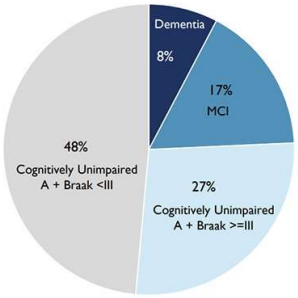
Alzheimer Disease as a Clinical-Biological Construct—An International Working Group Recommendation

Bruno Dubois, MD, MSc; Nicolas Villain, MD, PhD; Lon Schneider, MD, MSc; Nick Fox, MD, MA; Noll Campbell, PharmD, MSc; Douglas Galasko, MD, MSc; Miia Kivipelto, MD, PhD; Frank Jessen, MD; Bernard Hanseeuw, MD, PhD; Mercè Boada, MD, PhD; Frederik Barkhof, MD, PhD; Agneta Nordberg, MD, PhD; Lutz Froelich, MD, PhD; Gunhild Waldemar, MD, DMSc; Kristian Steen Frederiksen, MD, PhD; Alessandro Padovani, MD, PhD; Vincent Planche, MD, PhD; Christopher Rowe, MD; Alexandre Bejanin, PhD; Agustin Ibanez, PhD; Stefano Cappa, MD; Paulo Caramelli, MD, PhD; Ricardo Nitrini, MD, PhD; Ricardo Allegri, MD, PhD; Andrea Slachevsky, MD, PhD; Leonardo Cruz de Souza, MD, PhD; Andrea Bozoki, MD; Eric Widera, MD; Kaj Blennow, MD, PhD; Craig Ritchie, MD, PhD; Marc Agronin, MD; Francisco Lopera, MD; Lisa Delano-Wood, PhD; Stéphanie Bombois, MD, PhD; Richard Levy, MD, PhD; Madhav Thambisetty, MD, DPhil; Jean Georges, BA; David T. Jones, MD; Helen Lavretsky, MD, MSc; Jonathan Schott, MD, BSc; Jennifer Gatchel, MD, PhD; Sandra Swantek, MD; Paul Newhouse, MD; Howard H. Feldman, MD; Giovanni B. Frisoni, MD

NIA-AA criteria defined this group as "preclinical AD"

IWG recommended "asymptomatic at-risk for AD"

Consensus: **Don't test patients without symptoms yet...**



Courtesy of Howard Feldman (AlzForum)

Take Home Points

- Many new biomarkers are available for Alzheimer's and related diseases.
- Blood biomarkers are rapidly improving access to Alzheimer's diagnosis.
- Scaling implementation while ensuring appropriate use is the current challenge.
- Biomarkers for many non-AD neurodegenerative diseases are still needed.

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Yann Cobigo
Marilu Gorno-Tempini
Hilary Heuer
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Bruce Miller
Kate Possin
Howie Rosen

UCSF Collaborators (cont):
Bill Seeley
David Soleimani-Meigooni
Salvatore Spina
Adam Staffaroni

Non-UCSF Collaborators:
Brad Boeve
Jeff Dage
Brad Dickerson
Lea Grinberg
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4-Repeat Tau 4RTNI Neuroimaging Initiative

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ALLFTD — ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration

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