”How dementia biomarkers changed my practice and how they will change yours”
CCD, November, 2023

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- Professor of Medicine (Neurology), University of Toronto;
- Scientific Director, CCNA (Canadian Consortium on Neurodegeneration in Aging);
- Director, Kimel Family Centre for Brain Health and Wellness and Clinical Trials Unit, Baycrest.
- Adjunct Professor of Neurology, McGill University
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- Fellow in Cognitive Neurology, Baycrest Health Sciences

Medicine
UNIVERSITY OF TORONTO

CCNA CCNV
Canadian Consortium on Neurodegeneration in Aging
Consortium canadien en neurodégénérescence associée au vieillissement

Baycrest 100 YEARS 1918-2018

U of T NEUROLOGY

Funding Support for Dr. Chertkow

- Dr. Chertkow is supported by a research chair from Baycrest Health Science and University of Toronto.
- Canadian Institutes for Health Research
  - Foundation Grant Award 2015-23
  - CIHR: PI of operating grant for CCNA,plus "BRAIN" big data and dementia operating grant
- Weston Foundation
- NIH, Bright Focus
- The 11 partners of the Canadian Consortium on Neurodegeneration in Aging (CCNA)contribute to the national program. I am Scientific Director of CCNA.

Mitigating Bias: All recommendations for clinical therapy have been suggested by the Canadian Consensus Conference on Diagnosis and Treatment of Dementia

Faculty/Presenter Disclosure

- **Relationships with commercial interests past five years:**
- Dr. Chertkow is co-investigator on pharma-sponsored clinical trials of Roche (Gantenerumab,Graduate), Immunotec, Anavex Life Sciences, Lilly (Donanemab), Alector, Biogen (aducanumab).
- Previous industrial honoraria over five years for advisory boards (Deposited to Rotman Research Institute), received from:
  - Biogen Inc.
  - Esai Inc.
  - Eli Lilly Inc.
  - No Funding support has been received for this presentation

Chertkow lab- prior to pandemic

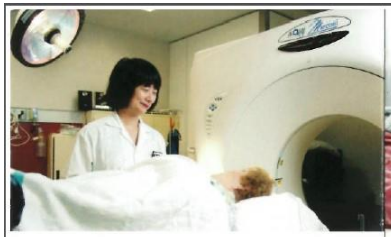
Paul Gauguin – “Where Do We Come From ? What Are We ? Where Are We Going ? “

Boston Museum of Fine Arts

My privileged position

- I have access to amyloid PET and tau PET done in the context of inclusion in pharma-sponsored clinical trials (Bank Family Clinical Trials Unit at Baycrest).
- I utilize (via Baycrest Memory Clinic) csf studies of amyloid beta 42, total-tau, phospho-tau- using clinical lab run by Dr. Mari De Marco at St. Pauls
- I have access to blood research Simoa studies of plasma GFAP, NfL, beta 42, total-tau, phospho-tau in collaboration with Dr. Cheryl Wellington, UBC (part of COMPASS-ND studies of CCNA).
- I get to look at many results emerging in the COMPASS-ND CCNA database – now partially released, soon full release.
- Many patients studied are also seen in the Ross Memory Disorders Clinic at Baycrest in Toronto.

COMPASS-ND national cohort



WHAT IS COMPASS–ND AND WHY SHOULD YOU VOLUNTEER?

COMPASS-ND is the largest Canadian study of dementia ever undertaken.

The goals of COMPASS-ND are: detecting dementia earlier; making diagnosis easier; predicting who is at risk for developing dementia.

Participating in COMPASS-ND does not prevent you from enrolling in drug studies. There are also therapeutic trials without drugs that are part of CCNA for which you may be eligible.

By enrolling in COMPASS-ND you will be making a valuable contribution to dementia research, which may lead to better treatments and prevention of dementia in the future.

WHAT WILL IT INVOLVE TO VOLUNTEER FOR COMPASS–ND?

This is a "longitudinal observational study". That means that we gather lots of information on each participant at the beginning, and then keep in touch with the participant and study partner over the coming years. We also invite you back after two years to have the same testing as you had at the beginning to assess any changes that may have occurred.

There are four or five visits involved at the start. Visits are arranged at your convenience at this Data Collection site. The research team will help cover your transportation costs.

The visits usually occur over three months, and involve the following procedures (each visit takes a morning).

VISIT #1: The study is explained in detail and the participant and study partner sign a consent form. A series of questions are asked about the participant's life and background. At the end of the visit, further forms are given to be filled out at home.

VISIT #2: More questions are asked, and we test hearing, vision, smell, walking, and strength. The doctor examines each participant, and we take samples of blood, urine, and saliva.

VISIT #3: Extended tests of thinking, memory, and attention are carried out by a psychologist over a three hour session.

VISIT #4: You are sent for an MRI brain scan. There are no injections involved. You lie i
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AND AFTER? WHAT HAPPENS THEN?

- If any of the tests find things that would affect your health, the information is transmitted to your own doctor.
- We will keep in touch with you each year, and ask you to return for reevaluation in two years.
- Brain Donation: None of us know what will happen to us in the future. If you (or any participant in COMPASS-
science tremendously to examine your brain. Most of our fundamental knowledge about Alzheimer's disease
comparing the brains of affected individuals with the brains of healthy individuals. So we encourage BRAIN D
COMPASS-ND. We have set up a set of brain banks across Canada to do specialized evaluation of the brains

Greetings!

You are reading this because your physician thinks that you or a family member might qualify to volunteer for the Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) study being carried out by the Canadian Consortium on Neurodegeneration in Aging (CCNA). You may have a problem with your memory, or simply be worried about memory loss, and you are old enough to be entered into this study.

CCNA Canadian Consortium on Neurodegeneration in Aging — CCNV Consortium canadien en neurodégénérescence associée au vieillissement

THANK YOU!

By volunteering to participate in our program, you have decided to actively contribute to finding a solution to Alzheimer's Disease and other Dementias, and the problem of memory loss in the elderly. The success of our program depends entirely on volunteers like you!

Please contact your local COMPASS-ND site for more information:

Address: _____

_____

Contact: _____

Telephone: _____

Fax: _____

Email: _____

CCNA Central Office
Jewish General Hospital
Lady Davis Research Institute
3755, Côte-Ste-Catherine Road,
Montreal (Quebec) H3T 1E2

Canadian Consortium on Neurodegeneration in Aging (CCNA)

The Comprehensive Assessment of Neurodegeneration and Dementia (COMPASS-ND) Study

www.ccna-ccnv.ca

Recruitment at 29 sites across Canada

DIAGNOSTIC CRITERIA FOR Probable Alzheimer's Disease (AD) [McKhann, Knopman, Chertkow et al, 2011]

Dementia established clinically, eg., deficit in two or more areas or cognition, interfering with daily life, progressing gradually

Insidious onset, worsening

No disturbance of consciousness

Onset any age

Absence of other brain or systemic disease that could account for the dementia

Not in presence of clear Vascular component, core features of DLB, FTD, other neuro illness

"The diagnosis of dementia due to Alzheimer's disease: Recommendations from the NIA and the Alzheimer's Association workgroup"-Guy M. McKhann, David S. Knopman, Howard Chertkow, et al., Alzheimer's & Dementia, 2011

Diagnosis of AD remains a clinical diagnosis, supported by lab tests.
Biomarker evidence can be supportive:
- **Biomarkers of Amyloid (a-beta) accumulation**
- **Biomarkers of neuronal degenereation or injury**

"We do not advocate the use of AD biomarker tests for routine diagnostic purposes at the present time"
- not standardized
- clinical criteria are good
- need more research
- access is limited

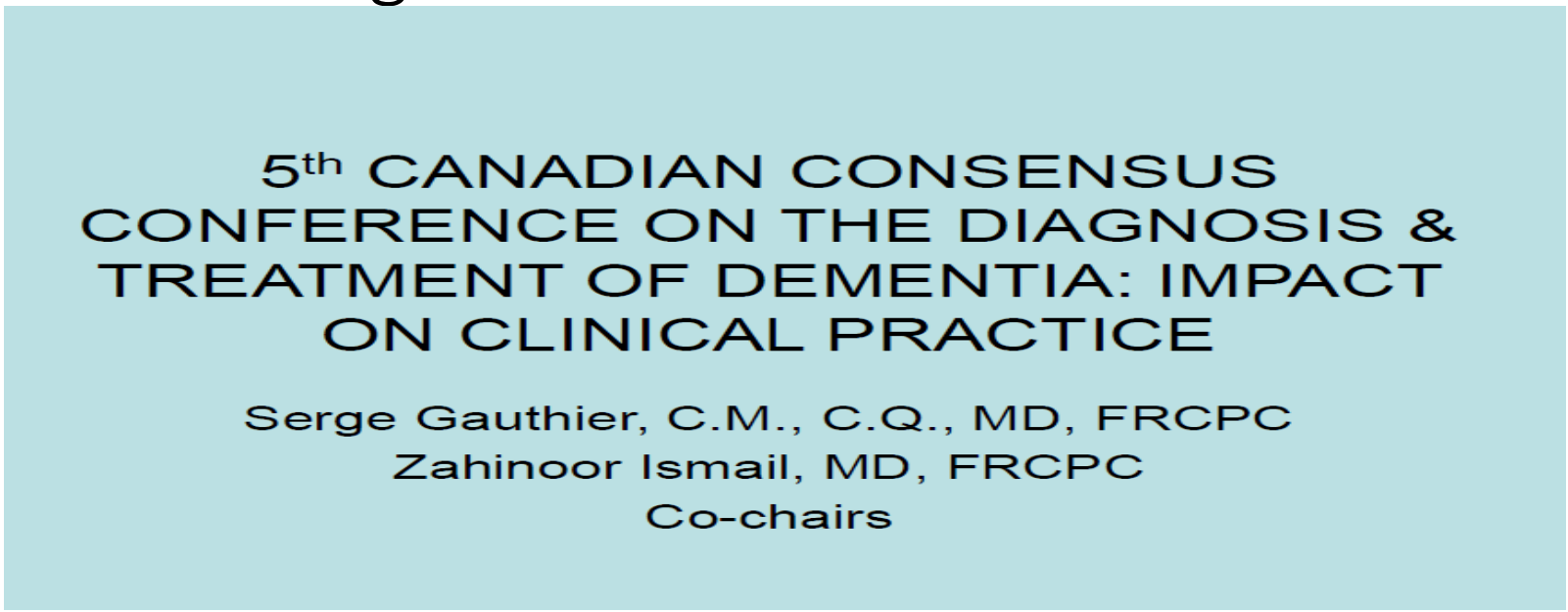
-but useful in clinical trials, research, and where available and "deemed appropriate by the clinician"

Similar guidelines from CCCDTD3-5 in Canada

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup
Marilyn S. Albert, Steven T. DeKosky, et al., Alzheimer's & Dementia, 2011

- "MCI of the Alzheimer's type": Mild memory symptoms (MCI). "It is ..important to incorporate this continuum of impairment into clinical and research practice."
- "MCI- Research criteria incorporating biomarkers"- biomarker evidence of AD (imaging and/or CSF= amyloid).

Alzheimer Disease dementia 2020 is still a clinical diagnosis



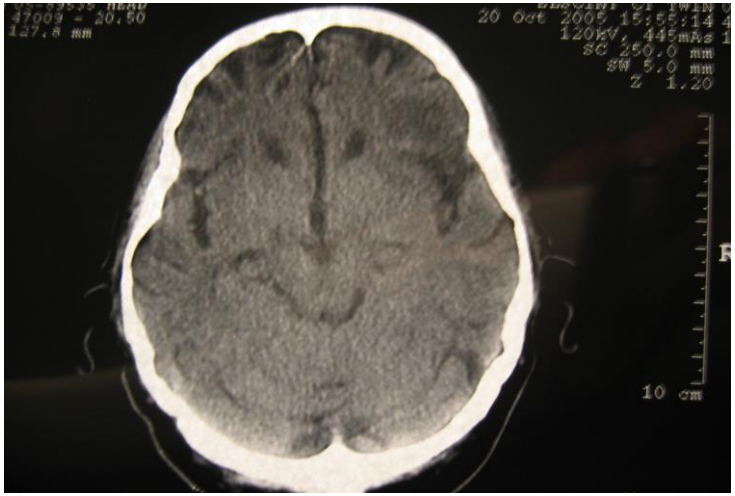
- A good clinician does not need biomarkers to make the diagnosis of AD.
- However: Imaging- to rule out other pathology, assess vascular contribution.

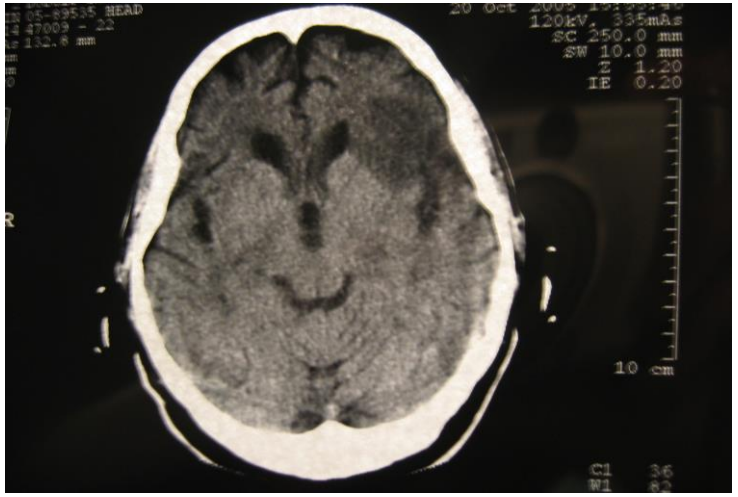
Click to edit Master title style

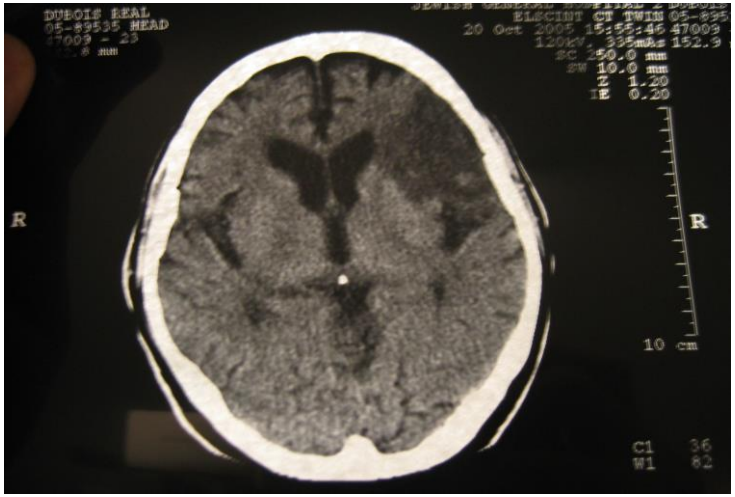
Standard evaluation in Memory Clinic done to exclude treatable causes of dementia and get the diagnosis

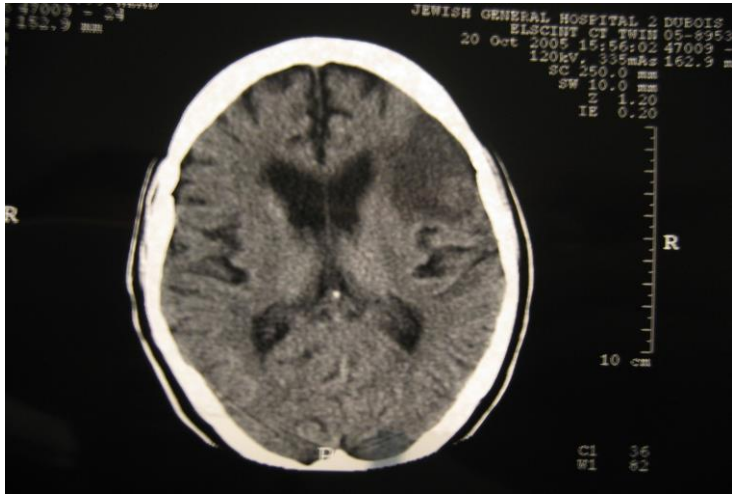
- **History**
- **Physical Exam and Mental Status (memory) testing**
- **Blood tests**
  - **VDRL, B12, Folate, Thyroid, metabolic screen, renal function**
- **Brain Imaging: CT scan sufficient, or MRI (to exclude tumor, hydrocephalus, infarcts, assess atrophy.**
- **Other tests not routinely done but useful in some cases:**
  - **EEG**
  - **Lumbar Puncture (Spinal tap) –especially for amyloid and tau**
  - **SPECT (Brain Blood flow) scan**
  - **PET (Positron Emission Tomography) brain scan**
  - **Genetic testing.**

Previous: Imaging to confirm clinically evident strokes as cause of cognitive decline









Case #1 (AA)

75 year old man with 13 years education; gradually progressive mild cognitive decline with memory, executive function loss, word-finding difficulty.

- Diagnosed “amnestic plus” MCI
- Chronic treated mild hypertension 140/90. No strokes.
- Family history of cardiac problems, stroke
- Exam – prominent grasp and primitive reflexes
- no lateralized weakness
- Blood tests, previous CT unremarkable

Case #1 (AA)

75 year old man with 13 years education; gradually progressive mild cognitive decline with memory, executive function loss, word-finding difficulty.

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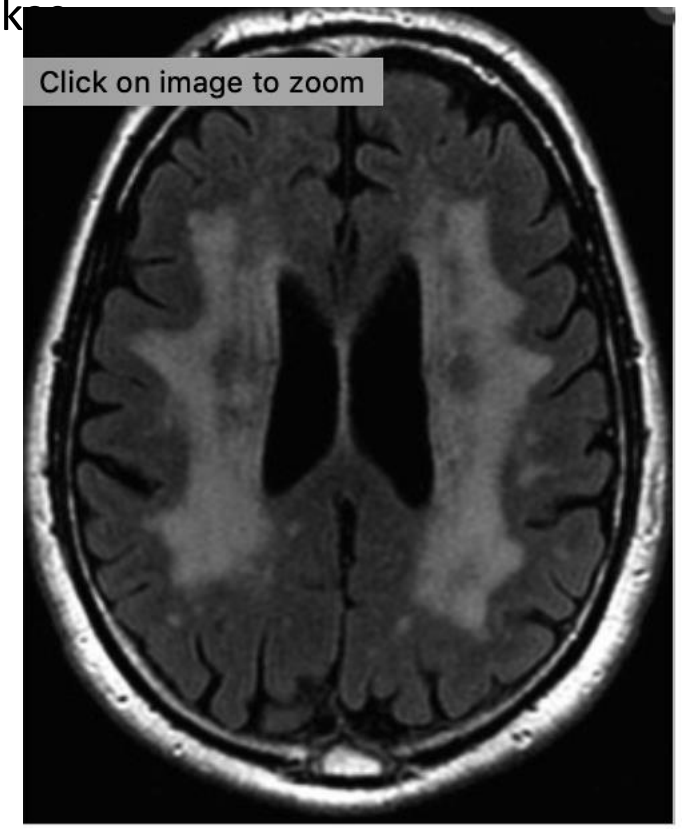
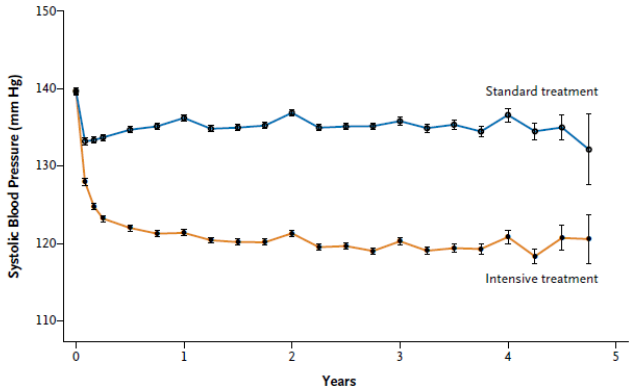


MRI shows confluent white matter changes, Fazekas 3
Diagnosis: Vascular MCI due to hypertension.
Treatment: More aggressive BP control

Systolic Blood Pressure Intervention Trial

N = 9361
Target group: age 50+, BP >130 mmHg and increased cardiovascular risk



Early interruption due to higher benefits intervention group (median follow-up 3.3 yrs)

Primary outcome was the first occurrence of myocardial infarction, acute coronary syndrome, stroke, heart failure, or death from cardiovascular causes (p<0.001)

SPRINT-MIND

Intensive blood pressure treatment significantly reduced the risk of MCI (19% lower rate) and combined outcome MCI + dementia (15% lower)

Oral presentation AAIC 2018

SPRINT Research Group, *NEJM 2016*

Critique of current clinical approach: We are missing pathology, we are misdiagnosing AD, we lack precision unless we use biomarkers on people who have dementia

Sensitivity and Specificity of clinical Diagnosis of probable AD (compared to brain pathological diagnosis after death) are only 70%

Why do we need biomarkers for Alzheimer's ?

J Neuropathol Exp Neurol
Copyright © 2012 by the American Association of Neuropathologists, Inc.
Vol. 71, No. 4
April 2012
pp. 266–273

ORIGINAL ARTICLE

Accuracy of the Clinical Diagnosis of Alzheimer Disease at National Institute on Aging Alzheimer Disease Centers, 2005–2010

Thomas G. Beach, MD, PhD, Sarah E. Monsell, PhD, Leslie E. Phillips, PhD, and Walter Kukull, PhD

	No AD pathology	Yes AD pathology	
No probable AD (clinical)	213	180	NPV=54 %
Probable AD (clinical)	88	438	PPV=83 %
	Specificity = 70.8%	Sensitivity = 70.9%	

- Clinical criteria for AD have poor diagnostic accuracy

doi:10.1093/brain/aww224 BRAIN 2016: 139; 2983–2993 | 2983

BRAIN
A JOURNAL OF NEUROLOGY

TDP-43 stage, mixed pathologies, and clinical Alzheimer's-type dementia

Bryan D. James,[1] Robert S. Wilson,[2,3] Patricia A. Boyle,[3] John Q. Trojanowski,[4] David A. Bennett[2] and Julie A. Schneider[2,5]

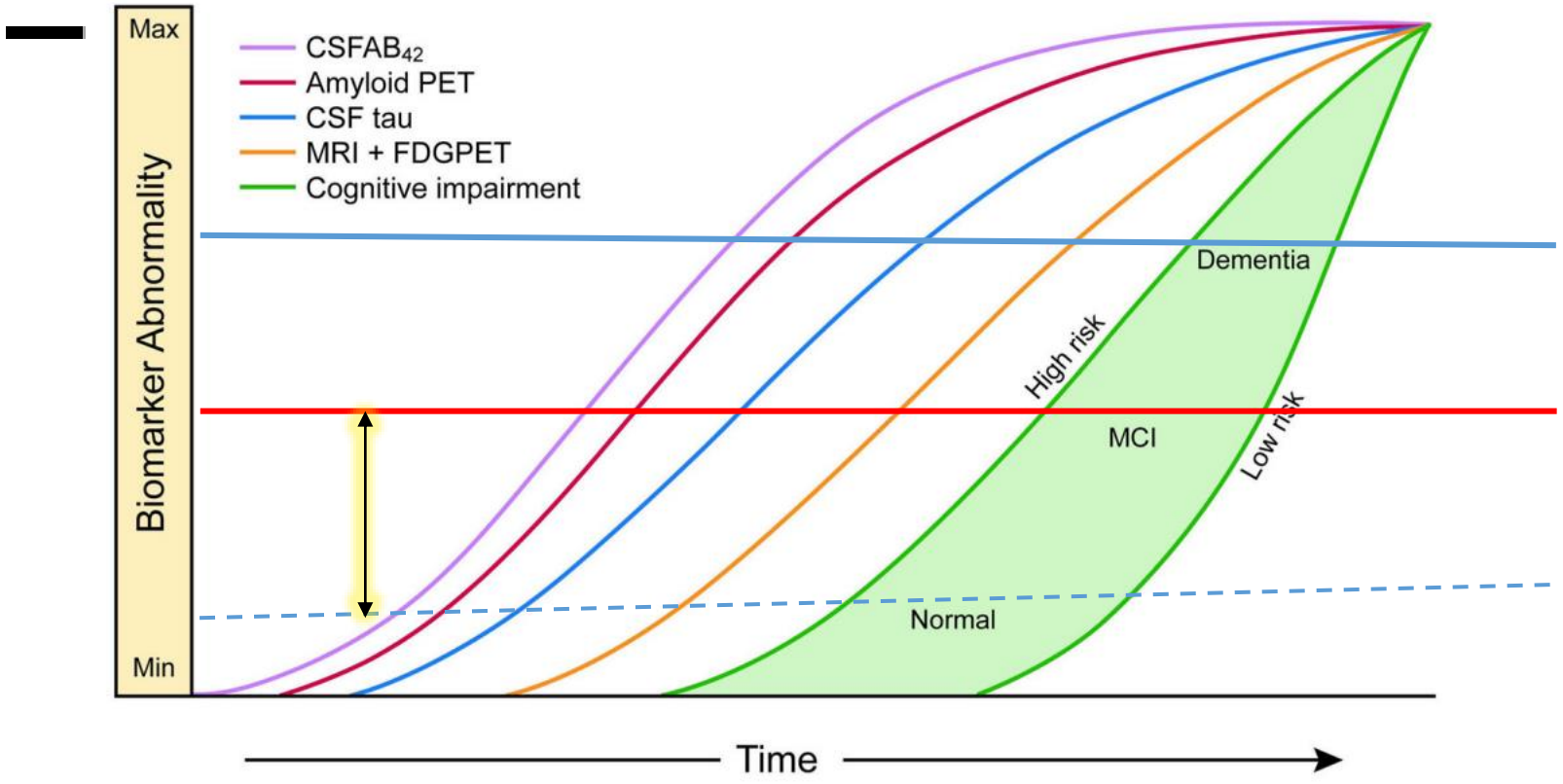
Clinically diagnosed late-onset AD cases have:

- Aβ plaques + PHF-tau – tangles 80 %
- TDP-43 inclusions 65 %
- α-synuclein / Lewy bodies 34 %
- Cerebrovascular pathology 30-57 %
- Hippocampal sclerosis 20 %

+ Neuronal and synaptic degeneration

- Late-onset Alzheimer-type dementia show multiple pathologies in different combinations

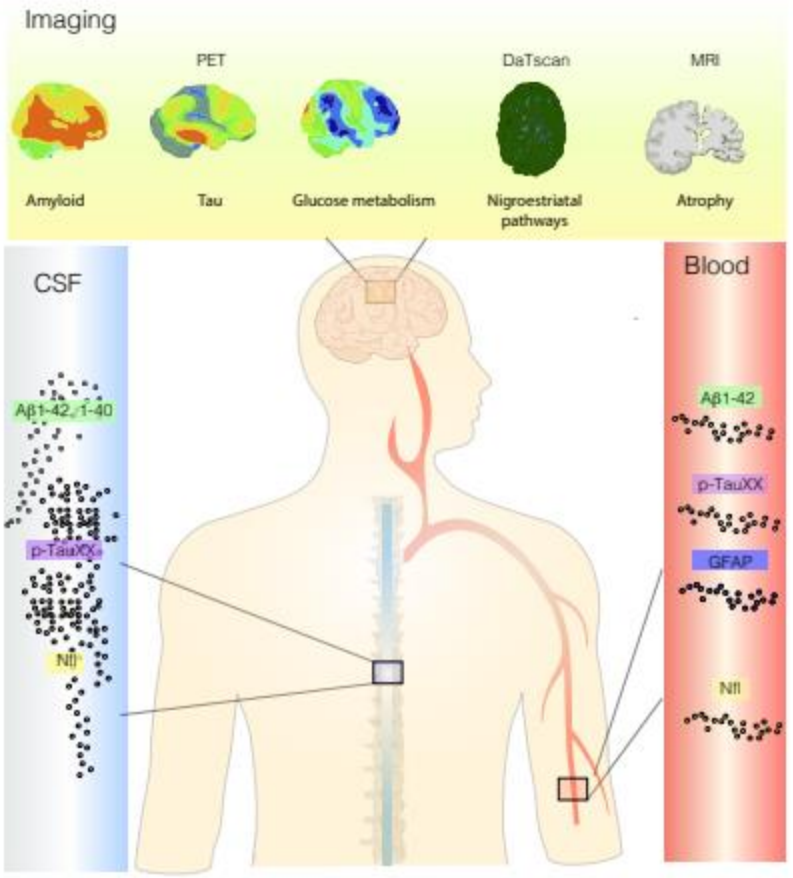
Hypothesized progression of AD biomarkers over time



Cliff Jack & colleagues, 2012

"If there's no abnormal amyloid, then it isn't Alzheimer Disease".- Dr. Clifford Jack, 2012

Visual overview of biomarker testing available on a research basis (and increasingly, clinical)

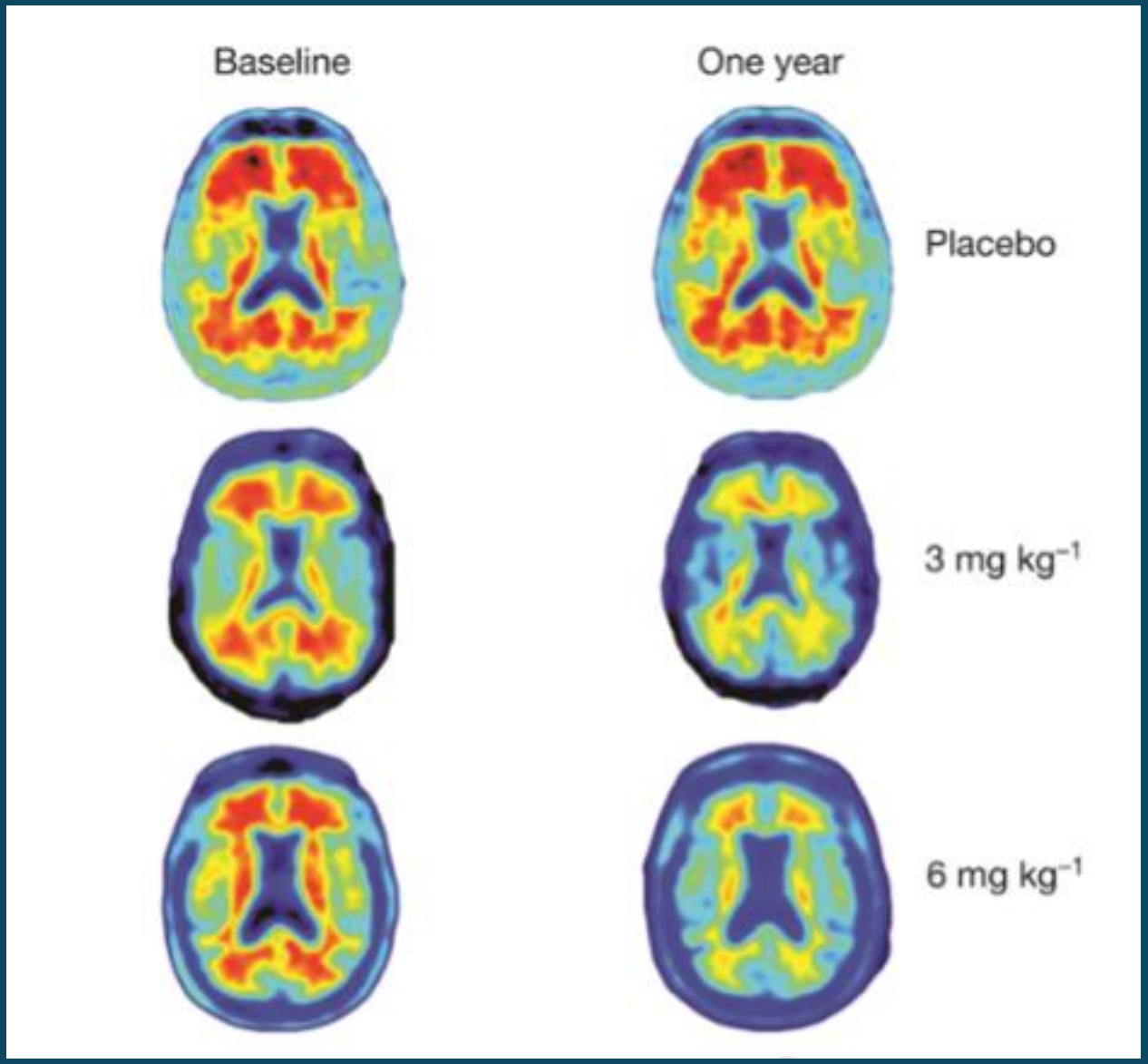


Visual overview of biomarker testing reviewed throughout Part II.

TABLE 1. AMYLOID-TAU-NEURODEGENERATION CLASSIFICATIONS	
NIA-AA Research Framework	
Amyloid (A)	Cerebrospinal fluid Aβ42, or Aβ42/Aβ40 ratio
	Amyloid-positron emission tomography
Tau (T)	Cerebrospinal fluid phosphorylated-tau
	Tau positron emission tomography
Neuro-degener-ation (N)	Anatomic MRI
	Fluorodeoxyglucose-positron emission tomography
	Cerebrospinal fluid total tau
Clinical Linkages for Individuals With Symptoms	
$A^+T^+N^-$	Prodromal Alzheimher's disease/mild cognitive impairment due to Alzheimer's disease
$A^+T^+N^+$	Alzheimer's disease dementia (can still be mixed dementia)
$A^-T^+N^-$	Cerebrovascular disease, prion disease, early tauopathies
$A^-T^+N^+$	Vascular dementia, tauopathies, dementia with Lewy bodies, primary age-related tauopathy
$A^-T^-N^+$	Limbic-predominant age-related TDP-43 encepha-lopathy

Gauthier and Rosa-Neto, Practical Neurology, June 2019

Aducanumab clearly leads to amyloid removal!



Sevigny,J. (2016) Nature, PMID 27582220

The proposed new NIA-AA 2023 AD criteria: A and T, less N.

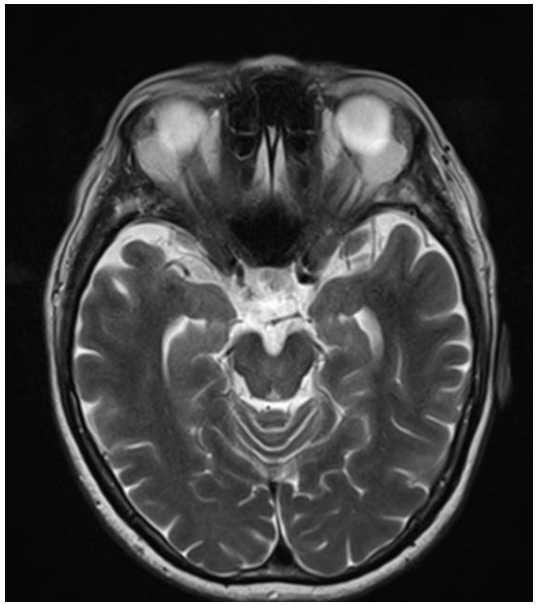
Biomarker category	fluid	imaging
Core Biomarkers		
A (Ab proteinopathy)	Ab42/40	Amyloid PET
T (AD tau proteinopathy)	ptau 181, 217	Tau PET
Non - specific biomarkers of tissue reaction involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MR, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD co-pathology		
V vascular brain injury		Anatomic infarction, WMH, abundant dilated perivascular spaces
S α-synuclein	αSyn-SAA*	

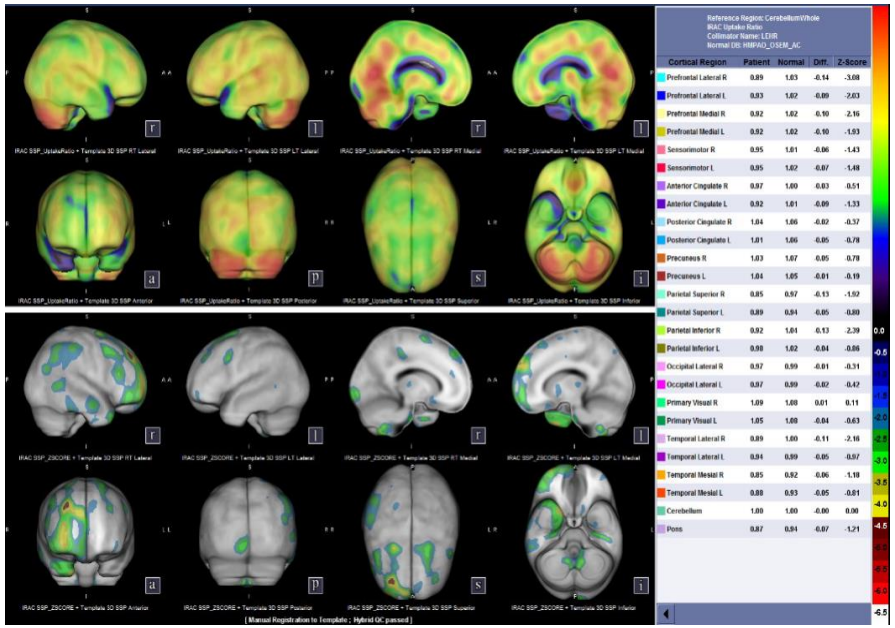
From ATN To ATNIVS. *In the proposed new scheme—which is currently a draft meant to solicit input from the ADRD research community—A and T are the core biomarkers for diagnosis and staging. The draft scheme also recognizes an expanded suite of additional markers that detect non-specific disease responses and co-pathologies. [Courtesy of NIA-AA working group.]*

Amyloid alone now = sufficient to diagnose Alzheimer Disease!

Case #2 (MP)

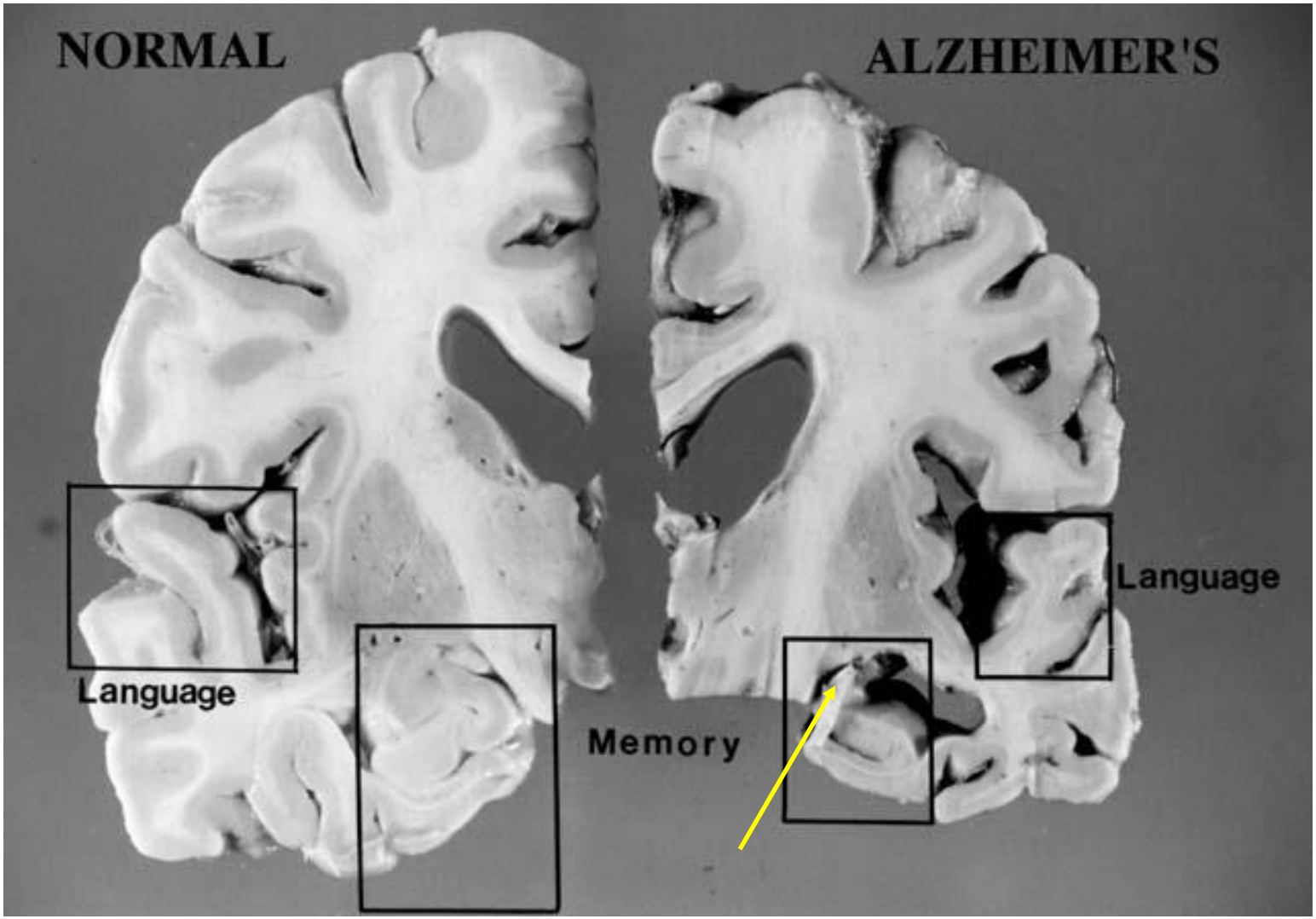
64 year old lady with high education; progressive cognitive decline in last 5 years with impaired IADLs; Episodic memory, attention and execution affected; positive family history; MoCA 18/30





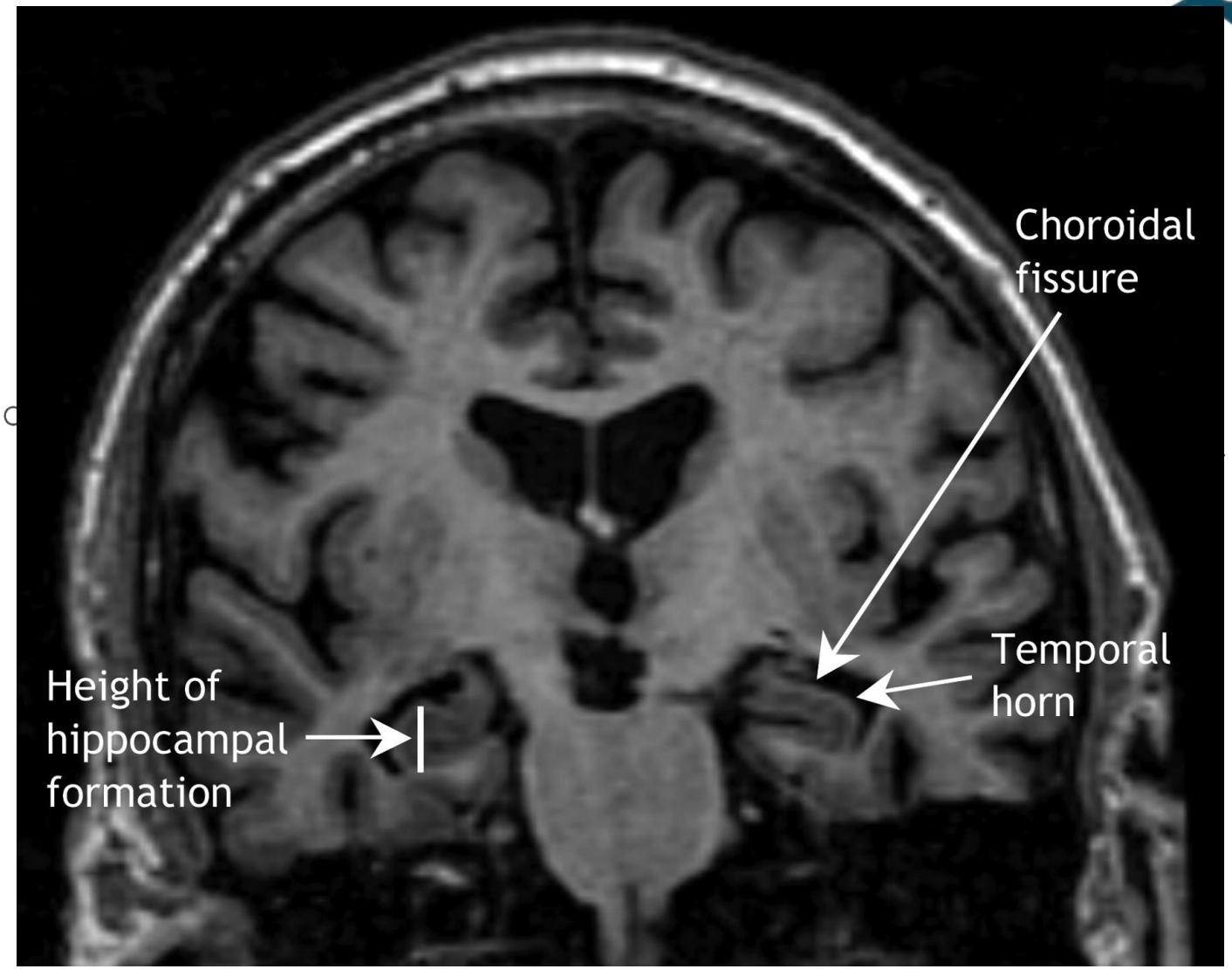
MRI showed gradually only mild atrophy of medial temporal lobes

Atrophy in Alzheimer's disease



Atrophy of the brain in AD: Medial temporal lobes are affected first and most severely

T1-weighted coronal magnetic resonance imaging scan showing extensive hippocampal atrophy (arrows).



Feldman, H. H. et al. CMAJ 2008;178:825-836.

Medial Temporal Atrophy Rating Algorithm

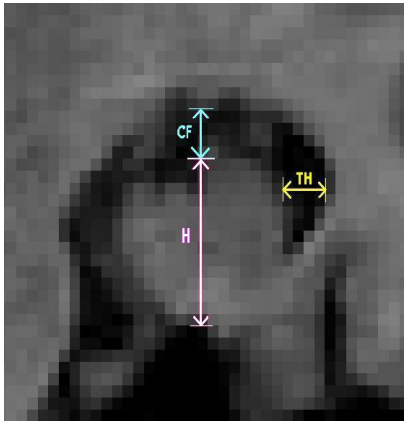
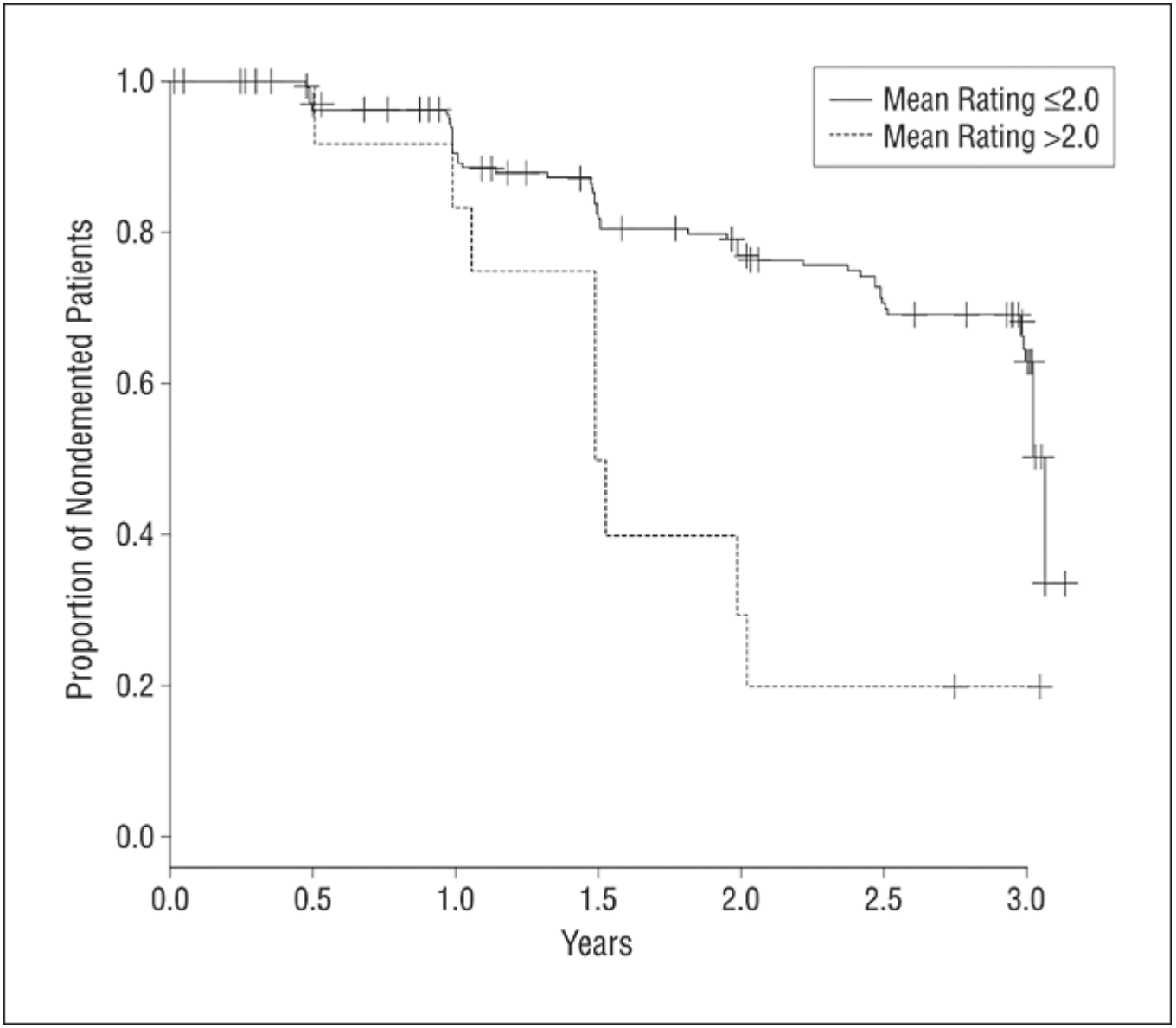


Table 1. Medial Temporal Atrophy Rating Algorithm

Score	Width of Choroidal Fissure	Width of Temporal Horn	Height of Hippocampus
0	Normal	Normal	Normal
1	Mildly widened	Normal	Normal
2	Moderately widened	Mildly widened	Mildly reduced
3	Markedly widened	Moderately widened	Moderately reduced
4	Markedly widened	Markedly widened	Markedly reduced

DeCarli, C. et al. Arch Neurol 2007;64:108-115.

Qualitative Estimates of Medial Temporal Atrophy, DeCarli et al., 2007



ST. PAUL'S HOSPITAL
PROVIDENCE HEALTH CARE

Department of Pathology and Laboratory Medicine

Dr. Mari DeMarco
St Paul's Hospital
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1081 Burrard St, Vancouver, BC V6Z 1Y6
Tel 604 806 8470 Fax 604 806 9681

Date of report September 15, 2022

Ordering physician Dr. Howard Chertkow
Baycrest-Kimel Family Bldg, Fax 416-785-2484

[redacted]

Neurodegenerative Profile, CSF

Results

Biomarker, Ratio, Profile	Result	Reference value
Aβ42	**892 ng/L**	> 1030 ng/L
Phospho tau	14 ng/L	< 28 ng/L
Total tau	162 ng/L	< 301 ng/L
Phospho tau/Aβ42 ratio	0.0157	< 0.024
Total tau/Aβ42 ratio	0.182	< 0.29

Interpretation **The biomarker profile is consistent with an amyloid beta pathology. Please advise if the clinical scenario warrants additional testing of the Abeta 42/40 ratio.**
Biomarker results require interpretation in the context of other medical information.

CSF analysis

A-beta 42: **739 ng/L (> 1030 ng/L)**

p-tau: **52 ng/L** (<28 ng/L)

Total tau: **471 ng/L** (<301 ng/L)

p-tau/A-beta 42: **0.0704** (<0.024)

Total tau/ A-beta 42: **0.637** (<0.29)

A+ T+ N+

The biomarker profile consistent with an **Alzheimer's** pathology, consistent with typical presentation of AD.

CSF analysis

A-beta 42: **739 ng/L (> 1030 ng/L)**

p-tau: **52 ng/L** (<28 ng/L)

Total tau: **471 ng/L** (<301 ng/L)

p-tau/A-beta 42: **0.0704** (<0.024)

Total tau/ A-beta 42: **0.637** (<0.29)

The biomarker profile consistent with an **Alzheimer's** pathology, consistent with typical presentation of AD.

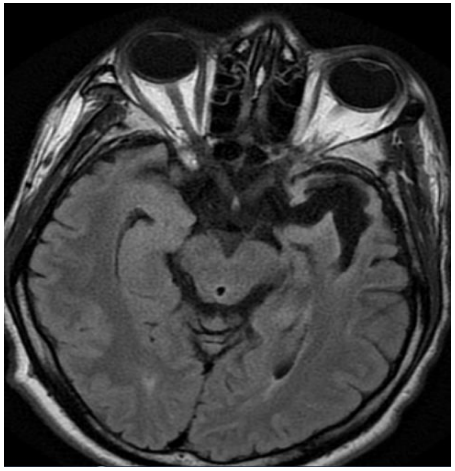
High likelihood of AD.

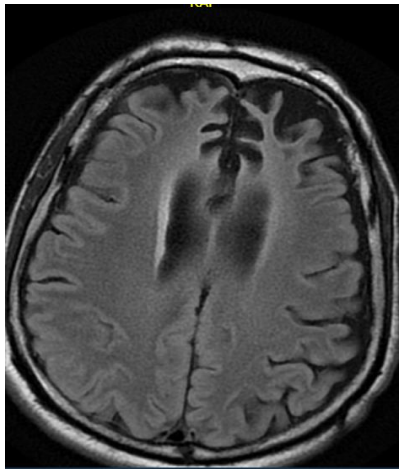
Patient enrolled into clinical trial of an anti-amyloid disease-modifying therapy – ongoing.

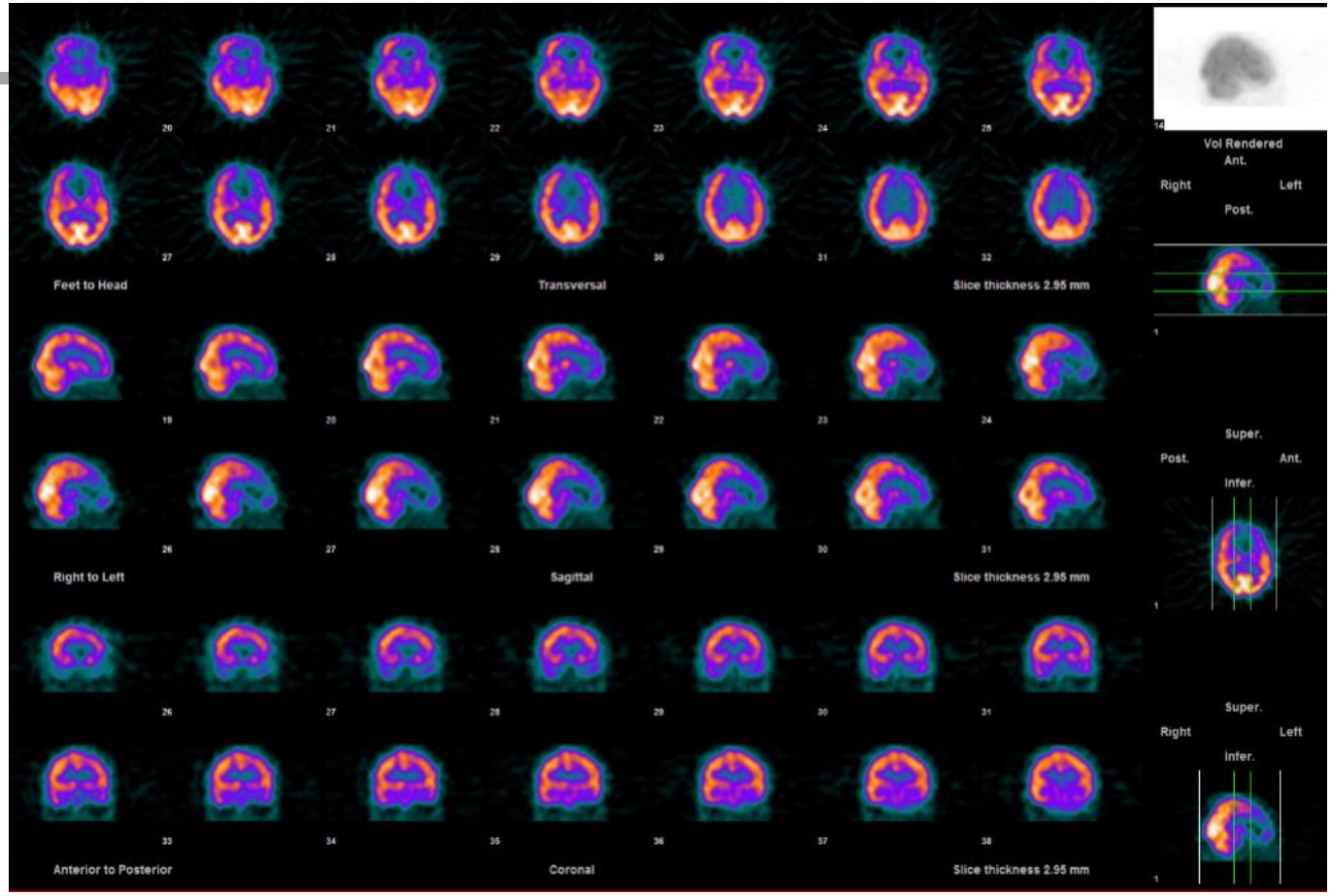
Case #3 (DG)

51 year old man with 12 years education; negative family history.

- Rapidly progressive behavioral abnormalities (apathy and withdrawal) alongside cognitive decline with memory, speech-language and executive difficulties for 6 months; MoCA 11/30.
- Normal blood workup, including asculitis, VDRL, HIV.







SPECT: Marked frontal abnormalities, decreased perfusion
?FTD

CSF analysis

A-beta 42: 892 ng/L (> 1030 ng/L)

p-tau: 34 ng/L (<28 ng/L)

Total tau: 162 ng/L (<301 ng/L)

p-tau/A-beta 42: 0.070 (<0.024)

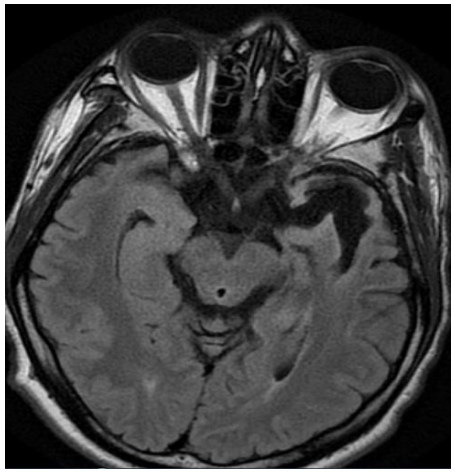
A+ T+ N+

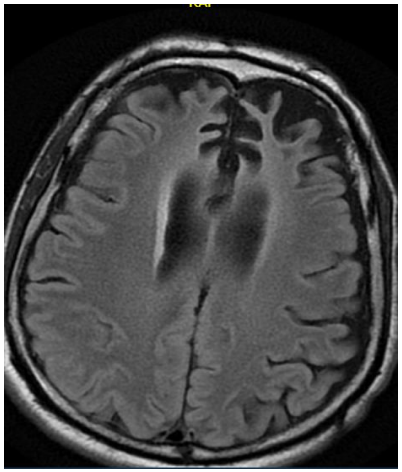
The biomarker profile consistent with an **amyloid beta** pathology, consistent with atypical presentation of AD.

Diagnosis: Alzheimer Disease, early onset, cause unknown – entered into anti-amyloid clinical trials.

Case #3 (DA)

59 year old man with 17 years education; rapidly progressive problems with memory, speech-language and executive difficulties for 18 months; MoCA 21/30





MRI Showing mild medial temporal lobe atrophy. SPECT normal.

CSF analysis

A-beta 42: 640 ng/L (> 1030 ng/L)

p-tau: 37 ng/L (<28 ng/L)

Total tau: 162 ng/L (<301 ng/L)

A+ T+ N+

The biomarker profile consistent with an **amyloid beta** pathology, consistent with atypical presentation of AD.

Diagnosis: Alzheimer Disease, mild.

Note: Simoa TDP43 shows elevation, 14,084 pg/mL (normal below 8,000).

Given high degree of certainty, he is opting for MAID when MMSE falls below 20

Academic question: Is TDP43 contributing to early age onset AD?

Typical dementia case with PET scans showing abnormal load of neurofibrilary tangles (a), amyloid (b) and presence of neuronal injury (c).

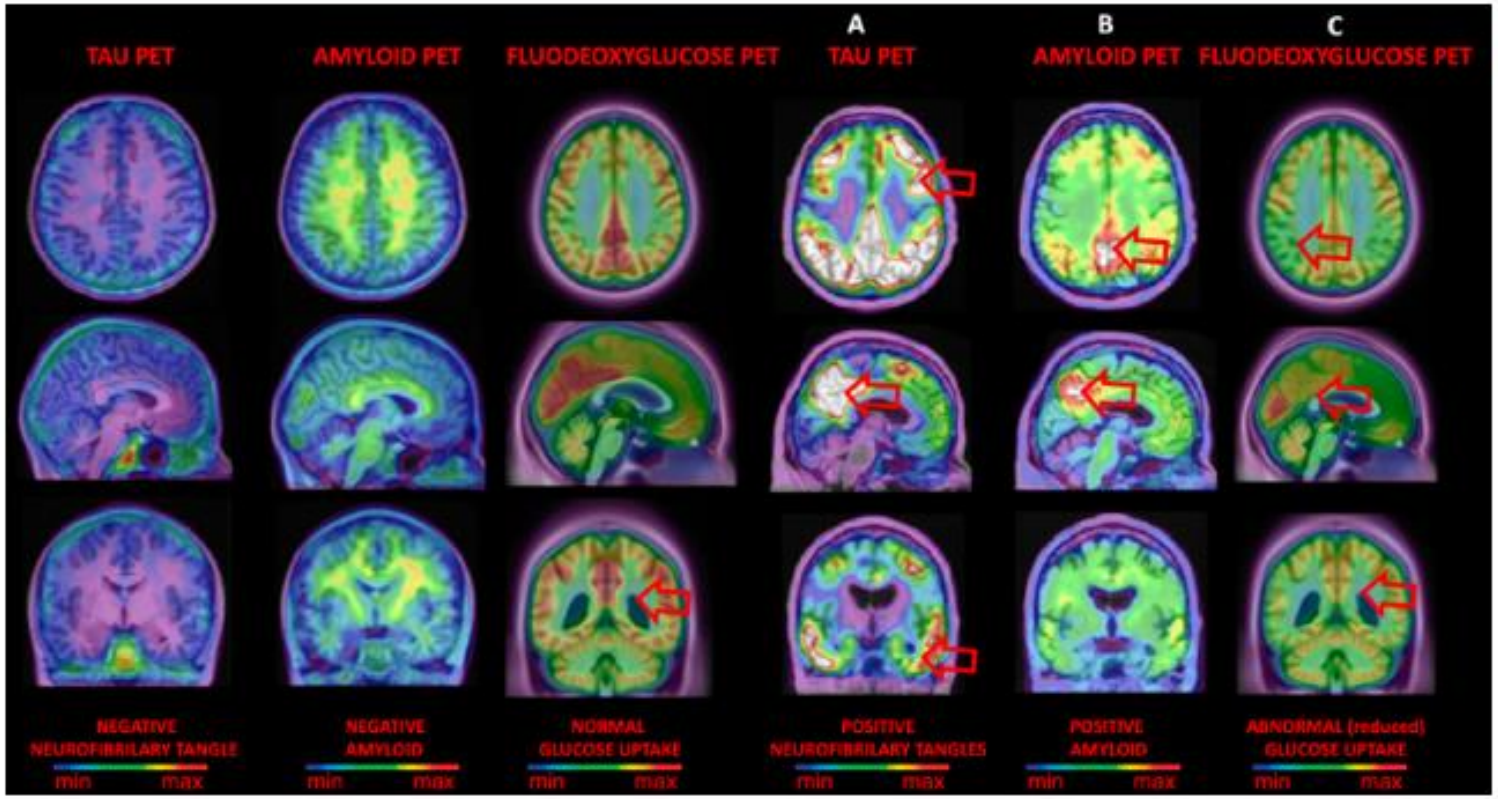
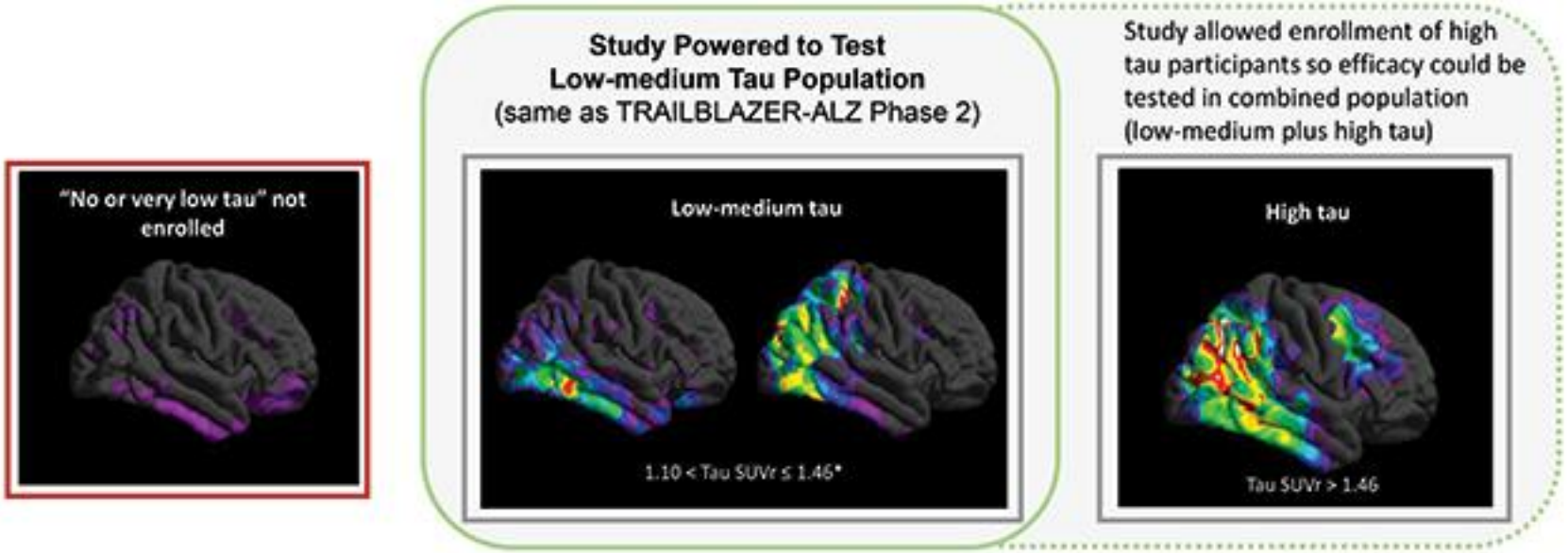


Figure 3. Typical dementia case with PET scans showing abnormal load of neurofibrilary tangles (a), amyloid (b) and presence of neuronal injury (c).



***Slice and Dice by Tau**. The Trailblazer-Alz2 trial focused on people with low to intermediate tangle load (middle), Gains were smaller in a high-tau group (right).*

- Tau PET : MTL and perirhinal uptake early in the AD disease.
- Donanemab Phase 3 Trailblazer-Alz2 – Lilly
- Tau PET level determines efficacy of the anti-amyloid drug.
- Tau PET as possible predictor of response to anti-amyloid drugs?

- Note: Starting two new trials of anti-tau medications in the Bank Clinial Trials Research Unit at Baycrest

PET AMYLOID PLAQUE BURDEN ASSESSMENT

PET Tracer

Neuraceq® (Florbetaben)

SECTION 1: AMYLOID PLAQUE BURDEN

1. Is the PET exam A β+ (positive)?

● Yes ○ No ○ Not Assessable

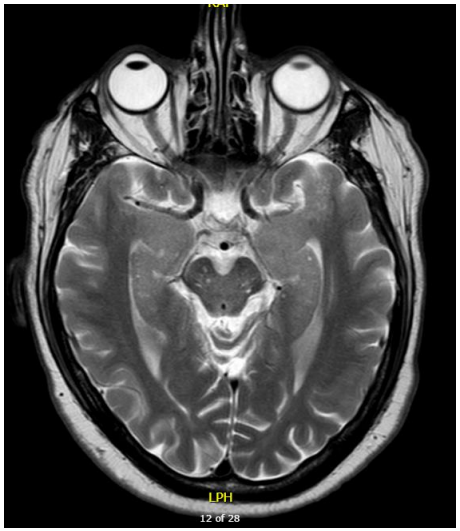
1a. If Not Assessable, please provide reason:

1b. If Yes, specify location(s) that most influenced decision (check all that apply):

Florbetaben (Neuraceq)	Flutemetamol (Vizamyl)	Florbetapir (Amyvid)	PIB	NAV4694
■ Lateral Temporal	❒ Frontal Lobes (axial, with optional sagittal plane view)	❒ Frontal Cortex (excluding midline)	❒ Frontal Cortex (excluding midline)	❒ Frontal Cortex (excluding midline)
■ Frontal Lobes	❒ Posterior Cingulate and Precuneus (sagittal, with optional coronal plane view)	❒ Medial Frontal Cortex (including Anterior Cingulate)	❒ Medial Frontal Cortex (including Anterior Cingulate)	❒ Medial Frontal Cortex (including Anterior Cingulate)
■ Posterior Cingulate/ Precuneus	❒ Lateral Temporal Lobes (axial, with optional	❒ Parietal Cortex (excluding midline)	❒ Parietal Cortex (excluding midline)	❒ Parietal Cortex (excluding midline)
■ Parietal Lobes		❒ Medial Parietal Cortex (Precuneus and/or Posterior Cingulate)	❒ Medial Parietal Cortex (Precuneus and/or Posterior Cingulate)	❒ Medial Parietal Cortex (Precuneus and/or Posterior Cingulate)
❒ Other Region (specify):		❒ Temporal Cortex	❒ Temporal Cortex	❒ Temporal Cortex
		❒ Occipital	❒ Occipital	❒ Occipital

Case #4 (WDC)

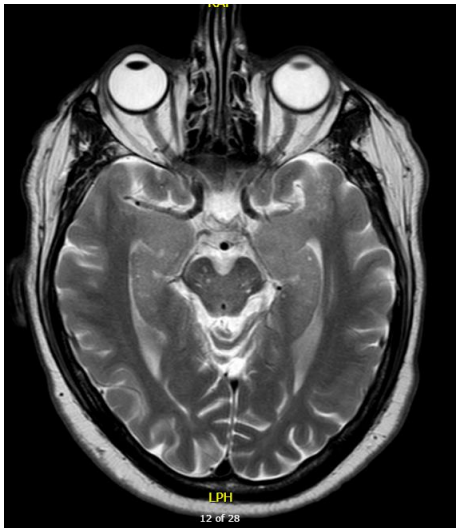
- 72 year old gentleman with slowly progressive episodic memory loss for 5 years
- Preserved executive function and language.
- Considered for inclusion in anti-amyloid clinical trials but….



Amyloid PET: Negative
Tau PET: Negative

Case #2 (WDC)

- 72 year old gentleman with slowly progressive episodic memory loss for 5 years
- Preserved executive function and language.
- Considered for inclusion in anti-amyloid clinical trials but….

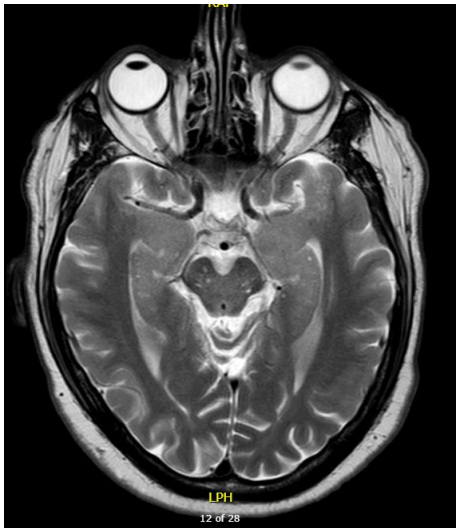


Amyloid PET: Negative
Tau PET: Negative

A- T- N-

Case #2 (WDC)

- 72 year old gentleman with slowly progressive episodic memory loss for 5 years
- Preserved executive function and language.
- Considered for inclusion in anti-amyloid clinical trials but….

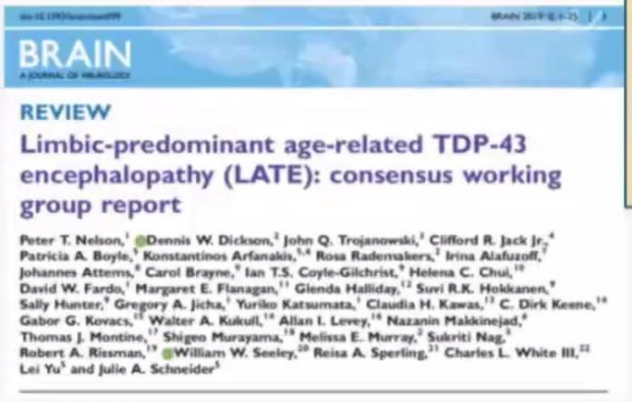


Amyloid PET: Negative
Tau PET: Negative

A- T- N-

Recent: TDP43 by Simoa (Wellington)for research:
TDP level elevated at 13,679 pg/mL!

LATE suspected as diagnosis


BRAIN

REVIEW

Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

Peter T. Nelson, Dennis W. Dickson, John Q. Trojanowski, Clifford R. Jack Jr., Patricia A. Boyle, Konstantinos Arfanakis, Rosa Rademakers, Irina Alafuzoff, Johannes Attems, Carol Brayne, Ian T.S. Coyle-Gilchrist, Helena C. Chui, David W. Fardo, Margaret E. Flanagan, Glenda Halliday, Sivi R.K. Hokkanen, Sally Hunter, Gregory A. Jicha, Yuriko Katsumata, Claudia H. Kawas, C. Dirk Keene, Gabor G. Kovacs, Walter A. Kukull, Allan I. Levey, Nazanin Makkinejad, Thomas J. Montine, Shigeo Murayama, Melissa E. Murray, Sukriti Nag, Robert A. Rissman, William W. Seeley, Reisa A. Sperling, Charles L. White III, Lei Yu and Julie A. Schneider

Based on work by
Drs Keith Josephs…
Dennis Dickson
(Mayo Clinic)

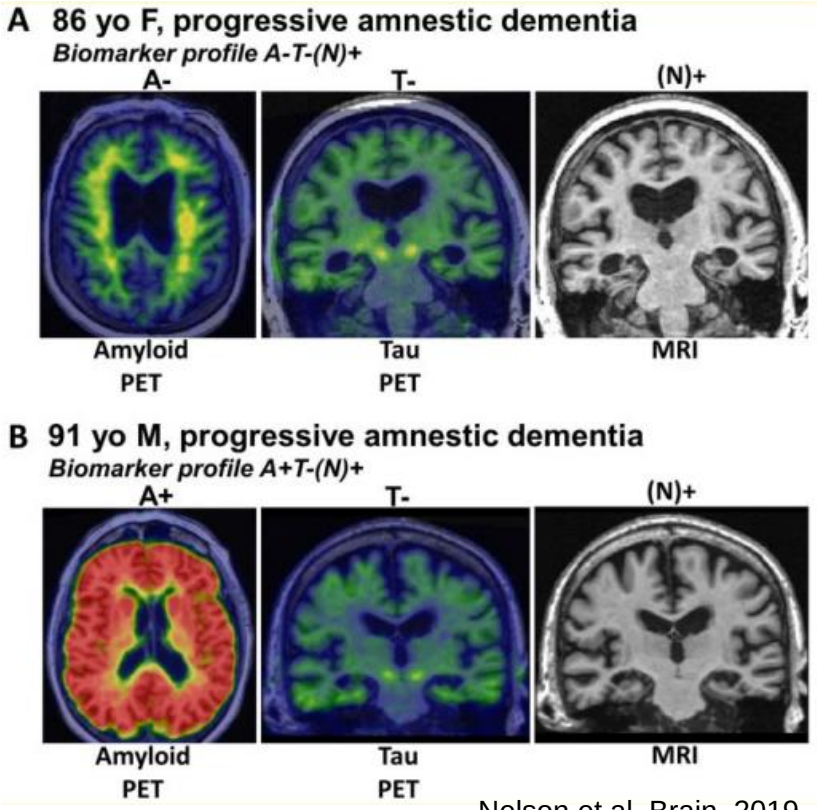
Neuropathology-based diagnosis, classification, and staging

LATE-NC featu

- A sampling [illegible]ging system for routine autopsy diagnosis is proposed to characterize the anatomical distribution of TDP-43 proteinopathy
  - Stage 1: amygdala only
  - Stage 2: + hippocampus
  - Stage 3: + middle frontal gyrus
- Hippocampal sclerosis pathology may be observed (and should be reported), but is neither necessary nor sufficient for diagnosis of LATE-NC

Diagnosis: Limbic-Associated TDP43 Encephalopathy

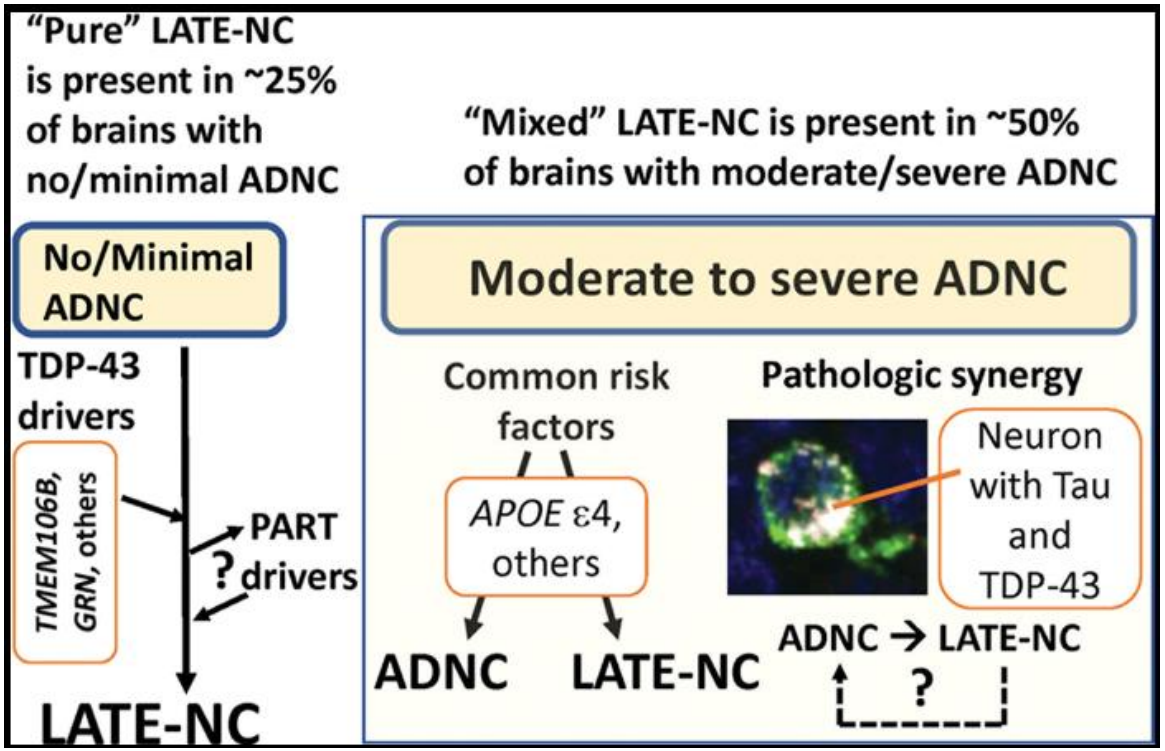
LATE



Nelson et al, Brain, 2019

Present in >20% (up to 50%) of individuals past age 80 years according to large community-based autopsy series.

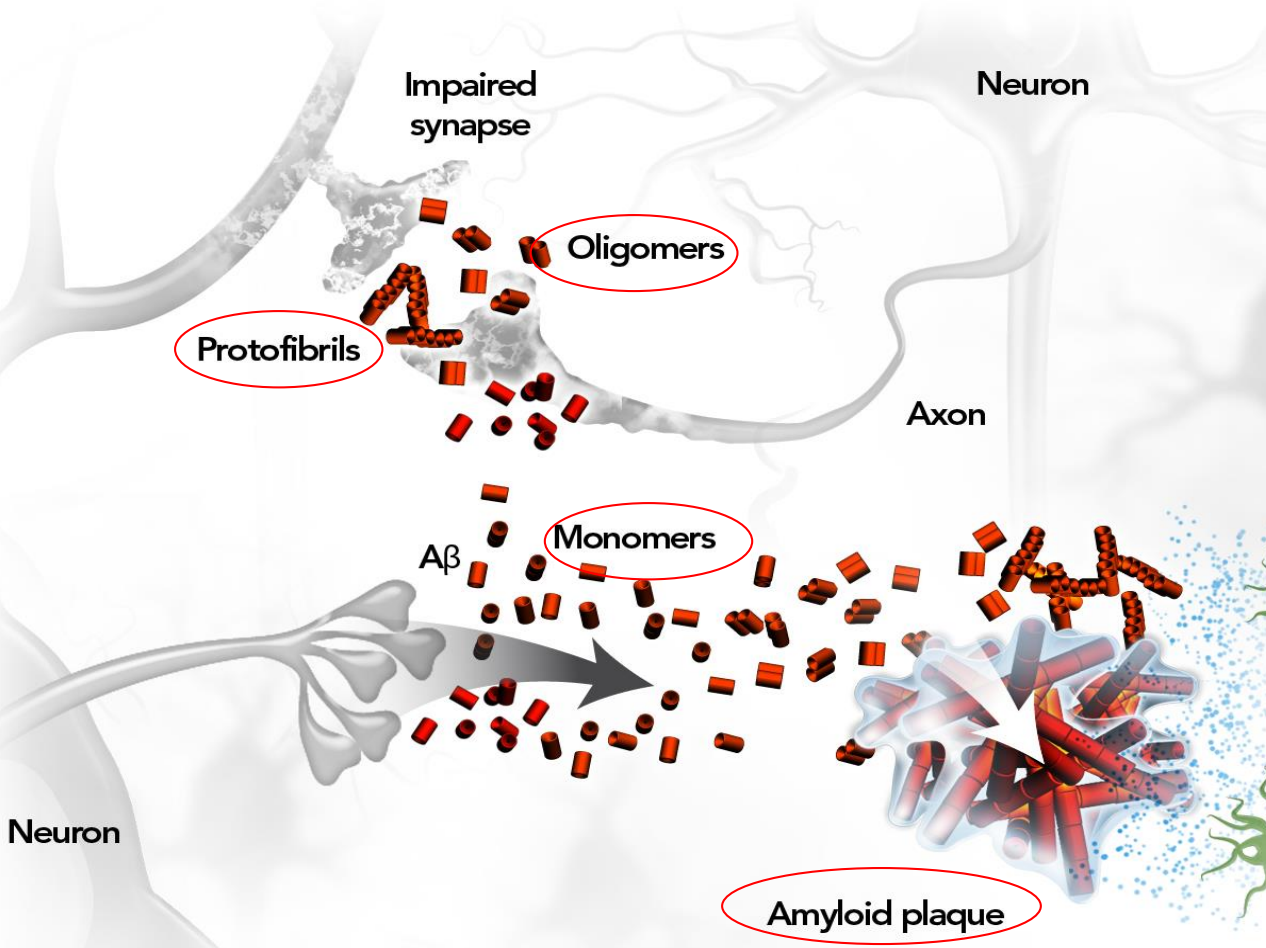
Associated with substantial disease-specific cognitive impairment, usually an amnestic dementia syndrome (‘dementia of the Alzheimer’s type’)



LATE-NC was seen in almost 40% of participants and often, but not always, coexisted with Alzheimer's disease neuropathology.

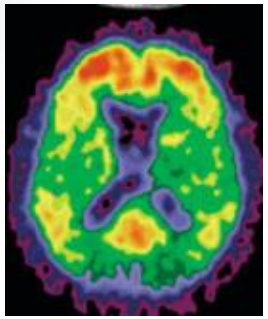
Nelson et al, Acta Neuropath, 2022

Amyloid Targets: Aβ Aggregates and Plaques



Soluble Species
Monomers
Oligomers

Insoluble Species
Protofibrils
Neuritic Plaques



In-vivo imaging of fibrillar amyloid

Mucke, 2009; LaFerla, 2007

January 2023: FDA approves Leqembi(lecanemab) under accelerated approval program

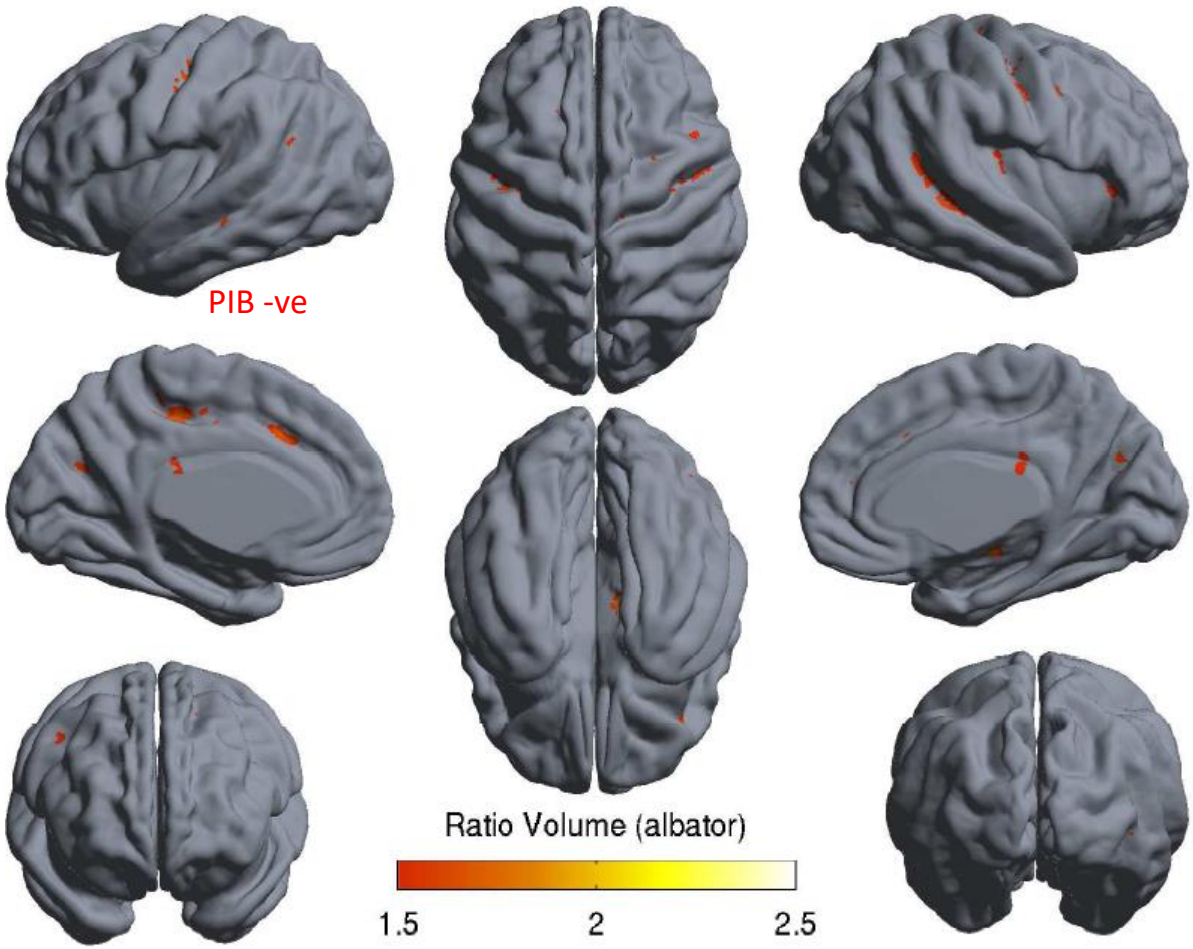
FDA Approves LEQEMBI™ (lecanemab-irmb) Under the Accelerated Approval Pathway for the Treatment of Alzheimer's Disease

JANUARY 6, 2023 • NEWS RELEASE

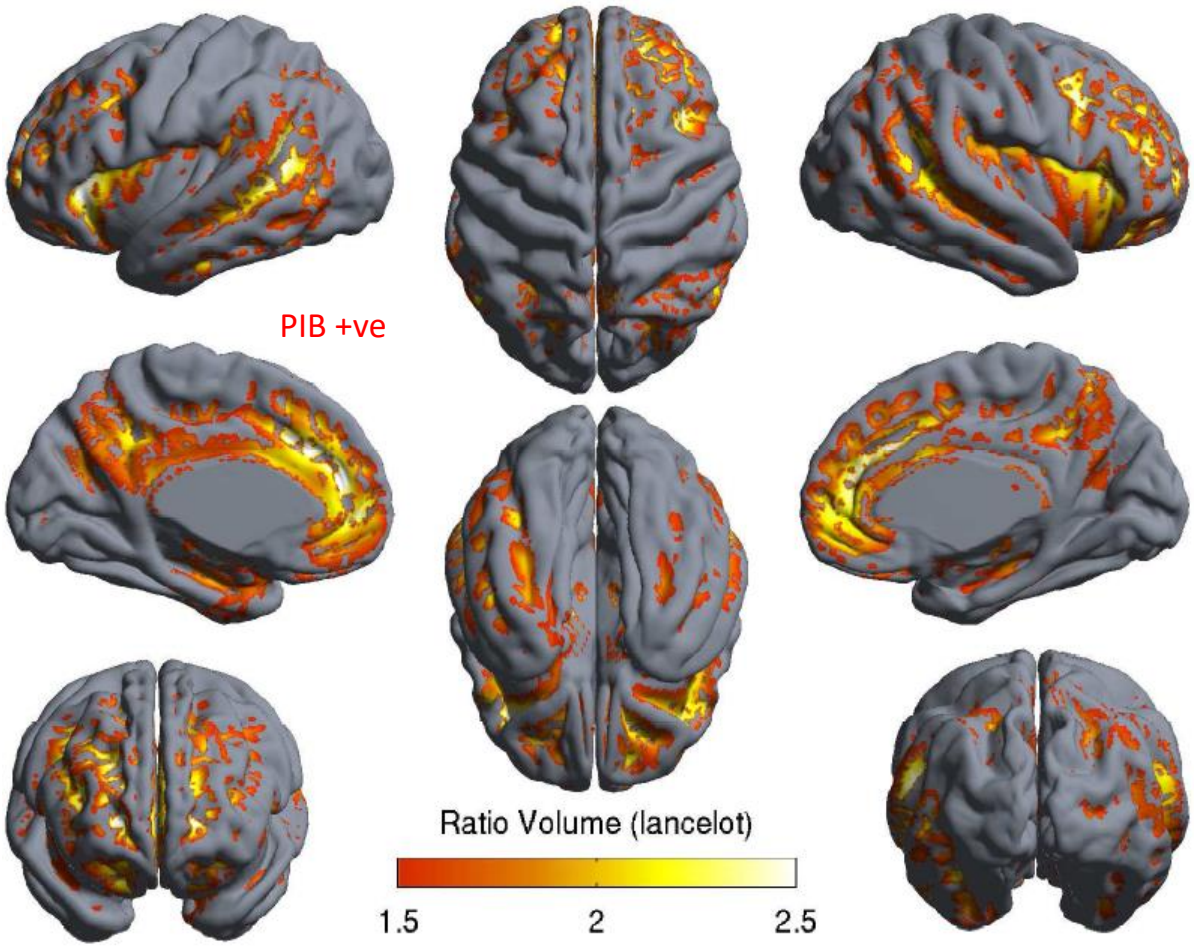
Accelerated Approval is based on Phase 2 data showing a reduction in amyloid-beta plaques in early AD patients treated with LEQEMBI™

Treatment with LEQEMBI should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials

TOKYO and CAMBRIDGE, Mass., Jan. 6, 2023 /PRNewswire/ -- Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") and Biogen Inc. (Nasdaq: BIIB, Corporate headquarters: Cambridge, Massachusetts, CEO: Christopher A. Viehbacher, "Biogen") announced today that under the Accelerated Approval Pathway the U.S. Food and Drug Administration (FDA) has approved lecanemab-irmb (Brand Name in the U.S.: LEQEMBI™) 100 mg/mL injection for



This is 3-d MRI reconstruction of an MCI subject with PIB PET injection PIB negative



This is 3-d MRI reconstruction of an MCI subject with PIB PET injection PIB positive

Why patients must have amyloid presence verified before anti-amyloid therapy

- Many individuals labelled “Alzheimer Disease” and even “Probable AD” in clinic, fail to show amyloid. These will not benefit from such therapy.
- The failed Bapineuzumab trials enrolled > 30% of individuals who were PET Aβ-negative thereby treating patients for a pathology they did not have.
- Monsell, Reiman et al, (2015) JAMA: 25% of patients clinically diagnosed with mild to moderate AD do not have amyloid in brain on post-mortem. Serrano-Pozo et al (Ann Neurol, 2014) but the figure lower, at 14%. These were subjects from research centres.
- Ideas Study (Rabinovici, 2019,JAMA,321;1286-94): Community physician diagnosed AD. Free access to amyloid PET.
  - Amyloid PET was +ve in 64% of these cases (NEG in 36%).

Evolving approach to clinical diagnosis

(Lahiri et al, 2023)

Diagnostic approach in 2023….

"Alzheimer Syndrome" = Cortical dementia, not FTD, diagnosed clinically (with MRI, lab tests)

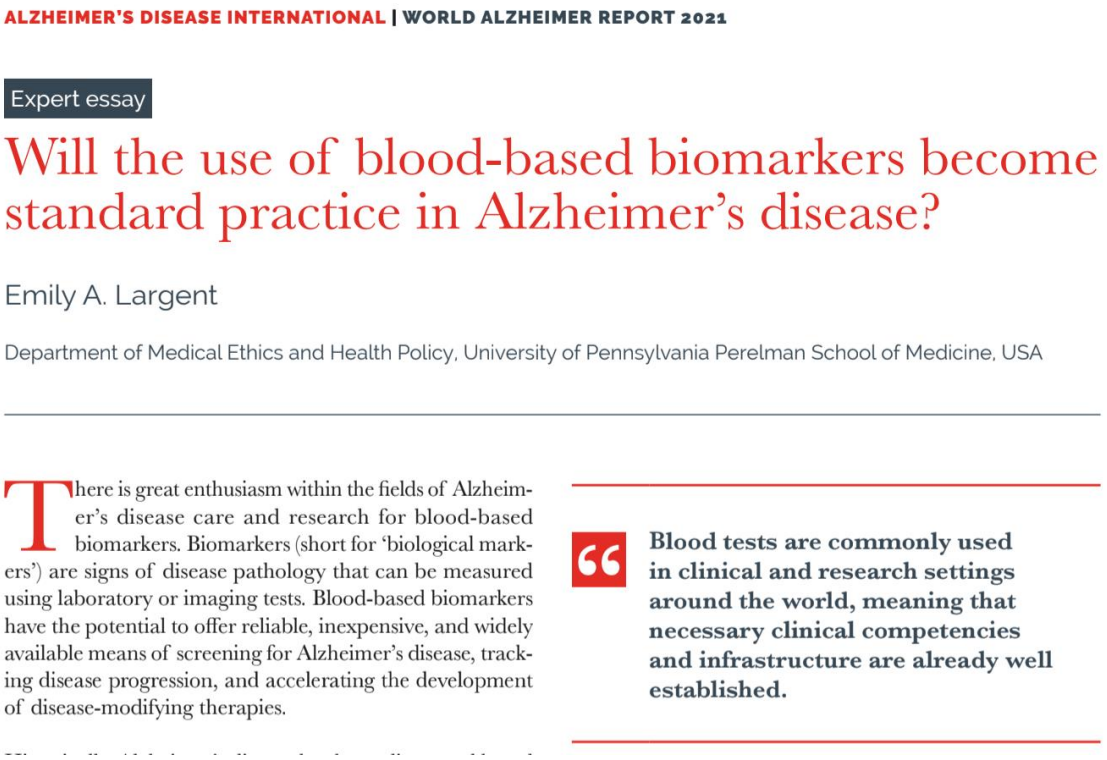
May be dementia
Or
MCI clinical criteria

2/3 = Alzheimer Disease with Amyloidopathy (or "MCI due to AD")

1/3 = No amyloidopathy = SNAP, LATE, PART, Hippocampal sclerosis, Tau-only AD, unsuspected vascular dementia, or Other.

Divergence has occurred between clinicians, and academic biomarker/imaging specialists.
Cliff Jack "If there isn't any amyloid, then its not Alzheimer Disease".

Will the use of blood-based biomarkers become standard practice in Alzheimer's disease?



ALZHEIMER'S DISEASE INTERNATIONAL | WORLD ALZHEIMER REPORT 2021

Expert essay

Will the use of blood-based biomarkers become standard practice in Alzheimer's disease?

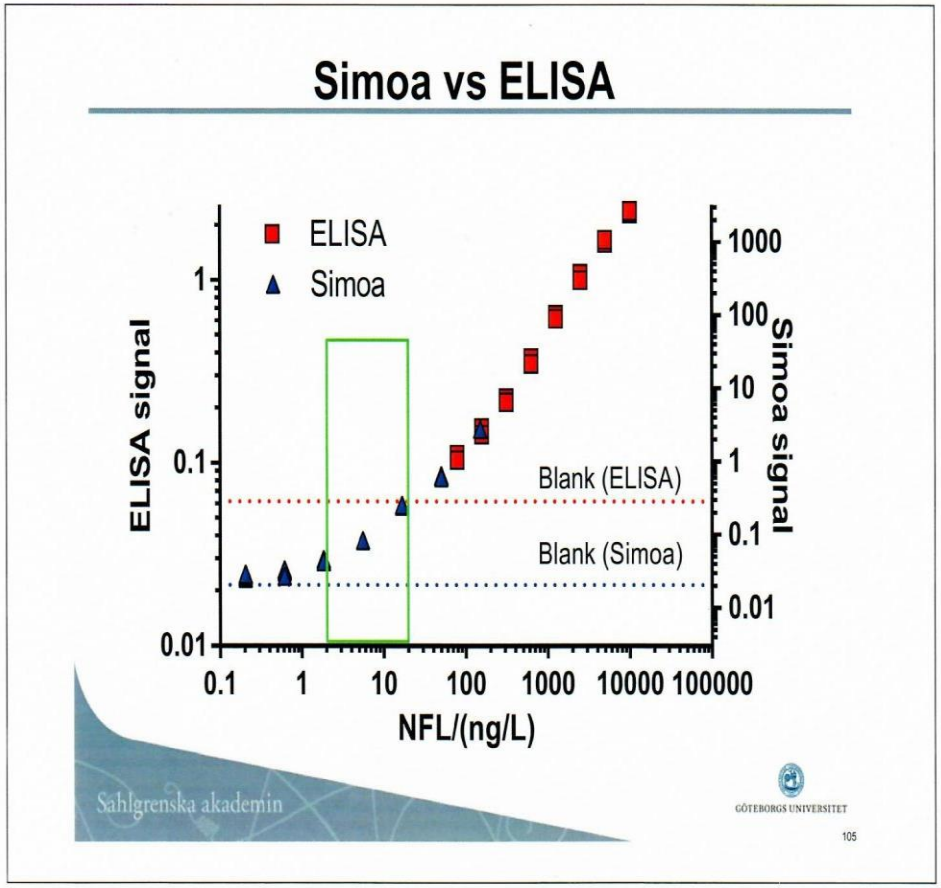
Emily A. Largent

Department of Medical Ethics and Health Policy, University of Pennsylvania Perelman School of Medicine, USA

There is great enthusiasm within the fields of Alzheimer's disease care and research for blood-based biomarkers. Biomarkers (short for 'biological markers') are signs of disease pathology that can be measured using laboratory or imaging tests. Blood-based biomarkers have the potential to offer reliable, inexpensive, and widely available means of screening for Alzheimer's disease, tracking disease progression, and accelerating the development of disease-modifying therapies.

> **Blood tests are commonly used in clinical and research settings around the world, meaning that necessary clinical competencies and infrastructure are already well established.**

Solution: Simoa (single molecular array) technology: A far more sensitive way to measure molecules in blood, csf



New developments: Plasma measures

ARTICLE CLASS OF EVIDENCE

High-precision plasma β-amyloid 42/40 predicts current and future brain amyloidosis

Suzanne E. Schindler, MD, PhD, James G. Bollinger, PhD, Vitaliy Ovod, MS, Kwasi G. Mawuenyega, PhD, Yan Li, PhD, Brian A. Gordon, PhD, David M. Holtzman, MD, John C. Morris, MD, Tammie L.S. Benzinger, MD, PhD, Chengjie Xiong, PhD, Anne M. Fagan, PhD, and Randall J. Bateman, MD

Correspondence
Dr. Bateman
batemanr@wustl.edu

Neurology® 2019;TBD:1-13. doi:10.1212/WNL.0000000000008081

Abstract

Objective

We examined whether plasma β-amyloid (Aβ)42/Aβ40, as measured by a high-precision assay, accurately diagnosed brain amyloidosis using amyloid PET or CSF p-tau181/Aβ42 as reference standards.

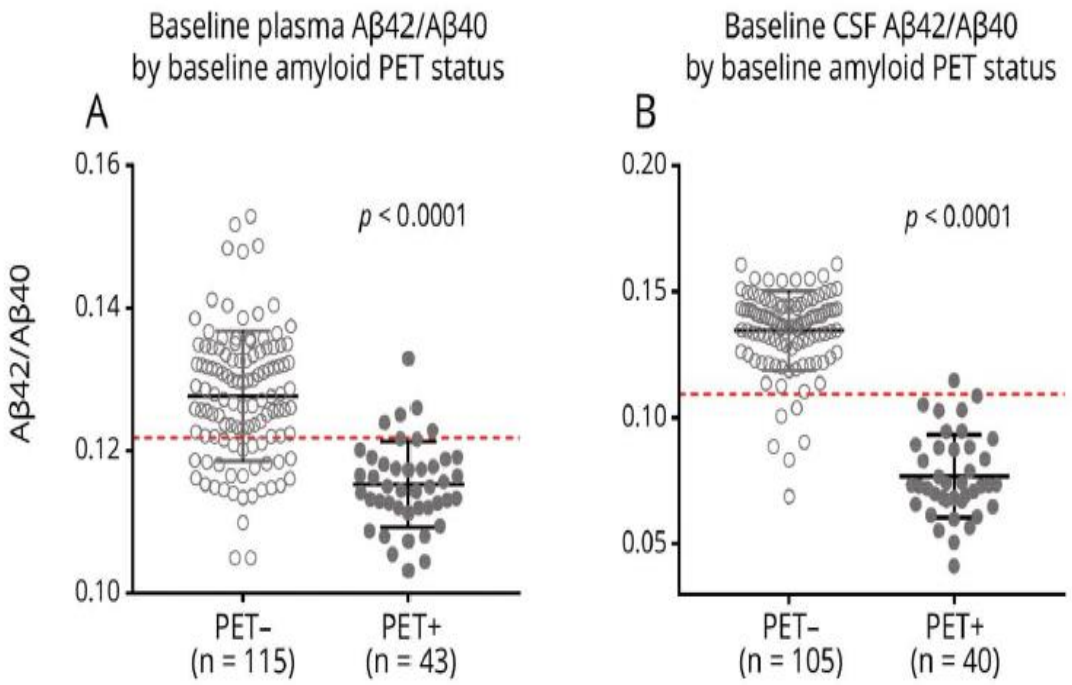
MORE ONLINE

→ **Class of Evidence**
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

Also see: Nakamura et al, (2018), Nature, 554; 249-54

Abeta42/40 ratio goes down in AD (with +ve amyloid PET) in plasma and csf

Figure 1 Correspondence of baseline plasma and CSF β-amyloid (Aβ)42/Aβ40 with baseline amyloid PET



Karikan, Pascoal et al, 2020 “Blood phosphorylated tau 181 as a biomarker for AD...” Lancet Neurology, 19;422-433

- Combination Gottenberg (Zetterberg, Blennow) and McGill (Rosa-Neto, Gauthier) collaboration.
- 4 cohorts tested, SIMOA Quanterix immunoassay.
- Plasma or serum can be used, about 5% level of csf.
- Best biomarker yet!
- High sensitivity to detect AD, MCI, “at-risk”.
- Specific for AD vs. other NDD
- Predicts atrophy ,future cognitive decline.
- Appears reliable, can repeat, inexpensive, no user-dependant factors, not affected by sex or demography or geography.
- Partially funded by CCNA

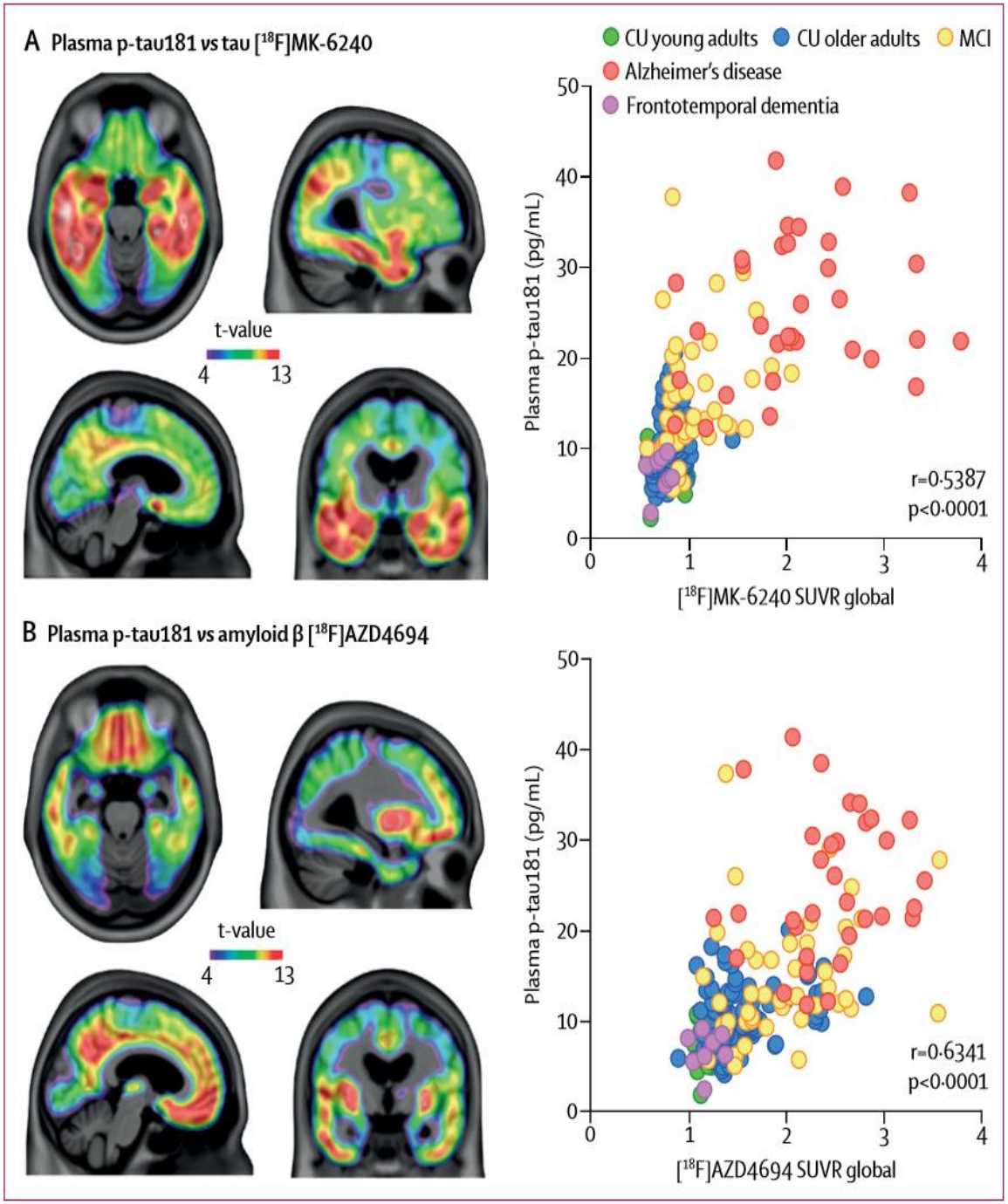


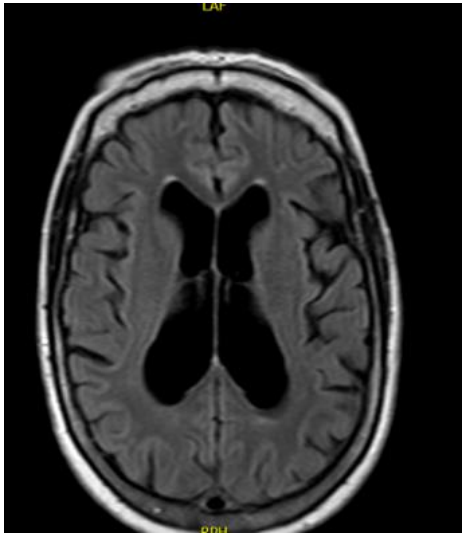
Figure 2: Associations between plasma p-tau181 concentration and PET tau and amyloid β load

Case #5 (HG)

- 82-year-old right-handed man, executive
- amnestic MCI, progressive slowly to dementia
- Decline in episodic memory, without word-finding or executive problems. No response to cholinesterase inhibitors.
- Family h/o dementia in mother .
- Consideration for anti-amyloid clinical trials

MRI Brain

- MRI (Brain)- Age-appropriate atrophy of cerebral cortex and few scattered microvascular changes



“AD dementia without amyloid”- +ve tau PET, negative amyloid PET

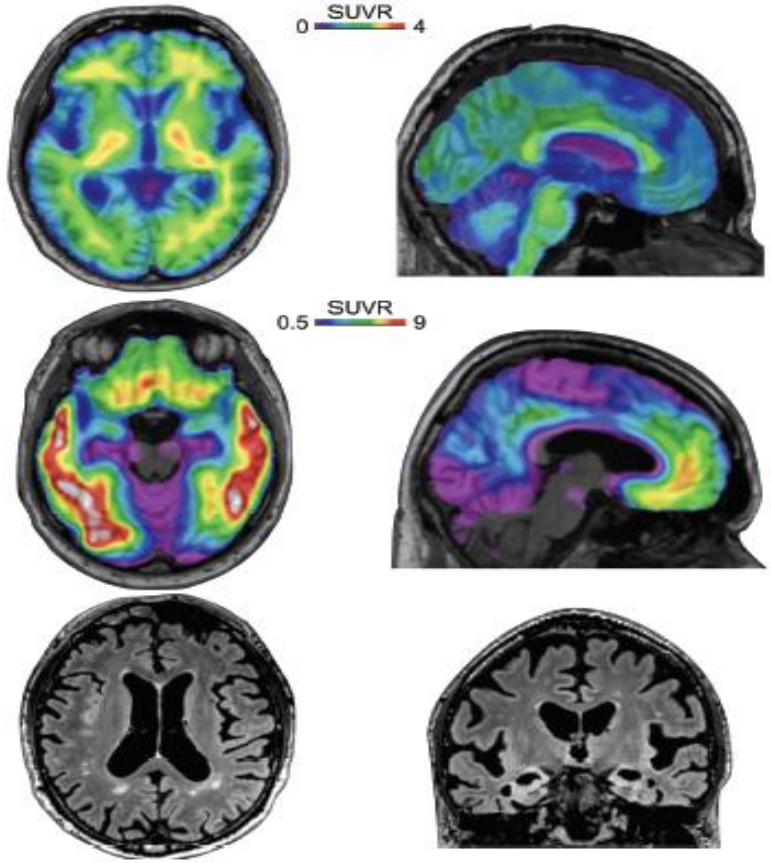
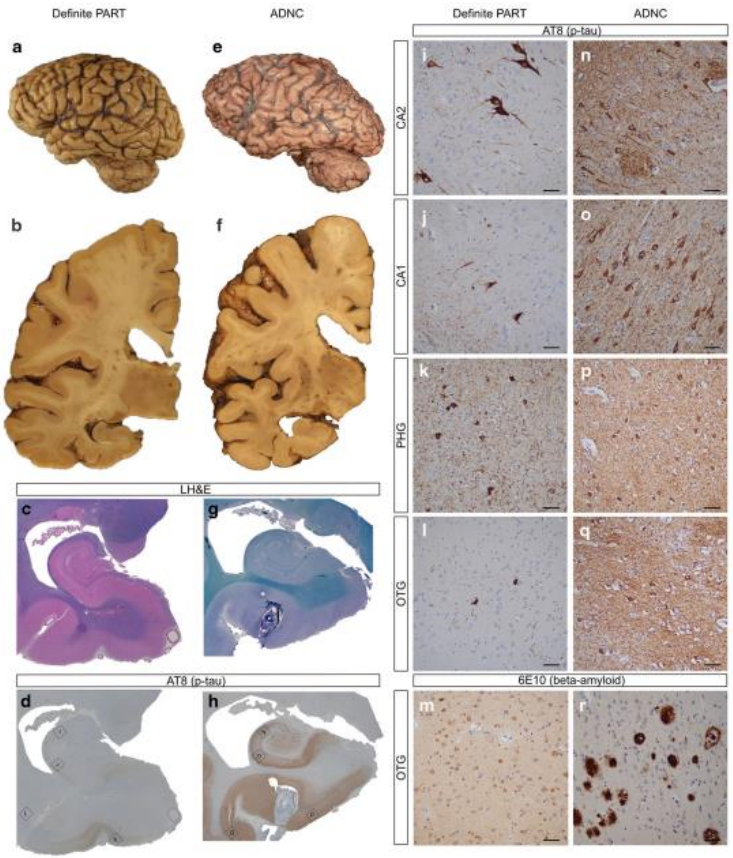


Figure. Amyloid positron emission tomography (PET), tau PET, and MRI from a man, age 80, with mild dementia (CDR 1) after a gradual cognitive decline over 5 years and clinical diagnosis of probable AD. The amyloid PET is read as negative, the tau PET positive on the temporal lobe, precuneus, inferior parietal cortex, orbitofrontal cortex, and amygdala (Braak V). The MRI shows mild general and hippocampal atrophy (Scheltens 4-5). White matter hyperintensities (WMH) are limited to the periventricular regions (Fazekas 1). This individual has a neurofibrillary tangle predominant dementia.

Diagnosis: PART-Primary Age Related Tauopathy

PART=Primary Age Related Tauopathy



- Possible subtype of AD (?Tangle-only dementia)
- Slowly progressive; late-onset.
- Many have no symptoms
- Significant proportion have antemortem diagnosis of AD
- 18% of cognitively normal with AD changes, and 5% of cognitively impaired elderly cases show PART

Hickman et al, Curr Neuro Neurosci Rep, 2021

Note: Anti tau (MAPT) ASO therapy in Phase 2 and 3 trials

Case #6 (LD)

- 72-year-old right-handed lady, nursery teacher
- Progressive changes in her speech and language since the age of 69 years
- Decline in word-finding ability while anxious, which later became continuous
- Difficulty speaking full sentences; phonemic and semantic errors
- Independent for driving, banking and cooking
- Family h/o dementia in mother

Verbal Expression:

- Spontaneous speech: slow, hesitant
  with word finding instances,
  semantic and phonemic
  paraphasias
- Repetition of words: flawless

- Repetition of sentences: spared for short and high predictability

- Naming to confrontation - moderately impaired
  - semantic substitutions (*unicorn: female horse*)
  - phonemic paraphasias (*stethoscope: stefostope*)
  - circumlocutory errors (*funnel: "when you want to pour water and you don't want to spill it"*)

Courtesy: Regina Jokel

Contd..

- Auditory comprehension: Entirely normal
- Cognitive Examination: Impaired working memory (Forward digit span of 4 which later declined to 2)

- Most likely diagnosis: logopenic PPA, not typical

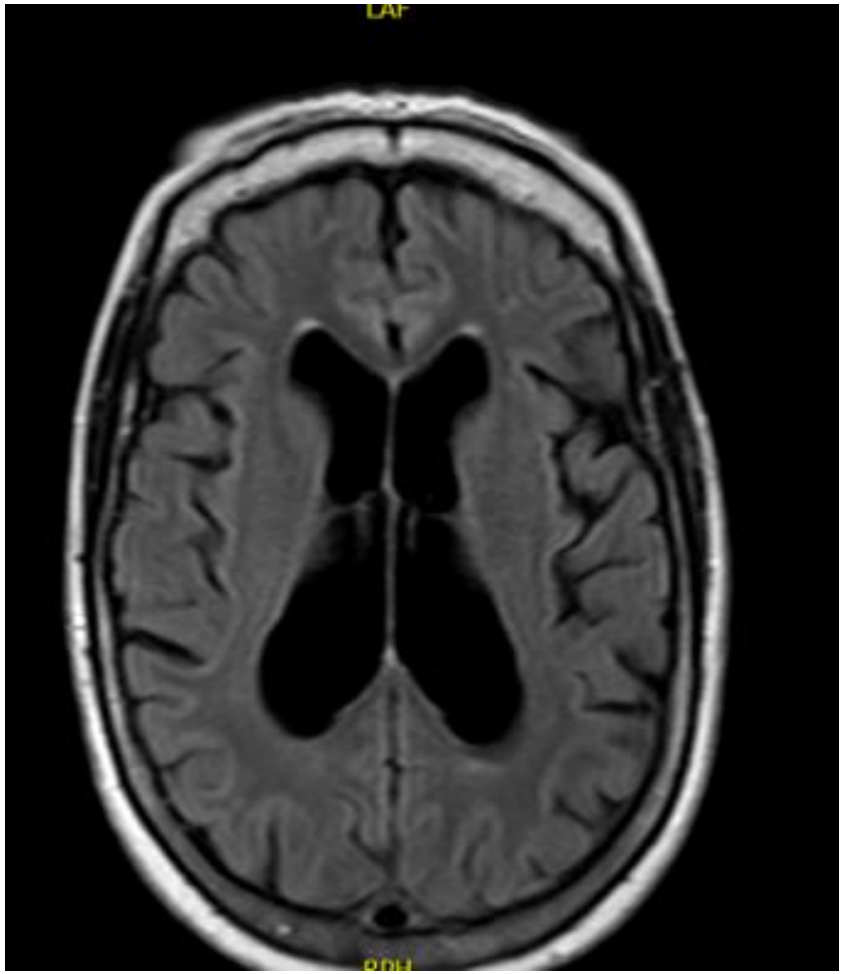
- Impaired word retrieval & naming
- Poor repetition of sentences (WM deficits)
- Slow hesitant spontaneous speech
- Simplified grammar and phonemic paraphasias
- Strong semantic knowledge and well preserved motor speech

Table 4 Diagnostic criteria for logopenic variant PPA

I. Clinical diagnosis of logopenic variant PPA
Both of the following core features must be present:
1. Impaired single-word retrieval in spontaneous speech and naming
2. Impaired repetition of sentences and phrases
At least 3 of the following other features must be present:
1. Speech (phonologic) errors in spontaneous speech and naming
2. Spared single-word comprehension and object knowledge
3. Spared motor speech
4. Absence of frank agrammatism
II. Imaging-supported logopenic variant diagnosis
Both criteria must be present:
1. Clinical diagnosis of logopenic variant PPA
2. Imaging must show at least one of the following results:
a. Predominant left posterior perisylvian or parietal atrophy on MRI
b. Predominant left posterior perisylvian or parietal hypoperfusion or hypometabolism on SPECT or PET
III. Logopenic variant PPA with definite pathology
Clinical diagnosis (criterion 1 below) and either criterion 2 or 3 must be present:
1. Clinical diagnosis of logopenic variant PPA
2. Histopathologic evidence of a specific neurodegenerative pathology (e.g. AD, FTLD-tau, FTLD-TDP, other)
3. Presence of a known pathogenic mutation

Gorno-Tempini et al, 2011

Asymmetric atrophy of the left peri-sylvian cortex and few scattered microvascular changes



CSF analysis

A-beta 42: 804 ng/L (> 1030 ng/L)

p-tau: 32 ng/L (<28 ng/L)

Total tau: 153 ng/L (<301 ng/L)

p-tau/A-beta 42: 0.0124 (<0.024)

Total tau/ A-beta 42: 0.190 (<0.29)

A+ T+ N-

The biomarker profile consistent with an **amyloid beta** pathology, consistent with atypical presentation of AD.

Patient elected for MAID, given biochemical support for AD

Patient #7 - LJF

- Mild Cognitive impairment
- Has vascular risk factors
- Hypertension, diabetes
- No CVA or TIA
- Stress and anxiety extreme.
- MRI- White matter changes, Fazekas 3
- SPECT scan normal

- Initial Conclusion: no NDD, possibly vascular MCI
- Diagnosis: Psychiatric, not NDD

CSF analysis

A-beta 42: 1451 ng/L (> 1030 ng/L)

p-tau: 16 ng/L (<28 ng/L)

Total tau: 188 ng/L (<301 ng/L)

p-tau/A-beta 42: 0.011 (<0.024)

Total tau/ A-beta 42: 0.13 (<0.29)

A- T- N-

The biomarker profile consistent with NO **amyloid beta** pathology.

CSF analysis

A-beta 42: 1451 ng/L (> 1030 ng/L)
p-tau: 16 ng/L (<28 ng/L)
Total tau: 188 ng/L (<301 ng/L)
p-tau/A-beta 42: 0.011 (<0.024)
Total tau/ A-beta 42: 0.13 (<0.29)

A- T- N-

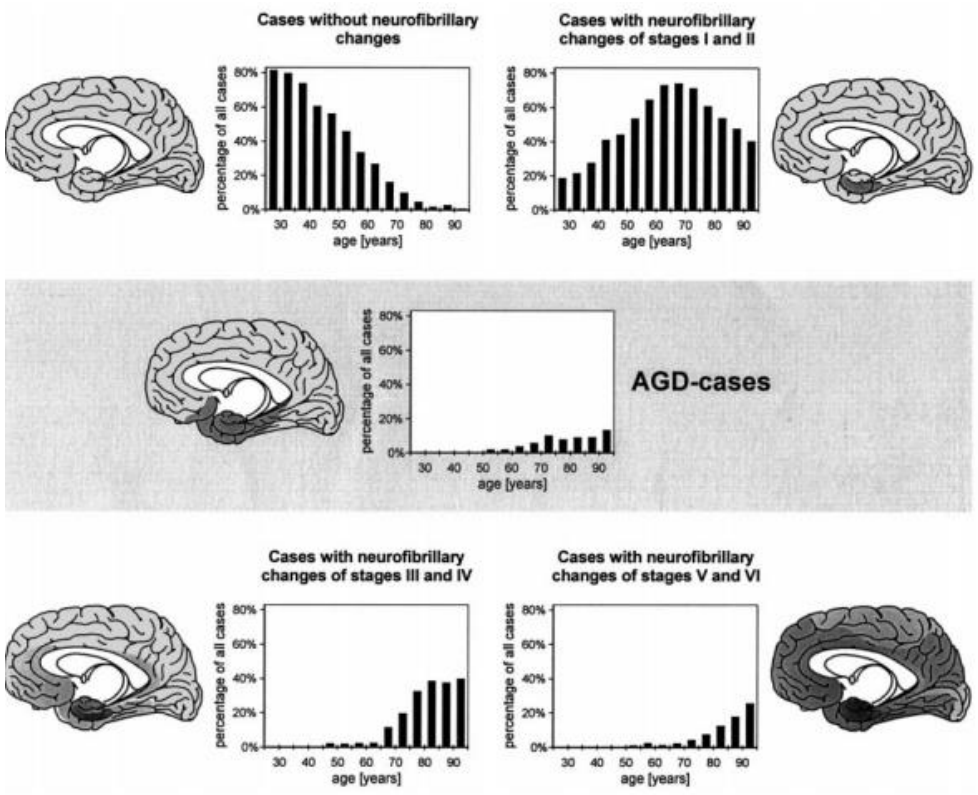
The biomarker profile consistent with NO **amyloid beta** pathology.

TDP43 by Simoa ELEVATED: 13,899 pg/mL.

Is this a combination of vascular MCI plus TDP43 NDD?

What we are still missing biomarkers for…

AGD



Slow cognitive decline in Old age

Rare in less than 70y

Found in people with normal cognition

Often mixed with ADNC

Braak & Braak, Journal o Neural Transmission, 1998

Hippocampal Sclerosis

Table 1. Demographic and Clinical Characteristics of Subjects With Hippocampal Sclerosis and Alzheimer Disease*

	Hippocampal Sclerosis (n = 16)	Alzheimer Disease (n = 32)
Sex		
Male	10	11
Female	6	21
Age at onset, mean ± SD, y	79.8 ± 5.6	77.3 ± 7.8
Age at death, mean ± SD, y	84.9 ± 4.9	83.2 ± 8.1
Duration of disease, mean ± SD, y	5.1 ± 2.6	5.9 ± 2.6
MMSE score, mean ± SD		
Initial	20.1 ± 6.3	19.0 ± 7.3
Closest to death	10.4 ± 8.9	11.6 ± 8.9
ECG abnormalities	2	14†
Diabetes mellitus	0	7†
Stroke	9	8†
Small vessel disease	4	2
White matter changes on CT	3	3
Valvular disease	2	1
History of arrhythmias	2	9
Hypertension	9	13
Head trauma	4	5
Coronary artery disease	5	12
Congestive heart failure	4	11

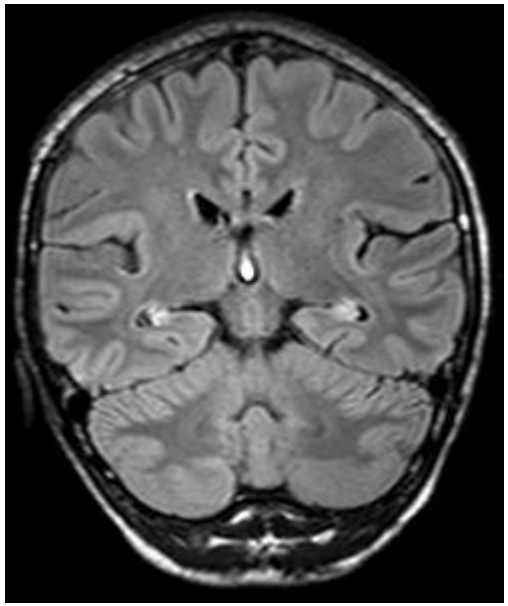
Leverenz, Arch Neurol, 2002

Table 1. Characteristics of hippocampal sclerosis dementia.

ID	Sex	Age*	Syndrome**	First dx***	Final dx***	Tau	TDP43	UBQ	FC	TC	HC	ERC
1	M	64	Amnesia	AD	HSD			P				
2	F	82	Amnesia	AD	AD		N	N	++	–	+++	+++
3	F	94	Amnesia	AD	AD	N	N	P	–	–	+++	+
4	M	55	Abnormal conduct	AD	AD	N	P	P	–	–	–	–
5	M	79	Amnesia	AD	AD		N		–	–	+++	+
6	M	69	Amnesia	AD	AD	N	P	P	+	++	+++	+++
7	F	74	Amnesia + abnormal conduct + irritability/agitation	AD	AD	N	P	P	++	++	+++	+++
8	M	64	Amnesia	AD	AD	N	N	P	–	–	+++	+
9	F	79	Amnesia + irritability/agitation	AD	FTD	N	P	P	++	++	+++	+++
10	F	79	Amnesia + abnormal conduct + parkinsonism	PSP	PSP		N		–	–	–	–
11	M	73	Amnesia + abnormal conduct + irritability/agitation	AD	AD	N	P	P	+	+	+++	+++
12	F	74	Amnesia + psychosis + irritability/agitation	AD	AD	N	N	N	+	+	+++	+
13	M	81	Amnesia + abnormal conduct + irritability/agitation	AD	FTD	N	P	P	+	+++	+++	+++
14	M	94	Amnesia	AD	AD	N	N	N	+	++	+++	++
15	M	55	Agnosia + abnormal conduct + irritability/agitation	DNOS	DNOS	N	P	P	–	–	+++	+
16	F	89	Normal	Normal	DNOS	N	P	P	–	–	–	–
17	F	82	Amnesia + aphasia + abnormal conduct + irritability/agitation	AD	AD	N	P	P	+	++	+++	+++
18	F	96	Amnesia + agnosia + apraxia	AD	AD	N	P	P	++	+++	+++	+++
19	M	79	Amnesia	AD	AD				–	–	+++	–
20	M	77	Executive dysfunction + abnormal conduct + parkinsonism	AD	AD	P	N	P	++	++	+++	+++
21	F	90	Amnesia + abnormal conduct	AD	AD	N	N	P	–	–	+++	+
22	F	83	Amnesia	AD	AD	N	N	P	–	+	+++	+++
23	M	82	Abnormal conduct + neglect of self-care + irritability/agitation	AD	AD	N	P	P	++	+++	+++	+++
24	M	83	Amnesia + neglect of self-care + irritability/agitation	AD	AD	N	P	P	–	–	+++	+++

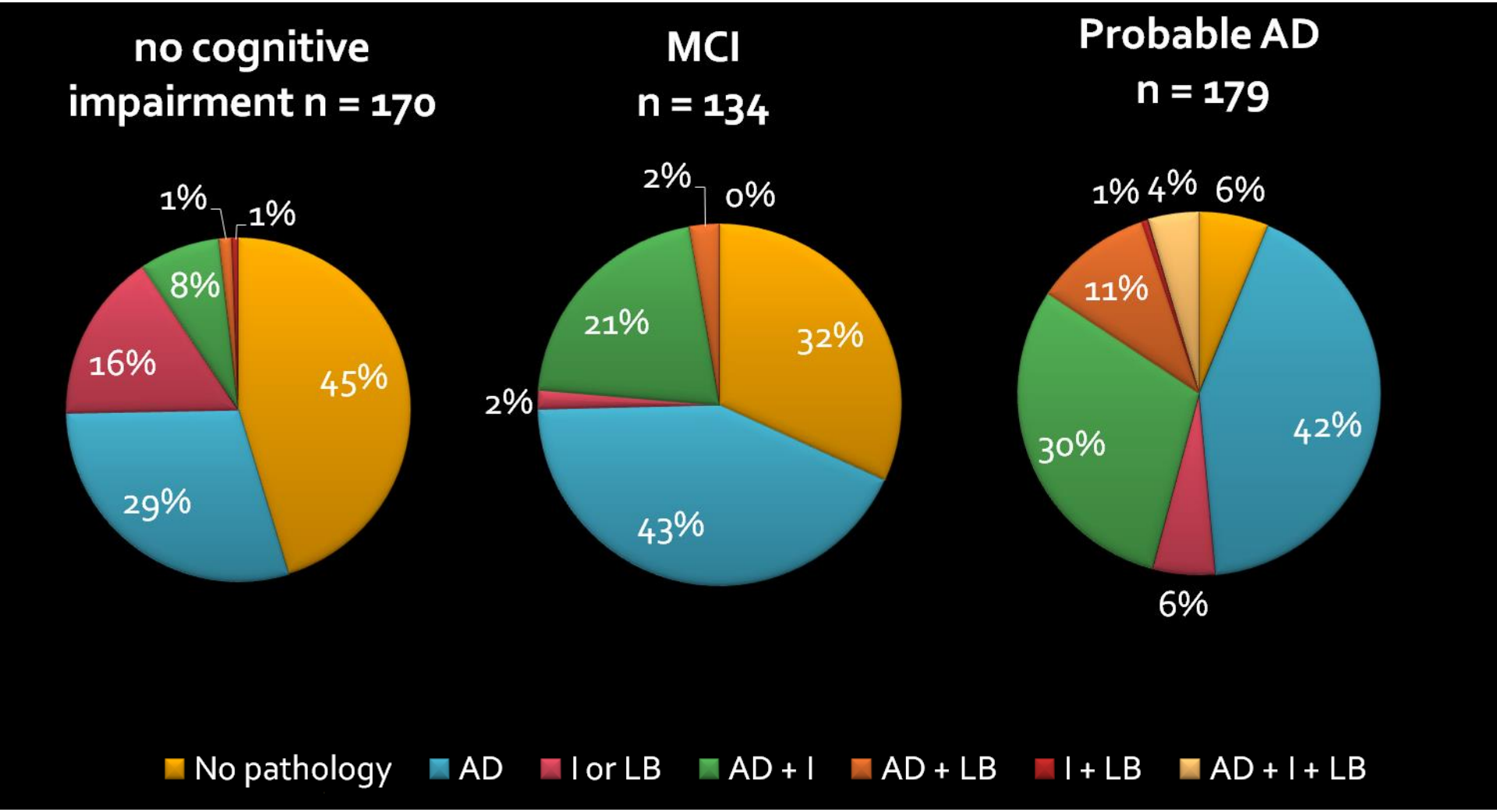
Onyike et al, Dement Neuropsychol 2013

Imaging in HS



- Increased T2 signal
- Hippocampal atrophy

The Mixed Neuropathology of Probable Alzheimer Disease and Mild Cognitive Impairment



Schneider et al Ann Neurol 2009;66:200-208

Conclusion

- ATN framework is now sliding from research into clinical use.
- Need to screen for amyloid prior to DMT will drive increased biomarkers. Ability to distinguish A+ from A- will be critical.
- Plasma biomarkers will be transformational
- Ability to confirm AD in atypical or young cases will help clinicians.
- Ability to exclude AD in psychiatric cases will help clinicians.
- Increased certainty of diagnosis and prognosis will increase “self-efficacy” but also increase MAID.
- Increasing use of biomarkes will shine a light on all those “Alzheimer Syndrome” patients who lack amyloid.

Evolving approach to clinical diagnosis

(Lahiri et al, 2023)

Diagnostic approach in 2023….

"Alzheimer Syndrome" = Cortical dementia, not FTD, diagnosed clinically (with MRI, lab tests)

May be dementia
Or
MCI clinical criteria

2/3 = Alzheimer Disease with Amyloidopathy (or "MCI due to AD")

1/3 = No amyloidopathy = SNAP, LATE, PART, Hippocampal sclerosis, Tau-only AD, unsuspected vascular dementia, or Other.

Divergence has occurred between clinicians, and academic biomarker/imaging specialists.
Cliff Jack "If there isn't any amyloid, then its not Alzheimer Disease".