Multimodal biomarkers and the NIA AA Research Framework

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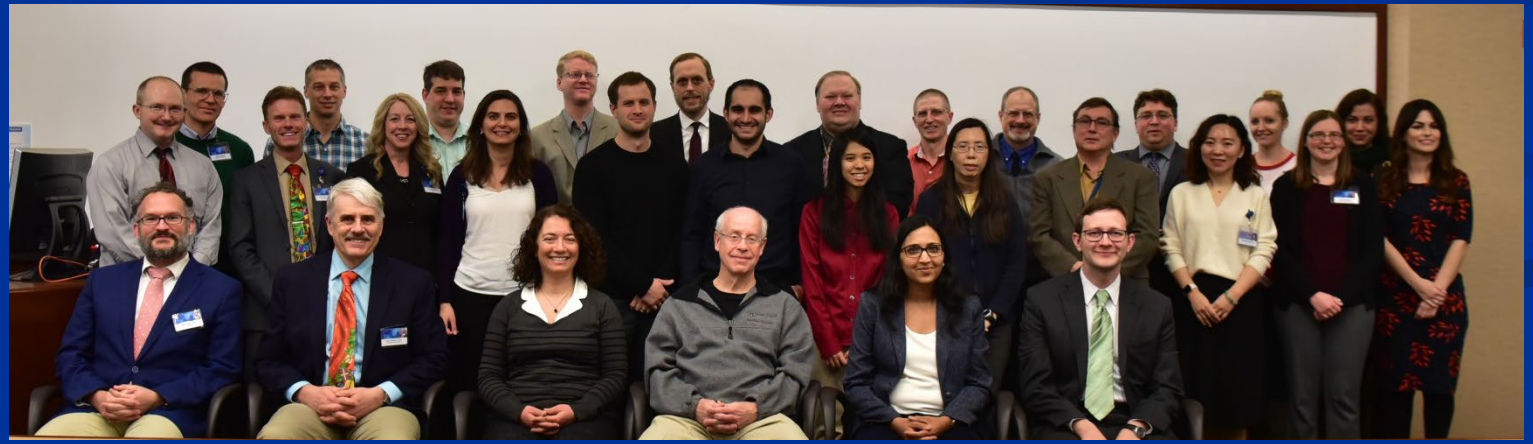
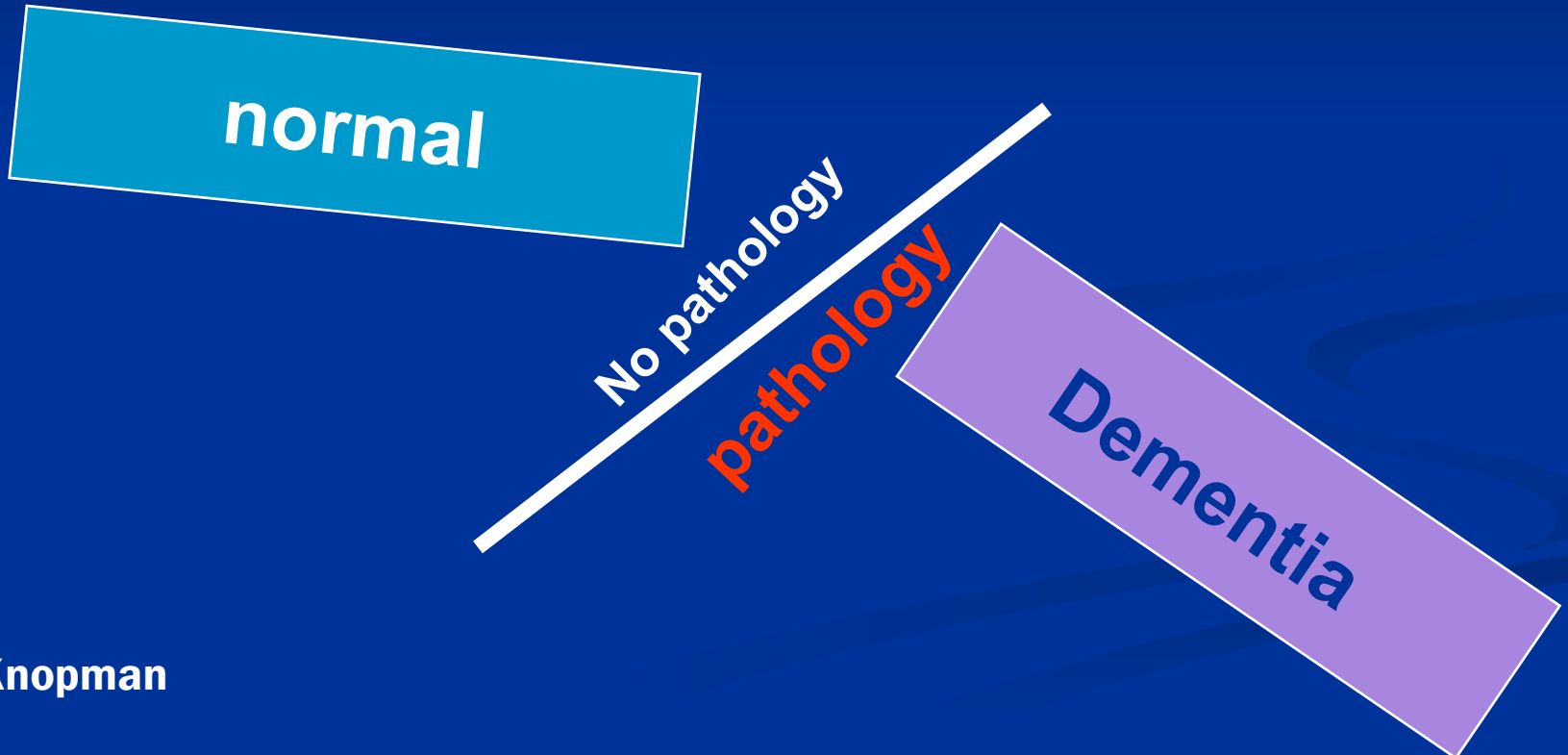


outline

- History of diagnostic criteria for Alzheimer's disease (AD)
- National Institute on Aging – Alzheimer's Association (NIA-AA) research framework
- NIA vs IWG
- Integration of plasma biomarkers into NIA-AA research framework

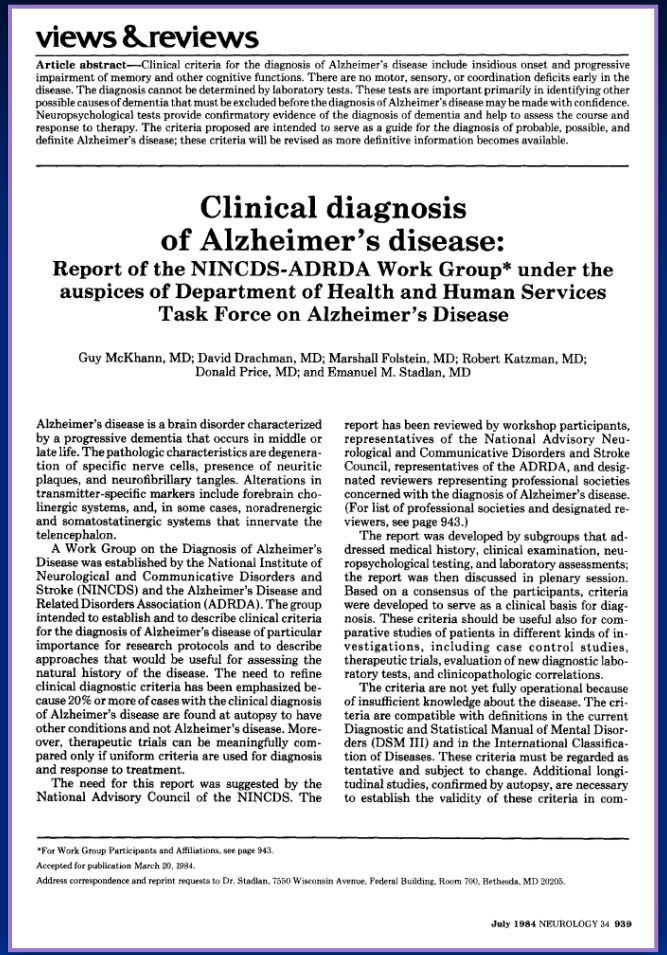
Relationship between normal state and dementia

The two-state view of early 1980's



D Knopman

NINCDS-ADRDA Criteria 1984



views & reviews

Article abstract—Clinical criteria for the diagnosis of Alzheimer's disease include insidious onset and progressive impairment of memory and other cognitive functions. There are no motor, sensory, or coordination deficits early in the disease. The diagnosis cannot be determined by laboratory tests. These tests are important primarily in identifying other possible causes of dementia that must be excluded before the diagnosis of Alzheimer's disease may be made with confidence. Neuropsychological tests provide confirmatory evidence of the diagnosis of dementia and help to assess the course and response to therapy. The criteria proposed are intended to serve as a guide for the diagnosis of probable, possible, and definite Alzheimer's disease; these criteria will be revised as more definitive information becomes available.

Clinical diagnosis of Alzheimer's disease:

Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease

Guy McKhann, MD; David Drachman, MD; Marshall Folstein, MD; Robert Katzman, MD; Donald Price, MD; and Emanuel M. Stadlan, MD

Alzheimer's disease is a brain disorder characterized by a progressive dementia that occurs in middle or late life. The pathologic characteristics are degeneration of specific nerve cells, presence of neuritic plaques, and neurofibrillary tangles. Alterations in transmitter-specific markers include forebrain cholinergic systems, and, in some cases, noradrenergic and somatostatinergic systems that innervate the telencephalon.

A Work Group on the Diagnosis of Alzheimer's Disease was established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA). The group intended to establish and to describe clinical criteria for the diagnosis of Alzheimer's disease of particular importance for research protocols and to describe approaches that would be useful for assessing the natural history of the disease. The need to refine clinical diagnostic criteria has been emphasized because 20% or more of cases with the clinical diagnosis of Alzheimer's disease are found at autopsy to have other conditions and not Alzheimer's disease. Moreover, therapeutic trials can be meaningfully compared only if uniform criteria are used for diagnosis and response to treatment.

The need for this report was suggested by the National Advisory Council of the NINCDS. The report has been reviewed by workshop participants, representatives of the National Advisory Neurological and Communicative Disorders and Stroke Council, representatives of the ADRDA, and designated reviewers representing professional societies concerned with the diagnosis of Alzheimer's disease. (For list of professional societies and designated reviewers, see page 943.)

The report was developed by subgroups that addressed medical history, clinical examination, neuropsychological testing, and laboratory assessments; the report was then discussed in plenary session. Based on a consensus of the participants, criteria were developed to serve as a clinical basis for diagnosis. These criteria should be useful also for comparative studies of patients in different kinds of investigations, including case control studies, therapeutic trials, evaluation of new diagnostic laboratory tests, and clinicopathologic correlations.

The criteria are not yet fully operational because of insufficient knowledge about the disease. The criteria are compatible with definitions in the current Diagnostic and Statistical Manual of Mental Disorders (DSM III) and in the International Classification of Diseases. These criteria must be regarded as tentative and subject to change. Additional longitudinal studies, confirmed by autopsy, are necessary to establish the validity of these criteria in com-

*For Work Group Participants and Affiliations, see page 943.

Accepted for publication March 20, 1984.

Address correspondence and reprint requests to Dr. Stadlan, 7550 Wisconsin Avenue, Federal Building, Room 700, Bethesda, MD 20205.

- McKhann et al 1984: clinical-pathologic entity
  - *Probable AD* diagnosis in life after exclusions
  - *Definite AD* only at autopsy
  - Over time, however, amnestic dementia became equated with AD – ie non-specific clinical presentation equated with one specific neuropathology

Neuropath 1990s+: Pathologic heterogeneity of aging & dementia

- Alzheimer disease (plaques and tangles)
- Alpha synuclein (Lewy body disease)
- Limbic Associated TDP Encephalopathy (LATE disease)
- Cerebrovascular disease
- Argyrophillic grain disease

==========

- All increase in prevalence with age
- Co-occurrence common; isolated pathology rare in old age
- All can be assoc. with dementia: "AD" syndromes not specific for AD
- All can be present in cognitively unimpaired

Biomarker era: earliest disease specific biomarkers, CSF then amyloid PET

ELSEVIER

Neuroscience Letters 273 (1999) 5–8

Neuroscience Letters

www.elsevier.com/locate/neulet

Cerebrospinal fluid tau and Aβ42 as predictors of development of Alzheimer's disease in patients with mild cognitive impairment

N. Andreasen[a,*], L. Minthon[b], E. Vanmechelen[c], H. Vanderstichele[c], P. Davidsson[d], B. Winblad[e], K. Blennow[d,f]

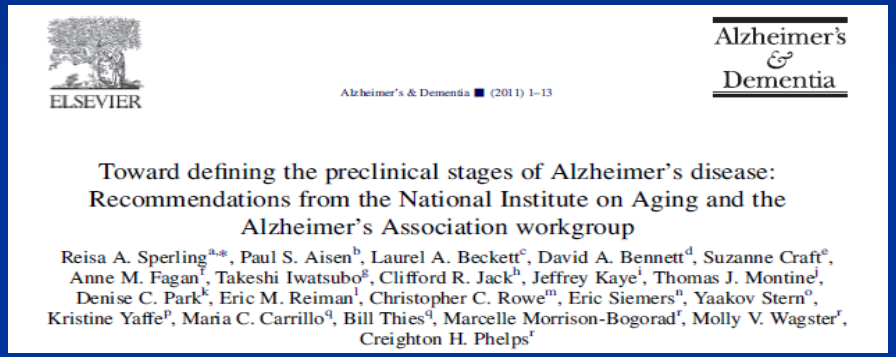
Imaging Brain Amyloid in Alzheimer's Disease with Pittsburgh Compound-B

William E. Klunk, MD, PhD,[1] Henry Engler, MD,[2] Agneta Nordberg, MD, PhD,[3,4] Yanming Wang, PhD,[5] Gunnar Blomqvist, PhD,[2] Daniel P. Holt, BS,[5] Mats Bergström, PhD,[2] Irina Savitcheva, MD,[2] Guo-feng Huang, PhD,[5] Sergio Estrada, PhD,[2] Birgitta Ausén, MSCI,[4] Manik L. Debnath, MS,[1] Julien Barletta, BS,[6] Julie C. Price, PhD,[5] Johan Sandell, PhD,[2] Brian J. Lopresti, BS,[5] Anders Wall, PhD,[2]

Ann Neurol 2004;55:306–319

History of diagnostic criteria for AD – incorporating biomarkers

- IWG (2007, 2010, 2014): clinical-biomarker construct
- NIA-AA 2011: 3 separate committees & 3 sets of guidelines



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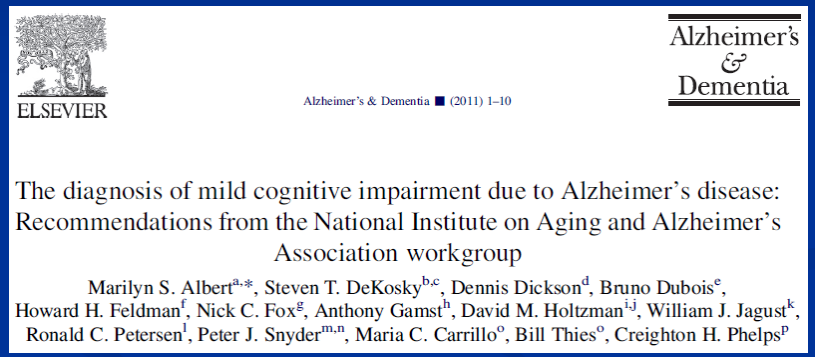
Alzheimer's & Dementia ■ (2011) 1–13

Alzheimer's & Dementia

Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

Reisa A. Sperling[a,*], Paul S. Aisen[b], Laurel A. Beckett[c], David A. Bennett[d], Suzanne Craft[e], Anne M. Fagan[f], Takeshi Iwatsubo[g], Clifford R. Jack[h], Jeffrey Kaye[i], Thomas J. Montine[j], Denise C. Park[k], Eric M. Reiman[l], Christopher C. Rowe[m], Eric Siemers[n], Yaakov Stern[o], Kristine Yaffe[p], Maria C. Carrillo[q], Bill Thies[q], Marcelle Morrison-Bogorad[r], Molly V. Wagster[r], Creighton H. Phelps[r]



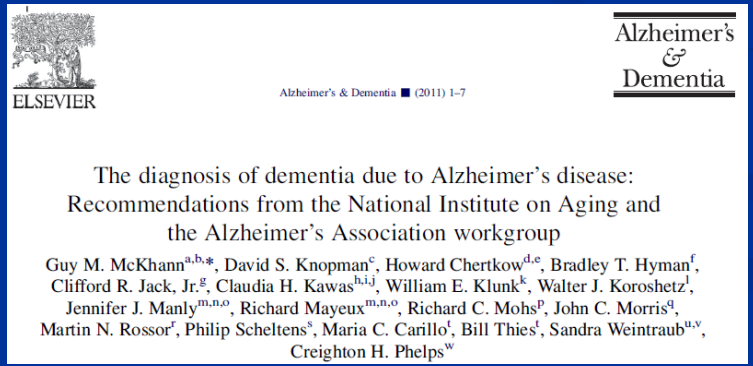
ELSEVIER

Alzheimer's & Dementia ■ (2011) 1–10

Alzheimer's & Dementia

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging and Alzheimer's Association workgroup

Marilyn S. Albert[a,*], Steven T. DeKosky[b,c], Dennis Dickson[d], Bruno Dubois[e], Howard H. Feldman[f], Nick C. Fox[g], Anthony Gamst[h], David M. Holtzman[i,j], William J. Jagust[k], Ronald C. Petersen[l], Peter J. Snyder[m,n], Maria C. Carrillo[o], Bill Thies[o], Creighton H. Phelps[p]



ELSEVIER

Alzheimer's & Dementia ■ (2011) 1–7

Alzheimer's & Dementia

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging and the Alzheimer's Association workgroup

Guy M. McKhann[a,b,*], David S. Knopman[c], Howard Chertkow[d,e], Bradley T. Hyman[f], Clifford R. Jack, Jr.[g], Claudia H. Kawas[h,i,j], William E. Klunk[k], Walter J. Koroshetz[l], Jennifer J. Manly[m,n,o], Richard Mayeux[m,n,o], Richard C. Mohs[p], John C. Morris[q], Martin N. Rossor[r], Philip Scheltens[s], Maria C. Carillo[t], Bill Thies[t], Sandra Weintraub[u,v], Creighton H. Phelps[w]

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- History of diagnostic criteria for Alzheimer's disease (AD)
- National Institute on Aging – Alzheimer's Association (NIA-AA) research framework
- NIA vs IWG
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ELSEVIER

CrossMark

Alzheimer's & Dementia 14 (2018) 535-562

Alzheimer's & Dementia

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

Contributors[†]: Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

Core principles of NIA AA research framework

- Separation of syndrome (impairment) from biology (etiology)
  - Amnestic dementia and AD are not synonymous
- Biological definition
  - Term AD refers to pathologic change (plaques & tangles – not to a syndrome(s)
  - Symptoms are a result of the disease process, not its definition
- AD defined by biomarkers in vivo – built on AT(N) construct
- Alzheimer's disease exists on a continuum not as discrete clinically defined entities

Jack et al Alz & Dem 2018

Operationalization: how to create orderly, common use framework? AT(N) biomarker grouping

- B-amyloid plaques or associated pathologic state: A
  - CSF Aβ 42, or 42/40 ratio
  - Amyloid PET
- Aggregated AD tau or associated pathologic state: T
  - CSF phosphorylated tau
  - Tau PET
- Neuronal injury and neurodegeneration: (N)
  - Structural MRI
  - FDG PET
  - CSF total tau CSF

Jack et al Neurology 2016

AT(N) Biomarker Profiles & Categories

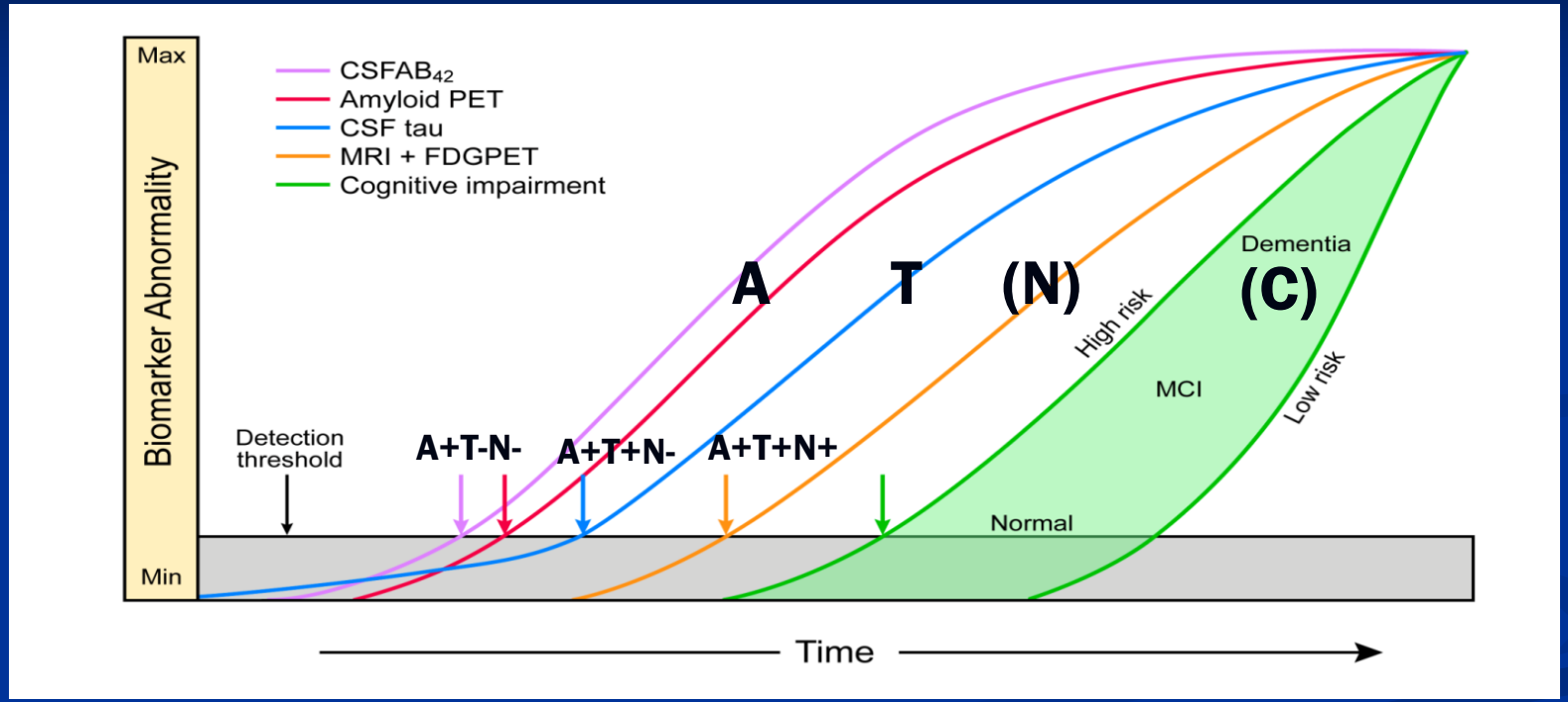
- Each biomarker group (AT(N)) *can be* dichotomized
- 8 "profiles"
- 3 "biomarker categories"
  - Normal biomarkers
  - Alzheimer's continuum
  - Non-AD pathologic change (SNAP)

Jack et al Alz & Dem 2018

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	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non-Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

Biomarker profiles: implicit disease staging

A-T-(N)- → A+T-(N)- → A+T+(N)- → A+T+(N)+



Jack et al, Lancet Neurology 2010 & 2013

Integrating syndromal cognitive staging with biomarker profiles

		Cognitive stage		
		Cognitively Unimpaired	**Mild Cognitive Impairment**	**Dementia**
Biomarker Profile	**$A^- T^- N^-$**	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
	$A^+ T^- N^-$	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
	$A^+ T^+ N^-$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI(Prodromal AD)	Alzheimer's disease with dementia
	$A^+ T^+ N^+$			
	$A^+ T^- N^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
	$A^- T^+ N^-$	non-Alzheimer's pathologic change, cognitively unimpaired	non-Alzheimer's pathologic change with MCI	non-Alzheimer's pathologic change with dementia
	$A^- T^- N^+$			
	$A^- T^+ N^+$			

Jack et al Alz & Dem 2018

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	$A^- T^- N^+$			
	$A^- T^+ N^+$			

Integrating syndromal cognitive staging with biomarker profiles

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$A^- T^- N^+$			
$A^- T^+ N^+$			

Biggest controversy for 2018 NIA AA framework: What is the definition of AD? How should the term AD be used?

Two camps

- Biological definition is appropriate
- Biological definition is not appropriate

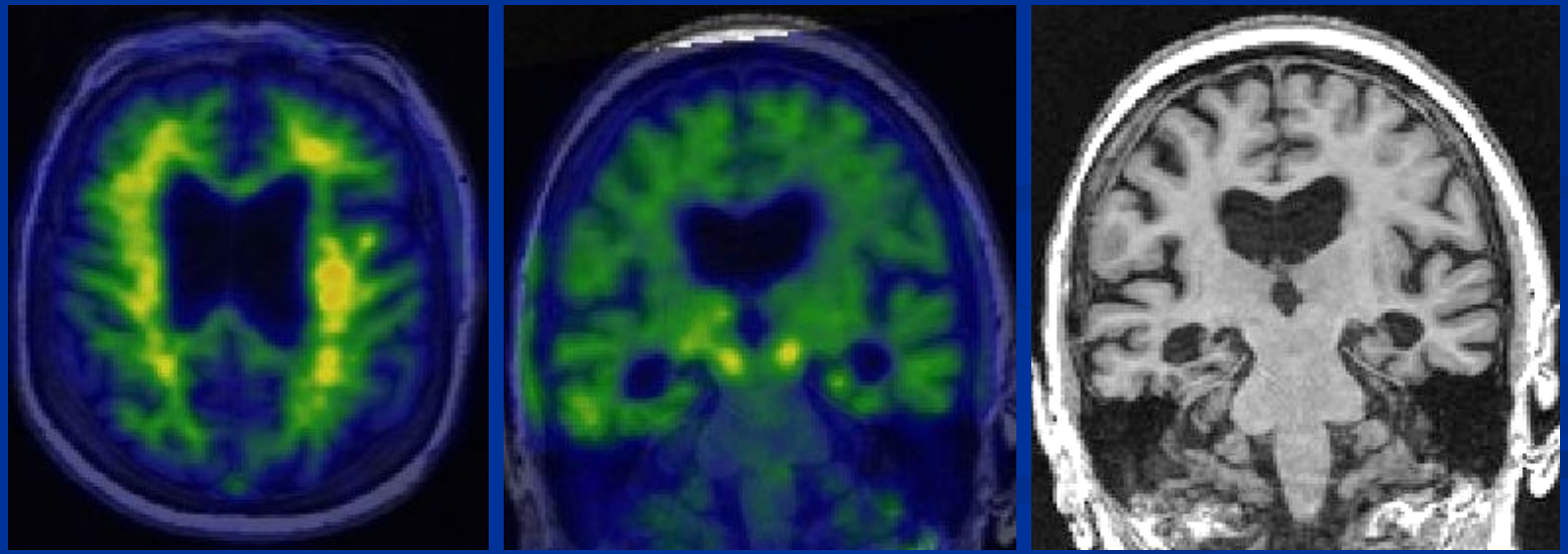
Consequence of defining AD as progressive amnestic dementia – illustrations of usefulness of biological definition of AD

- frequent mismatches between clinical diagnosis of "probable AD" (progressive amnestic dementia) & neuropathologic and biomarker diagnoses (*Beach 2012*; Sensitivity 70-87%; Specificity 44-70%)
- Failure modes of defining AD as a syndrome
  - Progressive amnestic syndrome due to non AD pathology
  - AD can present with non amnestic syndromes
  - Clinical definition of AD does not acknowledge preclinical disease

Amnestic Dementia Phenotype - yes: AD Biology - no

86 yo, F, progressive amnestic dementia. Clinic Dx "AD". Biomarker profile A-T-N+, suspected non-Alzheimer's pathologic change with dementia. Autopsy, Hipp Scl with TDP43 (LATE Dz)

A- **T-** **(N)+**



Jack et al Alz & Dem 2018

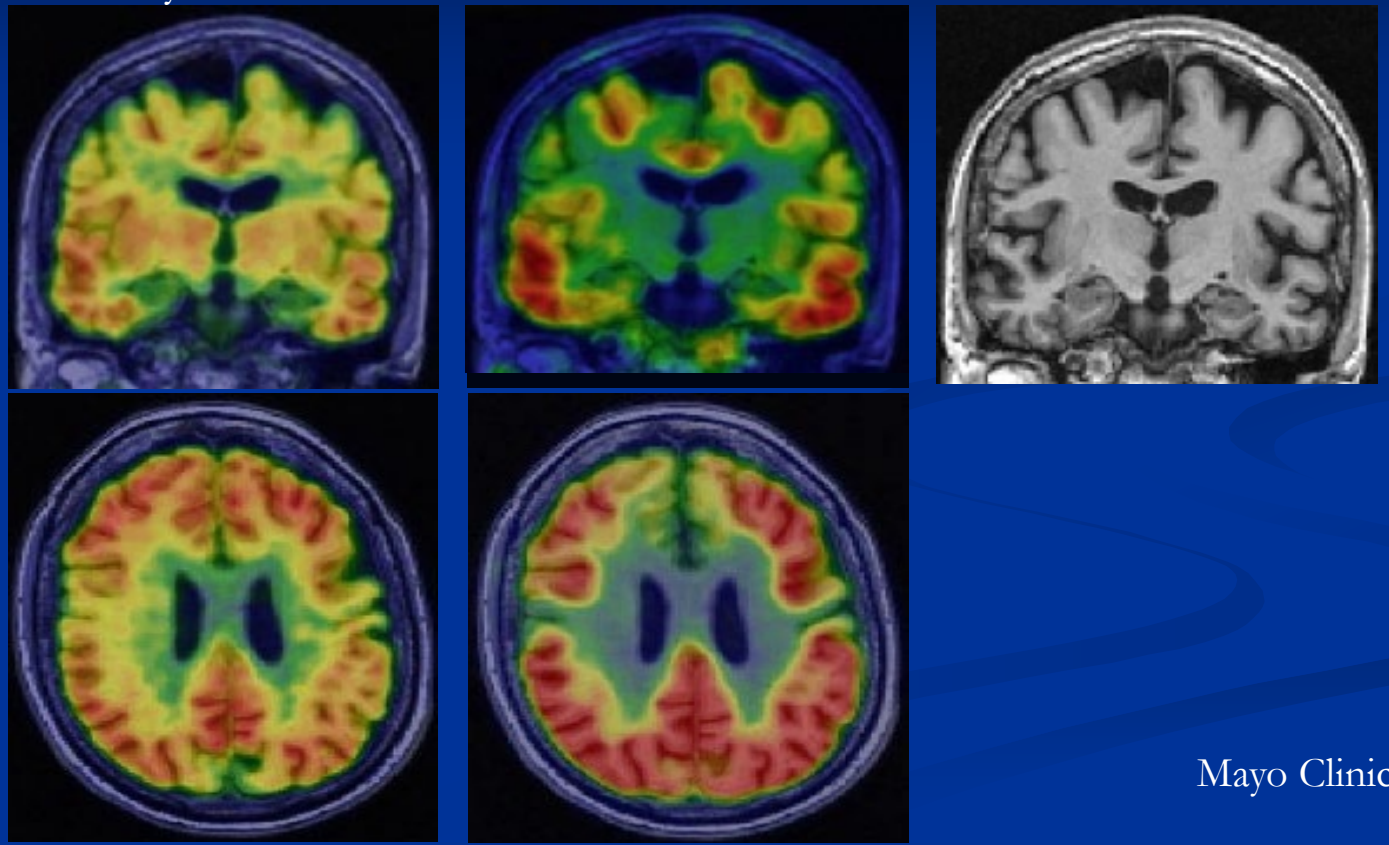
Amnestic Dementia Phenotype - no: AD Biology - yes

52 yo, F, behavioral/dysexecutive presentation, memory intact, limbic Sparing EOAD

Amyloid PET

Tau PET

MR



Mayo Clinic ADRC

outline

- History of diagnostic criteria for Alzheimer's disease (AD)
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IWG

Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS–ADRDA criteria

Bruno Dubois*, Howard H Feldman*, Claudia Jacova, Steven T DeKosky, Pascale Barberger-Gateau, Jeffrey Cummings, André Delacourte, Douglas Galasko, Serge Gauthier, Gregory Jicha, Kenichi Meguro, John O'Brien, Florence Pasquier, Philippe Robert, Martin Rossor, Steven Salloway, Yaakov Stern, Pieter J Visser, Philip Scheltens

2007

Revising the definition of Alzheimer's disease: a new lexicon

Bruno Dubois, Howard H Feldman, Claudia Jacova, Jeffrey L Cummings, Steven T DeKosky, Pascale Barberger-Gateau, André Delacourte, Giovanni Frisoni, Nick C Fox, Douglas Galasko, Serge Gauthier, Harald Hampel, Gregory A Jicha, Kenichi Meguro, John O'Brien, Florence Pasquier, Philippe Robert, Martin Rossor, Steven Salloway, Marie Sarazin, Leonardo C de Souza, Yaakov Stern, Pieter J Visser, Philip Scheltens

2010

Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria

Bruno Dubois, Howard H Feldman, Claudia Jacova, Harald Hampel, José Luis Molinuevo, Kaj Blennow, Steven T DeKosky, Serge Gauthier, Dennis Selkoe, Randall Bateman, Stefano Cappa, Sebastian Crutch, Sebastiaan Engelborghs, Giovanni B Frisoni, Nick C Fox, Douglas Galasko, Marie-Odile Habert, Gregory A Jicha, Agneta Nordberg, Florence Pasquier, Gil Rabinovici, Philippe Robert, Christopher Rowe, Stephen Salloway, Marie Sarazin, Stéphane Epelbaum, Leonardo C de Souza, Bruno Vellas, Pieter J Visser, Lon Schneider, Yaakov Stern, Philip Scheltens, Jeffrey L Cummings

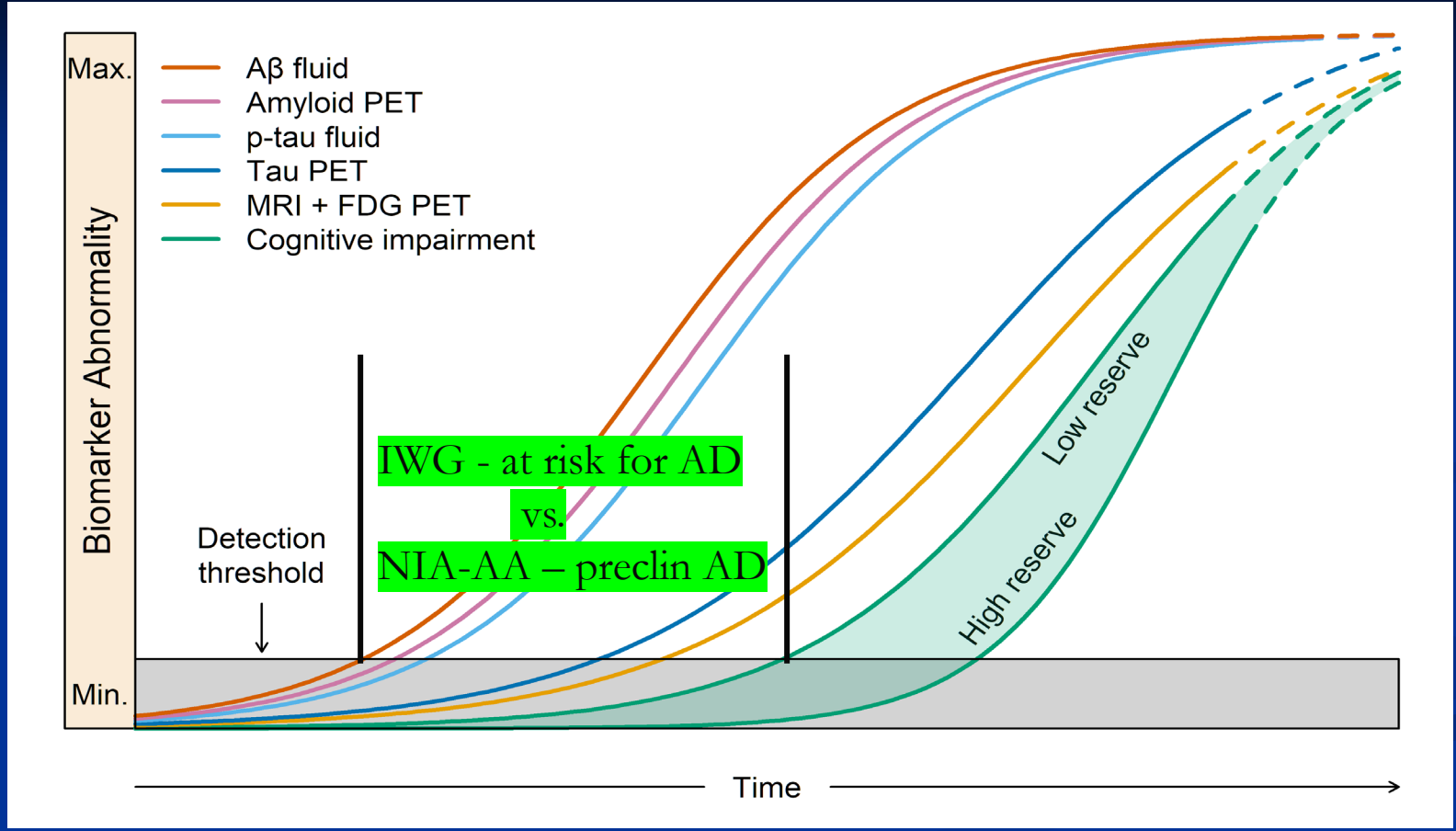
2014

Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group

Bruno Dubois*, Nicolas Villain*, Giovanni B Frisoni, Gil D Rabinovici, Marwan Sabbagh, Stefano Cappa, Alexandre Bejanin, Stéphanie Bombois, Stéphane Epelbaum, Marc Teichmann, Marie-Odile Habert, Agneta Nordberg, Kaj Blennow, Douglas Galasko, Yaakov Stern, Christopher C Rowe, Stephen Salloway, Lon S Schneider, Jeffrey L Cummings, Howard H Feldman

2021

NIA-AA vs IWG



Modified from Jack et al Lancet Neurology 2010, 2013, 2022

AT(N) classification and clinical progression in subjective cognitive decline Ebenau et al Neurology 2020

Table 2 Clinical progression in 8 ATN biomarker profiles

		Clinical progression details				Cox proportional hazard models	
	N	Total progression, n (%)	MCI, n	AD, n	Other dementia, n	Progression to dementia[a]	Progression to MCI or dementia[a]
A–T–N–	175	9 (5)	7	0	2[b]	1 (reference)	1 (reference)
A–T–N+	17	0 (0)	0	0	0	[e]	[e]
A–T+N–	66	5 (8)	2	1	2[c]	3.2 (0.5–19.3)	1.0 (0.3–3.1)
A–T+N+	7	1 (14)	0	1	0	18.5 (1.6–211.4)	3.6 (0.4–29.7)
A+T–N–	28	7 (25)	4	3	0	9.7 (1.6–59.3)	5.3 (2.0–14.4)
A+T–N+	7	0 (0)	0	0	0	[e]	[e]
A+T+N–	35	18 (51)	8	8	2[d]	20.2 (3.7–110.2)	9.1 (3.6–22.5)
A+T+N+	7	6 (86)	3	3	0	62.3 (9.5–408.4)	30.9 (9.6–99.3)

N= 693 Amsterdam cohort

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Major limitation of biological definition (until recently), major reason for "research framework" terminology

- Problem: CSF and PET imaging are invasive, expensive – limits use to specialty clinics or clinical trials
- Solution: plasma biomarkers

plasma A

LETTER

2018

doi:10.1038/nature25456

High performance plasma amyloid-β biomarkers for Alzheimer's disease

Akinori Nakamura[1], Naoki Kaneko[2], Victor L. Villemagne[3,4], Takashi Kato[1,5], James Doecke[6], Vincent Doré[3,6], Chris Fowler[4], Qiao-Xin Li[4], Ralph Martins[7], Christopher Rowe[3,4], Taisuke Tomita[8], Katsumi Matsuzaki[9], Kenji Ishii[10], Kazunari Ishii[11], Yutaka Arahata[5], Shinichi Iwamoto[2], Kengo Ito[1,5], Koichi Tanaka[2], Colin L. Masters[4] & Katsuhiko Yanagisawa[1]

ELSEVIER

Alzheimer's & Dementia ■ (2017) 1-9

Alzheimer's & Dementia

Theoretical Article

Amyloid β concentrations and stable isotope labeling kinetics of human plasma specific to central nervous system amyloidosis

Vitaliy Ovod[a,1], Kara N. Ramsey[a,1], Kwasi G. Mawuenyega[a], Jim G. Bollinger[a], Terry Hicks[a], Theresa Schneider[a], Melissa Sullivan[a], Katrina Paumier[a], David M. Holtzman[a,b,c], John C. Morris[a,c], Tammie Benzinger[d,c], Anne M. Fagan[a,b,c], Bruce W. Patterson[e], Randall J. Bateman[a,b,c,*]

Published online: April 6, 2018

Research Article

SOURCE DATA | TRANSPARENT PROCESS | OPEN ACCESS

EMBO Molecular Medicine

Amyloid blood biomarker detects Alzheimer's disease

Andreas Nabers[1,†], Laura Perna[2,†], Julia Lange[1], Ute Mons[2], Jonas Schartner[1], Jörn Güldenhaupt[1], Kai-Uwe Saum[2], Shorena Janelidze[3], Bernd Holleczek[4], Dan Rujescu[5], Oskar Hansson[3,6], Klaus Gerwert[2,*] & Hermann Brenner[2,7]

plasma (N)

JAMA Neurology | Original Investigation

Association of Plasma Neurofilament Light With Neurodegeneration in Patients With Alzheimer Disease

Niklas Mattsson, MD, PhD; Ulf Andreasson, PhD; Henrik Zetterberg, MD, PhD; Kaj Blennow, MD, PhD; for the Alzheimer's Disease Neuroimaging Initiative

2017

Neuroscience Letters 650 (2017) 60–64

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

Plasma neurofilament light chain levels in Alzheimer's disease☆

Wenjun Zhou[a,1], Jie Zhang[b,*,1], Fanlong Ye[b], Guangzheng Xu[c], Hang Su[d], Yindan Su[e], Xiangyang Zhang[f,**], Alzheimer's Disease Neuroimaging Initiative

[a] Department of Respiratory Medicine, Zhongshan Hospital, Fudan University, Shanghai, China
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[d] Shanghai Mental Health Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[e] The Affiliated High School to Hangzhou Normal University, Hangzhou, China
[f] Beijing HuiLongGuan Hospital, Peking University, Beijing, China

Plasma and CSF neurofilament light

Relation to longitudinal neuroimaging and cognitive measures

Michelle M. Mielke, PhD, Jeremy A. Syrjanen, MS, Kaj Blennow, MD, PhD, Henrik Zetterberg, MD, PhD, Prashanthi Vemuri, PhD, Ingmar Skoog, MD, PhD, Mary M. Machulda, PhD, Walter K. Kremers, PhD, David S. Knopman, MD, Clifford Jack, Jr., MD, Ronald C. Petersen, MD, PhD, and Silke Kern, MD, PhD

Neurology® 2019;93:e252-e260. doi:10.1212/WNL.0000000000007767

Plasma neurofilament light chain in the presenilin 1 E280A autosomal dominant Alzheimer's disease kindred: a cross-sectional and longitudinal cohort study

Yakeel T Quiroz*, Henrik Zetterberg*, Eric M Reiman*, Yinghua Chen, Yi Su, Joshua T Fox-Fuller, Gloria Garcia, Andres Villegas, Diego Sepulveda-Falla, Marina Villada, Joseph F Arboleda-Velasquez, Edmarie Guzmán-Vélez, Clara Vila-Castelar, Brian A Gordon, Stephanie A Schultz, Hillary D Protas, Valentina Ghisays, Margarita Giraldo, Victoria Tirado, Ana Baena, Claudia Munoz, Silvia Rios-Romenets, Pierre N Tariot, Kaj Blennow†, Francisco Lopera†

JAMA Neurology | Original Investigation

Association Between Longitudinal Plasma Neurofilament Light and Neurodegeneration in Patients With Alzheimer Disease

2019

Niklas Mattsson, MD, PhD; Nicholas C. Cullen, BSc; Ulf Andreasson, PhD; Henrik Zetterberg, MD, PhD; Kaj Blennow, MD, PhD

Lewczuk et al. Alzheimer's Research & Therapy (2018) 10:71
https://doi.org/10.1186/s13195-018-0404-9

Alzheimer's Research & Therapy

RESEARCH Open Access

Plasma neurofilament light as a potential biomarker of neurodegeneration in Alzheimer's disease

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plasma T

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IMMEDIATE COMMUNICATION

Diagnostic performance and prediction of clinical progression of plasma phospho-tau181 in the Alzheimer's Disease Neuroimaging Initiative

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Featured Article

Plasma phospho-tau181 increases with Alzheimer's disease clinical severity and is associated with tau- and amyloid-positron emission tomography

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nature medicine

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Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration

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nature medicine

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Plasma P-tau181 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia

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JAMA | Original Investigation

Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders

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Update of AT(N) multimodal biomarker system in NIA AA framework

- Incorporate plasma biomarkers
- Eliminate assumption of equivalence between imaging and fluid biomarkers
- Clinical applicability: updated system must be practical, usable in clinical setting to meet needs of era of disease modifying treatments

AD biomarker harmonization

- The Alzheimer's Association QC program: https://www.gu.se/en/neuroscience-physiology/the-alzheimers-association-qc-program-for-csf-and-blood-biomarkers
- International Federation of Clinical Chemistry and Laboratory Medicine working group for CSF and plasma proteins: https://www.ifcc.org/ifcc-scientific-division/sd-working-groups/csf-proteins-wg-csf/
- Global Biomarker Standardization Consortium: https://www.alz.org/research/for_researchers/partnerships/gbsc
- The Centiloid Project: Standardizing quantitative amyloid plaque estimation by PET: Klunk et al Alz and Dem 2015

Integrating clinical presentation (6 numeric stages) with biomarker staging: Independent sources of information

Clinical staging

Biomarker staging

	1	2	3	4	5	6
A+T-(N)-						
A+T+(N)-						
A+T+(N)+						