NIA-AA Research Framework: Towards a Biological Definition of Alzheimer's Disease

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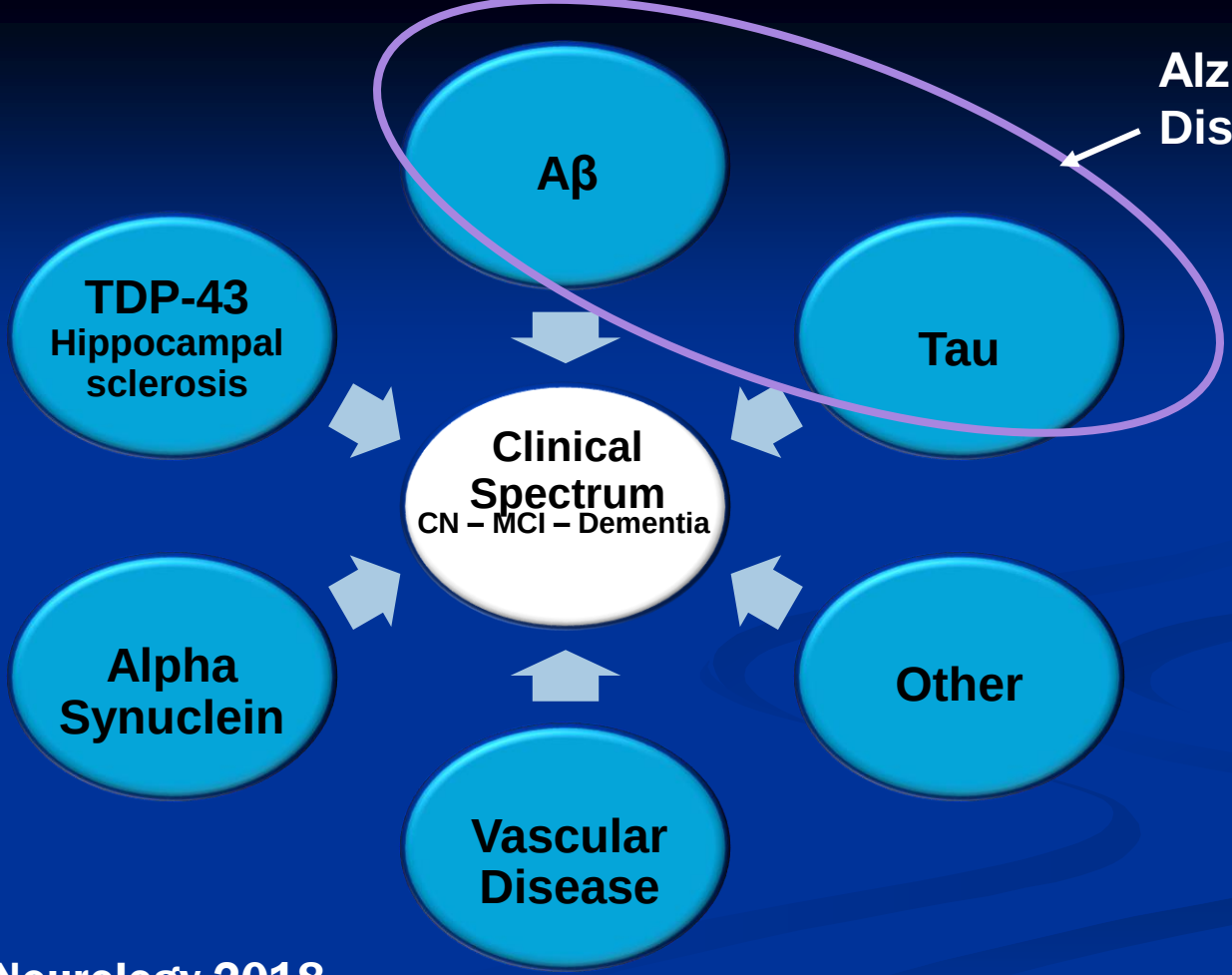
Dementia vs Alzheimers disease

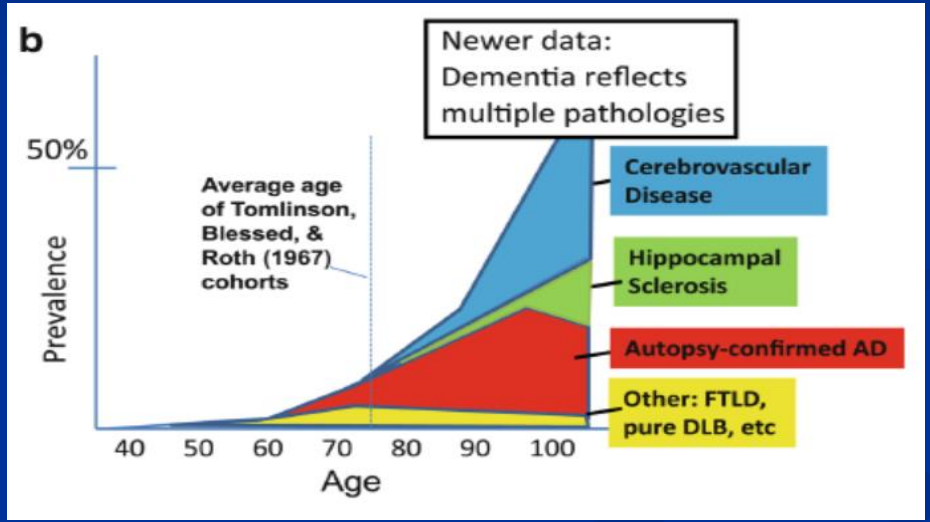
- **Alzheimers and dementia often used interchangeably but not correct**
- **Dementia = set of symptoms**
- **Alzheimer's disease = a pathologic process**
- **dementia** – progressive loss of intellectual abilities serious enough to interfere with daily life (loss of independence)
- **Alzheimer's disease -** most common etiology contributing to dementia but other age related conditions usually contribute



From Petersen, Neurology 2018

Pathological heterogeneity in old age

- Most demented (& many cognitively unimpaired) have multiple pathologies: AD (plaques and tangles), LB, CVD, HS, grain disease, TDP43
- Nelson, Acta Neuropath 2011



- Pure AD is uncommon in elderly (Markesbery 2006, Schneider 2009, Sonnen 2011)

evolution of diagnostic criteria for AD

- McKhann et al 1984: clinical- pathologic entity
  - possible/probable AD in life after exclusions
  - Definite AD only at autopsy
  - Over time, however, amnestic dementia became equated with AD
- IWG (2007, 2010, 2014) & NIA-AA (2011): clinical-biomarker
- NIA-AA 2011: 3 separate sets of diagnostic guidelines
  - Symptomatic – MCI, dementia – intended for clinical & research use
  - Preclinical AD – intended for research use

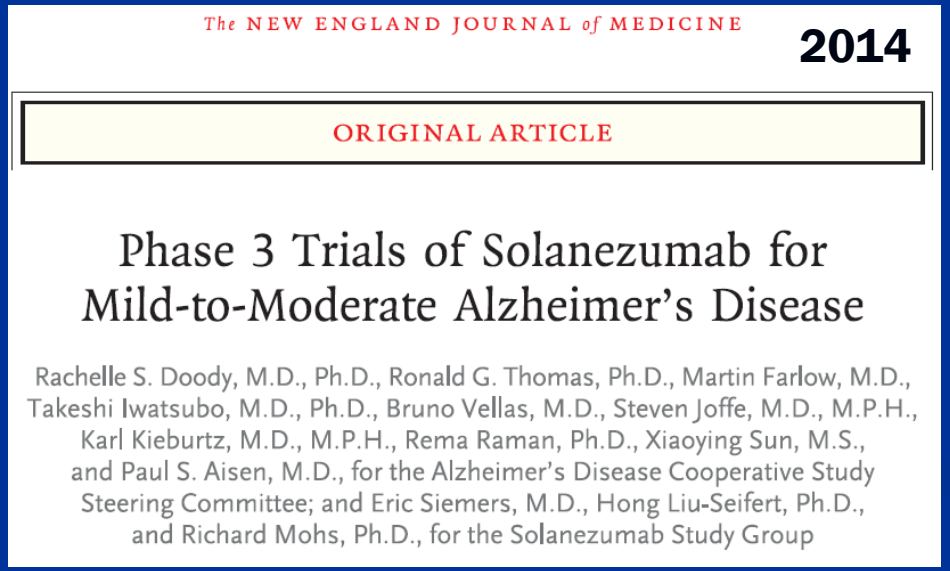
Why update 2011 NIA AA guidelines?

- 2011 presented a compartmentalized view of AD
  - AD is a continuum, not 3 separate entities
- Harmonize definition of AD across continuum
  - Prob AD – 2011 retained clinical definitions from McKhann 1984
- Harmonize implementation of biomarkers across continuum
- Introduction of tau PET – integrate into framework
- Increasing acceptance that certain biomarkers are valid proxies for AD pathologic changes
- Increasing recognition of frequent mismatches betw clinical dx of "AD" & neuropath dx (*Beach 2012*; Se 70-87%; Sp 44-70%)

Why update 2011 NIA AA guidelines?

30% error rate not tolerable "when it matters"

- clinical trials of disease modifying interventions
  - Symptomatic - need for diagnostic specificity (clinical dx 30% error)
  - Pre clinical - intervention to prevent symptom onset

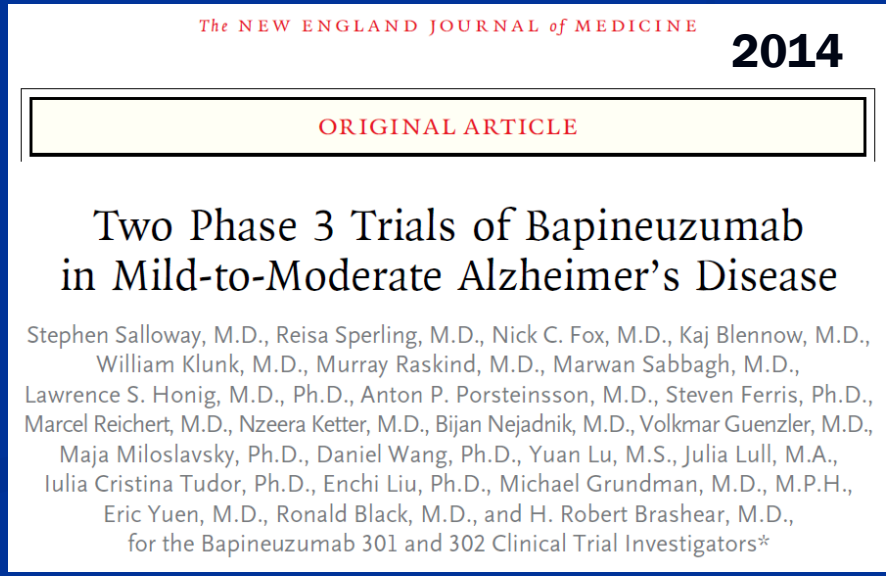


The NEW ENGLAND JOURNAL of MEDICINE 2014

ORIGINAL ARTICLE

Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer's Disease

Rachelle S. Doody, M.D., Ph.D., Ronald G. Thomas, Ph.D., Martin Farlow, M.D., Takeshi Iwatsubo, M.D., Ph.D., Bruno Vellas, M.D., Steven Joffe, M.D., M.P.H., Karl Kieburtz, M.D., M.P.H., Rema Raman, Ph.D., Xiaoying Sun, M.S., and Paul S. Aisen, M.D., for the Alzheimer's Disease Cooperative Study Steering Committee; and Eric Siemers, M.D., Hong Liu-Seifert, Ph.D., and Richard Mohs, Ph.D., for the Solanezumab Study Group



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ORIGINAL ARTICLE

Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease

Stephen Salloway, M.D., Reisa Sperling, M.D., Nick C. Fox, M.D., Kaj Blennow, M.D., William Klunk, M.D., Murray Raskind, M.D., Marwan Sabbagh, M.D., Lawrence S. Honig, M.D., Ph.D., Anton P. Porsteinsson, M.D., Steven Ferris, Ph.D., Marcel Reichert, M.D., Nzeera Ketter, M.D., Bijan Nejadnik, M.D., Volkmar Guenzler, M.D., Maja Miloslavsky, Ph.D., Daniel Wang, Ph.D., Yuan Lu, M.S., Julia Lull, M.A., Iulia Cristina Tudor, Ph.D., Enchi Liu, Ph.D., Michael Grundman, M.D., M.P.H., Eric Yuen, M.D., Ronald Black, M.D., and H. Robert Brashear, M.D., for the Bapineuzumab 301 and 302 Clinical Trial Investigators*

ELSEVIER

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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

Guiding principles

- OBJECTIVE: update a scheme for *defining* and *staging* the disease across its entire spectrum with which the research community can *communicate findings in a common manner*
- *Research* framework, not intended for general clinical care
- 2 use cases – *observational* and *interventional* research

What is the definition of AD? BIOLOGICAL

- Separation of syndrome from disease
- Term AD refers to pathologic change – not to a syndrome(s)
- AD is identified at post mortem by pathologic changes and in vivo by biomarkers
  - Symptoms are part of the disease continuum not its definition
  - major shift in thinking

What biomarker profile(s) define AD? guiding principles

- only biomarkers that are specific for hallmark AD proteinopathies (i.e. Ab and pathologic tau) were considered as potential biomarkers defining the presence of the disease
- Specifications: must function equally well throughout the disease spectrum
  - early through late life onset
  - from pre symptomatic through symptomatic phases
  - for both typical and atypical clinical presentations

Definition of Alzheimer's spectrum

- "Alzheimer's pathologic change " - biomarker evidence of B-amyloid alone
  - applied when tau biomarker normal or not available
  - ample data supporting causal/early role for Ab
- "Alzheimer's disease" - biomarker evidence of both amyloid and pathologic tau is required
  - Harmonizes in vivo and neuropath definition
- not regarded as separate entities but earlier and later phases of "Alzheimer's continuum" (umbrella term)

Operationalization: how to create orderly, common use framework?
AT(N) biomarker grouping, Neurology 2016

- B-amyloid plaques or associated pathologic state: A
  - CSF Ab 42 (low), or better low 42/40 ratio
  - Amyloid PET
- Aggregated 3R/4R tau or associated pathologic state: T
  - CSF phosphorylated tau (high)
  - Tau PET
- Neuronal injury and neurodegeneration: (N)
  - Structural MRI
  - FDG PET
  - CSF total tau (high)

AT(N) biomarker profiles & categories

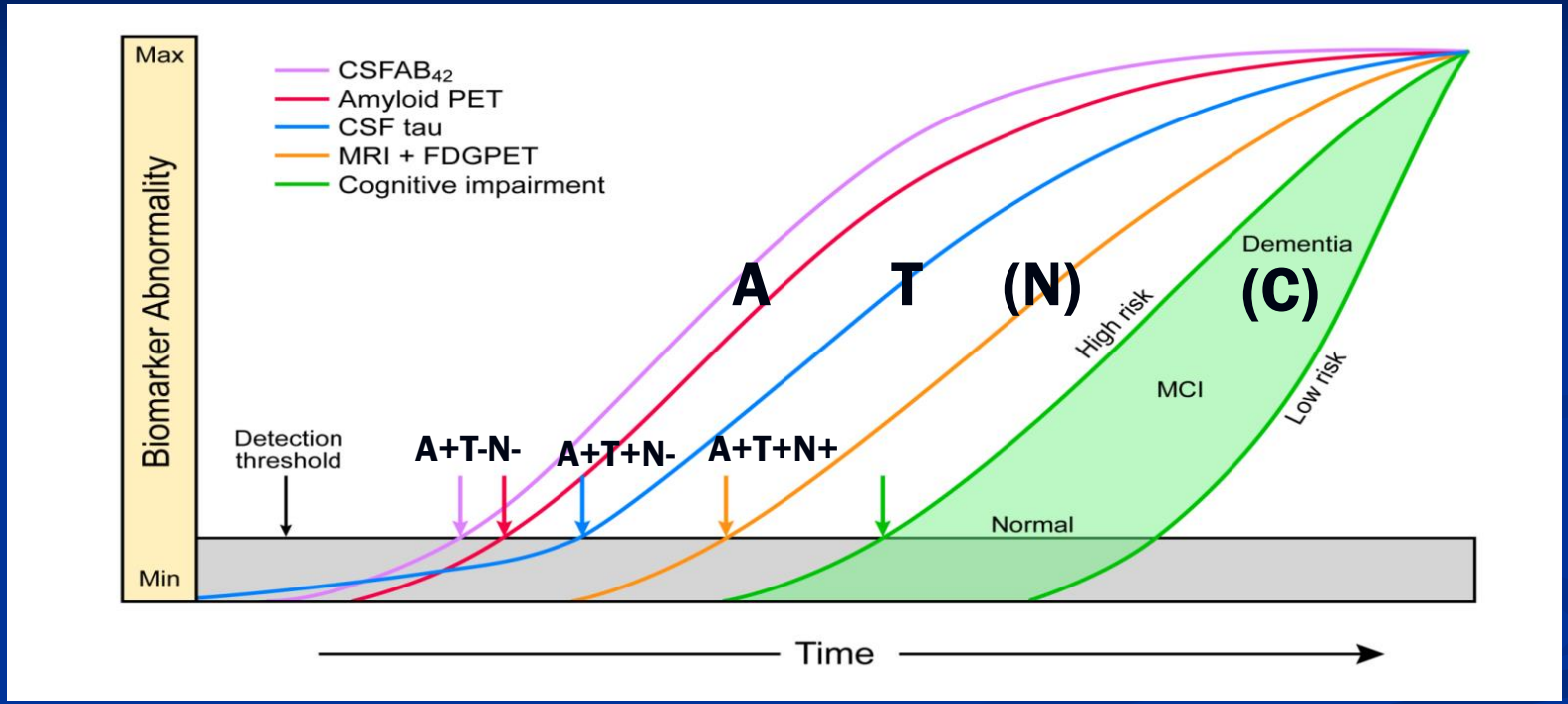
- Each biomarker group (AT(N)) *can be* dichotomized

  8 "profiles"
- 3 "biomarker categories";
  - normal biomarkers
  - Alzheimer's continuum
  - Non AD pathologic change (SNAP)

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	

dynamic biomarker model: modified amyloid cascade

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



Jack et al, Lancet Neurology 2010, 2013, Neuron 2013

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AT(N) biomarker profile *evolution*

- B-amyloid plaques or associated pathologic state: A
  - CSF Ab 42, or better low 42/40 ratio
  - Amyloid PET
  - *Plasma Ab42/40*
  - *Retinal imaging*
- Aggregated 3R/4R tau or associated pathologic state: T
  - CSF phosphorylated tau
  - Tau PET
  - *Plasma P-tau*
- Neuronal injury and neurodegeneration (N)
  - Structural MRI
  - FDG PET
  - *CSF or plasma NFL*
  - *UCB-J PET*
- *Vascular*
- *Inflammation*
- *Alpha synuclein*
- *TDP 43*

T tau CSF /plasma?

Defining vs staging

- measures used to define AD must be specific vs. measures used to stage need not be → different roles
- **Definition**
  - **A:** Aβ biomarkers determine whether or not an individual is in the Alzheimer's continuum
  - **T:** Pathologic tau biomarkers determine if someone who is in the Alzheimer's continuum has AD
- **Staging severity**
  - **(N):** Neurodegenerative/ neuronal injury biomarkers
  - **(C):** cognitive symptoms

framework cognitive staging - 2 schemes

- Syndromal categorical cognitive staging
  - Cognitively unimpaired (CU), MCI, dementia - largely same as 2011
  - Independent from biomarkers
  - Includes all members of cohort
- Numeric clinical staging (1-6)
  - avoids traditional syndromal labels
  - Applicable *only* to those in the Alzheimer's continuum

Early Alzheimer's Disease: Developing Drugs for Treatment

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Billy Dunn at 301-796-2250 or (CBER) Office of Communication, Outreach, and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

February 2018
Clinical/Medical

Nomenclature: Syndromal cognitive staging combined with biomarker profiles

Biomarker Profile	Cognitive stage: Cognitively Unimpaired	Cognitive stage: Mild Cognitive Impairment	Cognitive stage: Dementia
$A^- T^-(N)^-$	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
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Controversy: What is the definition of AD? How should the term AD be used?

- Biological definition is appropriate
- Biological definition is not appropriate

What is the alternative to a biological definition of AD?

- Often not precisely articulated but usually some sort of cognitive impairment/dementia syndrome
- Possible clinical definitions
  - AD = dementia
  - AD = amnestic dementia

Consequence of defining AD as dementia

- MAPT mutation carriers = AD
- Progranulin mutation carriers = AD
- CJD = AD
- Huntington's disease = AD
- Multiple strokes = AD
- The obstructive hydrocephalus variant of AD
- The MS variant of AD
- The brain tumor variant of AD

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A Critique of the 2018 National Institute on Aging's. Research Framework: Toward a biological definition of Alzheimer's disease

Department of Social Work,

Abstract

Shame on the National Institute on Aging (NIA) for sponsoring a new way of defining Alzheimer's disease based on biomarkers (plaques and tangles). Heiko Braak in 2011 after dissecting 2,332

Conclusion:

"Alzheimer's disease is likely caused by a mosaic that includes: viral (HIV/AIDS, herpes simplex virus type I, varicella zoster virus, cytomegalovirus, Epstein-Barr virus), bacteria (syphilis and lyme-disease/borrelia), parasites (toxoplasmosis, cryptococcosis and neurocysticercosis), fungi (Candida glabrata), infections (possibly prions), and vascular (stroke, multiple-infarct dementia, hydrocephalus, injury and brain tumors)."

What is the alternative to a biological definition of AD?

- Often not precisely articulated but usually some sort of cognitive impairment/dementia
- Possible clinical definitions
  - AD = dementia
  - AD = amnestic dementia

some insist AD means dementia syndrome

- Preclinical AD not valid concept, symptoms required, at risk for AD
  - Response: Preclinical dz. is universal in medicine. At risk for AD?
- Use of term AD to mean syndrome too engrained to change
  - Response: change always possible, education needed – e.g. addiction
- Biological definition premature, biomarkers not yet well studied
  - Response: CSF 20 yrs, routine in Europe, commercial test available. Amyloid PET > 10 yrs, MRI FDG 30-35 yrs
- Biological definition devalues research without biomarkers

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- Biological definition devalues research without biomarkers
  - Response – next slide

Clinical research without biomarkers

- clinical research without biomarkers does not have to label dementia syndrome as AD to be valuable
  - "Rehabilitate use of the term dementia" – Jagust
- clinical research without biomarkers provides information about risk factors for *clinically defined* syndromes & societal burden of cognitive disability – but not AD
  - amnestic multi domain dementia *is not* synonymous with the presence of b-amyloid deposition and neurofibrillary degeneration (i.e. AD)
  - absence of amnestic dementia *is not* synonymous with the absence of b-amyloid deposition and neurofibrillary degeneration (i.e. AD)

Clinical research without biomarkers

- "recommend that a clinically ascertained syndrome consistent with what has historically been labeled "probable or possible AD" be referred to as **Alzheimer's clinical syndrome**, but *not* as *Alzheimer's disease* or some modified form of *Alzheimer's disease* (e.g. possible or probable AD")"
- terminology applies to both mildly impaired and demented individuals
- terminology is consistent with our position that a dementia syndrome can be due to a variety of diseases, one is AD
- Consistent with FTLD field – eg CBS vs CBD

definition of AD vs mechanisms underlying AD

- NIA AA framework does not require A and T to be causal
  - framework can serve as a hypothesis testing platform for disease models where A and T are present as epiphenomena as well as models where they are causal
- BUT it is A and T proteinopathies that define AD as a unique disease among the many that can lead to dementia
- No "amyloid free" or "tau free" Alzheimers disease
  - "amyloid free" or "tau free" dementia yes, AD no

Conclusions

- Recommend biological definition of AD: separation of syndrome from pathologic change
  - AD is defined by AD neuropathologic change (plaques/tangles) or its biomarkers, not by presence or nature of clinical symptoms
- Why
  - Better understanding of the sequence of events in Alzheimer's continuum that lead to cognitive impairment
  - Better understanding of the multi factorial etiology of dementia
  - a more precise approach to therapeutic interventional trials