The development and evolution of a classification system for AD biomarkers: from A to AN to ATN

ADC meeting 2016, Baltimore

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From A to AN:
NIA-AA 2011 biomarker categorization

- Operationalizable with either imaging or CSF
- Neurodegeneration is related to tau in AD

- B-amyloid plaques (A)
  - CSF Ab 42
  - Amyloid PET
- Tau related neurodegeneration/ neuronal injury (N)
  - CSF phosphorylated tau and total tau
  - Structural MRI
  - FDG PET

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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

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Staging categories for preclinical AD research

Stage	Description	Aβ (PET or CSF)	Markers of neuronal injury (tau, FDG, sMRI)	Evidence of subtle cognitive change
Stage 1	Asymptomatic cerebral amyloidosis	Positive	Negative	Negative
Stage 2	Asymptomatic amyloidosis + "downstream" neurodegeneration	Positive	Positive	Negative
Stage 3	Amyloidosis + neuronal injury + subtle cognitive/behavioral decline	Positive	Positive	Positive

An Operational Approach to National Institute on Aging–Alzheimer's Association Criteria for Preclinical Alzheimer Disease

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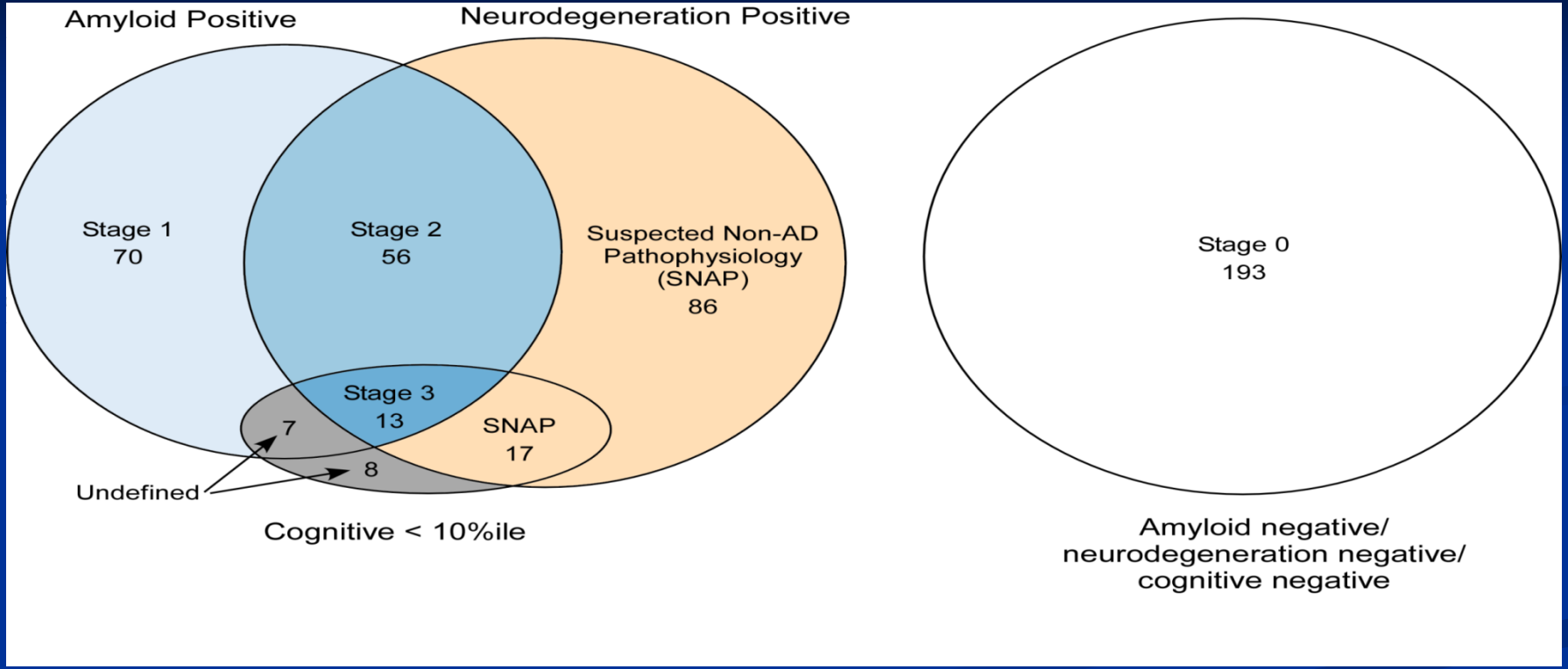
Annals Neurol 2012

Objectives

- Operationalize NIA-AA criteria: amyloid PET, FDG, MRI
- How do clincally normal participants distribute in the NIA-AA preclinical scheme?

Prevalence of 450 CN in MCSA by NIA-AA Preclinical Stage

Jack et al, Annals Neurol 2012



0 – 43%; 1 - 16%; 2 – 12%; 3 – 3%'; SNAP – 23%; Unclassif – 4%

Suspected non-Alzheimer's pathophysiology (SNAP)

- SNAP is a biomarker based construct denoting amyloid negative neurodegeneration positive individuals
- Suspected to be pathologically heterogeneous, composed of a variety of non-AD etiologies common in aging
- Common in CN and MCI elderly ~ 25%
- APOE4 is infrequent compared to amyloid positive (A+N- and A+N+) individuals

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NIA-AA staging +SNAP: 2-class AN biomarker categorization

- A-N- stage 0
- A+N- preclinical stage 1
- A+N+ preclinical stage 2/3
- A-N+ suspected non-Alzheimers pathophysiology, (SNAP) - heterogeneous non-AD catch all category

NIA-AA staging +SNAP

- enabled research community to communicate in a common language
- recognition that findings are consistent across studies

CN

- Knopman 2012
- Vos 2013
- Roe 2013
- Van Harten 2013
- Mormino 2014
- Toledo 2014
- Vos 2016
- Burnham 2016

MCI

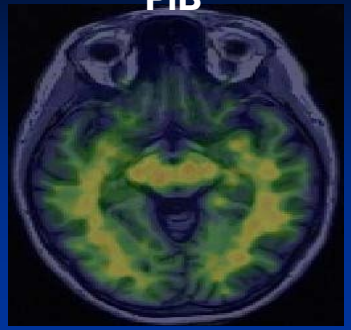
- Prestia 2013
- Petersen 2013
- Caroli 2015
- Vos 2015
- Wisse 2015

Is 2-class AN categorization the most precise way to think about biomarkers in 2016?

- tau PET, new enabling technology → rethink categorization
- weakness of NIA-AA plus SNAP - grouping CSF ptau along with t-tau, MRI, FDG into same "N" category
- solution
  - Biomarkers specific for aggregated tau (T)
  - Biomarkers of neurodegeneration/neuronal injury without conditioning on presumed association with tauopathy (N)
- Identify T and N that is and isn't associated with each other
- From AN to ATN

CN PiB -

PiB



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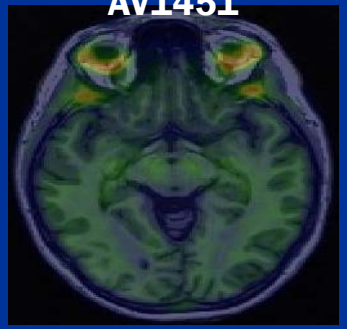

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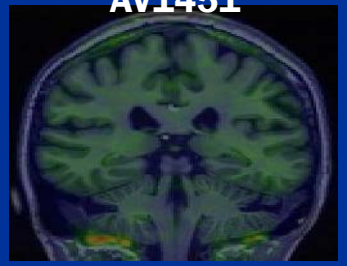
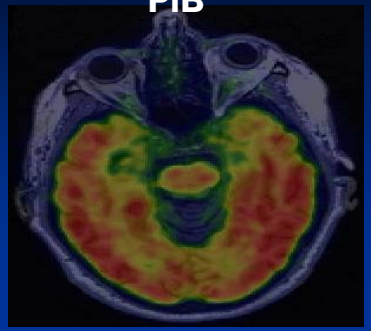


CN PiB +

PiB



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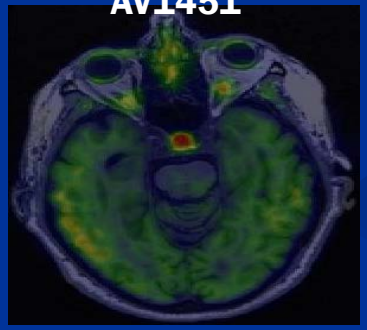

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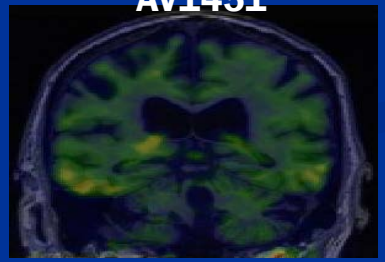

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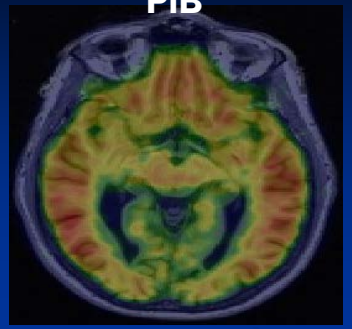
PiB



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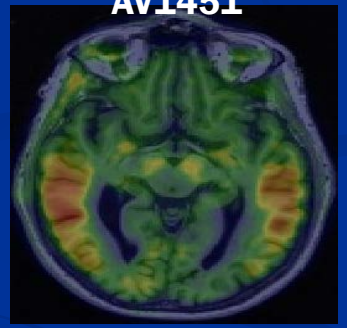

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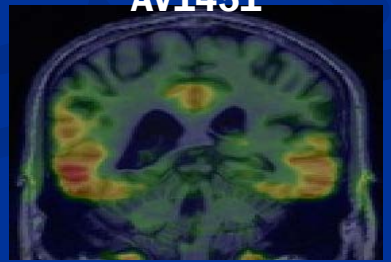

A/T/N: An unbiased descriptive classification scheme for Alzheimer disease biomarkers

OPEN

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ABSTRACT

Biomarkers have become an essential component of Alzheimer disease (AD) research and because of the pervasiveness of AD pathology in the elderly, the same biomarkers are used in cognitive aging research. A number of current issues suggest that an unbiased descriptive classification scheme for these biomarkers would be useful. We propose the "A/T/N" system in which 7 major AD biomarkers are divided into 3 binary categories based on the nature of the pathophysiology that each measures. "A" refers to the value of a β-amyloid biomarker (amyloid PET or CSF $A\beta_{42}$); "T," the value of a tau biomarker (CSF phospho tau, or tau PET); and "N," biomarkers of neurodegeneration or neuronal injury ([^{18}F]-fluorodeoxyglucose–PET, structural MRI, or CSF total tau). Each biomarker category is rated as positive or negative. An individual score might appear as A+/T+/N−, or A+/T−/N−, etc. The A/T/N system includes the new modality tau PET. It is agnostic to the temporal ordering of mechanisms underlying AD pathogenesis. It includes all individuals in any population regardless of the mix of biomarker findings and therefore is suited to population studies of cognitive aging. It does not specify disease labels and thus is not a diagnostic classification system. It is a descriptive system for categorizing multidomain biomarker findings at the individual person level in a format that is easy to understand and use. Given the present lack of consensus among AD specialists on terminology across the clinically normal to dementia spectrum, a biomarker classification scheme will have broadest acceptance if it is independent from any one clinically defined diagnostic scheme. *Neurology*® 2016;87:1–9

3-class categorization: ATN biomarker grouping

- B-amyloid plaques or assoc. pathophysiology (A) - specific
  - CSF Ab 42 (low), or better low 42/40 ratio
  - Amyloid PET
- Aggregated tau or assoc. pathophysiology (T) - specific
  - CSF phosphorylated tau (high)
  - Tau PET
- Neuronal injury and neurodegeneration (N) – non specific
  - Structural MRI
  - FDG PET
  - CSF total tau (high)

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ATN

- Each biomarker category is binary – 8 combinations/profiles

A-/T-/N-
A+/T-/N-
A+/T+/N-
A+/T-/N+
A+/T+/N+
A-/T+/N-
A-/T-/N+
A-/T+/N+

Analogy: TNM colon cancer staging

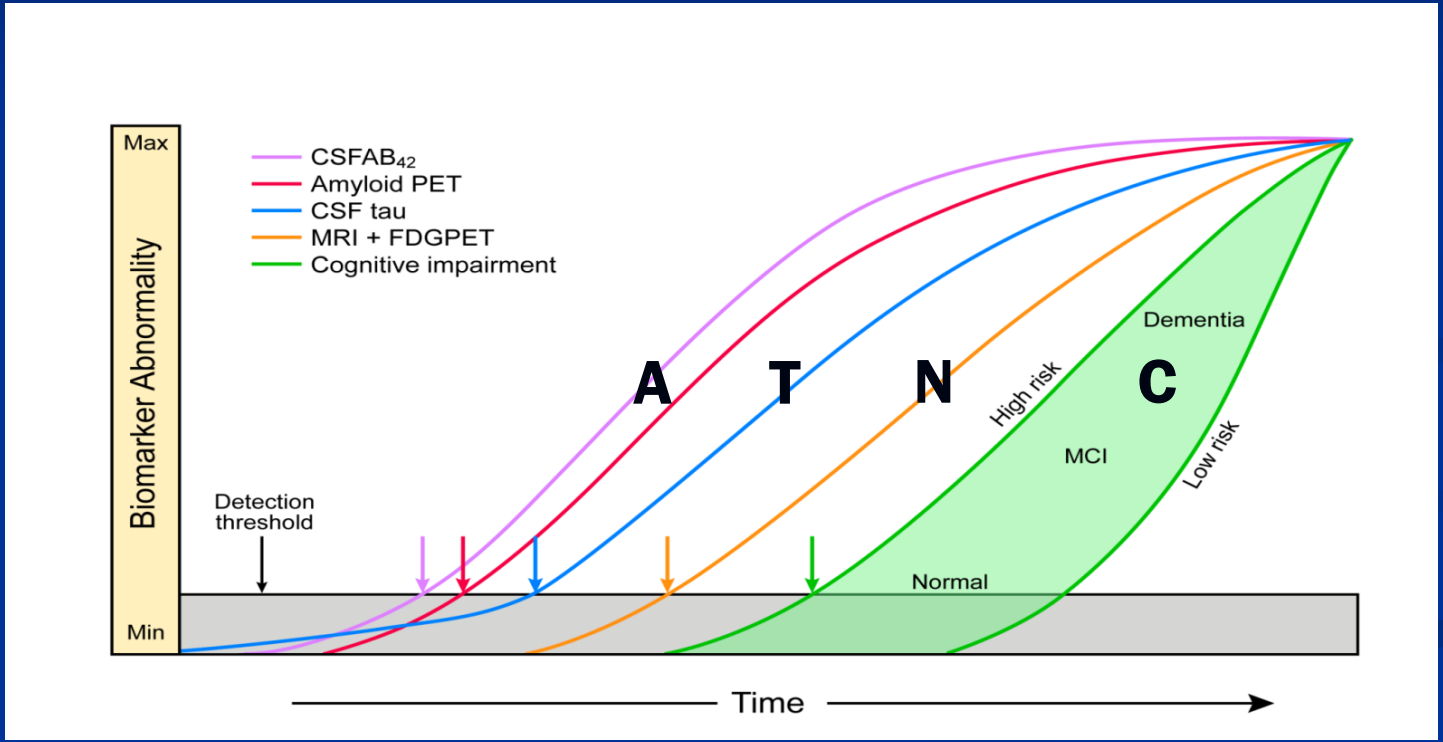
- **Tumor (T)** how far the primary tumor has grown into the wall of the colon or rectum, and if it has expanded into nearby areas.
- **Lymph node (N)** extent of spread to nearby lymph nodes.
- **Metastasis (M)** to other organs
- A number (0-4) is assigned to each factor, a higher number indicates increasing severity

ATN operationalization

- Individuals can be fully classified by CSF alone or imaging alone
- within a given research study, use one biomarker per category, not either/or mixtures of 2 or 3
- Extensions – vascular A/T/N/V……LB, TPD43, etc
  - Marchant 2012, Vemuri 2015

Application will include clinical: ATNC

A/T/N/Cn, A/T/N/Cm, A/T/N/Cd



Lancet Neurology, Feb, 2013

Does ATN work?

- Operationalization
  - Quantitative imaging methods – pipelines
  - Cutpoints
- application

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Alzheimer's & Dementia

Featured Article

Defining imaging biomarker cut points for brain aging and Alzheimer's disease

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Age and sex specific prevalences of cerebral β-amyloidosis, tauopathy and neurodegeneration among clinically normal individuals aged 50–95 years – in review

- ATN in 389 clinically normal MCSA participants
- People in every group – ie all needed to characterize population
- Dramatic changes in ATN prevalences with aging
- By age 85 prevalence of A−T−N− about 10%
  - 90% have abnormal biomarker profiles

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Age and sex specific prevalences of cerebral β-amyloidosis, tauopathy and neurodegeneration among clinically normal individuals aged 50–95 years – in review

- tau and neurodegeneration are discordant in
  - majority of SNAP (where N+ is defined by MR)
  - majority of NIA-AA stage 2/3 individuals
  - value of scoring T and N separately
- proportion of SNAP with evidence of tauopathy is 50% at age 65 and 39% at age 80 → tau (PART) does contribute to SNAP

Likely objections to ATN

- argument
- rebuttal

CSF p and t tau should not be placed in different categories

- Argument: Both are increased in AD and not in primary tauopathies
- rebuttal: Kaj Blennow
  - marked temporary increase in T-tau with normal P-tau in TBI & stroke (Hesse 2001; Ost,2006)
  - T tau not p tau elevated in also CJD
- T tau – measure of active neuronal injury (N)
- P tau – measure of pathophysiology assoc with NFT burden (T)

Neurodegenerative/neuronal injury category is misnamed because MRI, FDG, t tau disagree with each other often

- Jagust 2009; Toledo 2014;Alexopoulos 2014; Vos 2016
- Rebuttal: what is the rational substrate of …..
  - Atrophy: cumulative loss of dendritic spines, synapses, neurons
  - elevated CSF t tau: active injury to neurons
  - Hypometabolism: loss spines, synapses, neurons and dysfunction of neurons
- rebuttal: each measures different aspects of the same construct –

  loss of structure or function of, or injury to neurons
- Free recall vs cued recall – does disassociation mean these aren't both measures of memory

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Summary: ATN

- descriptive system for categorizing multi domain biomarker findings at individual level in format that is easy to understand and use
- Includes tau PET
- Includes all individuals in population
- Can be used with any clinical classification system
- Allows investigators to communicate in a common language
- unifying conceptual approach to biomarkers

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