Topic #1

The latest advances in the understanding of the pathophysiology of Alzheimer's Disease and the development of disease-modifying therapies

Gary Romano
On behalf of the EFPIA Working Group

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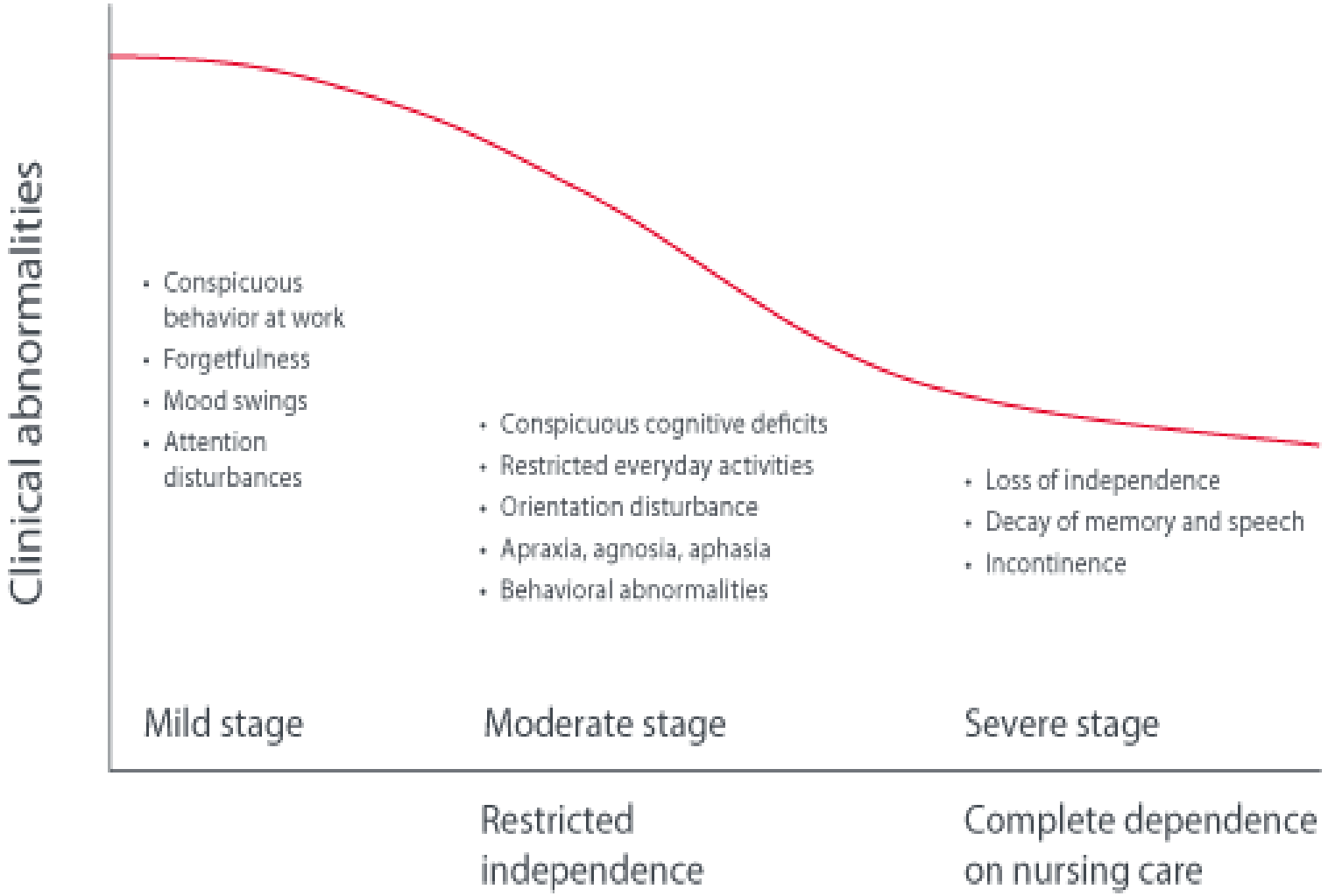
London UK

Disclosure

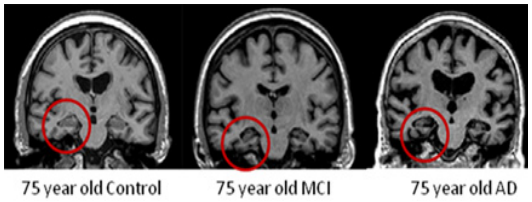
- Gary Romano is the Head of AD clinical development for Janssen R&D.

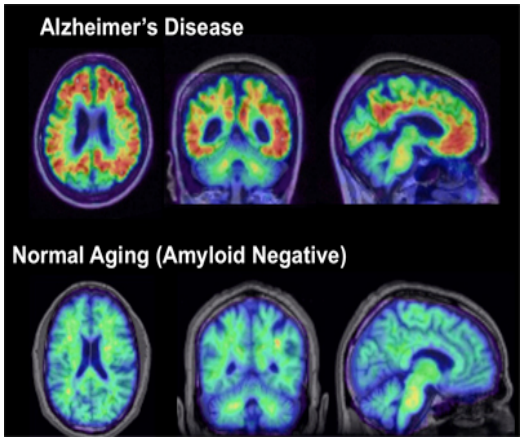
Historically AD diagnosis was based on clinical symptoms alone ….and trials were necessarily focused on the dementia stages

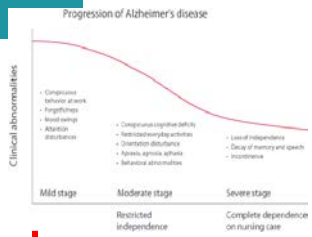


Biomarker and neuropathological studies have since shown that the pathophysiological processes of AD begin more than a decade before clinical symptomatology

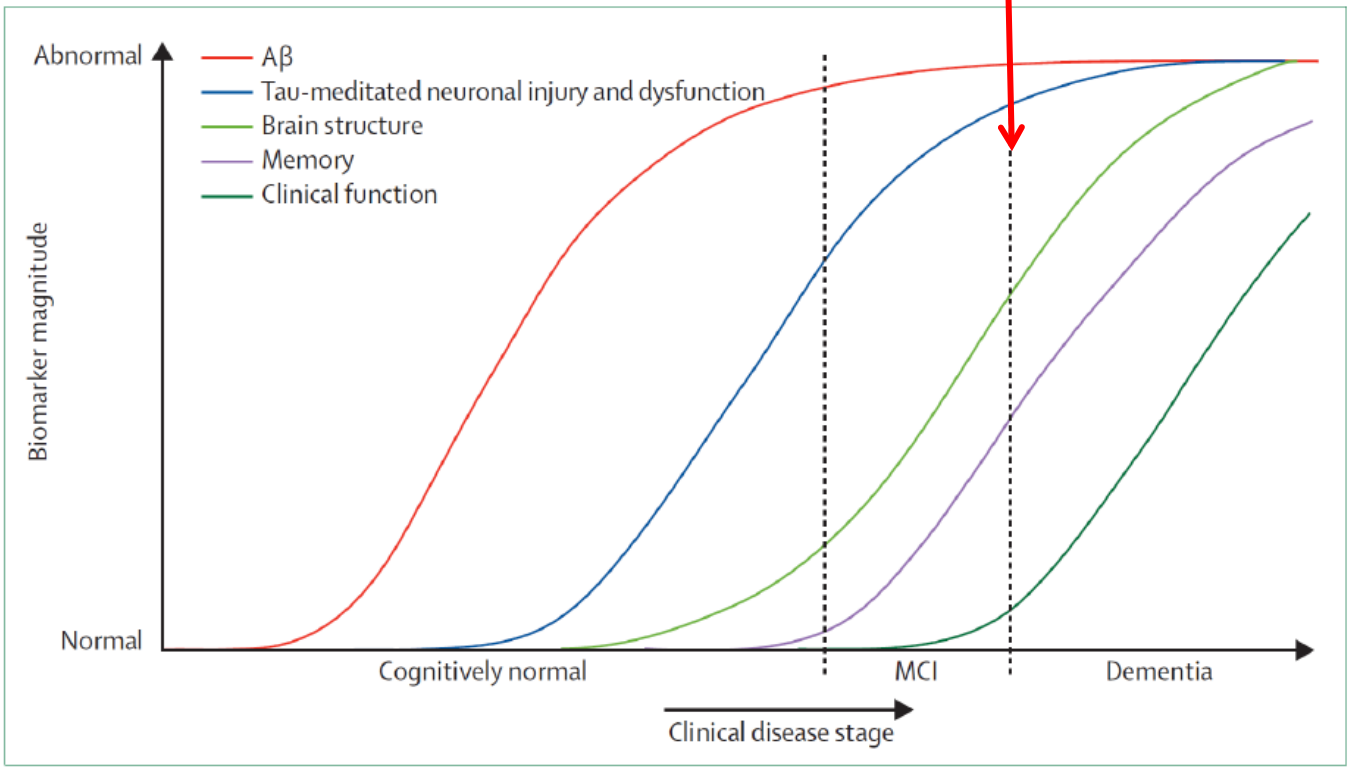
ADNI
Alzheimer's Disease Neuroimaging Initiative







end stage disease



Amyloid pathology and early neuronal degeneration

Widespread neurodegeneration and irreversible neuronal loss with progressive cognitive and functional impairment

IWG-2 and National Institute of Aging – Alzheimer's Association establish research criteria for early, asymptomatic stage of AD based on presence of pathological biomarkers

IWG-2 criteria for asymptomatic at risk for AD (A plus B)

A Absence of specific clinical phenotype (both are required)
- Absence of amnestic syndrome of the hippocampal type
- Absence of any clinical phenotype of atypical AD

B In-vivo evidence of Alzheimer's pathology (one of the following)
- Decreased $A\beta_{1-42}$ together with increased T-tau or P-tau in CSF
- Increased retention on fibrillar amyloid PET

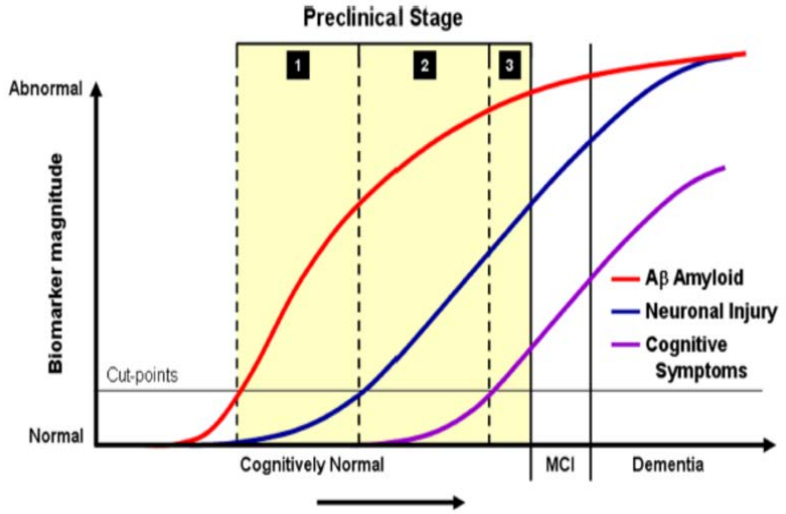
Lancet Neurol 2014; 13: 614–29

Proposed staging of preclinical AD

Definitions for the preclinical stages of AD were recently outlined by the US National Institute on Aging:[1]

- Stage 1: Asymptomatic cerebral amyloidosis
- Stage 2: Amyloidosis + evidence of neurodegeneration or neuronal injury
- Stage 3: Amyloidosis + neurodegeneration + evidence of subtle cognitive decline

Alzheimers Dement. 2011 May ; 7(3): 280–292.



Preclinical AD ~ Asymptomatic at risk for Alzheimer's Dementia

May begin 10+ years before prodromal AD

“despite differences in methodology…the findings converge convincingly.”

	Progression to CDR ≥0·5, symptomatic AD		
	5-year progression	Uncorrected SHR (95% CI)*	p for comparisons with other groups
Normal group	2%	Ref	1: p=0·016; 2: p=0·0002; 3: p<0·0001; 5: p=0·20
Stage 1	11%	7·0 (1·4–34·1)	N: p=0·016; 2: p=0·061; 3: p=0·0004; 5: p=0·20
Stage 2	26%	18·1 (3·9–83·1)	N: p=0·0002; 1: p=0·061; 3: p=0·066; 5: p=0·0047
Stage 3	56%	49·2 (10·1–240·4)	N: p<0·0001; 1: p=0·0004; 2: p=0·066; 5: p<0·0001
SNAP group	5%	3·1 (0·6–17·6)	N: p=0·20; 1: p=0·20; 2: p=0·0047; 3: p<0·0001

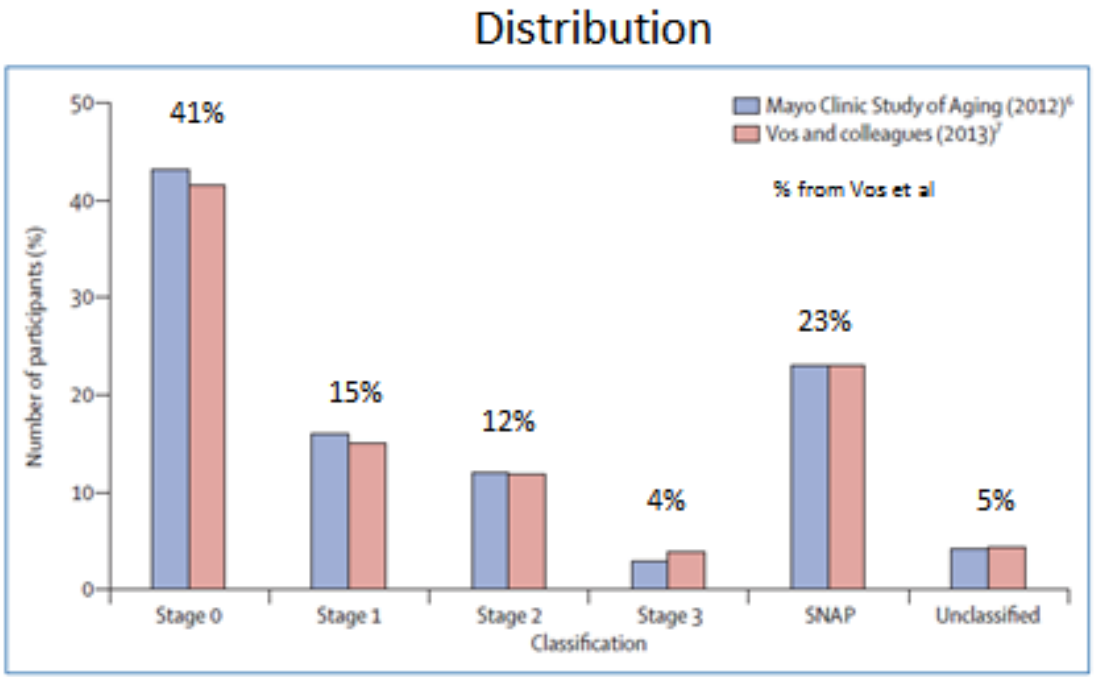
Vos et al
Lancet Neurology 2013

Table 3 **Proportion of participants who progressed to MCI/AD within 15 months by stage**

Comparison	Proportion progressed to MCI/ dementia within 15 mo, n (%)	p Value
Trend test stage 0-3	6 (5), 5 (11), 8 (21), 3 (43)	<0.001
Stage 0 vs 1-3	6 (5) vs 16 (18)	0.002
Stage 1 vs 2	5 (11) vs 8 (21)	0.26
Stage 2 vs 3	8 (21) vs 3 (43)	0.21
Stage 1-3 vs SNAP group	16 (18) vs 7 (10)	0.18
Stage 2 + 3 vs SNAP group	11 (24) vs 7 (10)	0.05
Stage 0 vs SNAP	6 (5) vs 7 (10)	0.15

Knopman et al
Neurology 2012

Do preclinical Alzheimer's disease criteria work?



- 31% would be screened positive by biomarkers for stage 1-3
- 16% would be screened positive by biomarkers for stage 2&3

"Despite the use of CSF analysis rather than neuroimaging to assess biomarkers and use of a convenience rather than a population-based sample, the frequencies coincide reasonably well (figure). As such, these two studies, although not definitive, provide strong support for the validity of the construct of preclinical AD."

www.thelancet.com/neurology Vol 12 October 2013

Ronald C Petersen
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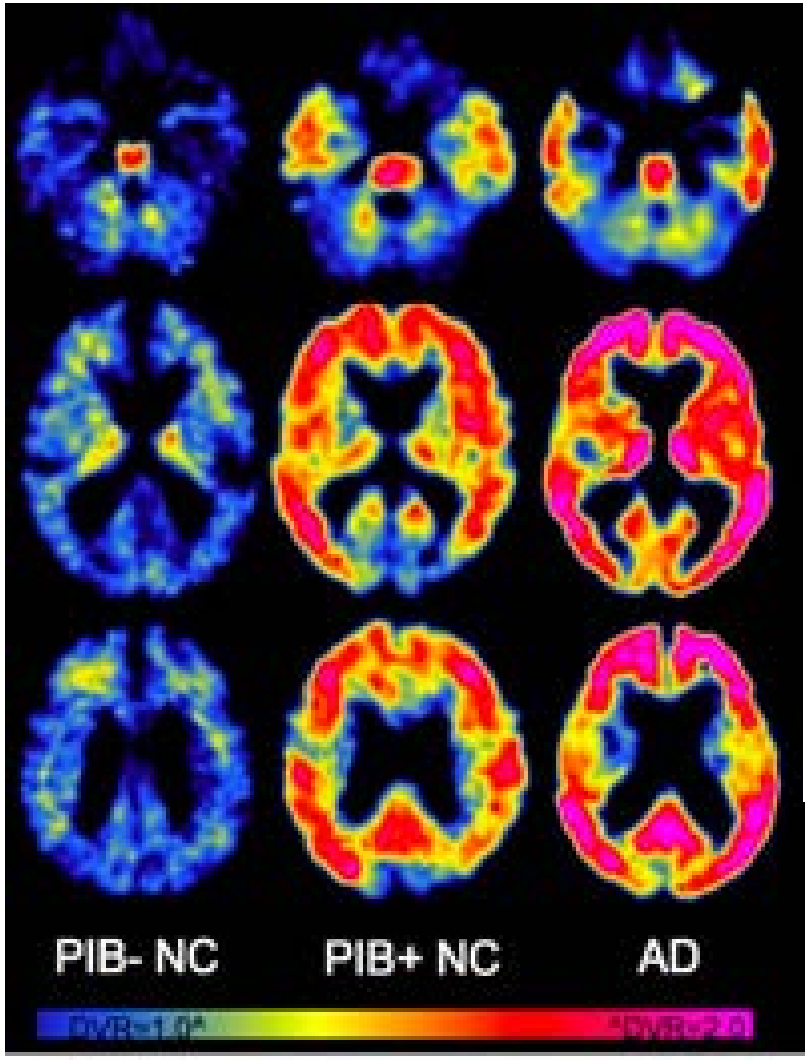
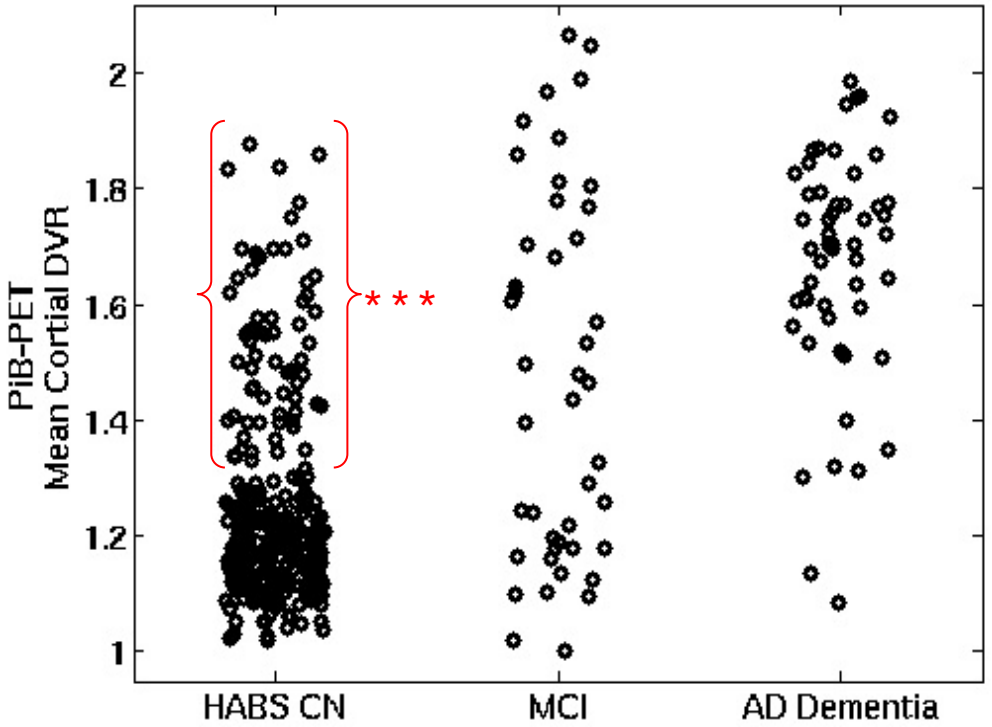
Amyloid detection using PET imaging in ‘Normal Controls’ MCI* and Demented AD patients**

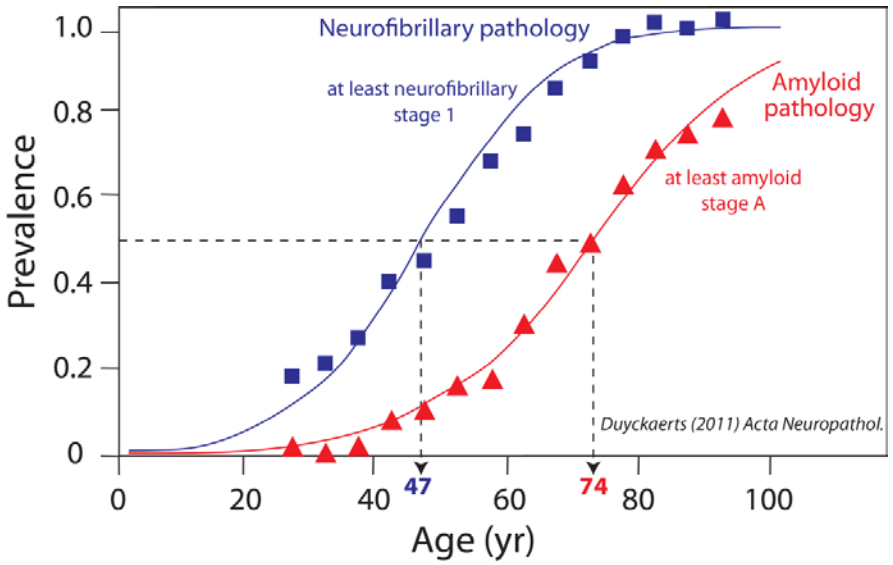




Harvard Aging Brain Study
Sperling, Johnson *NeuroMolecular Med* 2010

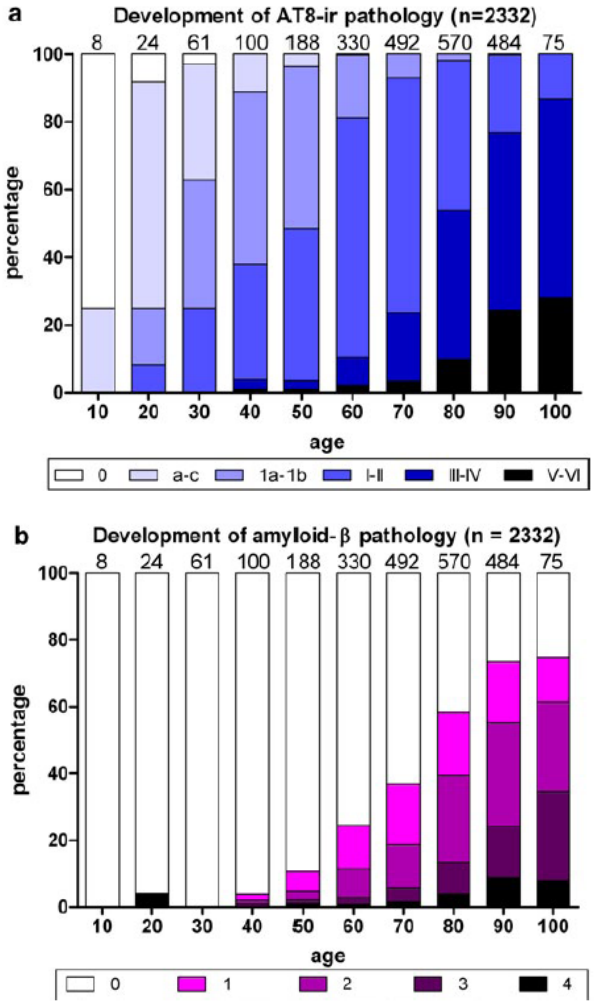
*Mild Cognitive Impairment
**clinically diagnosed, likely contains cases of non-AD pathology
***high levels of amyloid burden (above normal threshold)

Emerging evidence suggests that Tau aggregation pathology is also a very early event in pathogenesis



Duyckaerts (2011) Lancet Neurology 10, 774-775.

Regulatory framework needs to be open to alternative theories of molecular pathogenesis



Braak et al (2013), Acta Neuropath,126:631-41

May begin 10+ years before prodromal AD

Rationale for Targeting Preclinical AD (Asymptomatic At Risk for Alzheimer's Dementia)

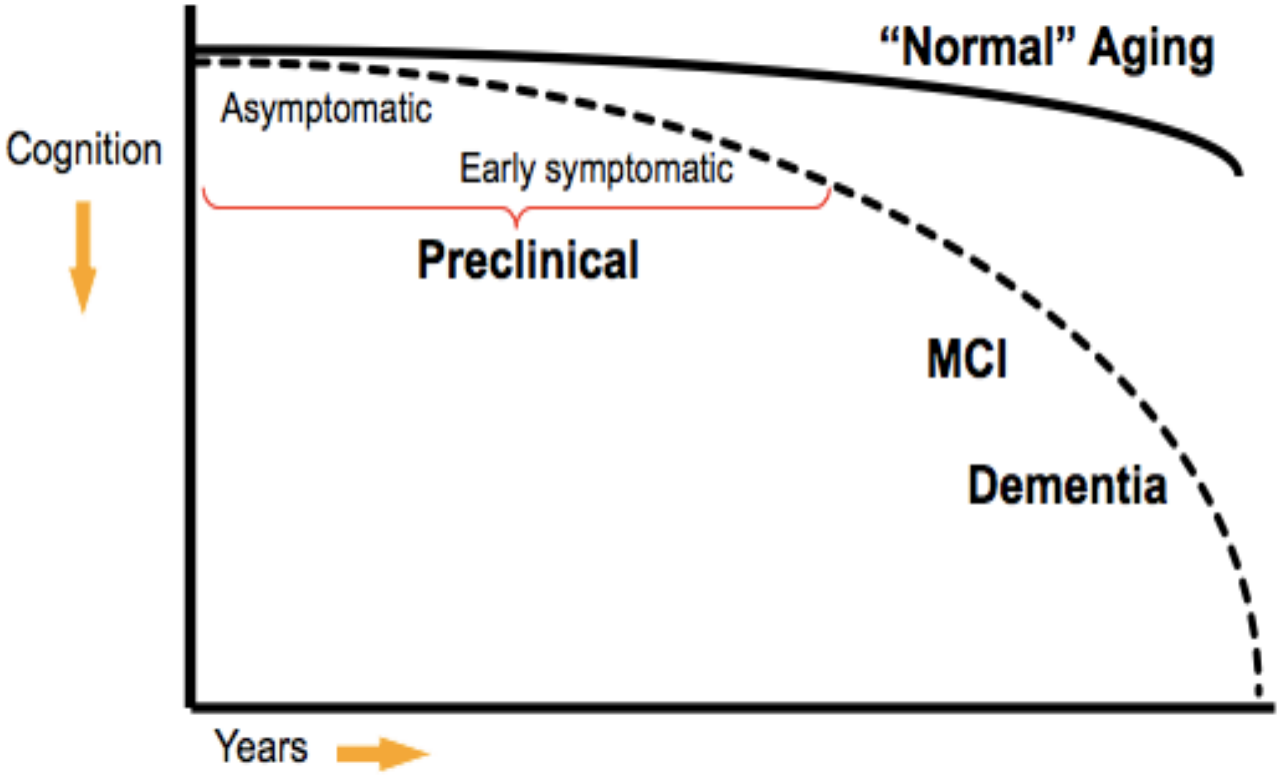
- Pathophysiological process of AD begins before onset of symptoms and dementia
  - New evidence indicates about 1/3 of asymptomatic older individuals harbor evidence of amyloid accumulation*
  - Developing work with tau markers (CSF, imaging) suggests tau pathology also begins in asymptomatic stage.
- Amyloid positive asymptomatic individuals*
  - Have AD-like structural and functional imaging abnormalities
  - Have subtle memory deficits, and faster rates of cognitive decline
  - Represent an older population at high risk for progression to AD dementia
  - Now amenable for a disease interception study

Reisa Sperling
*Harvard Ageing Study Group, others
AAIC, 2014

Clinical Trials in Preclinical AD are now feasible

- Reliable biomarker assays for diagnosis are available
  - CSF measures of Abeta and Tau/p-Tau
  - Amyloid PET ligands
- Asymptomatic subjects at risk can be accurately identified & recruited
  - Early disease stage registries/cohorts are being assembled
- Subtle cognitive decline can be measured with fit-for-purpose cognitive assessments in individuals who are asymptomatic at risk
  - E.g., PACC cognitive composite (Donohue et al, Neurology 2014)

The continuum of AD and normal aging



PATIENT OF TODAY

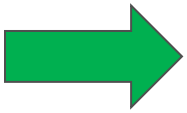
PATIENT OF TOMORROW

Summary

- AD pathophysiology begins decades before manifest clinical impairment
- Research criteria established for early, asymptomatic stage of AD by IWG-2 and NIA-AA
  - Based on presence of pathological biomarkers
  - Independent cohort studies provide strong support for the validity of the construct of preclinical AD.
- Clinical trials in preclinical AD are now feasible
- AD presents unique challenges to the development and registration of therapeutics for early disease interception
- Regulatory guidance can help to overcome these barriers to investment

Key Issues: Disease Intervention in Preclinical Alzheimer's presents unique challenges for drug development

- Trials in preclinical AD will require treatment of asymptomatic at-risk subjects who may not develop cognitive impairment for many years.
- Demonstration that disease interception in preclinical AD delays time to later stages of disease will take many years of observation.
- Clinical trials of long duration are likely to result in a large percentage of missing data, making it infeasible to assess long-term outcomes.



Regulatory guidance can help to lower these barriers to investment…

Key Issue: Trials in preclinical AD will require treatment of asymptomatic at-risk subjects who may not develop cognitive impairment for many years.

- From the Discussion Paper:
  - *"Preclinical AD refers to the pathophysiological stage when in vivo molecular biomarkers of AD are present, but clinical symptoms are absent"*
- *Question:*
  - *Does the Agency agree that for the purposes of a risk-benefit assessment preclinical AD should be considered a disease population?*

Key Issue: Demonstration that disease interception in preclinical AD delays time to later stages of disease will take many years of observation.

Questions:

- Does the Agency agree that stage specific endpoints based on clinically relevant phenotypic manifestations *at that stage of disease* might be sufficient for approval?
    - E.g. In preclinical AD, in which cognitive decline is the only manifestation of disease, would slowing of cognitive decline be sufficient for full approval?
- Does the Agency agree that demonstration of the clinical meaningfulness of such a cognitive treatment effect could be established through disease modeling based on data external to the drug trial?
    - E.g. data form observational studies linking cognitive decline to functional decline and/or time to dementia

Key Issue: Assessment of Efficacy in Preclinical AD

From Discussion Paper:

In section 4.5 (Assessment of Therapeutic Efficacy) specific recommendations for prodromal AD and dementia are provided. However, no specific recommendations are provided for assessment of efficacy in secondary prevention trials in Preclinical AD (asymptomatic at risk of AD or presymptomatic AD)

Question:

Does the Agency agree that the draft guidance should also include specific recommendations for the assessment of efficacy in secondary prevention trials in subjects with Preclinical AD?

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