Diagnosi preclinica e trattamento precoce

Orazio ZANETTI

Società Italiana di Gerontologia e Geriatria

U.O. Alzheimer - Centro per la Memoria

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ELSEVIER

Alzheimer's & Dementia 9 (2013) 63–75

Alzheimer's & Dementia

Review Articles

The global prevalence of dementia: A systematic review and metaanalysis

Martin Prince[a,*], Renata Bryce[a], Emiliano Albanese[a,b], Anders Wimo[c,d], Wagner Ribeiro[a,e], Cleusa P. Ferri[a,e]

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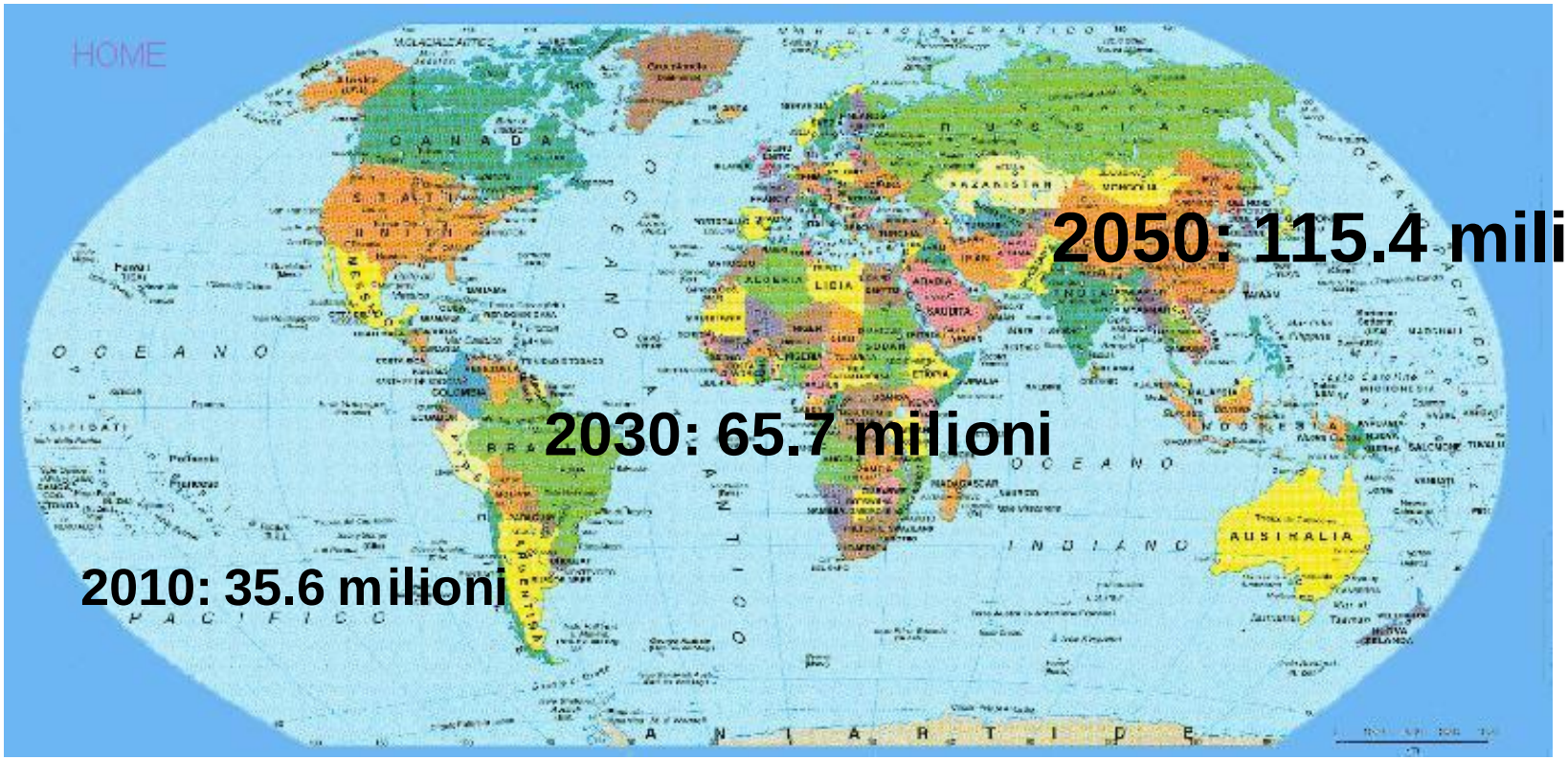
[e]Department of Psychiatry, Federal University of Sao Paulo, Sao Paulo, Brazil



SOMMARIO

- **AD preclinico: definizione**
- **I nuovi criteri diagnostici**
- **Verso terapie efficaci (*disease modifying*) precoci? (Prevenzione?)**
- **Aspetti etici e conclusioni**

SOMMARIO

- **AD preclinico: definizione**
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- **Verso terapie efficaci (*disease modifying*) precoci? (Prevenzione?)**
- **Aspetti etici e conclusioni**

Lo spettro della compromissione cognitiva

Normale “MCI” Demenza

Asintomatica

Fase preclinica-presintomatica

Paucisintomatica

Fase di predemenza

Demenza prodromica

Sintomatica

Demenza conclamata

Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade

Clifford R Jack Jr, David S Knopman, William J Jagust, Leslie M Shaw, Paul S Aisen, Michael W Weiner, Ronald C Petersen, John Q Trojanowski

Lancet Neurol 2010; 9: 119–28

Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade

Clifford R Jack Jr, David S Knopman, William J Jagust, Leslie M Shaw, Paul S Aisen, Michael W Weiner, Ronald C Petersen, John Q Trojanowski

Panel: Imaging and CSF biomarker categories in Alzheimer's disease

Brain Aβ-plaque deposition

- CSF $A\beta_{1-42}$
- PET Aβ imaging

Neurodegeneration

- CSF tau
- Fluorodeoxyglucose-PET
- Structural MRI

Aβ=β-amyloid.

Lancet Neurol 2010; 9: 119–28

Lancet Neurol 2010; 9: 119–28

Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade

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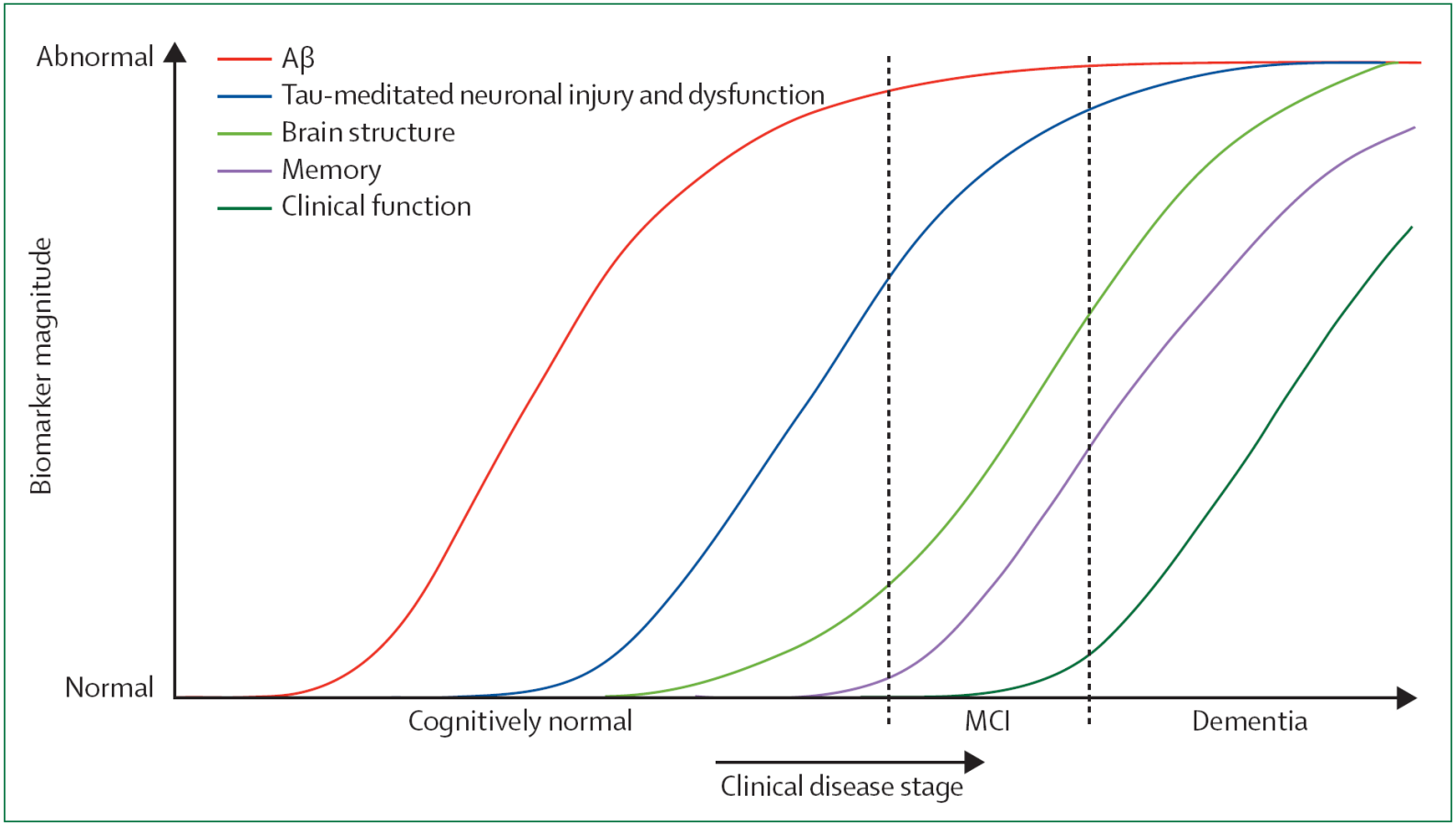

Figure 2: **Dynamic biomarkers of the Alzheimer's pathological cascade**

Aβ is identified by CSF $A\beta_{42}$ or PET amyloid imaging. Tau-mediated neuronal injury and dysfunction is identified by CSF tau or fluorodeoxyglucose-PET. Brain structure is measured by use of structural MRI. Aβ=β-amyloid. MCI=mild cognitive impairment.

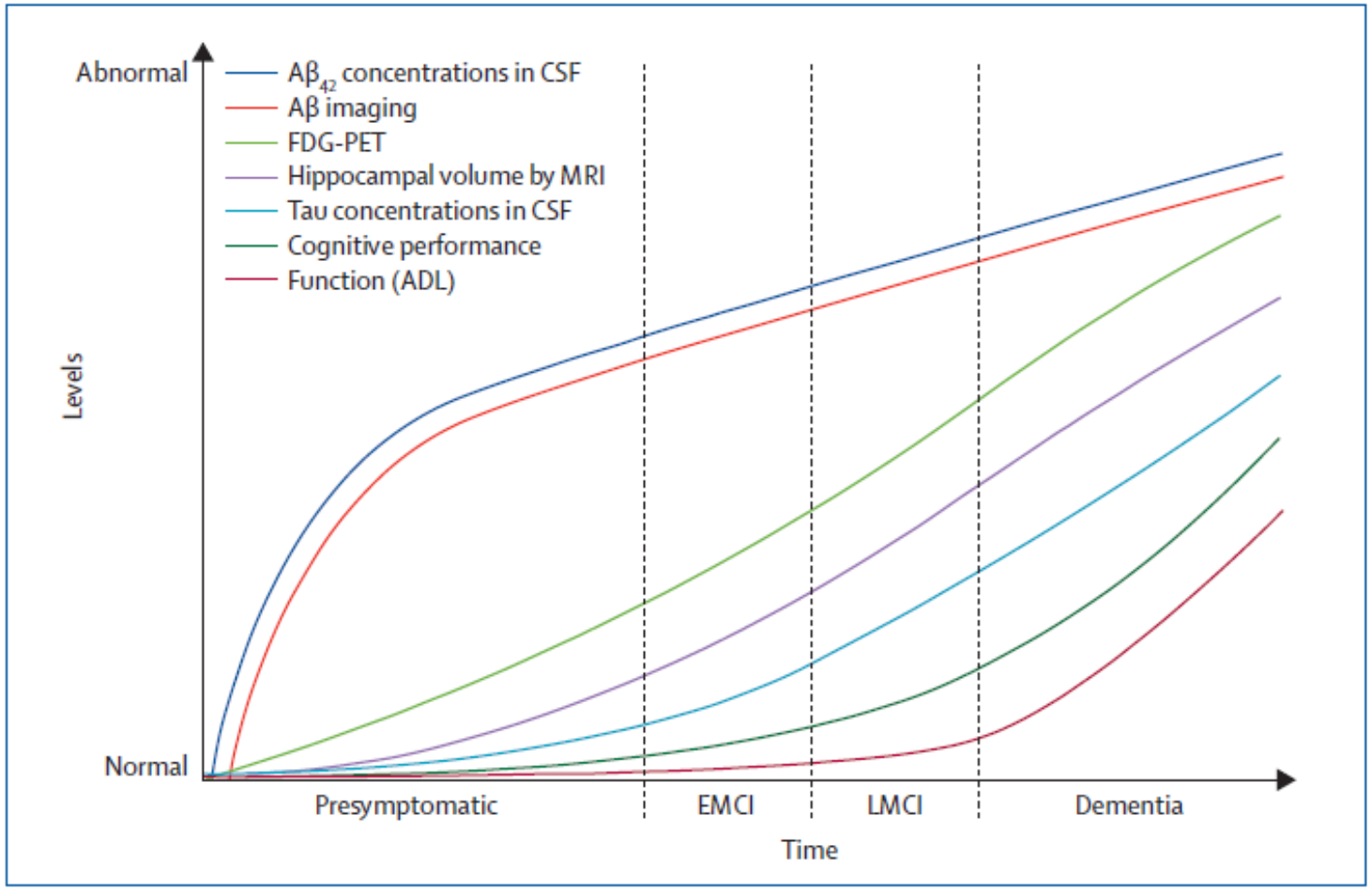

Figure: **Hypothetical progression of pathological and clinical events that lead to Alzheimer's disease, as detected by use of different imaging techniques, functional measures, or biomarkers**
Increases in the extent of pathological abnormality are shown for each imaging measure and biomarker. ADL=activities of daily living. EMCI=early MCI. FDG-PET=^{18}F-fluorodeoxyglucose PET. LMCI=late MCI.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 30, 2012 VOL. 367 NO. 9

Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

Randall J. Bateman, M.D., Chengjie Xiong, Ph.D., Tammie L.S. Benzinger, M.D., Ph.D., Anne M. Fagan, Ph.D., Alison Goate, Ph.D., Nick C. Fox, M.D., Daniel S. Marcus, Ph.D., Nigel J. Cairns, Ph.D., Xianyun Xie, M.S., Tyler M. Blazey, B.S., David M. Holtzman, M.D., Anna Santacruz, B.S., Virginia Buckles, Ph.D., Angela Oliver, R.N., Krista Moulder, Ph.D., Paul S. Aisen, M.D., Bernardino Ghetti, M.D., William E. Klunk, M.D., Eric McDade, M.D., Ralph N. Martins, Ph.D., Colin L. Masters, M.D., Richard Mayeux, M.D., John M. Ringman, M.D., Martin N. Rossor, M.D., Peter R. Schofield, Ph.D., D.Sc., Reisa A. Sperling, M.D., Stephen Salloway, M.D., and John C. Morris, M.D., for the Dominantly Inherited Alzheimer Network

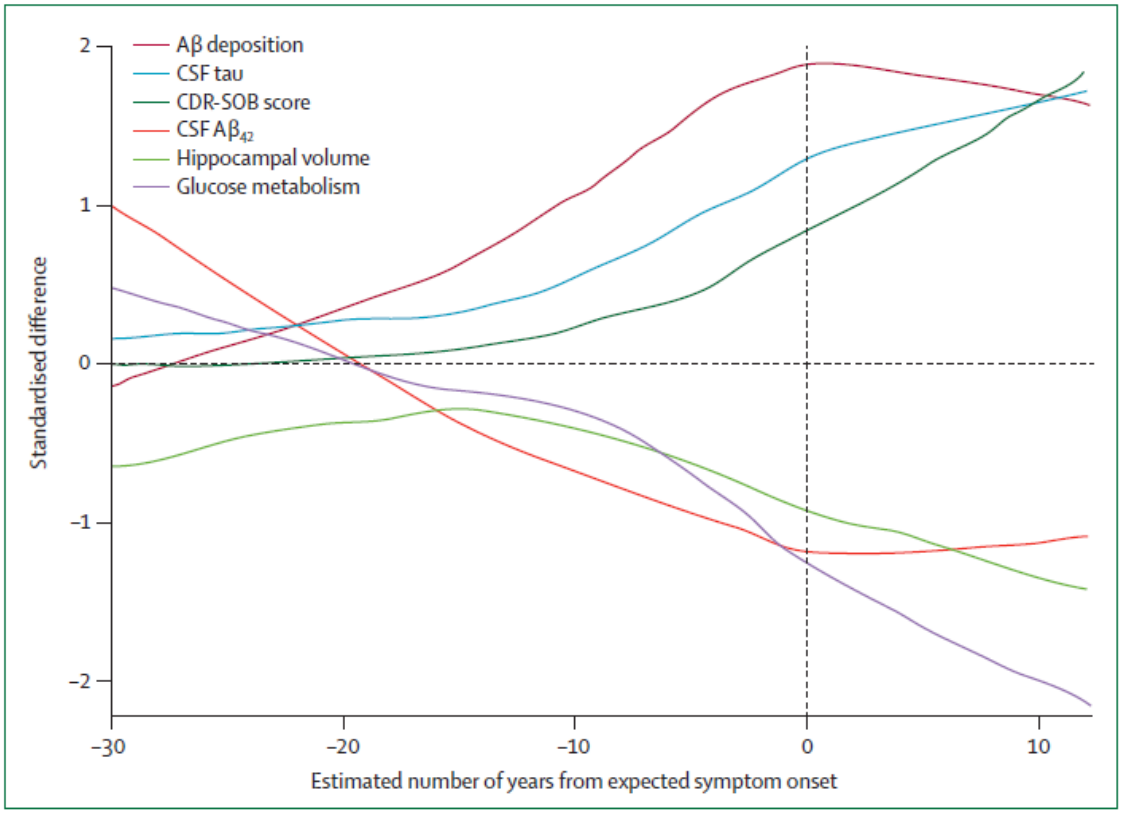

Figure 4: **Temporal ordering of biomarkers in carriers of autosomal-dominant mutations**
Cross-sectional data from the Dominantly Inherited Alzheimer's Network (DIAN) study.[54] Temporal ordering is
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ELSEVIER

Alzheimer's & Dementia ■ (2011) 1–6

Alzheimer's & Dementia

Introduction to the recommendations from the National Institute on Aging and the Alzheimer's Association workgroup on diagnostic guidelines for Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], Marilyn S. Albert[b], David S. Knopman[a], Guy M. McKhann[b], Reisa A. Sperling[c], Maria C. Carrillo[d], Bill Thies[d], Creighton H. Phelps[e]

4. Relevance to clinical practice

The recommendations of the three working groups differ in terms of current relevance to clinical practice. The core clinical criteria of the recommendations regarding AD dementia and MCI because of AD are intended to guide diagnosis in the clinical setting. However, the recommendations of the preclinical AD workgroup are intended purely for research purposes, and do not have any clinical utility at this time.

Tre "percorsi" diagnostici: AD, AD prodromica (MCI because of [due to] AD), **AD preclinica**

Alzheimer's & Dementia 2011; 7: 257-262

ELSEVIER

Alzheimer's & Dementia 7 (2011) 280–292

Alzheimer's & Dementia

Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

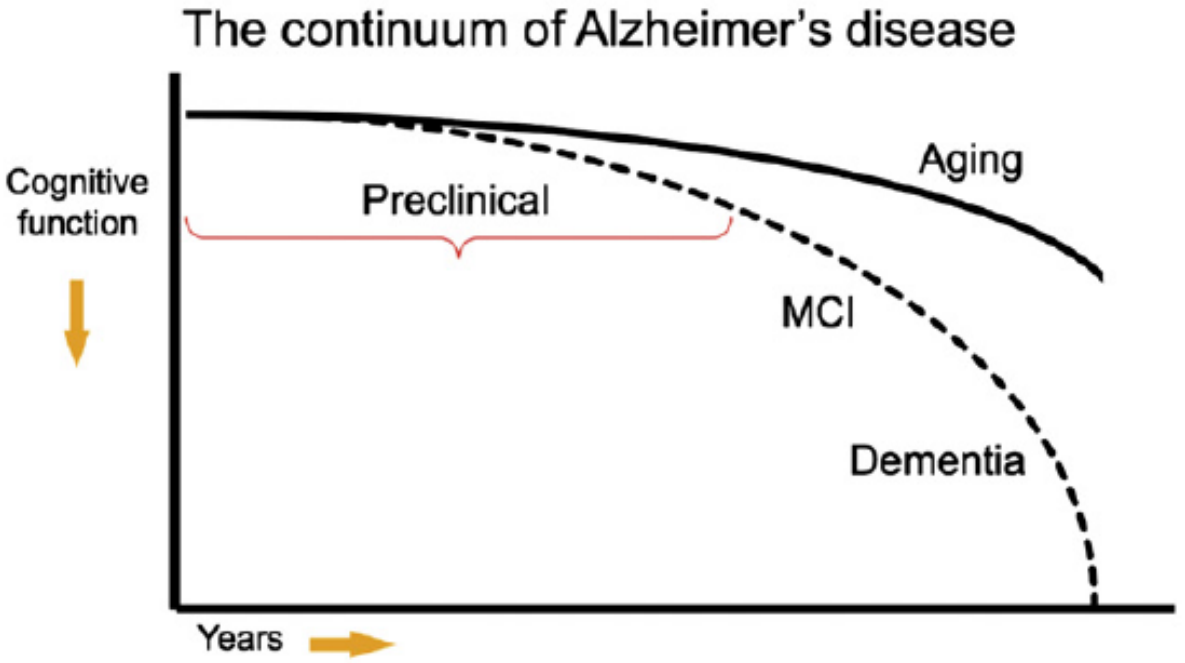
Reisa A. Sperling[a,*], Paul S. Aisen[b], Laurel A. Beckett[c], David A. Bennett[d], Suzanne Craft[e], Anne M. Fagan[f], Takeshi Iwatsubo[g], Clifford R. Jack, Jr.[h], Jeffrey Kaye[i], Thomas J. Montine[j], Denise C. Park[k], Eric M. Reiman[l], Christopher C. Rowe[m], Eric Siemers[n], Yaakov Stern[o],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

AD preclinica

asp). A hypothetical intervention that delayed the onset of AD dementia by 5 years would result in a 57% reduction in the number of patients with AD dementia, and reduce the projected Medicare costs of AD from $627 to $344 billion dollars.

These criteria are intended

intended purely for research purposes, and have no clinical or diagnostic utility at the present time. We hope these criteria



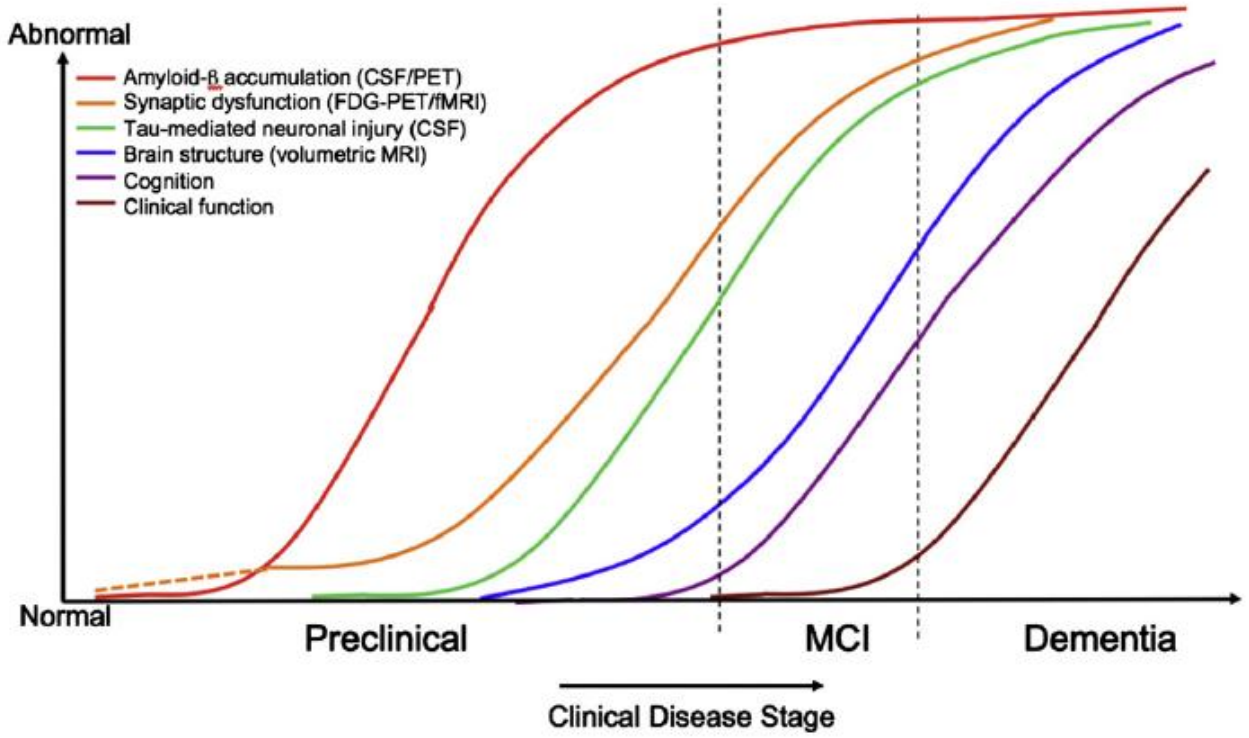

Abnormal
Amyloid-β accumulation (CSF/PET)
Synaptic dysfunction (FDG-PET/fMRI)
Tau-mediated neuronal injury (CSF)
Brain structure (volumetric MRI)
Cognition
Clinical function
Normal
Preclinical
MCI
Dementia
Clinical Disease Stage

Table 1
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

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose (18F); sMRI, structural magnetic resonance imaging.

- Stage 0
- SNAP group

Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study

Stephanie J B Vos, Chengjie Xiong, Pieter Jelle Visser, Mateusz S Jasielec, Jason Hassenstab, Elizabeth A Grant, Nigel J Cairns, John C Morris, David M Holtzman, Anne M Fagan

www.thelancet.com/neurology **Vol 12 October 2013**

Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study

Stephanie J B Vos, Chengjie Xiong, Pieter Jelle Visser, Mateusz S Jasielec, Jason Hassenstab, Elizabeth A Grant, Nigel J Cairns, John C Morris, David M Holtzman, Anne M Fagan

- 311 normal elderly participants (≥65 years old)
- **129 (41%) were classified as normal**
- 47 (15%) as STAGE 1
- 36 (12%) as STAGE 2
- 13 (4%) as STAGE 3
- **72 (23%) as *SNAP group***
- 14 (5%) as unclassified

Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study

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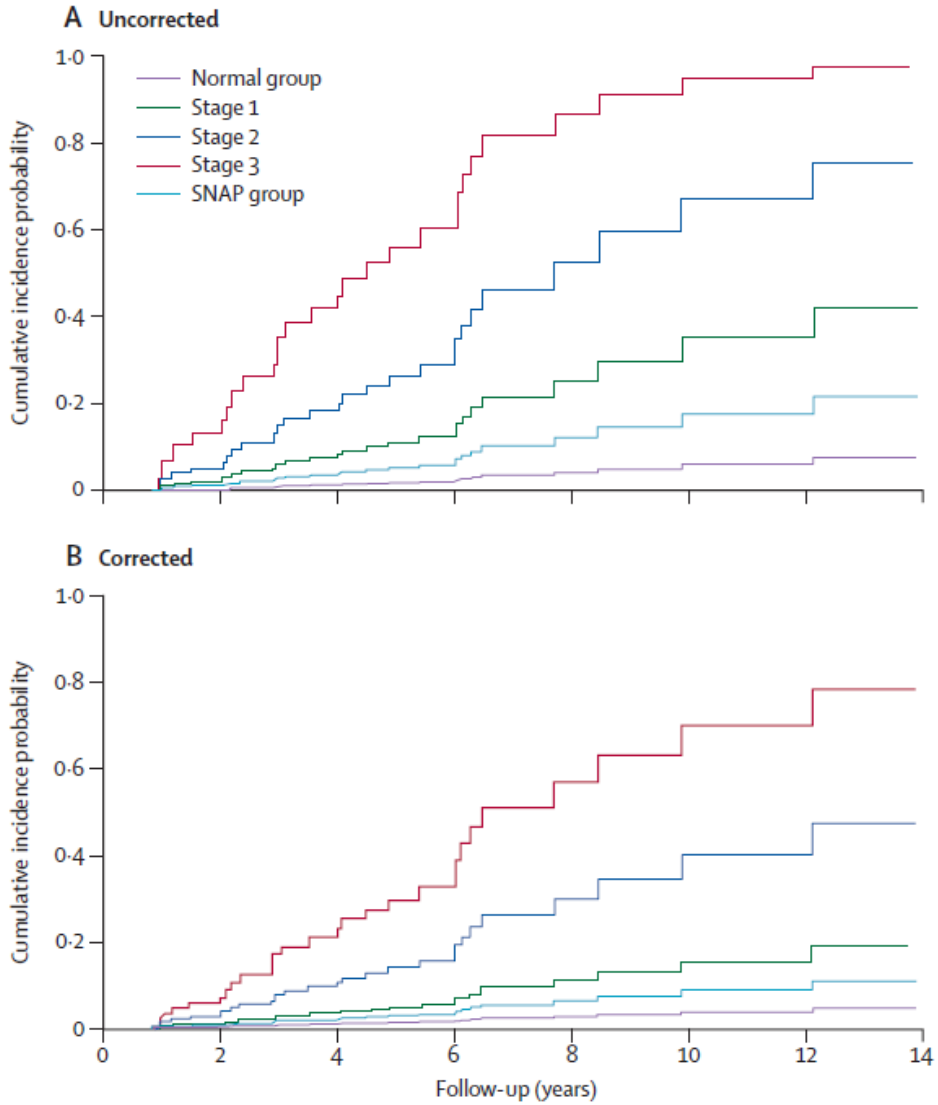
- The five years progression to at least 0.5 CDR symptomatic AD was:
- 2% for normal
- **11% for stage 1**
- **26% for stage 2**
- **56% for stage 3**
- 5% for SNAP



Number of participants

Normal	129	112	73	29	10	4	1	0
Stage 1	47	36	28	16	4	3	0	0
Stage 2	36	31	15	9	5	1	1	0
Stage 3	13	10	5	2	0	0	0	0
SNAP	72	61	28	15	11	6	6	2

Preclinical Alzheimer's disease and its outcome: a longitudinal cohort study

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www.thelancet.com/neurology **Vol 12 October 2013**

Panel 1: Preclinical AD stages and symptomatic AD

Normal group
CDR 0 (no dementia), no amyloid, no neuronal injury, no subtle cognitive decline

Preclinical AD stage 1
CDR 0 (no dementia), amyloid, no neuronal injury, no subtle cognitive decline

Preclinical AD stage 2
CDR 0 (no dementia), amyloid, neuronal injury, no subtle cognitive decline

Preclinical AD stage 3
CDR 0 (no dementia), amyloid, neuronal injury, subtle cognitive decline

SNAP group
CDR 0 (no dementia), no amyloid, neuronal injury, with or without subtle cognitive decline

Unclassified group
CDR 0 (no dementia), with or without amyloid, no neuronal injury, subtle cognitive decline

Symptomatic AD
CDR>0, memory and at least one other domain received a score of ≥0·5 and the clinician felt the cognitive impairments to be due to AD (probable AD according to NINDS-ADRDA criteria), no reference to biomarkers

AD=Alzheimer's disease. No amyloid=CSF amyloid-$\beta_{1\text{-}42}$ ($A\beta_{1\text{-}42}$) ≥459 pg/mL. Amyloid=CSF $A\beta_{1\text{-}42}$ <459 pg/mL. CDR 0=clinical dementia rating score of 0, no dementia. CDR 0·5=very mild impairment or very mild dementia. CDR 1=mild dementia. CDR 2=moderate dementia. CDR 3=severe dementia. No neuronal injury=CSF total tau (t-tau) ≤339 pg/mL and phosphorylated tau_{181} ($p\text{-}tau_{181}$) ≤67 pg/mL. Neuronal injury=CSF t-tau >339 pg/mL or $p\text{-}tau_{181}$ >67 pg/mL. SNAP=suspected non-Alzheimer pathophysiology. Subtle cognitive decline=episodic memory composite score in the lowest 10th percentile. No subtle cognitive decline=episodic memory composite score in the highest 90th percentile.

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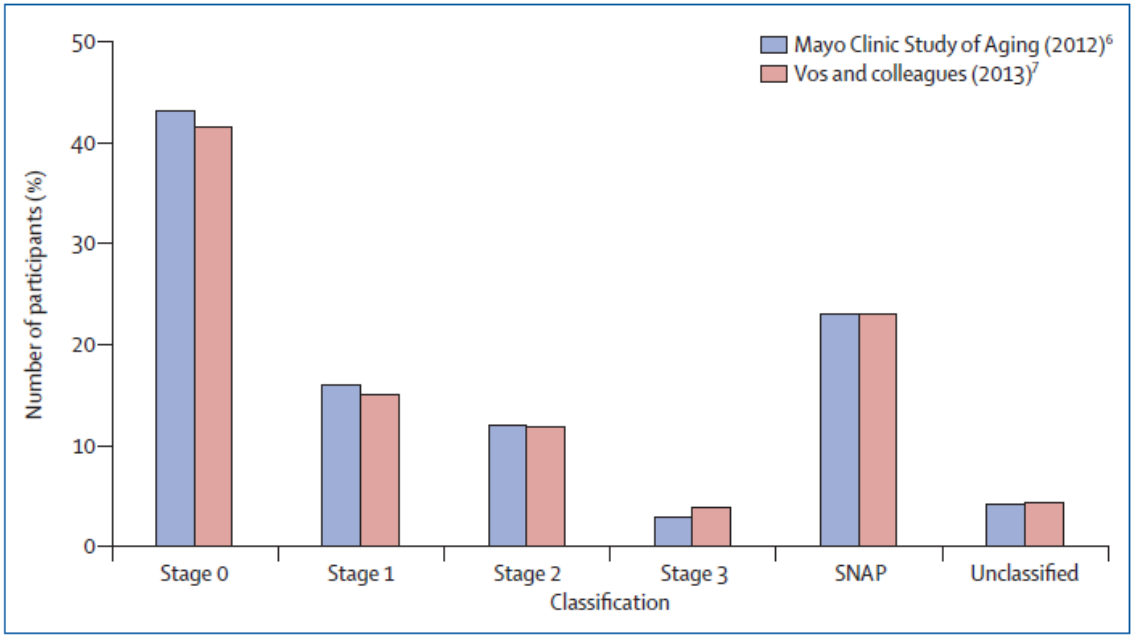

Figure: **Percentage of participants in each preclinical classification category in the Mayo Clinic Study of Aging and in the study by Vos and colleagues**
Neuroimaging was used in the Mayo Clinic Study of Aging[6] whereas CSF analysis was used in the study by Vos and colleagues.[7] SNAP=suspected non-Alzheimer's pathology.

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ARTICLES

Amyloid-first and neurodegeneration-first profiles characterize incident amyloid PET positivity

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Stephen D. Weigand, MS
David S. Knopman, MD
Val Lowe, MD
Prashanthi Vemuri, PhD
Michelle M. Mielke, PhD
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Ronald C. Petersen, MD, PhD

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ABSTRACT

Objective: To estimate the incidence of and to characterize cognitive and imaging findings associated with incident amyloid PET positivity.

Methods: Cognitively normal (CN) participants in the Mayo Clinic Study of Aging who had 2 or more serial imaging assessments, which included amyloid PET, FDG-PET, and MRI at each time point, were eligible for analysis (n = 207). Twelve subjects with Alzheimer disease dementia were included for comparison.

Results: Of the 123 CN participants who were amyloid-negative at baseline, 26 met criteria for incident amyloid PET positivity. Compared to the 69 subjects who remained stable amyloid-negative, on average these 26 did not differ on any imaging, demographic, or cognitive variables except amyloid PET (by definition) and task-free functional connectivity, which at baseline was greater in the incident amyloid-positive group. Eleven of the 26 incident amyloid-positive subjects had abnormal hippocampal volume, FDG-PET, or both at baseline.

Conclusions: The incidence of amyloid PET positivity is approximately 13% per year among CN participants over age 70 sampled from a population-based cohort. In 15/26 (58%), incident amyloid positivity occurred prior to abnormalities in FDG-PET and hippocampal volume. However, 11/26 (42%) incident amyloid-positive subjects had evidence of neurodegeneration prior to incident amyloid positivity. These 11 could be subjects with combinations of preexisting non-Alzheimer pathophysiologies and tau-mediated neurodegeneration who newly entered the amyloid pathway. Our findings suggest that both "amyloid-first" and "neurodegeneration-first" biomarker profile pathways to preclinical AD exist. *Neurology*® 2013;81:1–9

ELSEVIER

Alzheimer's & Dementia 9 (2013) 594–601

Alzheimer's & Dementia

Perspective

Revisiting the framework of the National Institute on Aging-Alzheimer's Association diagnostic criteria

Maria C. Carrillo[a,*], Robert A. Dean[b], François Nicolas[c], David S. Miller[d], Robert Berman[e], Zaven Khachaturian[f], Lisa J. Bain[g], Rachel Schindler[h], David Knopman[i]

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BOX 1

Biomarker and neuroimaging issues:

- Cutpoints for biomarker abnormalities are critical and need to be standardized to ensure diagnostic consistency.
- More data are needed on the predictive value of biomarkers for progression.
- Criteria need to address what to do when biomarkers conflict, are uninformative, or are inconsistent with clinical diagnosis.
- New biomarkers are needed that reflect stage rather than presence or absence of disease.
- Biomarkers that reflect effects of therapeutic interventions are needed.

2013

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Alzheimer's disease: clinical trials and drug development

Francesca Mangialasche, Alina Solomon, Bengt Winblad, Patrizia Mecocci, Miia Kivipelto

Alzheimer's disease is the most common cause of dementia in elderly people. Research into Alzheimer's disease therapy has been at least partly successful in terms of developing symptomatic treatments, but has also had several failures in terms of developing disease-modifying therapies. These successes and failures have led to debate about the potential deficiencies in our understanding of the pathogenesis of Alzheimer's disease and potential pitfalls in diagnosis, choice of therapeutic targets, development of drug candidates, and design of clinical trials. Many clinical and experimental studies are ongoing, but we need to acknowledge that a single cure for Alzheimer's disease is unlikely to be found and that the approach to drug development for this disorder needs to be reconsidered. Preclinical research is constantly providing us with new information on pieces of the complex Alzheimer's disease puzzle, and an analysis of this information might reveal patterns of pharmacological interactions instead of single potential drug targets. Several promising randomised controlled trials are ongoing, and the increased collaboration between pharmaceutical companies, basic researchers, and clinical researchers has the potential to bring us closer to developing an optimum pharmaceutical approach for the treatment of Alzheimer's disease.

Lancet Neurol 2010; 9: 702–16

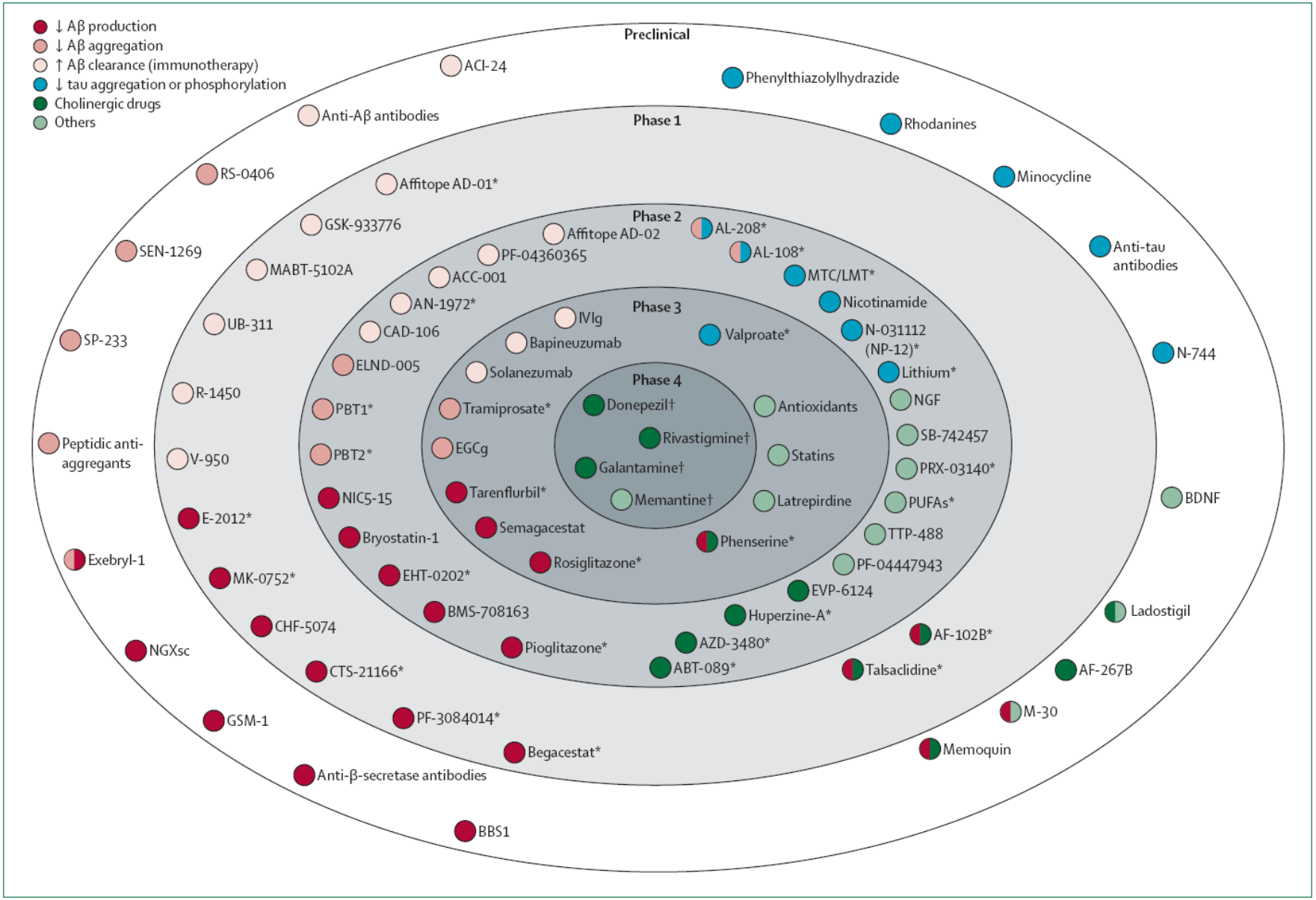

Figure: **Drug development in Alzheimer's disease**

Drugs being investigated for Alzheimer's disease therapy, reported according to the most advanced phase of study and main therapeutic properties (including data from studies in vitro and animal models). Aβ=amyloid β. BBS1=anti-β-site antibodies. BDNF=brain-derived neurotrophic factor. EGCg=epigallocatechin-3-gallate. IVIg=intravenous immunoglobulin. LMT=leuco-methylthioninium. MTC=methylthioninium chloride. NGF=nerve growth factor. NGXsc=NGX series compounds. PUFAs=polyunsaturated fatty acids. GSM=γ-secretase modulator. RCT=randomised controlled trial. *RCTs in Alzheimer's disease not ongoing. †Drugs approved for the treatment of Alzheimer's disease.

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JNHA: CLINICAL TRIALS AND AGING

THE POTENTIAL AND LIMITS FOR CLINICAL TRIALS FOR EARLY ALZHEIMER'S DISEASE AND SOME RECOMMENDATIONS

L.S. SCHNEIDER

Table 2
Model criteria and methods for phase II drug development trials for early or prodromal AD

Characteristic	Recommendation	Rationale
Experimental intervention (e.g., drug, antibody, psychotherapeutic, environmental)	Appropriate for MCI, early AD, and non-dementia patients who may not progress or may improve in their symptoms	Expect effectiveness over brief period, should be substantially safe considering participants have few symptoms, slow progression
Participant inclusion criteria	Episodic memory impairment as described (6), repeated memory assessments over several weeks. Trial should include biomarkers as stratification variables.	The need to rely on episodic memory impairment makes diagnosis dependent on actuarial tests. Repeated testing is needed to gain reliability in the diagnosis.
Exclusion criteria	Impairment in activities of daily living or dementia	Without these or similar criteria many would fulfill criteria for probable AD. Operationalization may be difficult
Methods	Multicenter, randomized, double-blinded, placebo-controlled trial. Randomization may be stratified by biomarker or cognitive severity	Needed to control for various known and unknown sources of bias
Durations	Based on expected drug actions. Brief for symptomatic effects, over 2 years for attenuation of progression	Patients with early AD are likely to show less change over time than mild AD patients
Primary outcome	Cognitive outcomes emphasizing memory function, different from tests used for early AD diagnosis	Early AD primarily defined by episodic memory impairment in the absence of many other symptoms
Secondary Outcome	CGIC, self-, informant- and clinician-rated, health-related QoL	Because ADLs are not likely to be impaired, and patients and informants notice impairment, self- and observer-rated global assessments and health-related QoL ratings are needed to assess further clinical significance
Statistics	Analysis based on stratification, repeated assessments of cognitive change over course of trial.	Assess outcomes based on biomarker status; repeated measures of cognitive outcomes to enhance precision and describe treatment effects

Ushering in the study and treatment of preclinical Alzheimer disease

Jessica B. Langbaum, Adam S. Fleisher, Kewei Chen, Napatkamon Ayutyanont, Francisco Lopera, Yakeel T. Quiroz, Richard J. Caselli, Pierre N. Tariot and Eric M. Reiman

Langbaum, J. B. *et al. Nat. Rev. Neurol.* 9, 371–381 (2013); published online 11 June 2013; corrected online 16 July 2013; doi:10.1038/nrneurol.2013.107

Key points

- The pathogenic cascade of Alzheimer disease (AD) is thought to begin at least one to two decades prior to cognitive impairment
- Disappointing results of several AD drugs in late-stage trials have suggested the need for early therapeutic intervention, calling for development of biomarkers and sensitive cognitive measures of preclinical disease
- The best established measurements for detection and tracking of preclinical and clinical AD include MRI, fluorodeoxyglucose PET, amyloid PET, and cerebrospinal fluid measures of amyloid-β_{42}, total tau, and phospho-tau
- Studies of individuals with inherited AD can provide insights into cognitive and biomarker changes that precede clinical manifestation of AD, and are suitable candidates for ongoing monitoring and early-intervention strategies
- We are entering an era of AD prevention research, with a number of preclinical AD treatment trials in the planning stages or under way for several at-risk, cognitively unimpaired populations

DIAN
Dominantly Inherited Alzheimer Network

Welcome

Welcome to the website of the Dominantly Inherited Alzheimer Network (DIAN). DIAN is an international research partnership of leading scientists determined to understand a rare form of Alzheimer's disease that is caused by a gene mutation. Understanding of this form of Alzheimer's disease may provide clues to decoding other dementias and developing dementia treatments.

Funded by a multiple-year research grant from the National Institute on Aging, DIAN currently involves thirteen outstanding research institutions in the United States, United Kingdom, Germany and Australia.

John C. Morris, M.D., Friedman Distinguished Professor of Neurology at Washington University School of Medicine in St. Louis, is the project's principal investigator.

DIAN is currently enrolling study participants who are biological adult children of a parent with a mutated gene known to cause dominantly inherited Alzheimer's disease.

Such individuals may or may not carry the gene themselves and may or may not have disease symptoms (click here for information about genetic testing).

To register for DIAN drug trials or DIAN, visit www.DIANExpandedRegistry.org.

DIAN

Site Staff MemberName	Site Staff Role (PI, SI, Psychometrician,Cog/ClinicalRaters, SC, Back-up SC, other)	Credentials/ Background	Years of ClinicalResearch (CR) Experience	Years ofCR Experience with AD Trials	Haveyoucompleted formal GCP training?	How manyregulated (FDA, EMA, etc.)studies are youcurrentlyworking on in yourrole	Whatpercentageof your time willyou be able to dedicate to thisstudy?
Giovanni B. Frisoni	PI	MD	23	8	yes	1 Phase 1 (enrolling); 2 Phase 3 (approved)	10%
Amalia C. Bruni	co-PI	MD	32	12	yes	2 phase 3	10%
Giuliano Binetti	co-PI	MD	20	20	no		10%
Orazio Zanetti	co-PI	MD	25	20	yes	1 Phase 2 enrolling; 1Phase 3approved; 1 Phase 2 approving	10%
Alessandro Padovani	co-PI	MD					

Alzheimer's Prevention Initiative

Lancet Neurol. 2012 Dec;11(12):1048-56.

Reiman EM, et al.: Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the presenilin 1 E280A kindred: a case-control study.

INTERPRETATION: Young adults at genetic risk for autosomal dominant Alzheimer's disease have functional and structural MRI findings and CSF and plasma biomarker findings consistent with Aβ(1-42) overproduction. Although the extent to which the underlying brain changes are either neurodegenerative or developmental remain to be determined, this study shows the earliest known biomarker changes in cognitively normal people at genetic risk for autosomal dominant Alzheimer's disease.

Alzheimer's Prevention Initiative

The study involves the experimental anti-amyloid antibody treatment crenezumab in approximately 300 people from an extraordinarily large extended family in Colombia, who share a rare genetic mutation that typically triggers Alzheimer's symptoms around age 45.

Ha già preso il largo negli Stati Uniti un ambizioso progetto di ricerca sulla prevenzione dell'Alzheimer, alimentato dai nuovi promettenti mezzi per identificare i soggetti a rischio e dalle misure preventive che potrebbero potenzialmente rallentare la progressione della malattia.

Il programma, chiamato **Alzheimer's Prevention Initiative** e coordinato da Eric Reiman e collaboratori

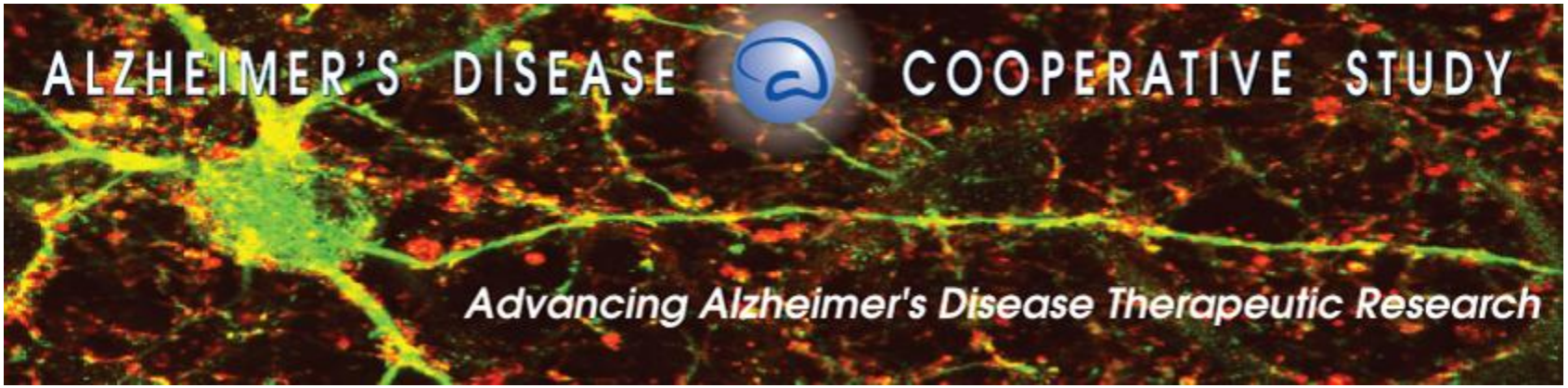
Ed è già iniziato l'arruolamento del primo dei due studi clinici del programma che coinvolgeranno ampie popolazioni di soggetti presintomatici ad altissimo rischio genetico di sviluppare una malattia di Alzheimer sintomatica. Uno studio coinvolgerà 2.000 persone residenti nell'area di Medellin, in Colombia, dove vive il gruppo di parenti più numeroso al mondo di portatori della mutazione E280A PS1, che conferisce un rischio estremamente elevato di sviluppare precocemente l'Alzheimer. I partecipanti dovranno avere un'età vicina a quella mediana di esordio clinico della malattia di Alzheimer legata a E280A PS1, che è di 47 anni.

L'altro studio,invece, riguarderà circa 50.000 cittadini nordamericani tra i 60 e gli 80 anni, di cui sarà analizzato il genotipo ApoE.

I due studi **dell'Alzheimer's Prevention Initiative** costituiranno il primo vero test della validità dell'ipotesi della cascata amiloide nella patogenesi della demenza di Alzheimer, secondo la quale l'accumulo della proteina amiloide giocherebbe un ruolo critico nello sviluppo della malattia. Questa ipotesi, però, resta ancora da dimostrare.

Ritardare l'esordio della demenza anche solo di 5 anni senza aumentare l'aspettativa di vita vuol dire aver la possibilità di dimezzare il numero di nuovi casi, dato che l'incidenza raddoppia ogni 5 anni dopo i 60.

THE A4 TRIAL



Anti-Amyloid Treatment in Asymptomatic AD – The A4 Trial

A4 is a new secondary prevention trial effort aimed at treating older individuals at risk for developing Alzheimer's disease (AD) dementia on the basis of **having biomarker evidence of amyloid**. We will test the hypothesis that decreasing amyloid burden during the preclinical stages of AD will impact "downstream neurodegeneration" and hopefully delay cognitive decline.

To enroll in A4, clinically normal older individuals (65 and older) will be screened with PET amyloid imaging. Those found to be “amyloid-positive” - and who meet other study criteria – will be able to enroll in the trial. Subjects will be treated for three years with the anti-amyloid drug or placebo. Ideally, we will follow them beyond treatment to determine the extent of the impact on the trajectory of cognitive decline.

We anticipate that A4 will be opening to enrollment later in 2013 and we expect to have site specific information in the summer. As soon as we have additional information to share about the A4 trial, it will be posted to this website. So, please check back with us frequently.

Thank you for your interest in the A4 clinical trial.

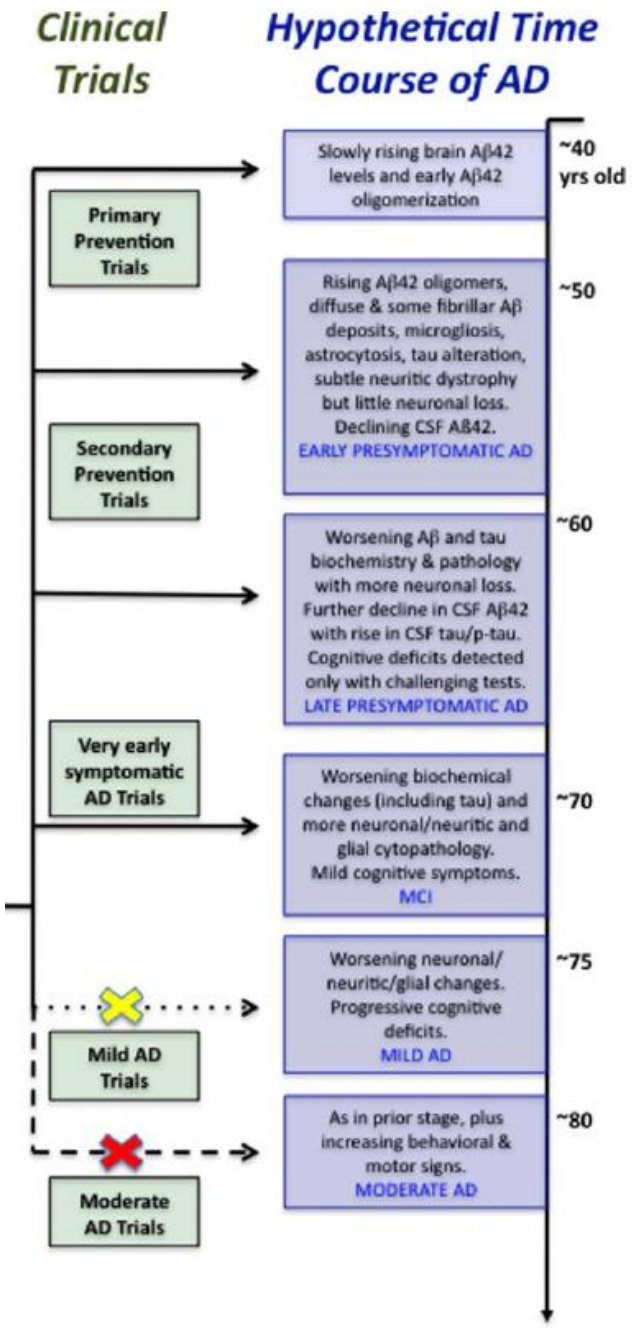
Anti-Amyloid Treatment in Asymptomatic AD – The A4 Trial

ANNALS SPECIAL EDITION: THERAPEUTIC PROSPECTS

The Therapeutics of Alzheimer's Disease: Where We Stand and Where We Are Heading

Dennis J. Selkoe, MD

ANN NEUROL 2013;74:328–336


Clinical Trials
Hypothetical Time Course of AD
Primary Prevention Trials
Secondary Prevention Trials
Very early symptomatic AD Trials
Mild AD Trials
Moderate AD Trials
Slowly rising brain Aβ42 levels and early Aβ42 oligomerization
~40 yrs old
Rising Aβ42 oligomers, diffuse & some fibrillar Aβ deposits, microgliosis, astrocytosis, tau alteration, subtle neuritic dystrophy but little neuronal loss. Declining CSF Aß42.
EARLY PRESYMPTOMATIC AD
~50
Worsening Aβ and tau biochemistry & pathology with more neuronal loss. Further decline in CSF Aβ42 with rise in CSF tau/p-tau. Cognitive deficits detected only with challenging tests.
LATE PRESYMPTOMATIC AD
~60
Worsening biochemical changes (including tau) and more neuronal/neuritic and glial cytopathology. Mild cognitive symptoms.
MCI
~70
Worsening neuronal/ neuritic/glial changes. Progressive cognitive deficits.
MILD AD
~75
As in prior stage, plus increasing behavioral & motor signs.
MODERATE AD
~80

SOMMARIO

- AD preclinico: definizione
- I nuovi criteri diagnostici
- Verso terapie efficaci (*disease modifying*) precoci? (Prevenzione?)
- **Aspetti etici e conclusioni**

OPINION

Preclinical Alzheimer disease—the challenges ahead

Reisa A. Sperling, Jason Karlawish and Keith A. Johnson

Abstract | There is growing recognition that the pathophysiological process of Alzheimer disease (AD) begins many years prior to clinically obvious symptoms, and the concept of a presymptomatic or preclinical stage of AD is becoming more widely accepted. Advances in biomarker studies have enabled detection of AD pathology *in vivo* in clinically normal older individuals. The predictive value of these biomarkers at the individual patient level, however, remains to be elucidated. The ultimate goal of identifying individuals in the preclinical stages of AD is to facilitate early intervention to delay and perhaps even prevent emergence of the clinical syndrome. A number of challenges remain to be overcome before this concept can be validated and translated into clinical practice.

Sperling, R. A. *et al. Nat. Rev. Neurol.* 9, 54–58 (2013); published online 27 November 2012; doi:10.1038/nrneurol.2012.241

- Ethical and practical concerns about disclosure of biomarker status in asymptomatic or very early symptomatic individuals need to be addressed. Solutions may vary by country. For example, in Australia, the current policy is nondisclosure of amyloid PET status, but as more is learned about the meaning of a positive amyloid scan, individuals may wish to be informed of their test results.

Alzheimer's Prevention Initiative: A Plan to Accelerate the Evaluation of Presymptomatic Treatments; Eric M. Reiman, MD, JessicaB.S. Langbaum, PhD, Adam S. Fleisher, MD,Richard J. Caselli, MD, Kewei Chen, PhD, Napatkamon Ayutyanont, PhD, Yakeel T.Quiroz, MA, Kenneth S. Kosik, MD, Francisco Lopera, MD, and **Pierre N. Tariot, MD**

Lancet Neurol 2013; 12: 207–16

Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers

Clifford R Jack Jr, David S Knopman, William J Jagust, Ronald C Petersen, Michael W Weiner, Paul S Aisen, Leslie M Shaw, Prashanthi Vemuri, Heather J Wiste, Stephen D Weigand, Timothy G Lesnick, Vernon S Pankratz, Michael C Donohue, John Q Trojanowski

1) **Amyloid deposition**
2) **Neurodegeneration - synaptic dysfunction**
3) **Neuronal loss – brain atrophy**

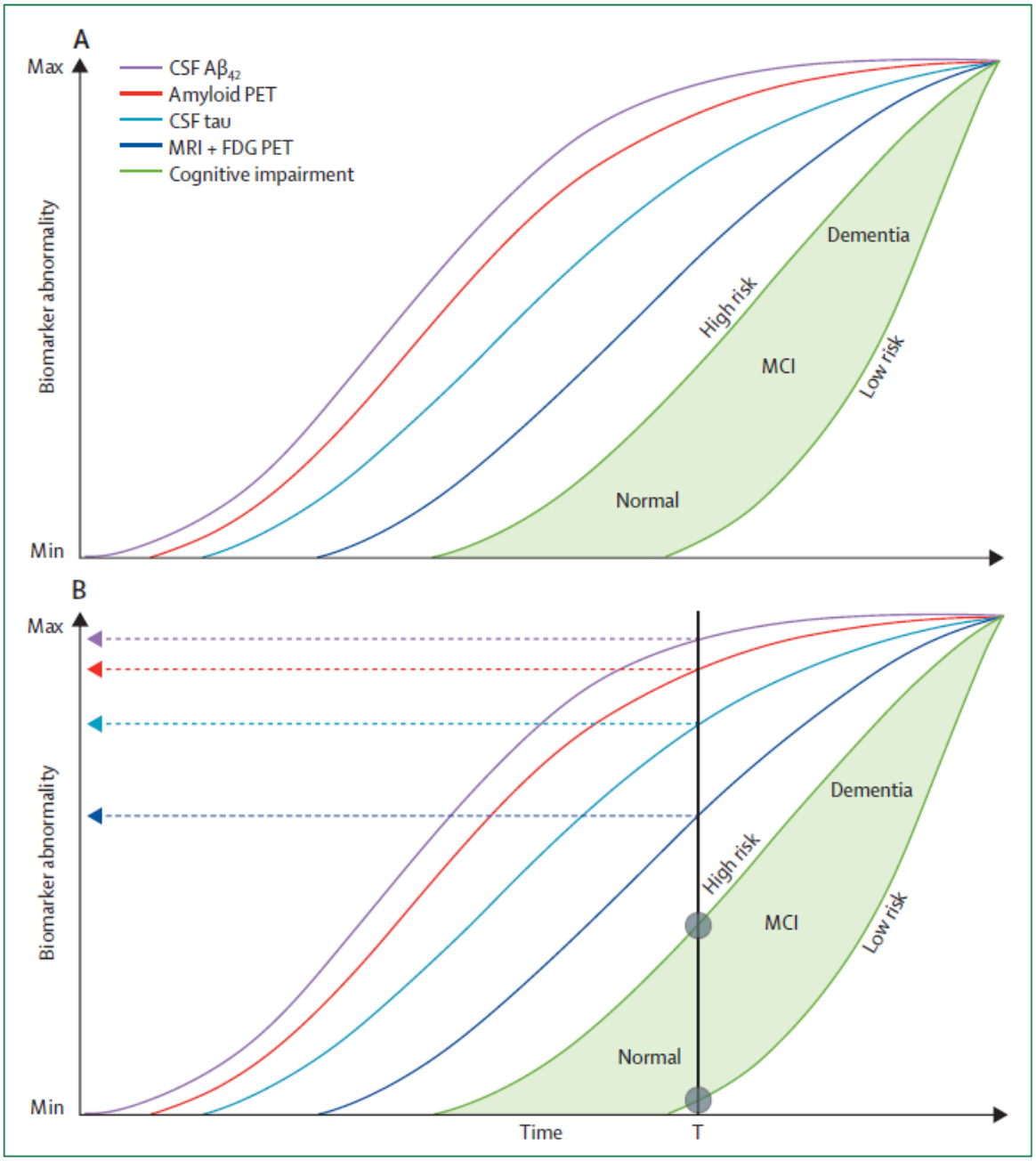


Figure 5: Revised model of dynamic biomarkers of the Alzheimer's disease pathological cascade

Lancet Neurol 2013; 12: 207–16

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Personal View

Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers

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Not all patients with MCI have AD pathology and progress to dementia.

MCI negative to amyloidosis and/or neurodegeneration should not progress to dementia.

Not all patients with AD pathology progress to dementia. → **[aspetti etici]**

Uncertain progress on the fuzzy boundaries od AD

Whitehouse P.J., George D.R.

JAD, 2011;26:1-5

“The myth of Alzheimer’s”

What you aren’t being told about today’s most dreaded diagnosis (2008)

“Sapessi tu quanti mulini, a guardar meglio sono veramente giganti; quante lucciole sono veramente lanterne!”

G. Bufalino: Quo pro quo.
Bompiani, Milano, 1991, p.48