Sin
SOCIETÀ ITALIANA DI NEUROLOGIA

8ª GIORNATA DELLO SPECIALIZZANDO IN NEUROLOGIA

SINdem
Associazione Autonoma Aderente alla SIN per le Demenze

La diagnosi di Malattia di Alzheimer: dalla ricerca alla pratica clinica

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NeuroMI
MILAN CENTER FOR NEUROSCIENCE

Demenza Pre-senile (di Alzheimer-Perusini)

Figure 2: **Alois Alzheimer**

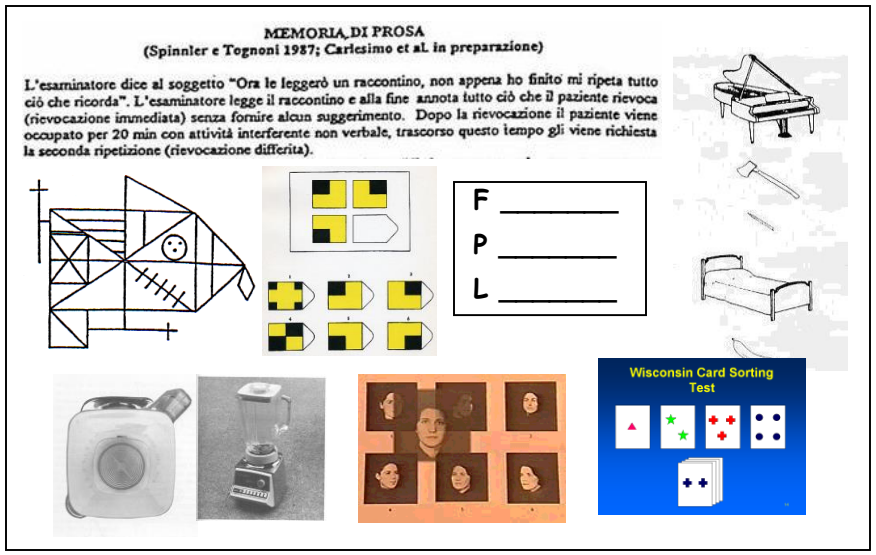
Alois Alzheimer visita Auguste Deter nel 1901 presso la Clinica Neurologica di Francoforte: Auguste ha allora 51 anni, muore nel 1906: Alzheimer e Perusini descrivono a Monaco il quadro autoptico

Clinical diagnosis of Alzheimer Disease

McKhann et al. **Neurology 1984**: Clinical diagnosis of Alzheimer's disease: report from the NINDS-ADRDA work group.

Clinical – pathological definition

Neuropsychology



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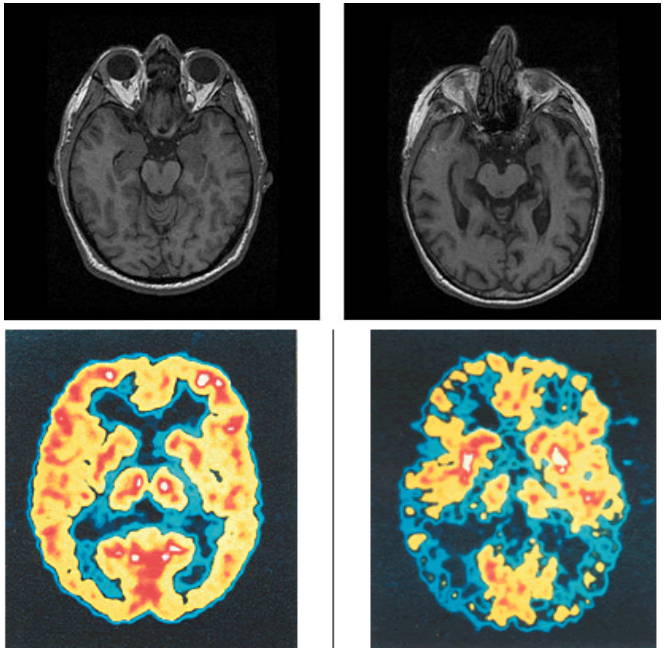
Imaging



Criteri di McKahn per Demenza di Alzheimer (1984)

A. Presenza di Demenza (sec. criteri DSM-III)

B. Iniziale e preminente deficit della Memoria

C. Esordio graduale ed evoluzione progressiva dei deficit cognitivi

D. Deficit cognitivi NON attribuibili ad altre cause

Criteri clinici e per esclusione

Malattia di Alzheimer probabile, certezza solo autoptica

AD: Aspetti Clinici

- Condizione clinica caratterizzata da un progressivo e ***isolato*** declino delle prestazioni cognitive
- Iniziale (e poi prevalente) **compromissione** della **MEMORIA**
  - **Varianti Non Amnestiche di AD**

VARIANTI Non Amnesiche AD

TRE Varianti AD (rare):

- AD con Disturbi ***Linguistici*** preminenti
  - afasia primaria progressiva tipo **Logopenico**
  - d.d. con afasie primarie progressive non fluenti da demenze fronto-temporali
- AD con Disturbi ***Visuo-spaziali*** preminenti (**Atrofia Corticale Posteriore**)
  - d.d. con demenza semantica, demenza corpi di Lewy
- AD con Disturbi ***Comportamentali*** preminenti
  - d.d. con varianti comportamentali delle demenze fronto-temporali

Elementi di ESCLUSIONE

- -Anamnestici:
  - esordio improvviso
  - precoce manifestazione di disturbi della marcia
  - crisi epilettiche precoci
  - cambiamenti comportamentali prevalenti

- Clinici:
  - segni neurologici focali (es. emiparesi, deficit sensoriali, deficit di campo visivo)
  - segni extrapiramidali precoci

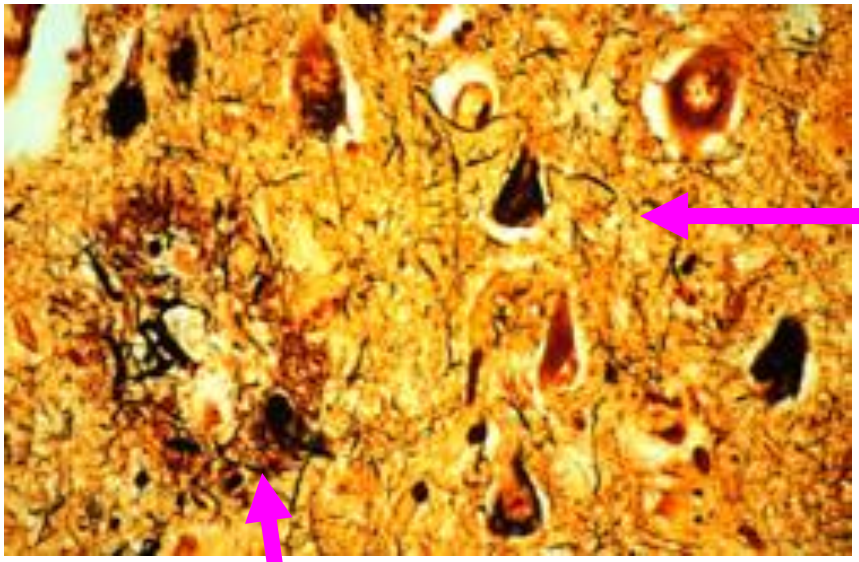
- Altri Disturbi abbastanza gravi da giustificare i deficit di memoria e i sintomi correlati
  - Esempi: demenze non AD, depressione maggiore, malattia cerebrovascolare, alterazioni metaboliche o tossiche, alterazione di segnale alla risonanza magnetica compatibile con segni vascolari o con infezioni

In vita: diagnosi di AD **POSSIBILE o PROBABILE**
(**su base clinica con/senza supporto strumentale**)

La diagnosi di CERTEZZA
(= Malattia di Alzheimer "DEFINITA")

- **Evidenza sia clinica che istopatologica (*biopsia cerebrale o autopsia*)**
  conteggio della densità delle **placche senili e dei gomitoli NF** a llivello di molteplici aree corticali: criteri di Braak
- **Evidenza sia clinica che *genetica*, per es. mutazioni sul cromosoma 1,14,21.**

NEUROPATOLOGIA DELL'ALZHEIMER

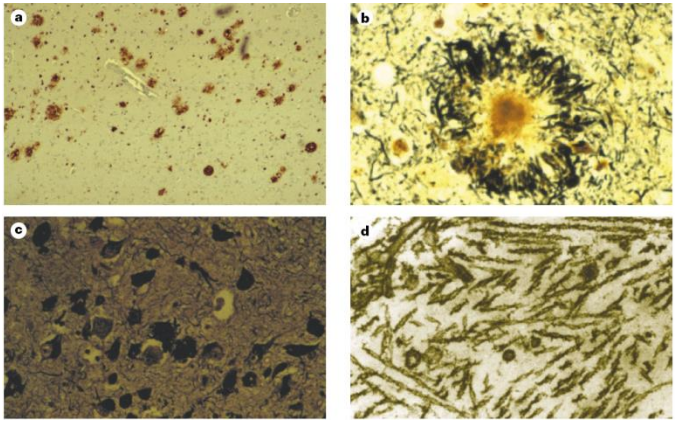


GROVIGLI NEUROFIBRILLARI

PLACCHE SENILI

PLACCHE SENILI:
Amiloide Aβ

GROVIGLI NEUROFIBRILLARI:
Proteina τ



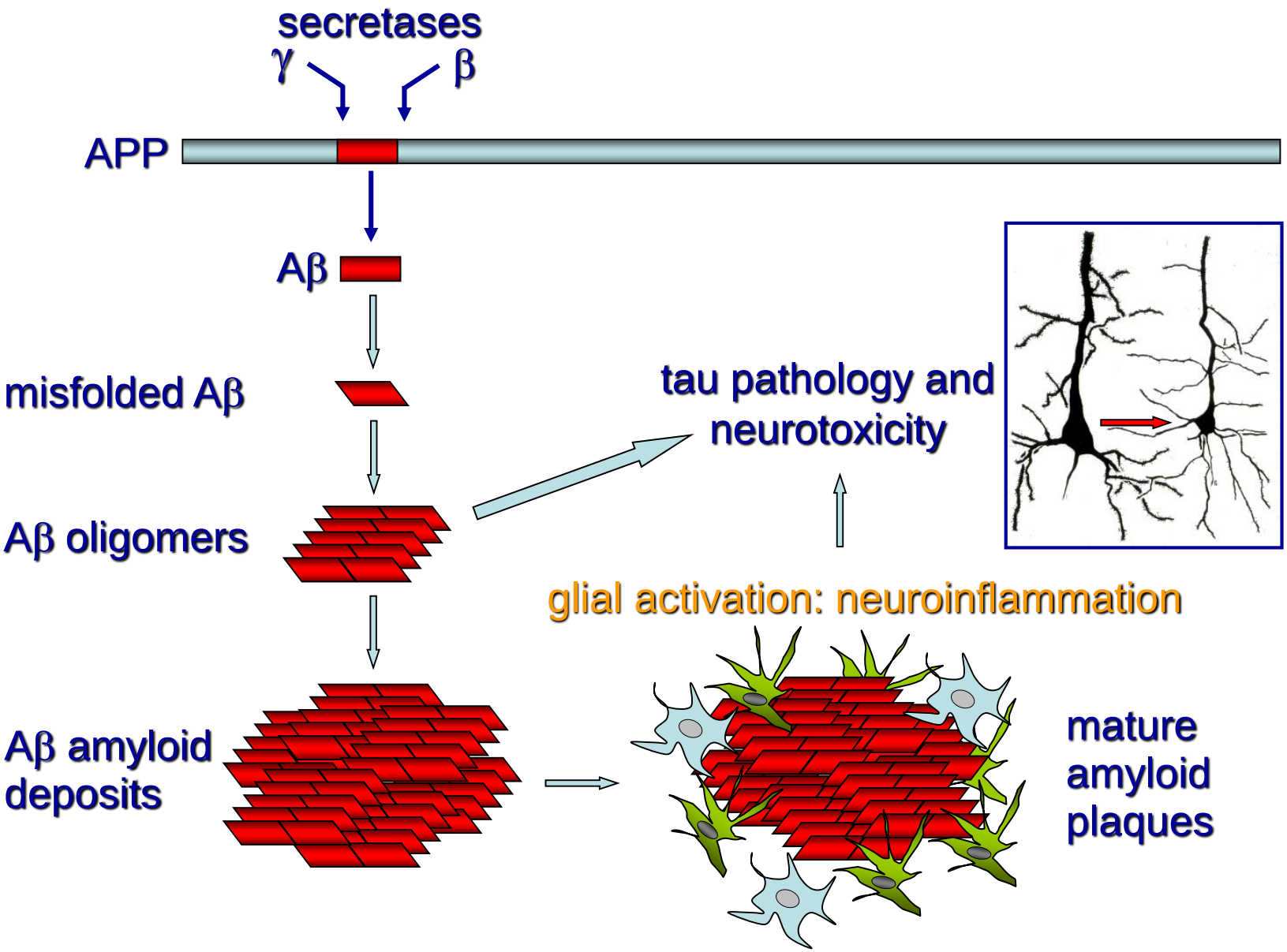
Genetic evidence for the primary role of Abeta

- Dose effect of Abeta production in Down syndrome
- Increased Abeta production in mutations of APP, PS1, PS2 and SORL1 genes
- Decreased Abeta production in protective APP A673T mutation (decreased BACE activity)
- Most genetic risk factors interact with Abeta processing and pathways

(Nat Genetics, Dec 2013 Meta-analysis of 74.000 individuals)

Aβ cascade hypothesis of AD

Hardy J. and Selkoe D. (2002) *Science* **297**:353-6



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Alzheimer's & Dementia 7 (2011) 263–269

Alzheimer's & Dementia

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

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],

Table 1
AD dementia criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (CSF tau, FDG-PET, structural MRI)
Probable AD dementia			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With three levels of evidence of AD pathophysiological process	Intermediate	Unavailable or indeterminate	Positive
	Intermediate	Positive	Unavailable or indeterminate
	High	Positive	Positive
Possible AD dementia (atypical clinical presentation)			
Based on clinical criteria	Uninformative	Unavailable, conflicting, or indeterminate	Unavailable, conflicting, or indeterminate
With evidence of AD pathophysiological process	High but does not rule out second etiology	Positive	Positive
Dementia-unlikely due to AD	Lowest	Negative	Negative

Alzheimers Dement. 2011 May ; 7(3): 270–279. doi:10.1016/j.jalz.2011.03.008.

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

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], and **Creighton H. Phelps**[p]

Summary of clinical and cognitive evaluation for MCI due to AD

Establish clinical and cognitive criteria
Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)
Objective evidence of Impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)
Preservation of independence in functional abilities
Not demented
Examine etiology of MCI consistent with AD pathophysiological process
Rule out vascular, traumatic, medical causes of cognitive decline, where possible
Provide evidence of longitudinal decline in cognition, when feasible
Report history consistent with AD genetic factors, where relevant

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

Lancet Neurol 2014; 13: 614–29

Panel 1: IWG-2 criteria for typical AD (A plus B at any stage)

A Specific clinical phenotype

- Presence of an early and significant episodic memory impairment (isolated or associated with other cognitive or behavioural changes that are suggestive of a mild cognitive impairment or of a dementia syndrome) that includes the following features:
  - Gradual and progressive change in memory function reported by patient or informant over more than 6 months
  - Objective evidence of an amnestic syndrome of the hippocampal type,* based on significantly impaired performance on an episodic memory test with established specificity for AD, such as cued recall with control of encoding test

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 tracer retention on amyloid PET
- AD autosomal dominant mutation present (in *PSEN1*, *PSEN2*, or *APP*)

Panel 2: IWG-2 criteria for atypical AD (A plus B at any stage)

A Specific clinical phenotype (one of the following)

- Posterior variant of AD (including)
  - An occipitotemporal variant defined by the presence of an early, predominant, and
  - progressive impairment of visuoperceptive functions or of visual identification of objects, symbols, words, or faces
  - A biparietal variant defined by the presence of early, predominant, and progressive difficulty with visuospatial function, features of Gerstmann syndrome, of Balint syndrome, limb apraxia, or neglect
- Logopenic variant of AD defined by the presence of an early, predominant, and progressive impairment of single word retrieval and in repetition of sentences, in the context of spared semantic, syntactic, and motor speech abilities
- Frontal variant of AD defined by the presence of early, predominant, and progressive behavioural changes including association of primary apathy or behavioural disinhibition, or predominant executive dysfunction on cognitive testing
- Down's syndrome variant of AD defined by the occurrence of a dementia characterised by early behavioural changes and executive dysfunction in people with Down's syndrome

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 tracer retention on amyloid PET
- Alzheimer's disease autosomal dominant mutation present (in *PSEN1*, *PSEN2*, or *APP*)

One disease, one set of criteria: The « IWG criteria »

A simplified algorithm is proposed:

In any condition and at any stage of the disease
the diagnosis of AD relies on clinico-biological entity:

characterized by a specific phenotype

Typical AD

- Amnestic syndrome of the Hipp. type

Atypical AD

Posterior variant
Logopenic variant
Frontal variant

with the presence of a patho-physiological marker

- CSF (both Aβ and Tau changes)

OR

- positive amyloid PET

Dubois et al, Lancet Neur, 2014

Le Malattie di Alzheimer: diverse isoforme di ABeta

Structural Variation in Amyloid-β Fibrils from Alzheimer's Disease Clinical Subtypes

Nature. 2017 January 12; 541(7636): 217–221

Wei Qiang[1,†], **Wai-Ming Yau**[1], **Jun-Xia Lu**[1,‡], **John Collinge**[2], and **Robert Tycko**[1,*]

Goldsbury C, Frey P, Olivieri V, Aebi U, Muller SA. Multiple assembly pathways underlie amyloid-β fibril polymorphisms. J Mol Biol. 2005; 352:282–298. [PubMed: 16095615]

). Meinhardt J, Sachse C, Hortschansky P, Grigorieff N, Fandrich M. Aβ(1–40) fibril polymorphism implies diverse interaction patterns in amyloid fibrils. J Mol Biol. 2009; 386:869–877. [PubMed: 19038266]

.. Zhang R, et al. Interprotofilament interactions between Alzheimer's Aβ(1–42) peptides in amyloid fibrils revealed by cryoEM. Proc Natl Acad Sci U S A. 2009; 106:4653–4658. [PubMed: 19264960]

:. Kodali R, Williams AD, Chemuru S, Wetzel R. Aβ(1–40) forms five distinct amyloid structures whose β-sheet contents and fibril stabilities are correlated. J Mol Biol. 2010; 401:503–517.

Stohr J, et al. Distinct synthetic Aβ prion strains producing different amyloid deposits in bigenic mice. Proc Natl Acad Sci U S A. 2014; 111:10329–10334. [PubMed: 24982137]

Cohen ML, et al. Rapidly progressive Alzheimer's disease features distinct structures of amyloid-β. Brain. 2015; 138:1009–1022. [PubMed: 25688081]

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

Lancet Neurol 2010; 9: 119–28

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

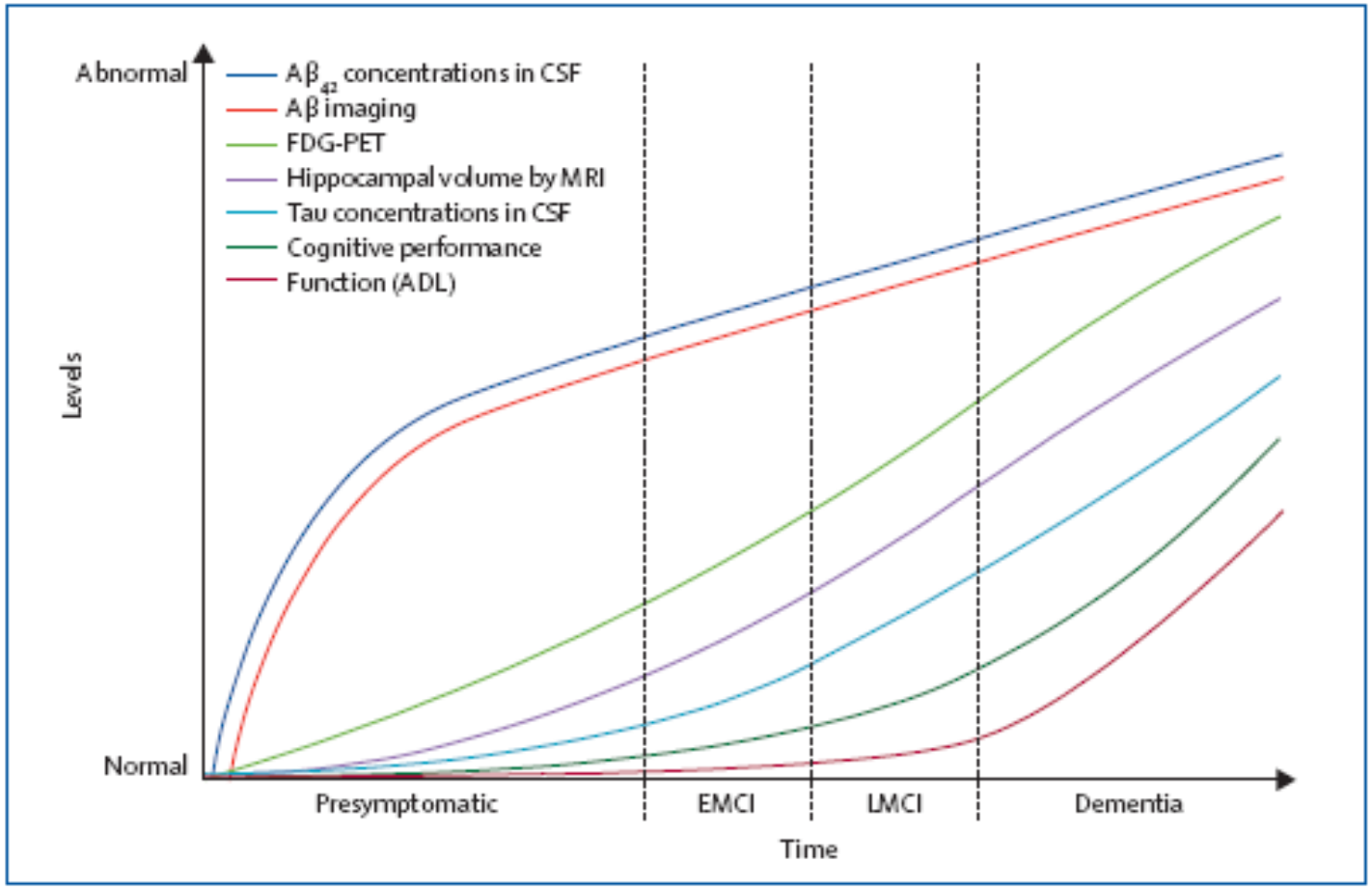

Figure: **Hypothetical progression of pathological and clinical events that lead to Alzheimer's disease, as detected by use of different imaging techniques, functional measures, or biomarkers**

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.

Alzheimer Disease (AD) vs Alzheimer Dementia

Preclinical AD

The long asymptomatic period between the first brain lesions and the first appearance of symptoms and which concerns normal individuals that later fulfil AD diagnostic criteria

Prodromal AD

The symptomatic predementia phase of AD, generally included in the mild cognitive impairment category; this phase is characterised by symptoms not severe enough to meet currently accepted diagnostic criteria for AD

AD dementia

The phase of AD where symptoms are sufficiently severe to meet currently accepted dementia and AD diagnostic criteria

CLINICAL-BIOMARKERS CONSTRUCT

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

OPEN

Clifford R. Jack, Jr., MD
David A. Bennett, MD
Kaj Blennow, MD, PhD
Maria C. Carrillo, PhD
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Reisa A. Sperling, MD
Bruno Dubois, MD, PhD

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 categorie di biomarcatori: classificazione ATN

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

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],

Table 4
Descriptive nomenclature: Syndromal cognitive staging combined with biomarkers

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

Normal

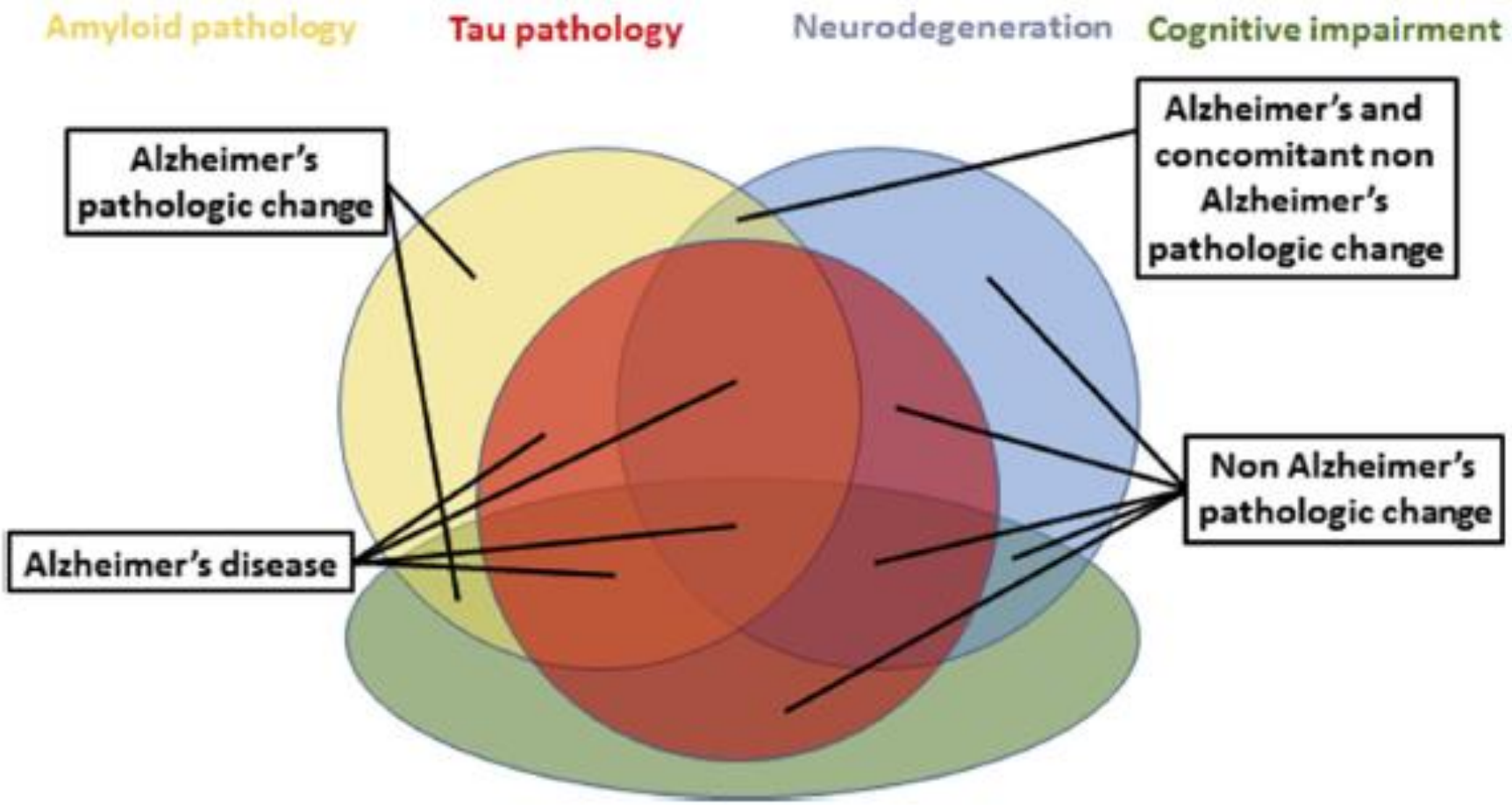
AD pat ch

AD

SNAP

SNAP: Suspected Non Alzheimer Pathology (Jack, Nat Rev Neurol 2016)

C.R. Jack Jr. et al. / Alzheimer's & Dementia 14 (2018) 535-562



NUOVA VISIONE DELLA MALATTIA DI ALZHEIMER

- Il termine AD indica la patogenesi – non la presentazione clinica
  - Una demenza amnestica non implica la malattia di Alzheimer all'autopsia
  - Presentazioni cliniche atipiche non escludono la malattia di Alzheimer

"Le malattie di Alzheimer"

- La malattia di Alzheimer è definite dai biomarcatori, non dal quadro clinico
  - I sintomi sono parte di un "disease continuum" e compaiono tardivamente
  - Rivoluzione concettuale:
    - AD inizialmente un **clinical-pathological construct** (1984)
    - poi un **clinical-biomarker construct** (2007-2014)
    - ora (2018) un **pathophysiological construct** del continuum di malattia

SPECIAL INVITED ARTICLE OPEN ACCESS

How early can we diagnose Alzheimer disease (and is it sufficient)?

The 2017 Wartenberg lecture

Ronald C. Petersen, PhD, MD

Neurology® 2018;91:395-402. doi:10.1212/WNL.0000000000006088

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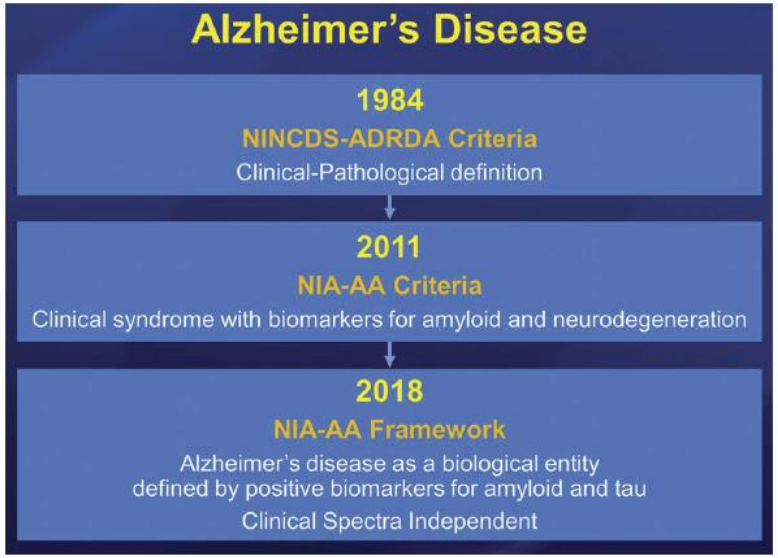
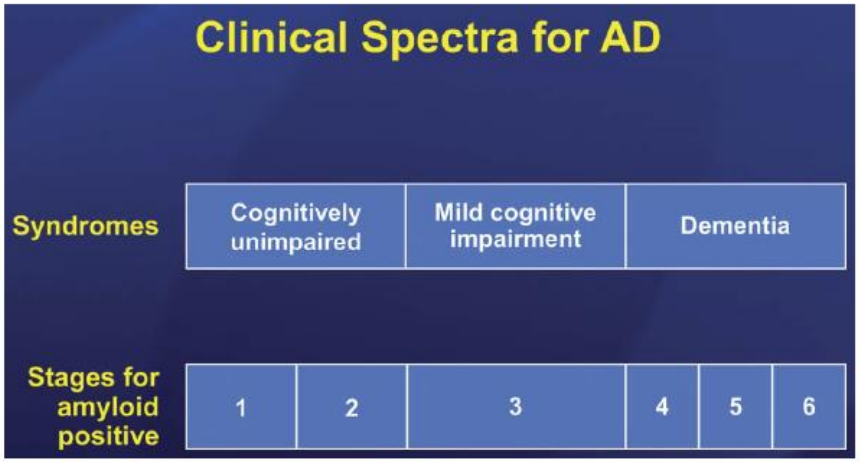
Figure 2 Temporal evolution of criteria and research frameworks for Alzheimer disease



Aβ = β-amyloid; MCI = mild cognitive impairment. Reproduced with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

Figure 4 Correspondence of clinical syndromes and stages for Alzheimer disease (AD) in the National Institute on Aging–Alzheimer's Association research framework



Aβ = β-amyloid; DSM-5 = *Diagnostic and Statistical Manual of Mental Disorders, 5th edition*; MCI = mild cognitive impairment. Reproduced with permission of Mayo Foundation for Medical Education and Research. All rights reserved.

Alzheimer disease biomarkers may aid in the prognosis of MCI cases initially reverted to normal

Lisa Vermunt, MD, Alegría J.L. van Paasen, BSc, Charlotte E. Teunissen, PhD, Philip Scheltens, MD, PhD, Pieter Jelle Visser, MD, PhD, and Betty M. Tijms, PhD, for the Alzheimer's Disease Neuroimaging Initiative

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Neurology® 2019;92:e2699-e2705. doi:10.1212/WNL.0000000000007609

Results

Seventy-seven (10%) out of 757 individuals with MCI reverted to NC and 61 of these individuals had follow-up data available. After 3.2 ± 2.2 years, 16 (24%) progressed to MCI, and 3 (5%) to dementia. Those who declined were older and had a higher amyloid PET burden and higher CSF tau levels.

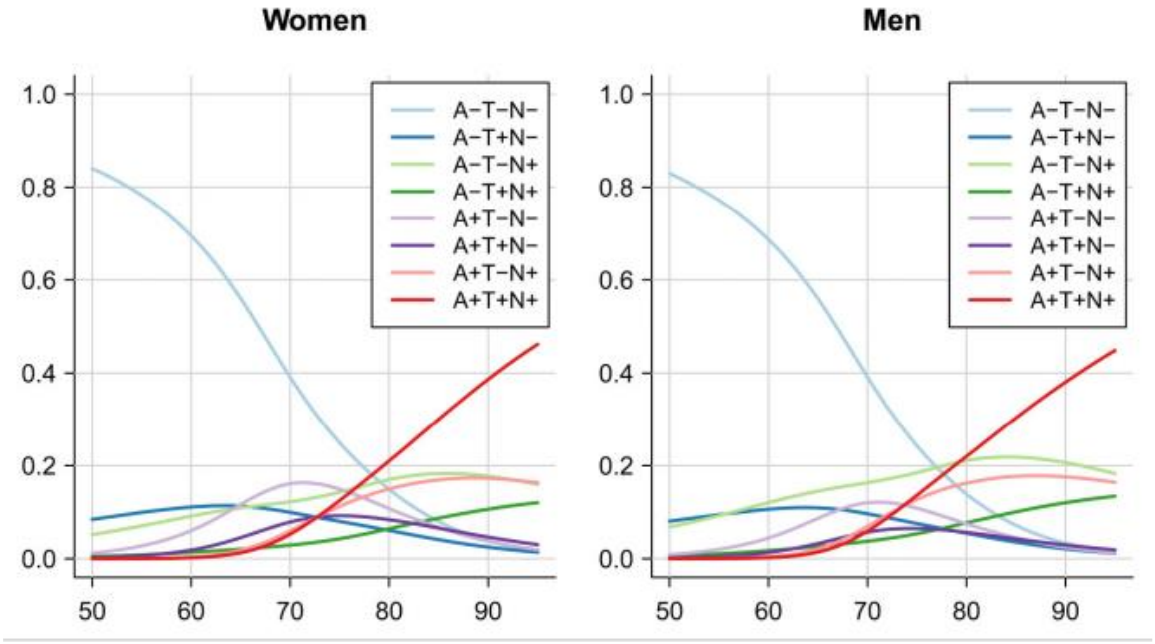
Conclusion

In MCI reverters, abnormal biomarkers for AD pathology are associated with subsequent decline. AD biomarkers may aid in the prognosis of reverting MCI.

Lancet Neurol. 2017 June ; 16(6): 435–444. doi:10.1016/S1474-4422(17)30077-7.

Age and sex specific prevalences of cerebral β-amyloidosis, tauopathy and neurodegeneration among clinically normal individuals aged 50-95 years: a cross-sectional study

Clifford R. Jack Jr, MD[1] [Prof], Heather J. Wiste, BA[2], Stephen D. Weigand, MS[2], Terry M. Therneau, PhD[2] [Prof], David S. Knopman, MD[3] [Prof], Val Lowe, MD[4] [Prof], Prashanthi Vemuri, PhD[1], Michelle M. Mielke, PhD[2] [Prof], Rosebud O. Roberts, MB, ChB[2,3] [Prof], Mary M. Machulda, PhD[6], Matthew L. Senjem, MS[5], Jeffrey L. Gunter, PhD[6], Walter A. Rocca, MD[2,3] [Prof], and Ronald C. Petersen, MD[2,3] [Prof]



BIOLOGICAL BASIS OF DEMENTIA

Degenerative process

Onset

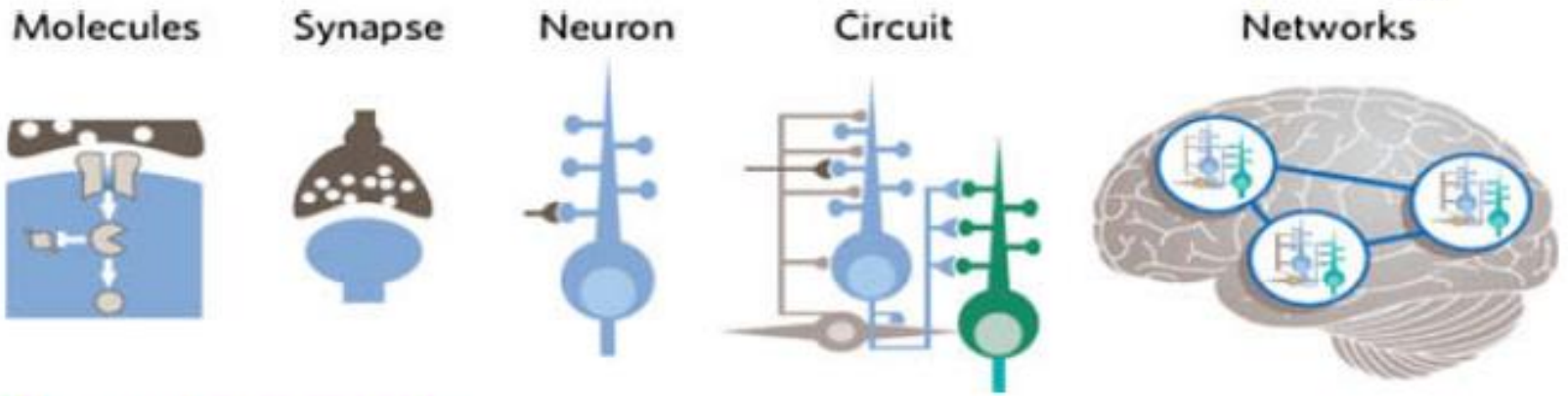
Slow progression

Common underlying mechanisms?

Symptoms

Heterogeneous

No good correlation with pathology



Neurodegeneration
(Death, damage, dysfunction)

Clinical expression

Cell vulnerability factors
- Cell defence systems
- Trophic factors
- Functional reserve

Compensatory mechanisms
- Genes
- Aging
- Associated lesions

risk or diagnosis of «preclinical Alzheimer Disease»?

Preclinical stage: preliminary statements

Biomarker

- AD pathology is characterized by amyloid and tau lesions in the brain
- In vivo evidence of A and T positivity provides the higher risk probability

Subjective cognitive decline is not a marker

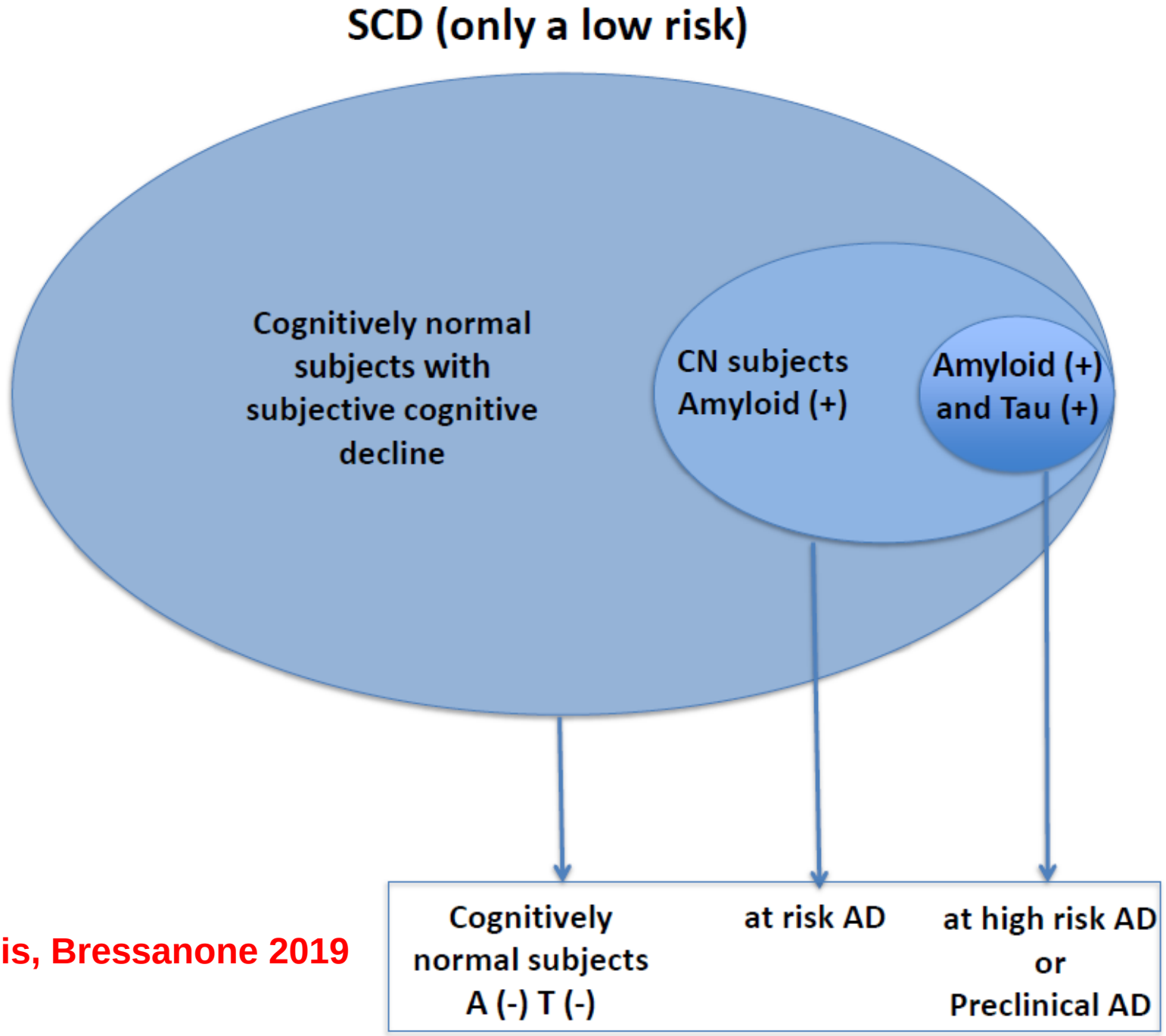
- Complaint is subjective; deficit is objective.
- Memory complainers are the rule over 60 years old: a few of them will have AD, the others not.
- SCD is a marker of ageing not of preclinical AD
- Among complainers, the most at risk are those who complain less (Cacciamani et al: 'Low cognitive awareness, but not complaint, is a good marker of preclinical AD'.

A-T-S Criteria

- **A(+) T(+) S(+) = AD**
  - both A and T are positive
  - S = symptoms objective and specific

- **A (+) T(+) S(-) = at-risk AD (AR-AD)**
  - Only 'at risk'
  - With a risk stratification (to be determined by strong epidemiological data) :
    - Absolute risk: G+ (even when A-T-S-)
    - Very high risk: A(+) T(+) = preclinical AD (?)
    - Moderate risk:
      - A(+) T(-)
      - A(-) T(+)
    - Modulating factors (?): ApoE4, cognitive reserve, neurodegeneration, low awareness / SCD

Dubois, Bressanone 2019



Dubois, Bressanone 2019

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Alzheimer's & Dementia ■ (2018) 1-7

Alzheimer's & Dementia

Perspective

The National Institute on Aging—Alzheimer's Association Framework on Alzheimer's disease: Application to clinical trials

Jeffrey Cummings*

Cleveland Clinic Lou Ruvo Center for Brain Health, Las Vegas, NV, USA

ATN classification of neurodegenerative disorders including those related to Alzheimer's disease (AD)

Amyloid (A)	Tau (T)	Neurodegeneration (N)	Comment	Trial population
Negative	Negative	Negative	Normal	Primary prevention trials; before amyloid is present
Positive	Negative	Negative	Alzheimer pathology; this defines preclinical AD before any changes associated with amyloid have begun	Secondary prevention trials; amyloid is present, tau is not; delay of tau spread as a potential outcome
Positive	Positive	Negative	AD; amyloid and tau changes are present; no evidence of neurodegeneration	Secondary prevention trials; amyloid and tau are present, neurodegeneration is not; delay in tau spread or development of neurodegeneration are potential outcomes
Positive	Positive	Positive	AD; amyloid, tau, and neurodegeneration This category will also include mixed dementia where AD co-exists with other brain disorders such as cerebrovascular disease. Comorbid conditions contribute to the neurodegeneration component.	Treatment trials; all three basic biomarkers are present; slowing of progression or delay to milestone are appropriate designs Combination treatment trials could include this population; for example, trials including AD and CVD
Positive	Negative	Positive	Alzheimer pathology plus some other cause of neurodegeneration	Combination treatment trials of anti-amyloid agent and drugs addressing concomitant pathology may be warranted
Negative	Negative	Positive	Not AD; neurodegeneration only	Non-AD trials such as VaD, some FTD
Negative	Positive	Negative	Not AD; elevated tau without neurodegeneration	Non-AD trials of CVD, prion disease, or early tauopathies
Negative	Positive	Positive	Not AD; elevated tau and neurodegeneration	Non-AD trials of VaD or tauopathies

New therapeutic strategies

- **Anti-amyloid drugs:**

  decrease production*: enzymatic inhibitors*

  removal: *immunotherapy*

- **Anti-TAU drugs**

PROBLEMI CON IMMUNOTERAPIA PASSIVA ANTI-AMILOIDE E NUOVE STRATEGIE

PAZIENTI GIUSTI ? Inclusione di pazienti non AD

Selezionare i pazienti postivi per accumulo di beta amiloide mediante biomarker (PET – liquor)

TROPPO TARDI ? inefficacia nei pazienti già dementi

Trattare prima: AD prodromico (MCI) o preclinico

TROPPO POCO ? non sufficiente rimozione di Abeta per effetti collaterali?

Dose titration, facilitare il passaggio attraverso la BEE (nanoparticelle?)

HOT TOPIC:

16:05	Discussant: Prof. Ildebrando Appollonio	**Speranze e fallimenti delle terapie "disease modifying" nella Malattia di Alzheimer** Benedetta Storti - *Università degli Studi di Milano-Bicocca*

SNAP: dalla Sclerosi Ippocampale a LATE

Primi 13 casi (da serie neuropatologica di 81 pz = 16%)

1. Demenza
2. Scarsa neuropatologia AD
3. Sclerosi ippocampale

TDP-43 anche in pz senza SLA o FTD

> 80 aa, con sclerosi ippocampale

Acta Neuropathol (1994) 88 : 212–221

REGULAR PAPER

D. W. Dickson · P. Davies · C. Bevona
K. H. Van Hoeven · S. M. Factor · E. Grober
M. K. Aronson · H. A. Crystal

Hippocampal sclerosis: a common pathological feature of dementia in very old (≥80 years of age) humans

Handbook of Clinical Neurology, Vol. 89 (3rd series)
Dementias
C. Duyckaerts, I. Litvan, Editors

Hippocampal sclerosis

Chapter 53

Neuropathology of hippocampal sclerosis

CATALINA AMADOR-ORTIZ AND DENNIS W. DICKSON*

BRAIN
Peter T. Nelson University of Kentucky, Lexington, KY, USA

REVIEW

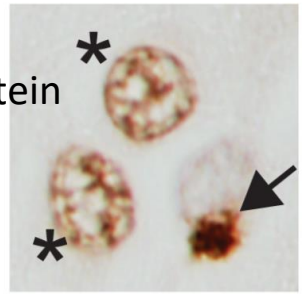
Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

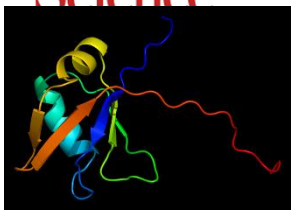
1994 — 2006 — 2007-8 — 2019

Ubiquitinated TDP-43 in Frontotemporal Lobar Degeneration and Amyotrophic Lateral Sclerosis

Manuela Neumann,[1,11*] Deepak M. Sampathu,[1*] Linda K. Kwong,[1*] Adam C. Truax,[1]
Matthew C. Micsenyi,[1] Thomas T. Chou,[2] Jennifer Bruce,[1] Theresa Schuck,[1] Murray Grossman,[3,4]
Christop [5] Eliezer Masliah [7]
Ian R. M Hans A. Kre
John Q.

Science





-Transactive response DNA binding protein
-Regolatore dell'espressione genica
-Nucleo → citoplasma in condizioni patologiche

doi:10.1093/brain/awz099 BRAIN 2019: 0; 1–25 |

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW

Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

Peter T. Nelson,[1] Dennis W. Dickson,[2] John Q. Trojanowski,[3] Clifford R. Jack Jr.,[4] Patricia A. Boyle,[5] Konstantinos Arfanakis,[5,6] Rosa Rademakers,[2] Irina Alafuzoff,[7] Johannes Attems,[8] Carol Brayne,[9] Ian T.S. Coyle-Gilchrist,[9] Helena C. Chui,[10] David W. Fardo,[1] Margaret E. Flanagan,[11] Glenda Halliday,[12] Suvi R.K. Hokkanen,[9] Sally Hunter,[9] Gregory A. Jicha,[1] Yuriko Katsumata,[1] Claudia H. Kawas,[13] C. Dirk Keene,[1] Gabor G. Kovacs,[15] Walter A. Kukull,[14] Allan I. Levey,[16] Nazanin Makkinejad,[6] Thomas J. Montine,[17] Shigeo Murayama,[18] Melissa E. Murray,[2] Sukriti Nag,[5] Robert A. Rissman,[19] William W. Seeley,[20] Reisa A. Sperling,[21] Charles L. White III,[22] Lei Yu[5] and Julie A. Schneider[5]

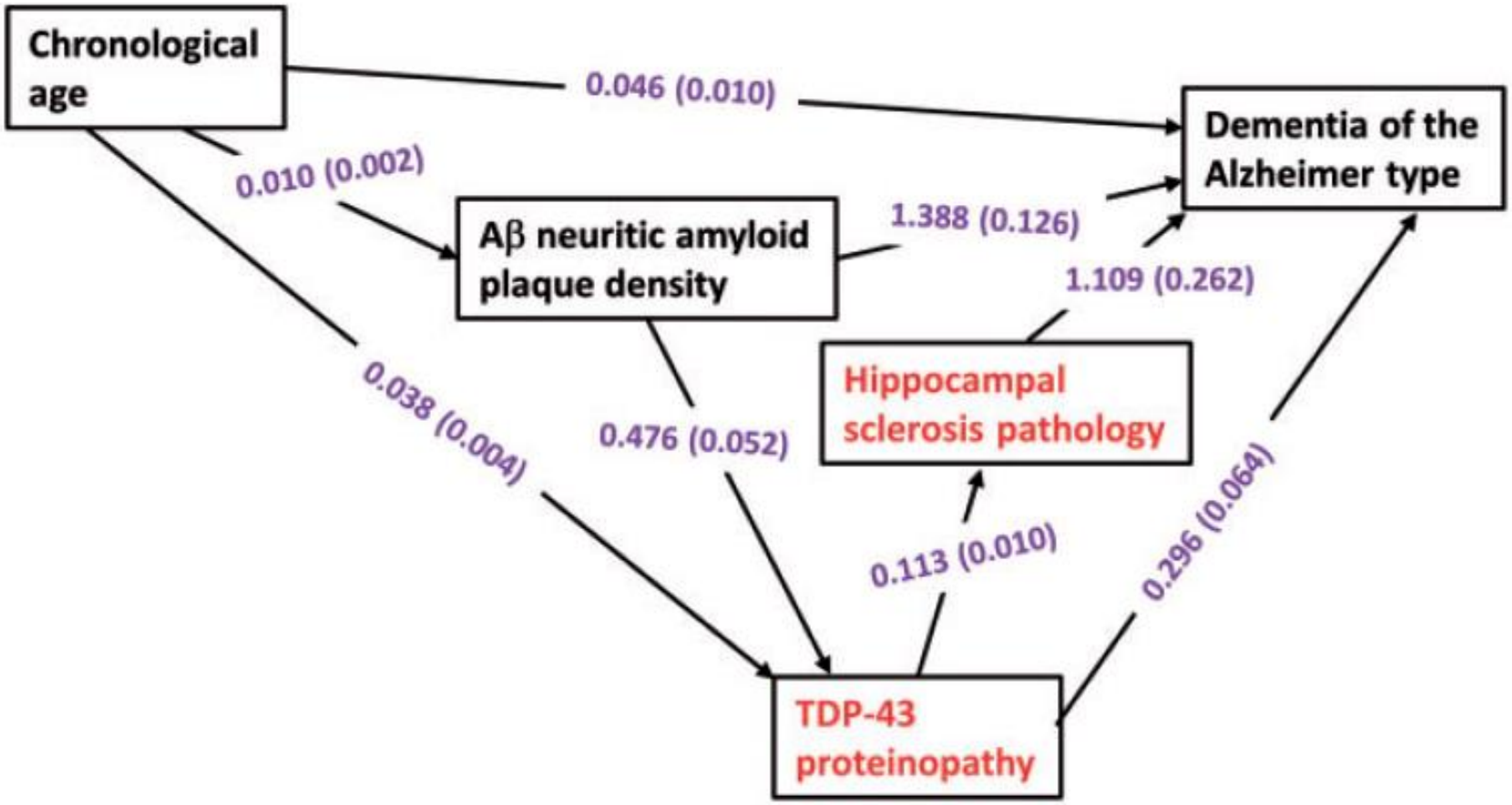
- LATE is associated with substantial disease-specific cognitive impairment, usually an amnestic dementia syndrome ('dementia of the Alzheimer's type')
- The overall public health impact of LATE is on the same order of magnitude as Alzheimer's disease neuropathological changes; the diseases are often comorbid, but which pathology is more severe varies greatly between individuals
- Genetic risk factors for LATE have some overlap with FTLD-TDP and with Alzheimer's disease
- There is no molecule-specific biomarker for LATE. This is an important area of need for use in clinical trials (including as a potential exclusion criterion for Alzheimer's disease clinical trials) and longitudinal studies of the clinical and pathological progression of LATE

Table 2 A statistical analysis of attributable risk from research volunteers in two clinical-pathological studies of ageing from Rush University

Neuropathological indices	Fraction attributable % (95% CI)[a]
Alzheimer's disease (ADNC)	39.4 (31.5–47.4)
Vascular disease pathology[b]	24.8 (17.3–32.1)
LATE-NC	**17.3** (13.1–22.0)
α-Synucleinopathy/Lewy body pathology	11.9 (8.4–15.6)

Shown are fractions of dementia of the Alzheimer type cases that were attributable to individual neuropathological indices in advanced age. In this sample, the mean age of death was 89.7 years (SD 6.5 years, range 65–108 years). For these analyses, multi-

Pathway analysis with Path coefficients (Standard error)
Sample: Rush University ROS-MAP autopsy cohorts (***n*** **= 1309**)



LATE ←→AD

- Sindrome amnesica
- Età avanzata
- Atrofia ippocampale
- Positività ApoE

- Sindrome amnesica
- Età avanzata
- Atrofia ippocampale
- Positività ApoE

LATE ←→AD

- Sindrome amnesica poco evolutiva
- Età avanzatissima
- Atrofia ippocampale severa / sclerosi
- Positività ApoE

- Sindrome amnesica
- Età avanzata
- Atrofia ippocampale
- Positività ApoE

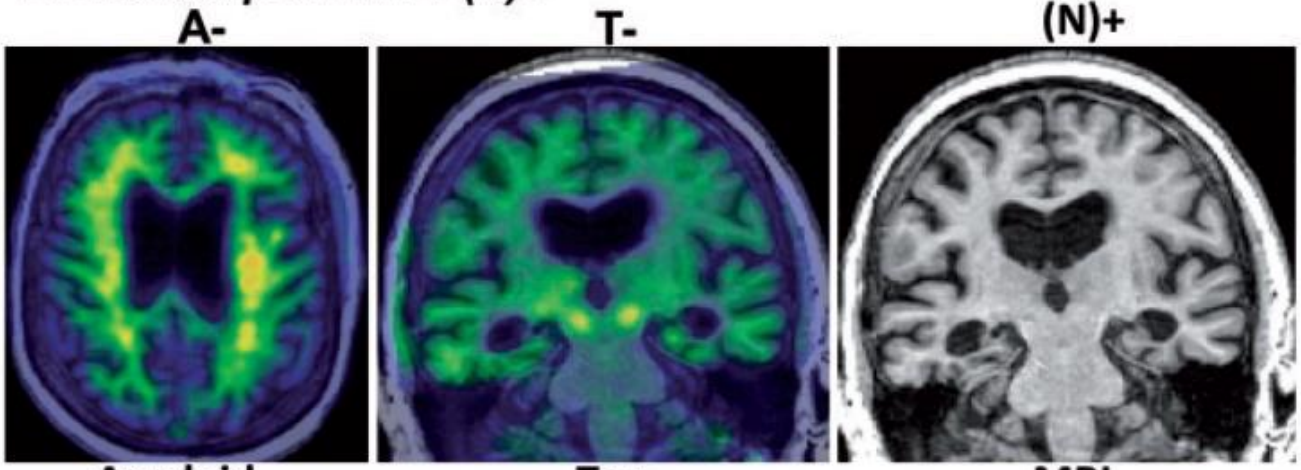
LATE ←→AD

- Sindrome amnesica poco evolutiva
- Età avanzata
- Atrofia ippocampale severa / sclerosi
- Positività ApoE
- A- / T- / N+
- A+ / T- / N+

- Sindrome amnesica
- Età avanzata
- Atrofia ippocampale
- Positività ApoE
- A+ / T+ / N+

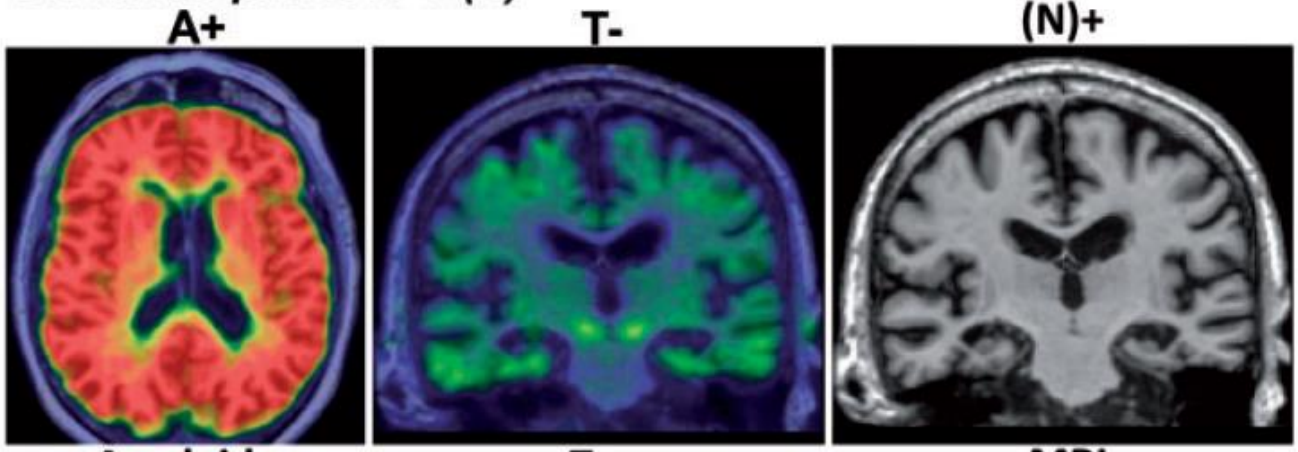
A **86 yo F, progressive amnestic dementia**

Biomarker profile A-T-(N)+



B **91 yo M, progressive amnestic dementia**

Biomarker profile A+T-(N)+



Trials preventivi in soggetti normali (AD preclinico)

• ADCS A4 (NCT02008357) • Eli Lilly	Solanezumab	Monoclonal antibody	• 1,150 asymptomatic individuals at risk of AD • 240 weeks	ADCS–PACC	July 2022
• DIAN-TU (NCT01760005) • Eli Lilly, Roche–Genentech and Janssen	• Solanezumab • Gantenerumab • Atabecestat	• Monoclonal antibody • Monoclonal antibody • BACE inhibitor	• 438 asymptomatic *APP* or *PSEN* mutation carriers • 208 weeks	DIAN-TU composite score	December 2023
• API Generation S1 (NCT02565511) • Novartis	• CAD106 • CNP520	• Aβ antigen • BACE inhibitor	• 1,340 asymptomatic homozygous *APOE*ε4* carriers • 60 months	• MCI diagnosis • APCC	May 2024
• API Generation S2 (NCT03131453) • Novartis	CNP520	BACE inhibitor	• 2,000 asymptomatic homozygous *APOE*ε4* carriers and heterozygous *APOE*ε4* carriers with brain amyloid accumulation • 60 months	• MCI diagnosis • APCC	July 2024

- **Atebecestat (Janssen) phase 3 in normal subjects: interrotto nel 2018 per tossicità epatica**

DIAGNOSI PRECLINICA SOLO PER RICERCA

Sfide dei trial pre-clinici

- Difficoltà di definire il livello di rischio e di monitore piccole alterazioni cognitive
- Necessità di marcatori biologici come end-points surrogati (PET – CSF – altri biomarcatori) ?
- Necessità di follow-up lungo (5-10 years?)
- Aspetti legali, etici, economici….

Journal of Alzheimer's Disease 69 (2019) 1–2
DOI 10.3233/JAD-190267
IOS Press

Editorial

One Step Forward Toward a Surrogate Endpoint for Clinical Trials of Alzheimer's Disease Drugs: The Results of PharmaCog WP5 (European ADNI)

Giovanni B. Frisoni[a,*], Olivier Blin[b] and Regis Bordet[c]

modules of PharmaCog was a longitudinal study of 150 mild cognitive impairment memory clinic patients followed longitudinally with clinical, imaging, and cerebrospinal fluid markers of progression with an ADNI-like design and ADNI-compatible data collection procedures [6].

AMA Journal of Ethics®
December 2016, Volume 18, Number 12: 1207-1217

HEALTH LAW

The Legal Implications of Detecting Alzheimer's Disease Earlier

Joshua Preston, Jaleh McTeigue, Caitlin Opperman, Jordan Dean Scott Krieg, Mikaela Brandt-Fontaine, Alina Yasis, and Francis X. Shen, JD, PhD

Early detection of Alzheimer's disease (AD) raises a number of challenging legal questions. In this essay, we explore some of those questions, such as: Is a neurological indicator of increased risk for AD a legally relevant brain state before there are any outward behavioral manifestations? How should courts address evidentiary challenges to the admissibility of AD-related neuroimaging? How should the government regulate the marketing of neuroimaging diagnostic tools? How should insurance coverage for the use of these new tools be optimized? We suggest that many voices and multidisciplinary perspectives are needed to answer these questions and ensure that legal responses are swift, efficient, and equitable.

Alzheimers Dement. 2016 May ; 12(5): 614–622. doi:10.1016/j.jalz.2016.01.009.

Ethical challenges in preclinical Alzheimer's disease observational studies and trials: results of the Barcelona summit

José L. Molinuevo[a], **Jordi Cami**[b], **Xavier Carné**[c], **Maria C. Carrillo**[d], **Jean Georges**[e], **Maria B. Isaac**[f], **Zaven Khachaturian**[g], **Scott Y. H. Kim**[h], **John C. Morris**[i], **Florence Pasquier**[j], **Craig Ritchie**[k], **Reisa Sperling**[l], and **Jason Karlawish**[m]

The ethical challenges

When considering preclinical AD trials, two ethical issues of special importance arise. First, because asymptomatic persons are exposed to novel agents for an extended period, the design of the trial must ensure that the potential benefits justify the burden and risk for the participants. Second, many prevention trials will enrich their study population through genetic and other biological risk factors that will be screened by genetic and/or imaging techniques. Since these tests are normally discouraged in routine clinical practice and therefore, a person would not normally receive this information unless participating in prevention trials, the issue of disclosure of such information must be carefully addressed

Risk-Benefit Considerations

Disclosure of Risk Marker Status

Safety of Disclosing Amyloid Status in Cognitively Normal Older Adults

Jeffrey M. Burns[1], **David K. Johnson**[1,2], **Edward Liebmann**[2], **Rebecca Bothwell**[1], **Jill K. Morris**[1], and **Eric D. Vidoni**[1]

RESULTS—Clinicians disclosed amyloid status to 97 cognitively normal older adults (27 had elevated cerebral amyloid). There was no difference in depressive symptoms across groups over time. There was a significant group by time interaction in anxiety, although post-hoc analyses revealed no group differences at any time point, suggesting a minimal non-sustained increase in anxiety symptoms immediately post-disclosure in the elevated group. Slight but measureable increases in test-related distress were present after disclosure and were related to greater baseline levels of anxiety and depression.

DISCUSSION—Disclosing amyloid imaging results to cognitively normal adults in the clinical research setting with pre- and post-disclosure counseling has a low risk of psychological harm.

Alzheimers Dement. 2017 September ; 13(9): 1024–1030.

Perspectives on Communicating Biomarker-Based Assessments of Alzheimer's Disease to Cognitively Healthy Individuals

Journal of Alzheimer's Disease 62 (2018) 487–498

Richard Milne[a,*], Eline Bunnik[b], Ana Diaz[c], Edo Richard[d], Shirlene Badger[a], Dianne Gove[c], Jean Georges[c], Karine Fauria[e], Jose-Luis Molinuevo[e], Katie Wells[f], Craig Ritchie[g] and Carol Brayne[a]

Difference between risk and diagnosis

Potential benefits and potential harms of knowing

«Guidelines» to the disclosure process

1. the communication should make it clear that it relates to a risk rather than a diagnosis
2. Information should provide clear details on risk level
3. Information should be accompained with suggestions for actions
4. Informations should be provided by experts with the necessary knowledge and skills
5. Informations should be provided face-to-face
6. Time should be allowed for questions before, during and after disclosure
7. Communication should occur consistenly accross settings (specialist, GP)
8. People with increased risk should be monitored following disclosure
9. Psychosocial support should be available

CHALLENGE FOR EARLY DIAGNOSIS OF AD

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Assessing the Preparedness of the U.S. Health Care System Infrastructure for an Alzheimer's Treatment

Jodi L. Liu, Jakub P. Hlávka, Richard Hillestad, Soeren Mattke

Key findings

- Alzheimer's disease is a progressive neurodegenerative disorder that leads to cognitive decline, dementia, and premature death. No disease-modifying treatment is available but encouraging results from clinical trials offer hope that one or more therapies will become available as early as 2020.
- This prospect raises the question of whether the U.S. health care system is prepared to handle the expected large number of patients. Around 15 million Americans with mild cognitive impairment, which could be an early sign of the disease, will have to be evaluated by specialists, undergo diagnostic testing, and be treated.
- A simulation analysis shows that projected capacity is insufficient to handle the expected case load and predicts patients would have to wait an average of 18.6 months for treatment in 2020. Approximately 2.1 million patients would develop Alzheimer's dementia between 2020 and 2040 while on waiting lists.
- The most pressing constraint is limited capacity of specialists to evaluate and diagnose patients, but access to imaging to confirm Alzheimer's disease and to infusion centers to deliver the treatment would also contribute to waiting times.
- Addressing capacity constraints requires solving a complex puzzle consisting of payment policy, regulatory requirements, workforce considerations, and capacity planning at the national and local levels, combined with awareness campaigns.
- No individual stakeholder will be able to put all the pieces together alone. This report intends to inform a discussion among stakeholders and create a sense of urgency to start collaborating on addressing the obstacles in a timely manner.

For more information on this publication, visit www.rand.org/t/RR2503.

Research Report

JAKUB P. HLÁVKA, SOEREN MATTKE, JODI L. LIU

Assessing the Preparedness of the Health Care System Infrastructure in Six European Countries for an Alzheimer's Treatment

KEY FINDINGS

- The burden of Alzheimer's disease in high-income countries is expected to approximately double between 2015 and 2050. Recent clinical trial results give hope that a disease-modifying therapy might become available in the near future. The therapy is expected to treat early-stage patients to prevent or delay the progression to dementia.
- This preventive treatment paradigm implies the need to screen, diagnose, and treat a large population of patients with mild cognitive impairment. There would be many undiagnosed prevalent cases that would need to be addressed initially, and then the longer-term capacity to address incident cases would not need to be as high as the short-term capacity.
- We use a simulation model to assess the preparedness of the health care system infrastructure in six European countries—France, Germany, Italy, Spain, Sweden, and the United Kingdom—to evaluate, diagnose, and treat the expected number of patients.
- Projected peak wait times range from five months for treatment in Germany to 19 months for evaluation in France. The first years without wait times would be 2030 in Germany and 2033 in France, and 2042 in the United Kingdom and 2044 in Spain. Specialist capacity is the rate-limiting factor in France, the United Kingdom, and Spain, and treatment delivery capacity is an issue in most of the countries.
- If a disease-modifying therapy becomes available in 2020, we estimate the projected capacity constraints could result in over 1 million patients with mild cognitive impairment progressing to Alzheimer's dementia while on wait-lists between 2020 and 2044 in these six countries.
- A combination of reimbursement, regulatory, and workforce planning policies, as well as innovation in diagnosis and treatment delivery, is needed to expand capacity and to ensure that available capacity is leveraged optimally to treat patients with early-stage Alzheimer's disease.

ITALY: EXPECTED PATIENTS AND HEALTH CARE SYSTEM CAPACITY

Millions of patients could seek diagnosis and treatment

Of the 20.6 million people age 55 and older in 2019,

16.4 MILLION could seek screening in a doctor's office

Of the 2.9 million who screen positive for MCI,

1.4 MILLION could seek a dementia specialist for evaluation (there are 9,501 neurologists, geriatricians, and geriatric psychiatrists, or 16.0 specialists per 100,000 people)

1.3 MILLION could be referred for biomarker testing

0.6 MILLION might test positive for biomarkers and return to the specialist to learn about treatment

0.5 MILLION could be recommended for infusion therapy

The primary aim of INTERCEPTOR is to identify a biomarker or a set of biomarkers able to predict with greatest accuracy, highest risks/costs ratio, lowest invasiveness and best availability on the territorial level, the conversion of diagnosis of MCI to dementia in a 3 years follow-up period.

This in order to initiate as soon as possible all those initiatives to contrast disease progression.

The secondary aim is to define an optimal organizational model, both in terms of transferability in clinical practice of diagnostic path defined of the primary objective and the sustainability of costs, to identify patients able to prescription of antidementia drug that now are in the course of experimentation by RCTs.

8 nov 2016
14 nov 2016
23 mar 2017
2 mag 2017
22 mag 2017
10 lug 2017
8 set 2017
20 set 2017
26 set 2017
20 dic 2017
19 gen 2018
8 feb 2018
22 mag 2018
29 mag 2018
30 LUG 2018 !

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I BIOMARCATORI INCLUSI NELLO STUDIO

Biomarker 1: Mini-Mental State Examination

Biomarker 2: Delayed Free Recall and Free and Cued Selective Reminding Test

Biomarker 3: Cerebro-Spinal-Fluid (CSF) p-tau e ratio tau/ABeta

Biomarker 4: (^{18}F)FDG-PET

Biomarker 5: at least the presence of one allele APOE ε 4

Biomarker 6: multiple six electroencephalogram (EEG) biomarkers into a diagnostic classification index

Biomarker 7: volumetric MRI

Frölich *et al. Alzheimer's Research & Therapy* (2017) 9:84
DOI 10.1186/s13195-017-0301-7

Alzheimer's Research & Therapy

RESEARCH Open Access

Incremental value of biomarker combinations to predict progression of mild cognitive impairment to Alzheimer's dementia

Lutz Frölich[1*], Oliver Peters[2], Piotr Lewczuk[3,4], Oliver Gruber[5], Stefan J. Teipel[6,7,8], Hermann J. Gertz[9], Holger Jahn[10], Frank Jessen[11,12,13], Alexander Kurz[14], Christian Luckhaus[15], Michael Hüll[16], Johannes Pantel[17], Friedel M. Reischies[2], Johannes Schröder[18], Michael Wagner[11], Otto Rienhoff[19], Stefanie Wolf[5], Chris Bauer[20], Johannes Schuchhardt[20], Isabella Heuser[2], Eckart Rüther[5], Fritz Henn[1], Wolfgang Maier[11], Jens Wiltfang[5] and Johannes Kornhuber[3,4]

Grazie per l'attenzione!

- **Domande?.....**