4° CONVEGNO NAZIONALE SUI CENTRI DIURNI ALZHEIMER

31 Maggio - 1 Giugno 2013

Stato dell'arte sui traccianti per amiloide

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Alzheimer's & Dementia 7 (2011) 270–279

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

Alzheimer's & Dementia

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], Creighton H. Phelps[p]

Biomarkers under examination for AD
Biomarkers of Aβ deposition
CSF $A\beta_{42}$
PET amyloid imaging
Biomarkers of neuronal injury
CSF tau/phosphorylated-tau
Hippocampal volume or medial temporal atrophy by volumetric measures or visual rating
Rate of brain atrophy
FDG-PET imaging
SPECT perfusion imaging
Less well validated biomarkers: fMRI activation studies, resting BOLD functional connectivity, MRI perfusion, MR spectroscopy, diffusion tensor imaging, voxel-based and multivariate measures
Associated biochemical change
Inflammatory biomarkers (cytokines)
Oxidative stress (isoprostanes)
Other markers of synaptic damage and neurodegeneration such as cell death

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Alzheimer's & Dementia

MCI criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
MCI–core clinical criteria	Uninformative	Conflicting/indeterminant/untested	Conflicting/indeterminant/untested
MCI due to AD—intermediate likelihood	Intermediate	Positive	Untested
		Untested	Positive
MCI due to AD—high likelihood	Highest	Positive	Positive
MCI—unlikely due to AD	Lowest	Negative	Negative

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

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

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], Martin N. Rossor[r], Philip Scheltens[s], Maria C. Carrillo[t], Bill Thies[t], Sandra Weintraub[u,v], Creighton H. Phelps[w]

Alzheimer's & Dementia

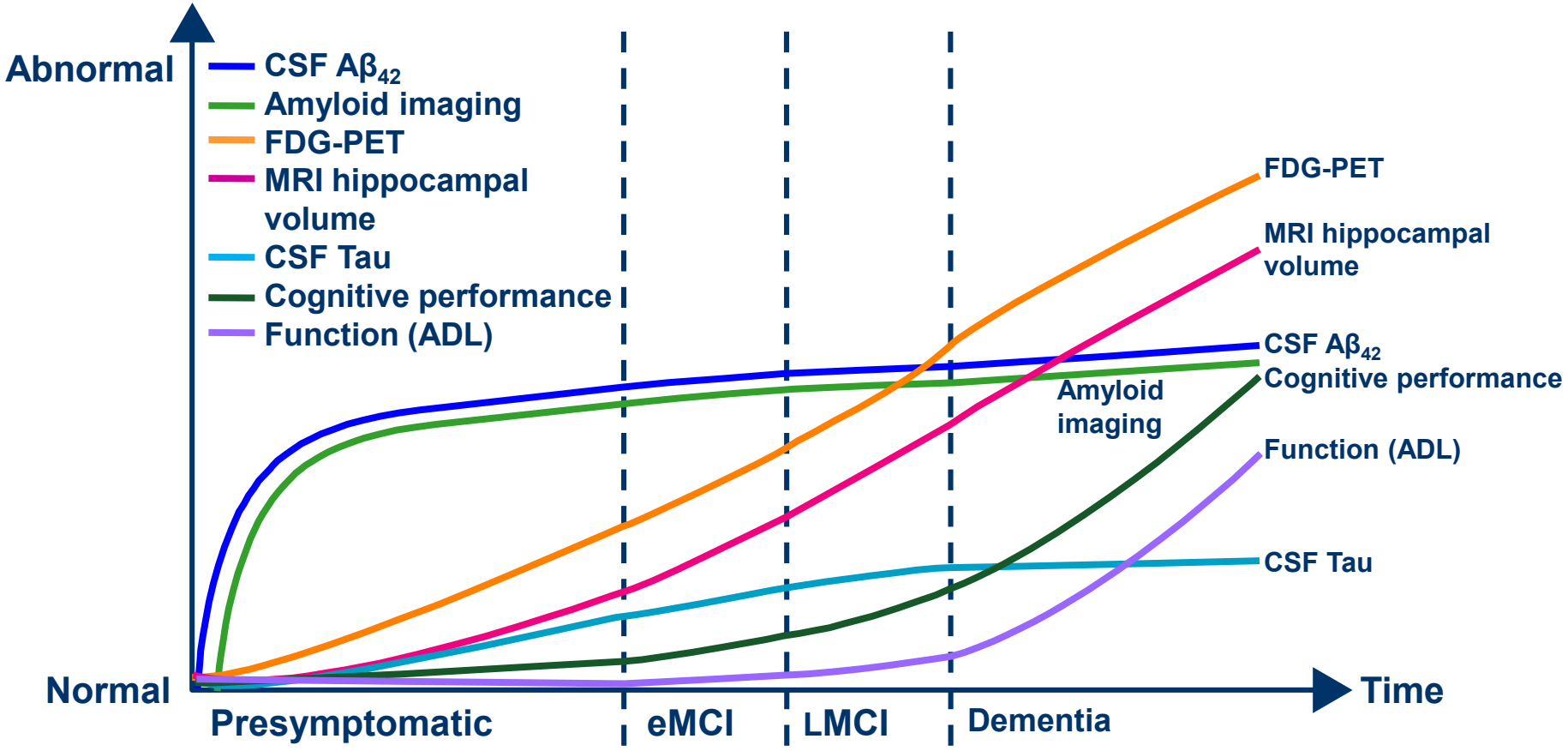
In persons who meet the core clinical Criteria for probable AD dementia biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process.

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

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid-beta; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, ^{18}fluorodeoxyglucose; MRI, magnetic resonance imaging.

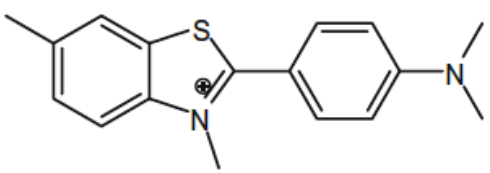
AD: Progressione



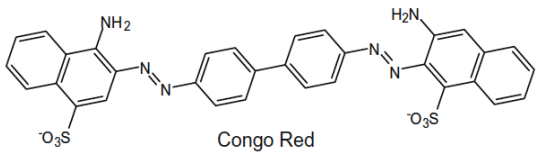
Aisen PS, Petersen RC, Donohue MC, et al. *Alzheimers Dement.* 2010;6:239-246.

Origine dei traccianti per amiloide

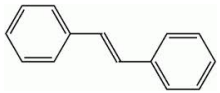
Colorazioni per amiloide



Thioflavin T



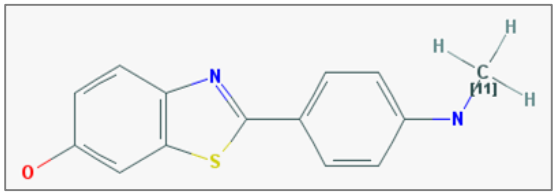
Congo Red



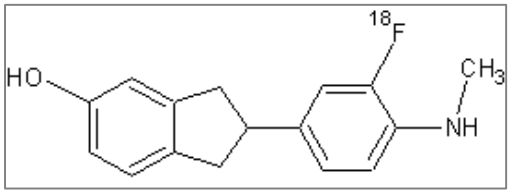
Stilbene

Traccianti per amiloide

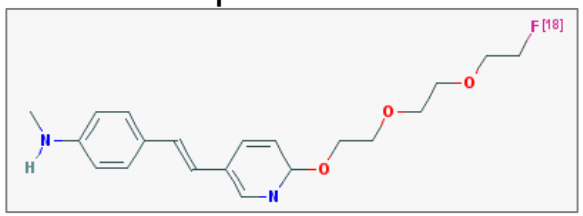
^{11}C- PiB



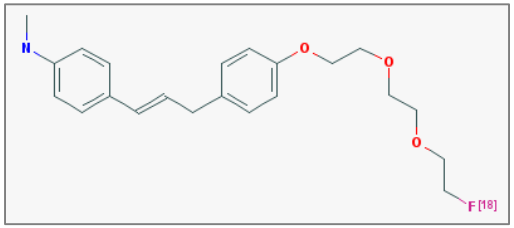
^{18}F-flutemetamol



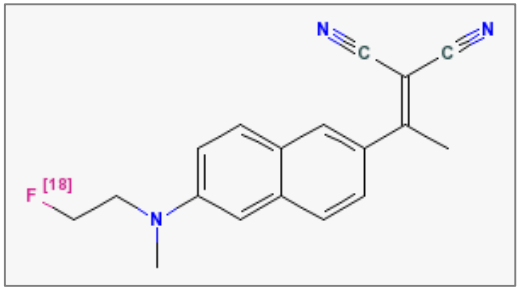
^{18}F-florbetapir



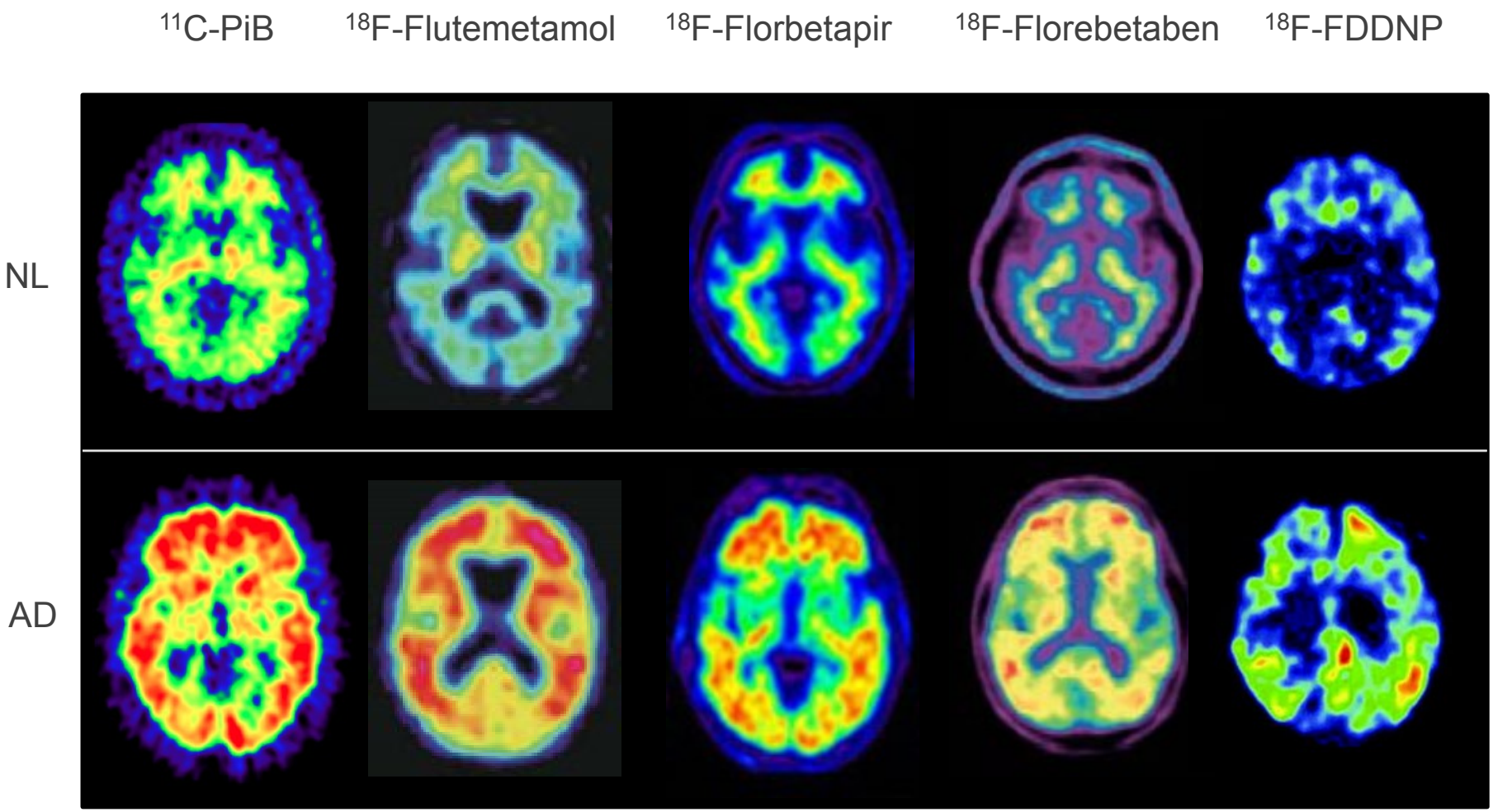
^{18}F-florbetaben



^{18}F-FDDNP

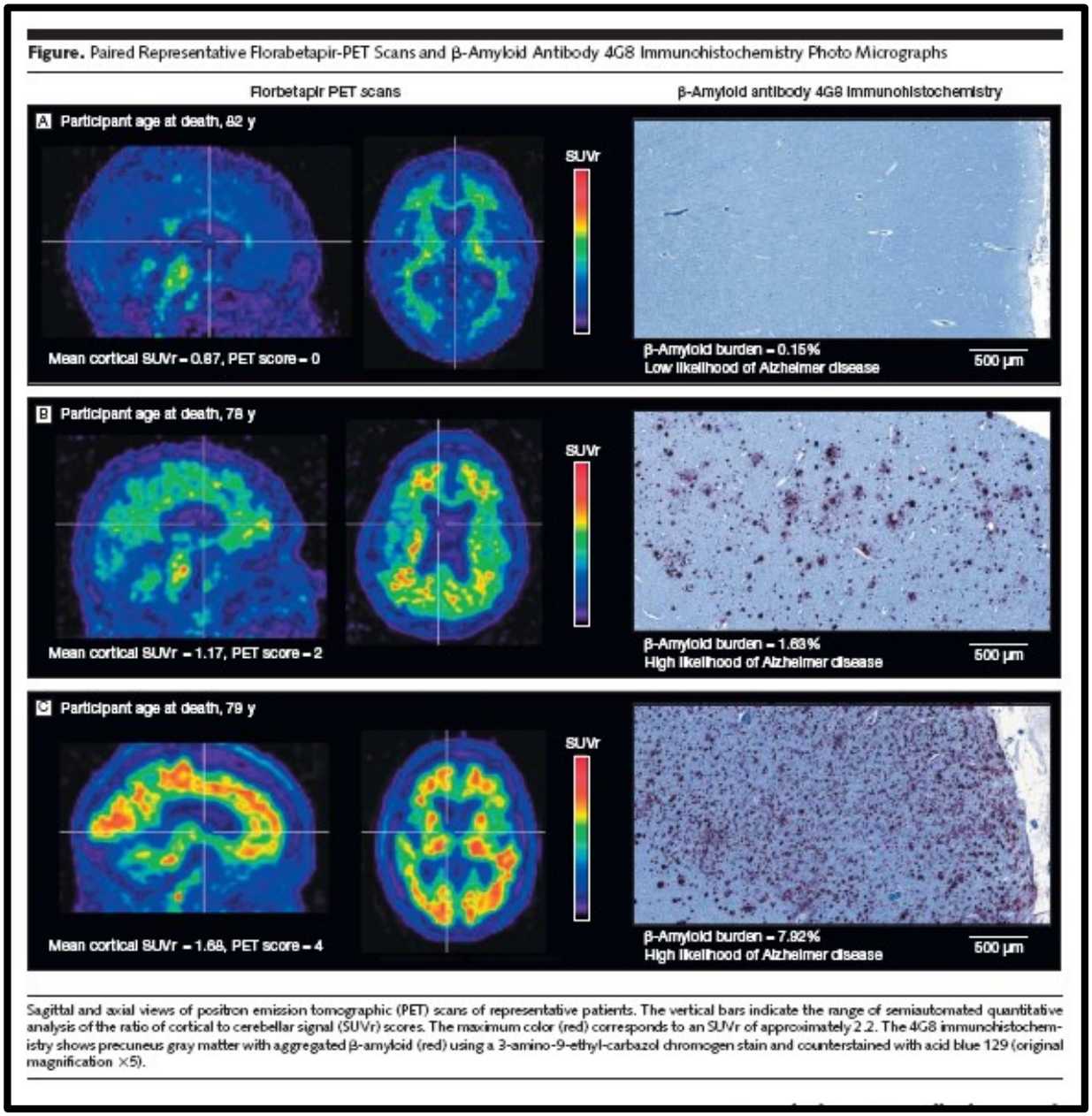


Traccianti PET per amiloide – Confronto AD vs soggetti normali



Klunk et al. Ann Neurol 2004; Wong et al. Mol Imaging Biol 2012; Wong et al. J Nucl Med 2010;
Rowe et al. Lancet Neurol 2008; Small et al. NEJM 2006

Traccianti PET per amiloide – Confronto con istopatologia



Clark CM et al. JAMA 2011.

Traccianti PET per amiloide – Accuratezza nella AD

Sensibilità elevata (>90%) nel rilevamento della deposizione di amiloide cerebrale

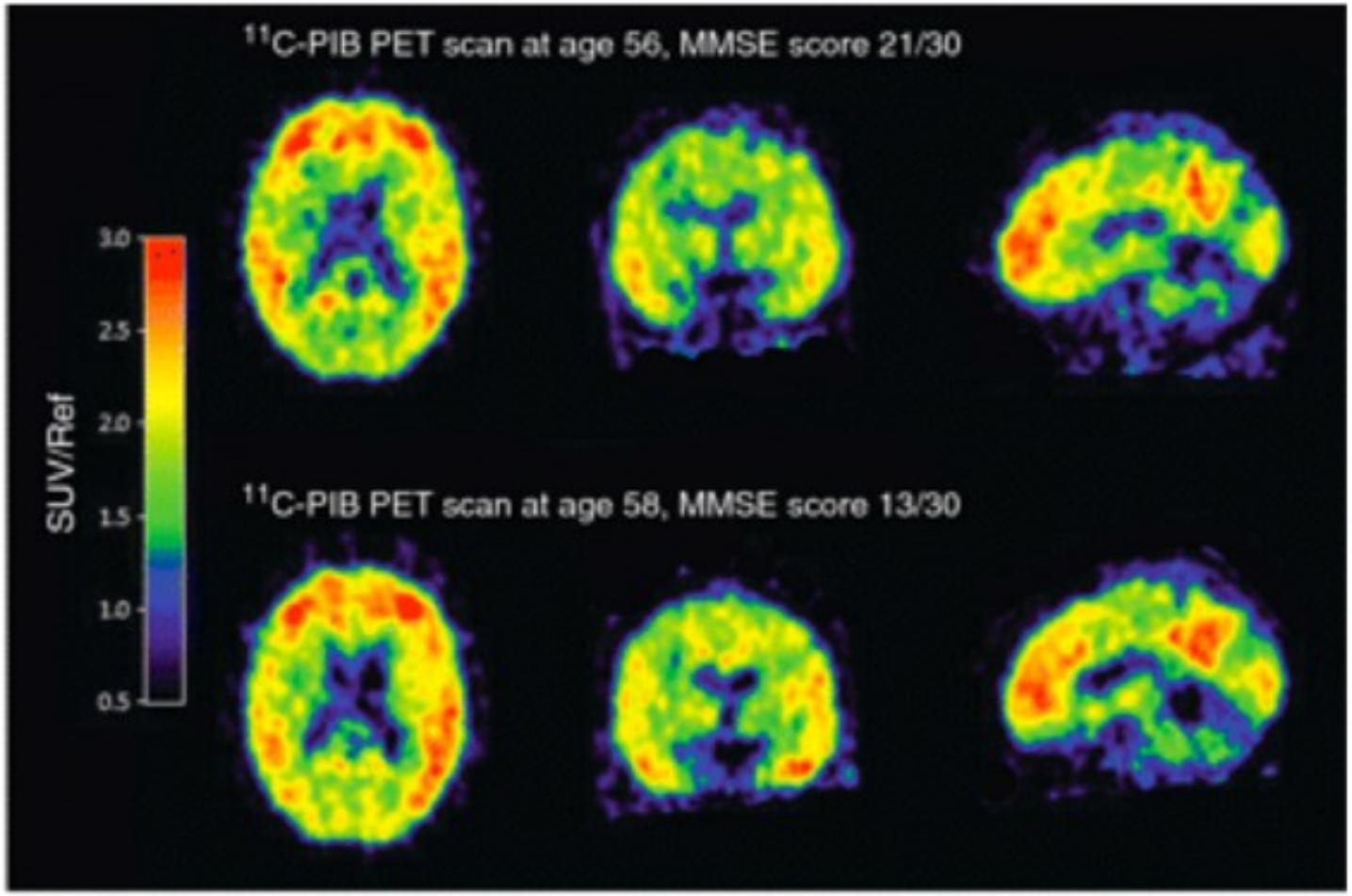
- ✓ Evidenza anche in stadi precoci di malattia, anche preclinici
- ✓ Pochi casi riportati di pazienti con AD e PET normale (Cairns et al. 2009)

Buona specificità

- ✓ No uptake nelle FTD (Rabinovici et al. 2007, Rowe et al. 2008)
- ✓ No uptake nel PD (Maetzler et al. 2008)
- ✓ Pazienti con DLB mostrano livelli di uptake elevati, congruenti con dati anatomopatologici (Edison et al. 2008)

Traccianti PET per amiloide – Studi longitudinali

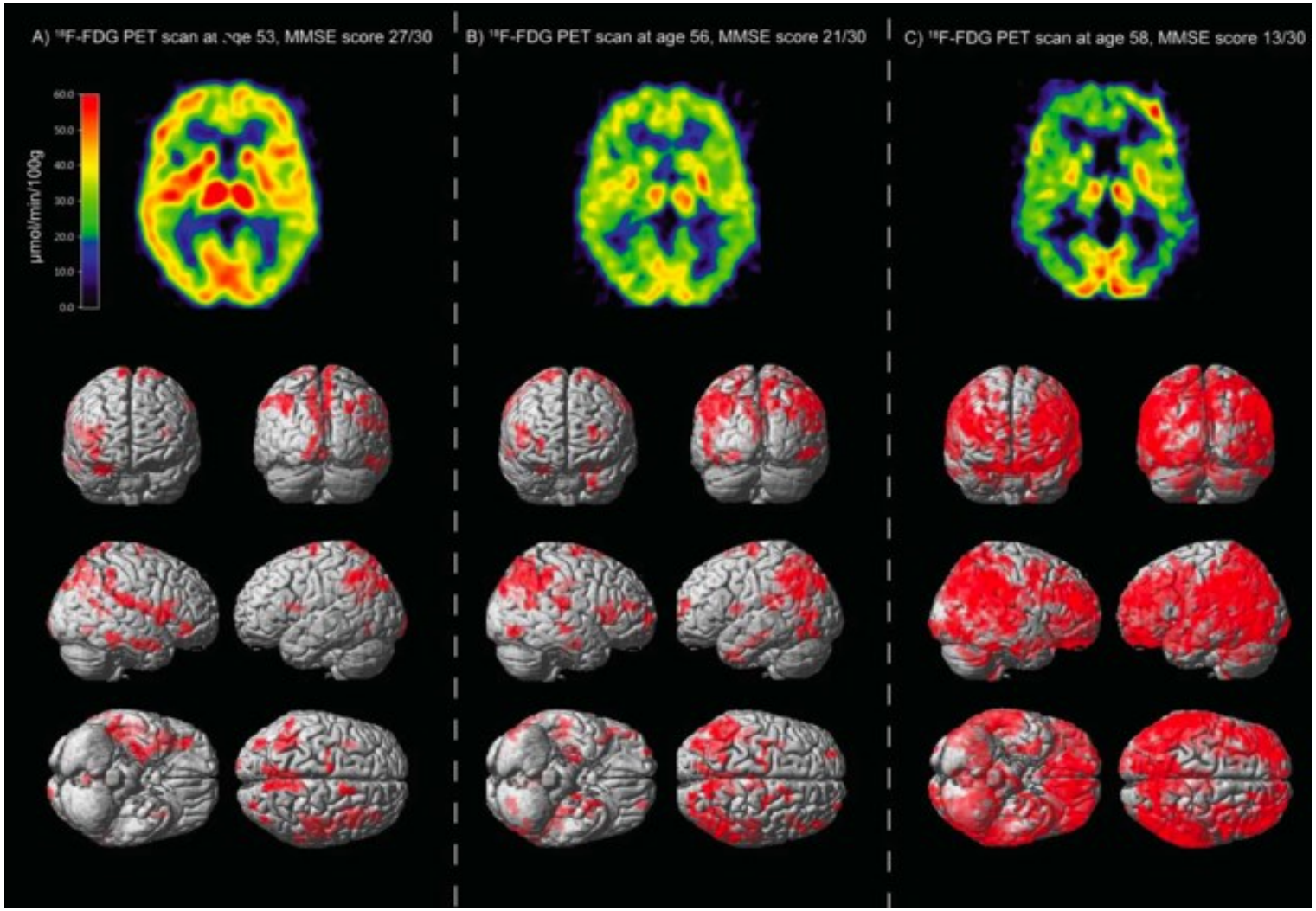
Pazienti con AD: livelli di ^{11}C-PiB uptake *elevati*, ma *stabili*



Kadir et al. Brain 2010

Traccianti PET per amiloide – Studi longitudinali

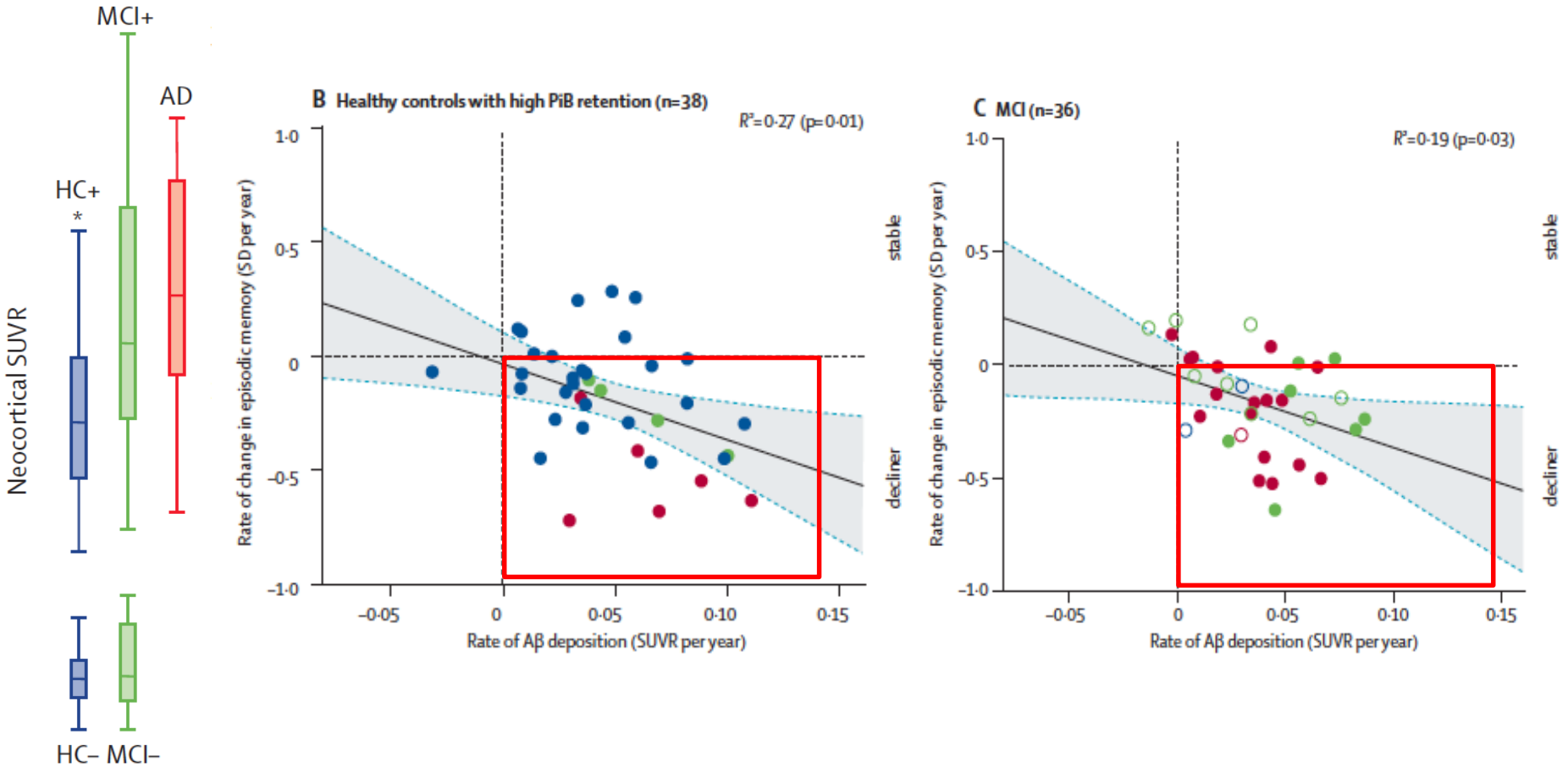
Pazienti con AD:
riduzione progressiva del metabolismo cerebrale di glucosio (^{18}F-FDG PET)



Kadir et al. Brain 2010

Traccianti PET per amiloide – Studi longitudinali

MCI – NL ^{11}C-PiB+ ⟶ Accumulo di Aβ nel tempo



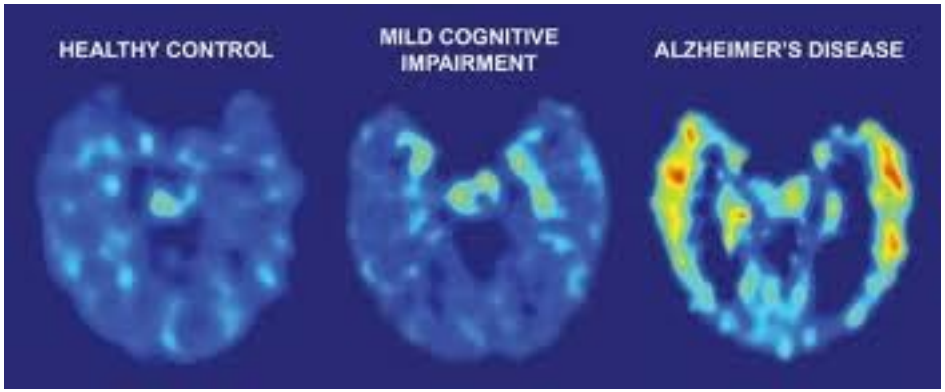
Villemagne et al. Lancet Neurol 2013

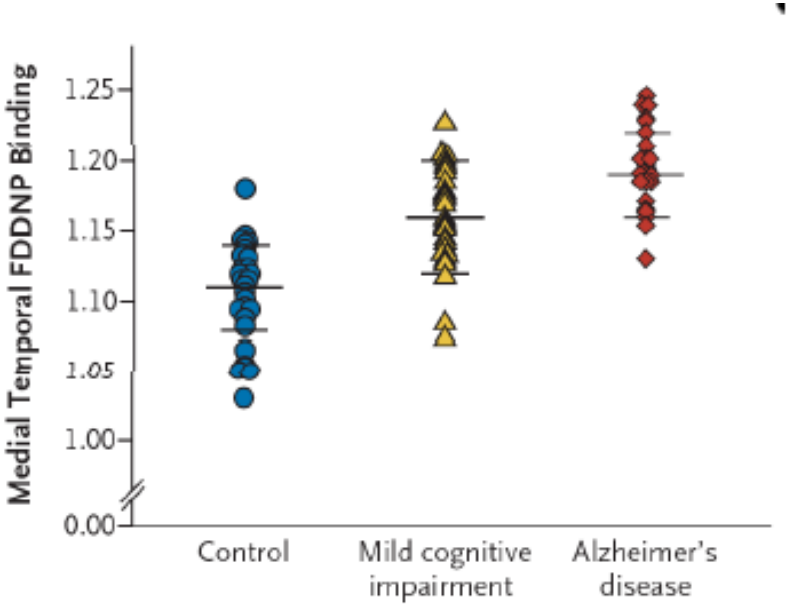
Traccianti PET per amiloide – Studi longitudinali

^{18}F-FDDNP

Sito di legame diverso sulla proteina amiloide

Affinità per i grovigli neurofibrillari di proteina tau



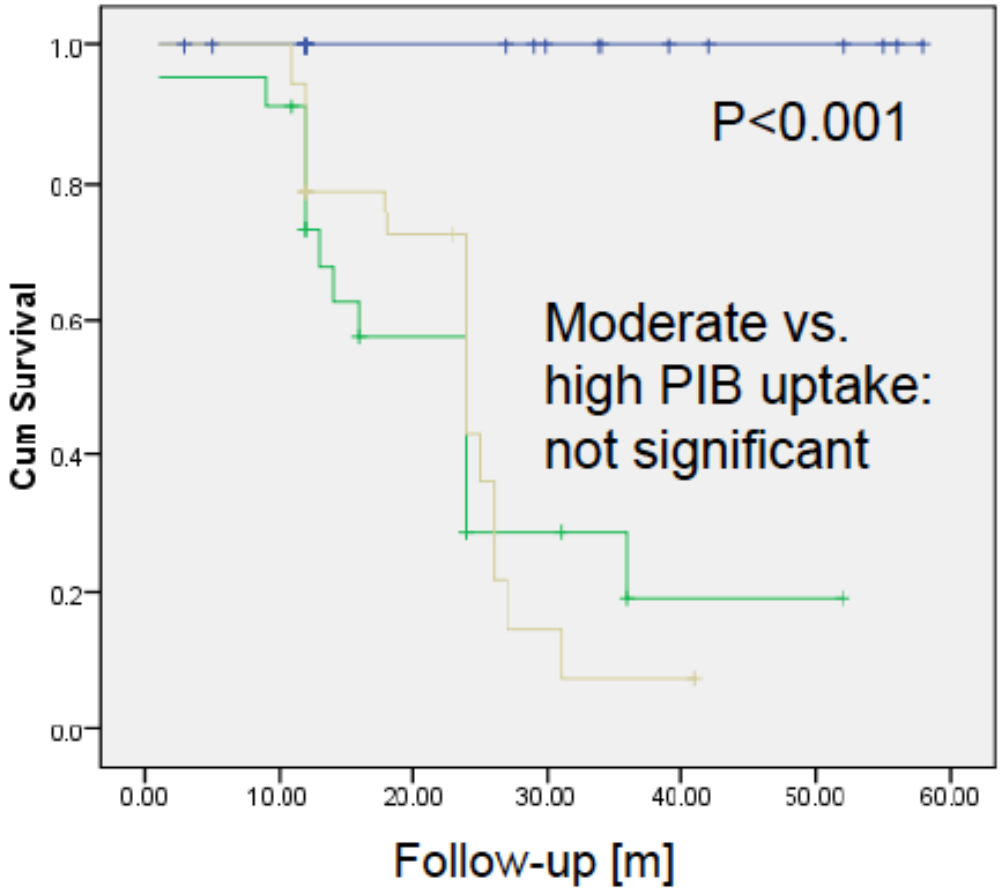


Small et al. NEJM 2006

Traccianti PET per amiloide – MCI

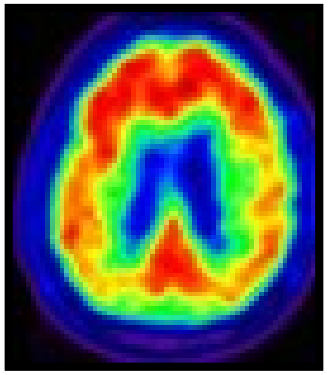
Valore predittivo negativo eccellente: quasi 100%

Valore predittivo positivo (demenza entro 2 anni): 50%



Herholz SNM 2010 Meeting

Utilizzo clinico dei traccianti PET per amiloide



AmyPET +

✖ Diagnosi di AD

✔ Presenza di amiloidosi cerebrale

Questioni irrisolte

- Alta prevalenza (20%) di individui cognitivamente normali amiloide-positivi (età-correlata)
  - 50-60 aa < 5%
  - 60-70aa 10%
  - 79-80aa 25%
  - 80-90aa >50%
- AmyPET positiva anche in altre condizioni patologiche
  - DLB
  - angiopatia amiloidea cerebrale

Appropriate use criteria for amyloid PET: A report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association

Keith A. Johnson[a], Satoshi Minoshima[b], Nicolaas I. Bohnen[c], Kevin J. Donohoe[d], Norman L. Foster[e], Peter Herscovitch[f], Jason H. Karlawish[g], Christopher C. Rowe[h], Maria C. Carrillo[i,*], Dean M. Hartley[i], Saima Hedrick[j], Virginia Pappas[j], William H. Thies[i]

Alzheimer's & Dementia

Preamble: (*i*) a cognitive complaint with objectively confirmed impairment; (*ii*) AD as a possible diagnosis, but when the diagnosis is uncertain after a comprehensive evaluation by a dementia expert; and (*iii*) when knowledge of the presence or absence of Aβ pathology is expected to increase diagnostic certainty and alter management.

Condizioni necessarie:

i. Il paziente deve essere stato valutato da un esperto in demenza, che abbia accertato oggettivamente (anche con utilizzo di test neuropsicologici) la presenza di un decadimento cognitivo
ii. Dopo attenta valutazione da parte dell'esperto in demenza, la causa di questo decadimento cognitivo deve essere incerta e "potrebbe" essere inclusa nella diagnosi differenziale AD o uno dei suoi stadi prodromici.
iii. La conoscenza della presenza o dell'assenza di patologia amiloidea deve aumentare il livello di confidenza diagnostica e comunque deve servire a modificare il percorso diagnostico del paziente.

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Alzheimer's & Dementia

Amyloid imaging is appropriate in the situations listed here for individuals with all of the following characteristics:

1. Patients with persistent or progressive unexplained MCI
2. Patients satisfying core clinical criteria for possible AD because of unclear clinical presentation, either an atypical clinical course or an etiologically mixed presentation
3. Patients with progressive dementia and atypically early age of onset (usually defined as 65 years or less in age)

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Alzheimer's & Dementia

Amyloid imaging is inappropriate in the following situations:

4. Patients with core clinical criteria for probable AD with typical age of onset
5. To determine dementia severity
6. Based solely on a positive family history of dementia or presence of apolipoprotein E (*APOE*)ε4
7. Patients with a cognitive complaint that is unconfirmed on clinical examination
8. In lieu of genotyping for suspected autosomal mutation carriers
9. In asymptomatic individuals
10. Nonmedical use (e.g., legal, insurance coverage, or employment screening)

Riflessioni

- Diagnosi precoce di AD
  - Trattamento adeguato
  - Sollievo dall'incertezza di non conoscere la natura dei sintomi
  - Possibilità di pianificazione dei propri affari e cure mediche
- I biomarkers sono una componente essenziale soprattutto nella diagnosi precoce della AD
- Procedura utile nei trials clinici
  - Corretto arruolamento dei pazienti
  - Proof-of-concept dell'effetto delle terapie anti-amiloide

Grazie per l’attenzione