LA DIAGNOSI PRECOCE DELLE MALATTIE NEURODEGENERATIVE
(biomarcatori a confronto)

Neuroimmagine funzionale

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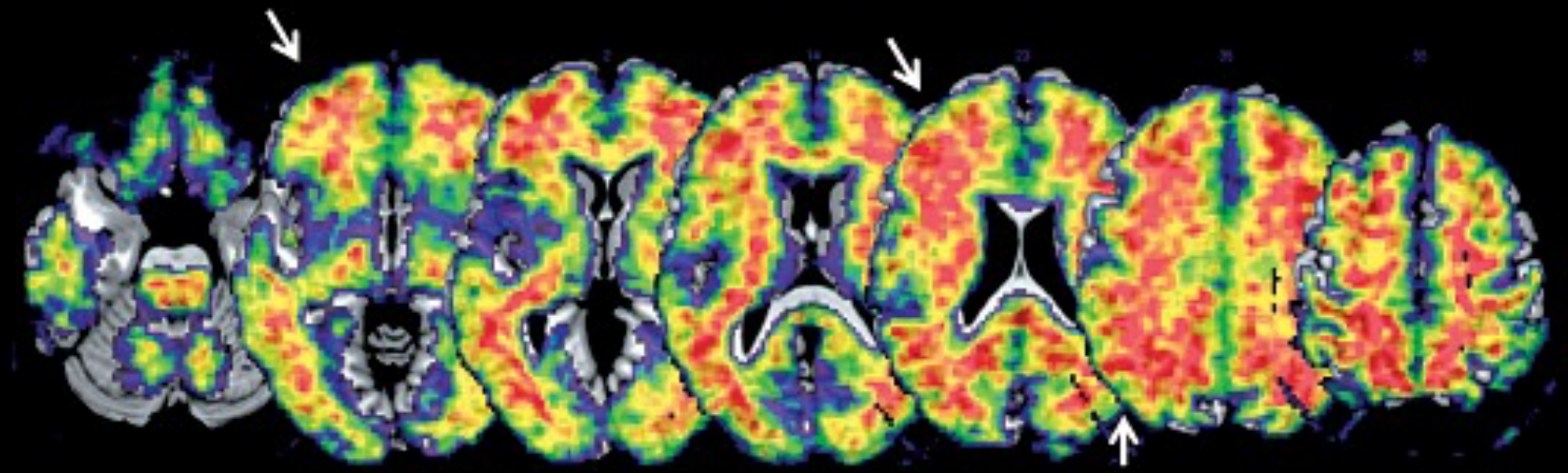
Member of Steering Committee of AIMN PET Adult Study Group, Italy
Member of Steering Committee of AIMN Neuroimaging Study Group, Italy



6° CONVEGNO su COGNITIVITA' MALATTIE NEUROLOGICHE
Torino, 10 novembre 2017 SALA CONGRESSI INTESA SANPAOLO
Via Santa Teresa, 1/G 10121 Torino

Dove ci moviamo?

Imaging biomarkers in Alzheimer's disease: added value in the clinical setting

1984

Task force NINCDS-ADRDA ha definito i criteri principali per la diagnosi clinica di malattia di Alzheimer fondata sulla storia ed esame clinico, test di laboratorio e valutazione neuropsicologica.

anche DSM-IV

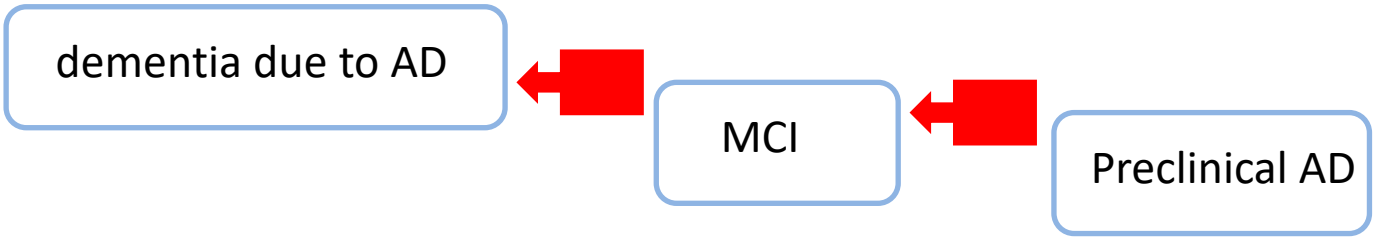
prevedeva

Definite AD
Probable
Possible

sensitivity and specificity about 80% and 70%

Last 20 years

CSF, MRI and PET technologies has allowed research and clinical **approach** to AD to move towards the **earliest** manifestations of the disease



Morbelli S. The Quarterly Journal of Nuclear Medicine and Molecular Imaging 2017 December;61(4):360-71

From 2007 to 2011

Lancet Neurol 2014; 13: 614–29

International Working Group-1 (IWG-1) (2007)
National Institute of Aging- Alzheimer Association criteria (NIAA) (2011)
International Working Group-2 (IWG-2) (2014)

Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria

Panel 4: IWG-2 criteria for the preclinical states of AD

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

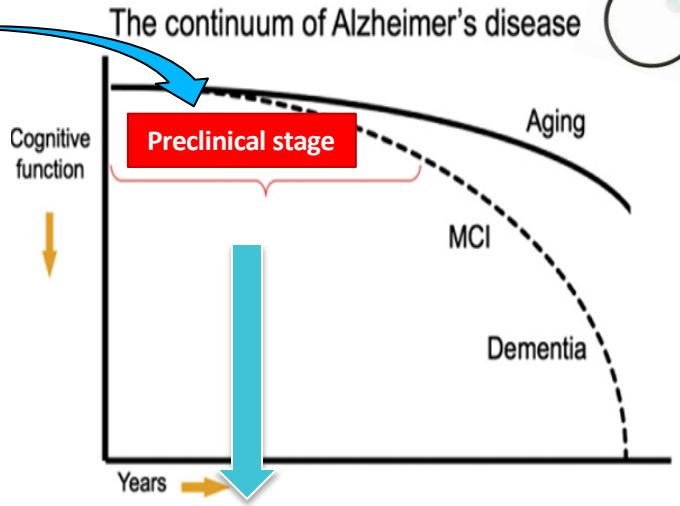
A Absence of specific clinical phenotype (both are required)
- Absence of amnestic syndrome of the hippocampal type
- Absence of any clinical phenotype of atypical AD

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

IWG-2 criteria for presymptomatic AD (A plus B)

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

B Proven AD autosomal dominant mutation in *PSEN1*, *PSEN2*, or *APP*, or other proven genes (including Down's syndrome trisomy 21)



Stage 1
Asymptomatic amyloidosis
-High Aβ PET retention
-Low CSF $A\beta_{42}$

Stage 2
Amyloidosis + Neurodegeneration
-Neuronal dysfunction on fMRI or PET
-High CSF total tau (t-tau)/phosphorylated (p-tau)
-Cortical thinning/hippocampal atrophy

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
-Evidence of cognitive decline
-Poor performance on more challenging cognitive tests
-Does not yet meet criteria for MCI

Sperling RA et al. *Alzheimer Dement*. 2011; 7:280-292.

Due tipi di biomarkers

'**new lexicon**' (Dubois et al., Lancet Neurol 2010)

	Pathophysiological markers	Topographical markers
Cerebrospinal fluid		
Amyloid β_{42}	Yes	No
Total tau, phospho-tau	Yes	No
PET		
Amyloid tracer uptake	Yes	No
Fluorodeoxyglucose	No	Yes
Structural MRI		
Medial temporal atrophy	No	Yes

AD=Alzheimer's disease.

biomarkers for amyloid-beta deposition

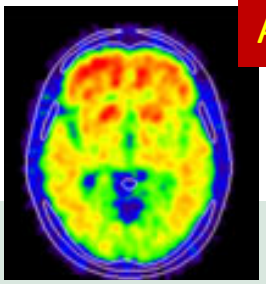
biomarkers for tau-mediated neural injury

To differentiate the biomarkers of AD **diagnosis** from those of AD **progression**.

Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria

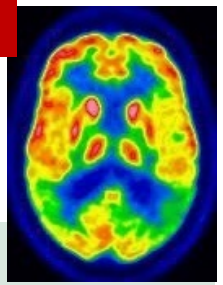
Lancet Neurol 2014; 13: 614–29

Panel 5: Definition of AD biomarkers



Amiloyd

FDG



Diagnostic marker

- Pathophysiological marker
- Reflects in-vivo pathology
- Is present at all stages of the disease
- Observable even in the asymptomatic state
- Might not be correlated with clinical severity
- Indicated for inclusion in protocols of clinical trials

Progression marker

- Topographical or downstream marker
- Poor disease specificity
- Indicates clinical severity (staging marker)
- Might not be present in early stages
- Quantifies time to disease milestones
- Indicated for disease progression

Biomarkers della patologia di Alzheimer sono ristrette a quelli indicanti la specifica presenza della patologia Tau (CSF o PET tau) o della patologia amiloidea (CSF e amyloid PET).
Questi biomarkers hanno la necessaria **specificità** per la diagnosi di AD **in ogni punto del continuum della malattia.**

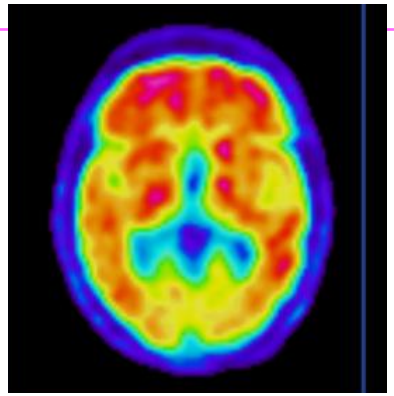
Markers topografici dei cambiamenti metabolici, non avendo una sufficiente specificità patologica, possono essere usati per misurare la progressione di malattia

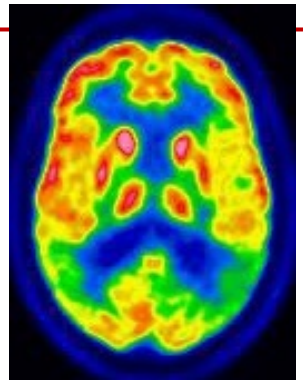
Beta amyloide PET

FDG PET

Definisce la presenza di amiloide
Caratteristiche di specificità
Statico
Presenza di malattia
Da sola no diagnosi

Tracciante metabolico (sinapsi)
Caratteristiche di sensibilità
Dinamico
Progressione di malattia
Da sola no diagnosi



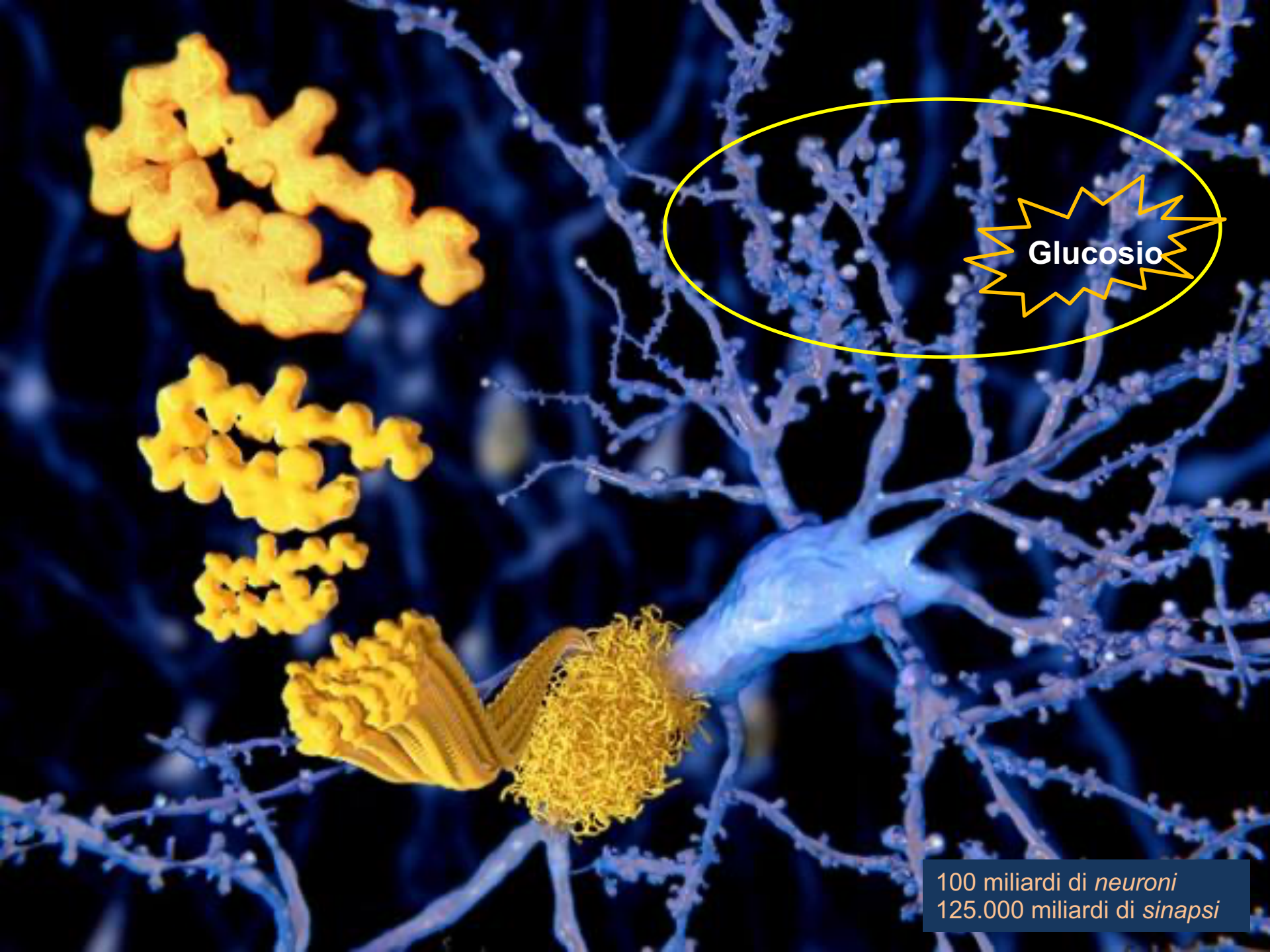


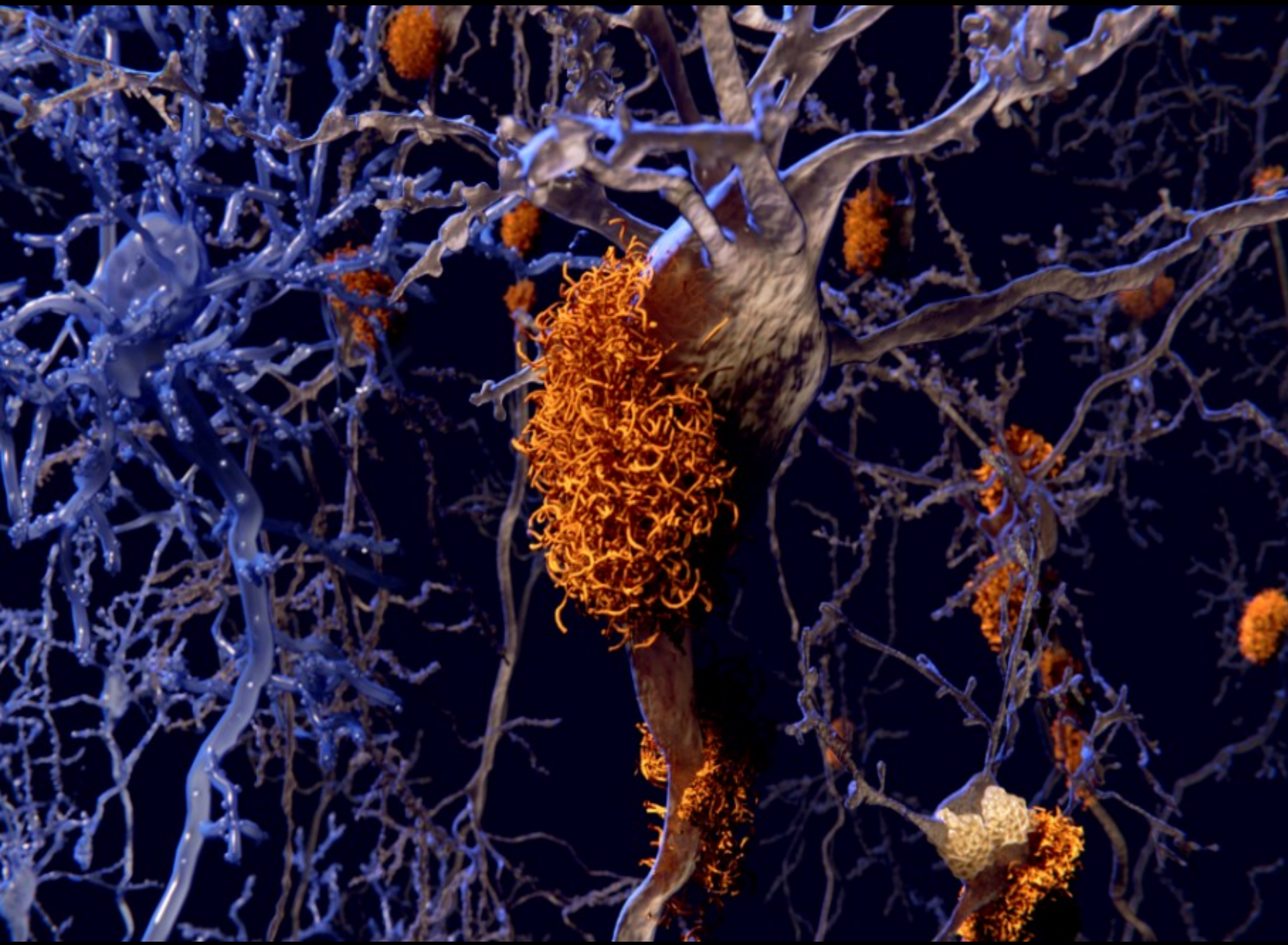
The **combination of a specific cognitive profile**, consistent with typical or atypical AD, **and a positive pathophysiological marker moves** the patient **from** an undetermined status of **MCI to** that of **prodromal AD**.

The concept of MCI remains useful for cases that are negative for pathophysiological biomarkers.

18F-FDG-PET e diagnosi precoce

Cosa legge FDG-PET?


Glucosio
100 miliardi di *neuroni*
125.000 miliardi di *sinapsi*

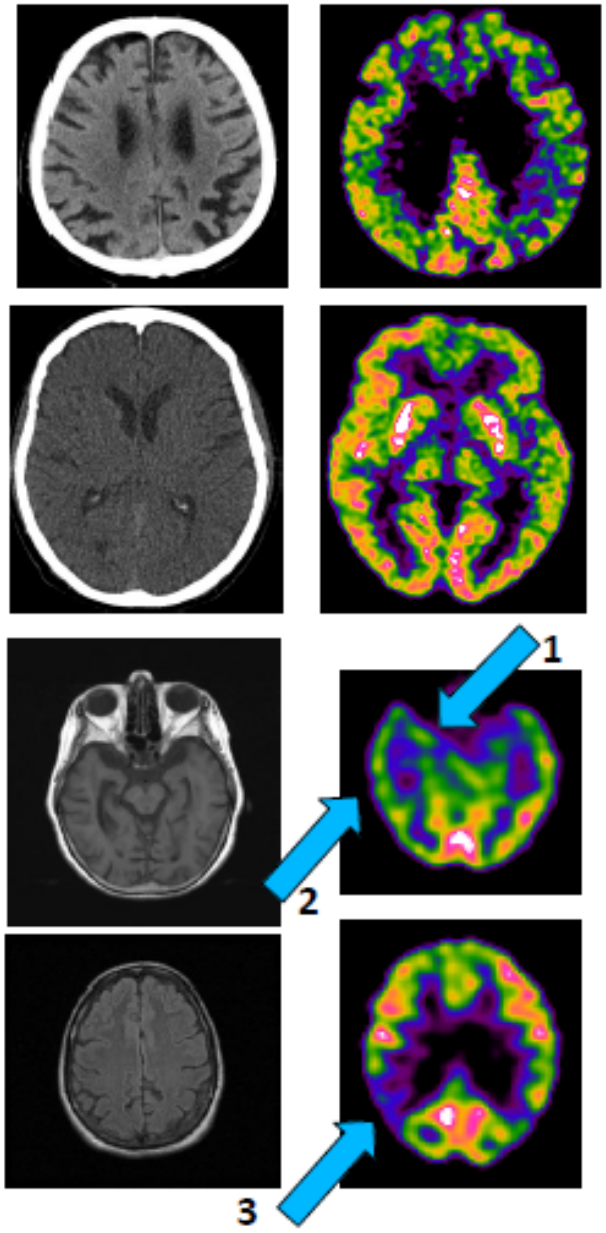


Quali sono i fenomeni che causano ipometabolismo del glucosio nelle malattie neurodegenerative ?

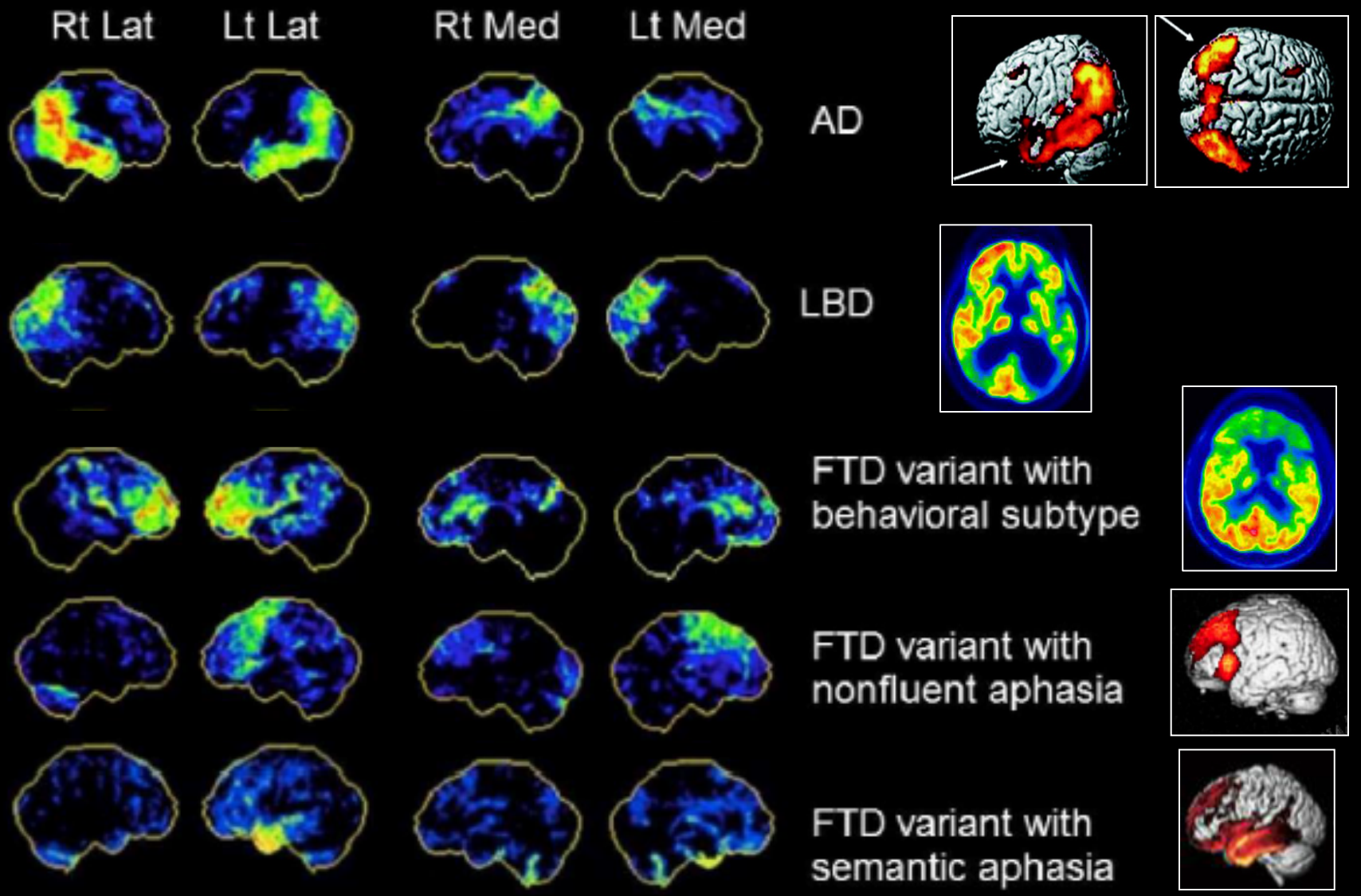
1. Atrofia (‘effetto volume parziale’)

2. Ridotto consumo metabolico dovuto a degenerazione sinaptica e perdita neuronale dei neuroni corticali

3. Ridotto consumo metabolico dovuto a perdita neuronale di neuroni distanti (deafferentazione-diaschisi)



Pattern topografici caratteristici di FDG-PET nelle principali demenze

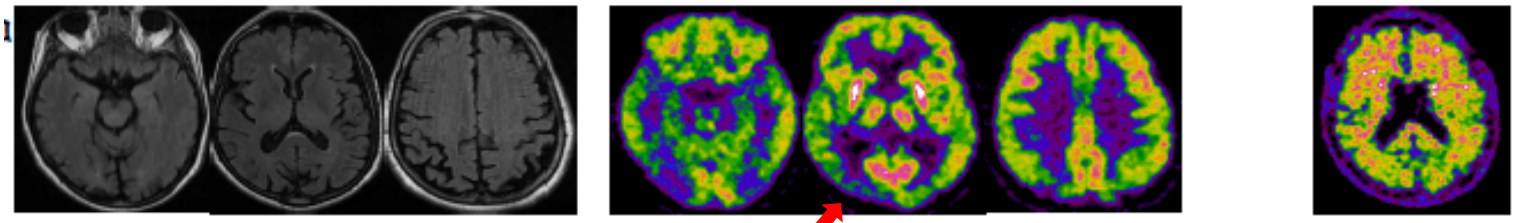


Taswell et al., J Nucl Med 2015

A.Cistaro. IRMET. Turin

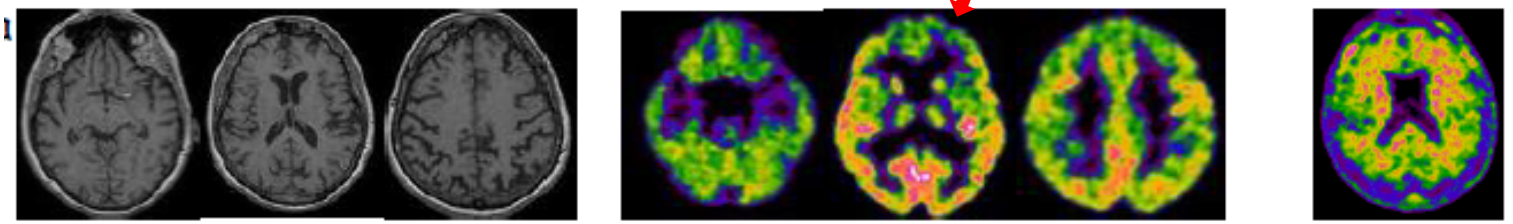
Posterior Variant AD

Donna. 75aa.
mdMCI
Visuo-spaziale
MMSE=27



Frontal variant AD

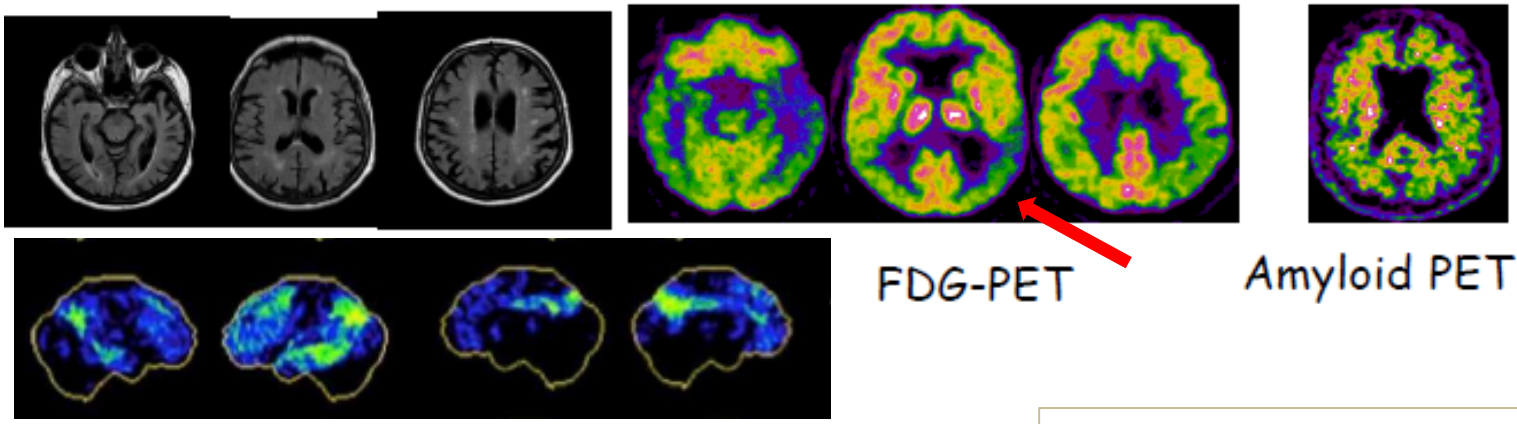
Donna. 74aa.
mdMCI
BPSD
MMSE=24



MRI

Logopenic variant AD

Uomo. 77aa.
demenza
linguaggio
MMSE=20



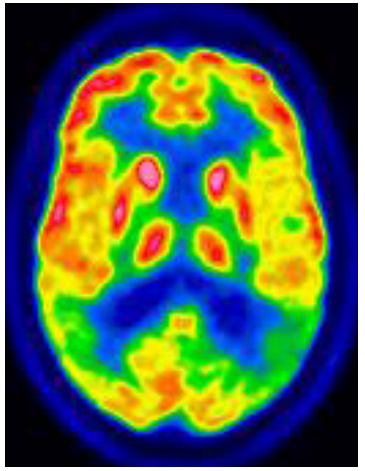
FDG-PET

Amyloid PET

F. Nobili. San Martino Hospital. Genoa

Findings in AD dementia

Hypometabolismin **the parieto-temporal association** area, **posterior cingulate** cortices, and **precuneus**.



Brain fluorodeoxyglucose (FDG) PET in dementia

Takashi Kato[a,b,*], Yoshitaka Inui[a], Akinori Nakamura[b], Kengo Ito[a,b,c]

Ageing Res Rev. 2016 Sep;30:73-84

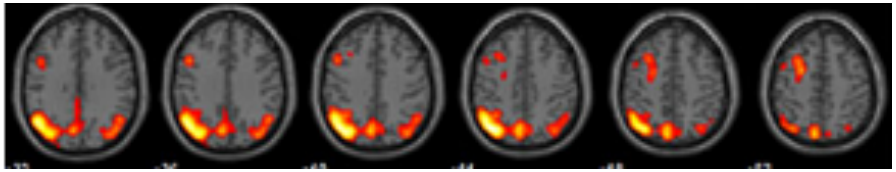
Early-onset AD (onset <65 years) exhibit **more severe** hypometabolism than patients with late-onsetAD (onset >65 years) .

This phenomenon likely reflects the different subtypes of AD and greater cognitive reserves in younger compared with older subjects.

Findings in MCI

Hypometabolism in the inferior parietal lobe, precuneus, and posterior cingulate is a predictor of conversion from MCI to AD dementia

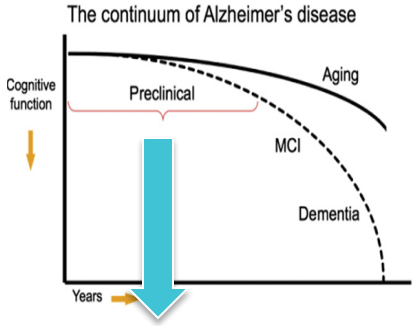
MCI → AD podromico



Un FDG scan negativo esclude forma neurodegenerativa

D. Perani. Clin Transl Imaging 2013

FDG PET in the preclinical or presymtomatic stage of AD



Mosconi et al., 2010

FDG PET may predict conversion of cognitively normal individuals to those with MCI.

Stage 1
Asymptomatic amyloidosis
-High Aβ PET retention
-Low CSF $A\beta_{42}$

Stage 2
Amyloidosis + Neurodegeneration
-**Neuronal dysfunction** on fMRI or **PET**
-High CSF total tau (t-tau)/phosphorylated (p-tau)
-Cortical thinning/hippocampal atrophy

Stage 3
Amyloidosis + Neurodegeneration + Subtle Cognitive Decline
-Evidence of cognitive decline
-Poor performance on more challenging cognitive tests
-Does not yet meet criteria for MCI

MCI → AD

Some people will not progress beyond Stage 1 or Stage 2.

People in Stage 3 may be more likely to progress to MCI and AD.

Sperling RA et al. *Alzheimer Dement*. 2011; 7:280-292.

Hypometabolism in the **parieto-temporal, posterior cingulate cortices/precuneus** is suggestive of AD patho-physiology

in normal subjects

- con rischio clinico per AD (subjective memory complaint) *(Mosconi et al., 2007)*
- con fattori di rischio genetico per late-onset AD (ApoE-4) *(Langbaumet al., 2010; Small et al., 1995)*
- KIBRA CC *(Corneveaux et al., 2010)* influences episodic memory and modulates the activation of the hippocampus during memory retrieval
- soggetti con familiarità per AD *(Mosconi et al., 2007, 2014)*
- in AD autosomica dominante, approximately 10 years before the expected onset of symptoms *(Bateman et al., 2012; Kennedy et al.,1995).*

Regions : medial temporal and parietal areas *(Ewers et al., 2014)*
hippocampus *(de Leonet et al., 2001; Mosconi et al., 2008)*

Limited evidence suggests that tau-related pathology precedes cerebral metabolic dysfunction (Dowling et al., 2015).

^{18}F-FDG PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI) (Review)

Cochrane Database of Systematic Reviews 2015, Issue 1. Art. No.: CD010632.

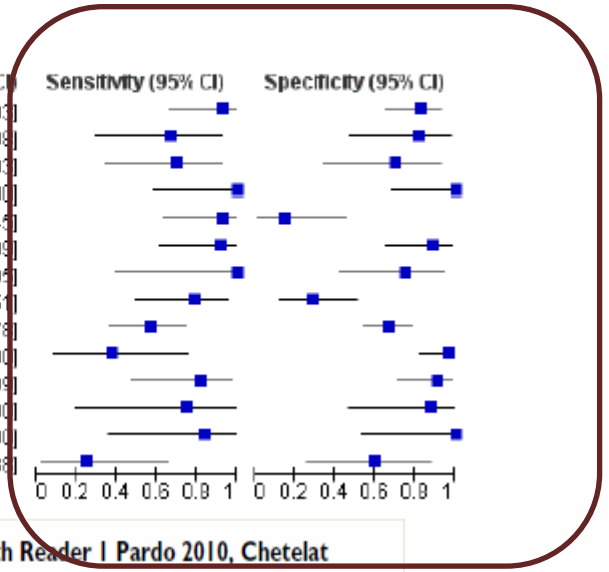
Smailagic N, Vacante M, Hyde C, Martin S, Ukoumunne O, Sachpekidis C.

14 studi (421 pts with MCI)

databases to January 2013 (1999 to 2013)

Study 1° AIM PET scans can potentially predict the decline of **mild cognitive Impairment** (MCI) **to** Alzheimer's disease dementia

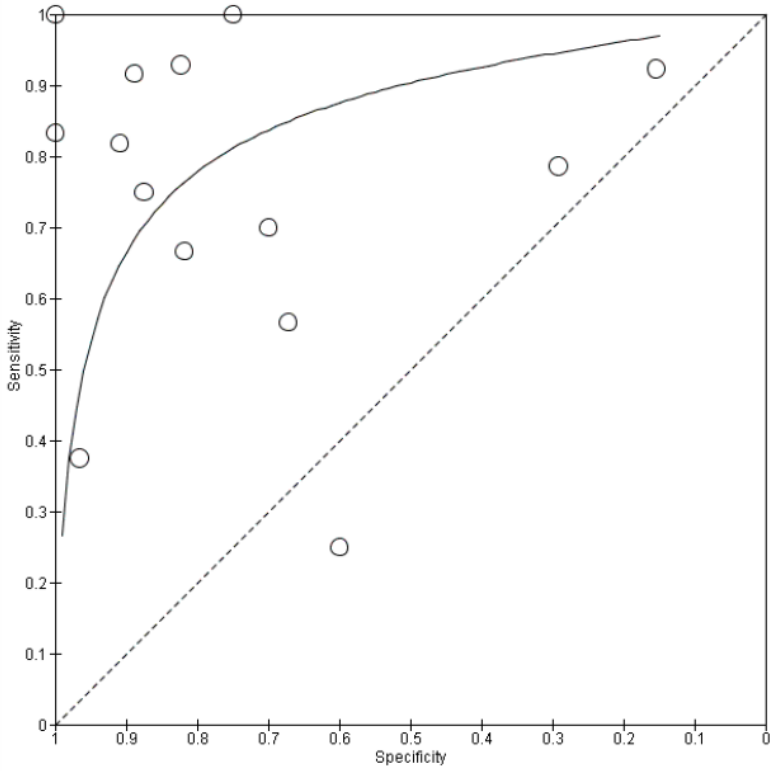
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Anchisi 2005	13	6	1	28	0.93 [0.66, 1.00]	0.82 [0.65, 0.93]
Arnâiz 2001	6	2	3	9	0.67 [0.30, 0.93]	0.82 [0.48, 0.98]
Berent 1999	7	3	3	7	0.70 [0.35, 0.93]	0.70 [0.35, 0.93]
Chételat 2003	7	0	0	10	1.00 [0.59, 1.00]	1.00 [0.69, 1.00]
Clerici 2009	12	11	1	2	0.92 [0.64, 1.00]	0.15 [0.02, 0.45]
Drzezga 2005	11	2	1	16	0.92 [0.62, 1.00]	0.89 [0.65, 0.99]
Fellgiebel 2007	4	3	0	9	1.00 [0.40, 1.00]	0.75 [0.43, 0.95]
Galluzzi 2010	11	17	3	7	0.79 [0.49, 0.95]	0.29 [0.13, 0.51]
Herholz 2011	17	21	13	43	0.57 [0.37, 0.75]	0.67 [0.54, 0.78]
Mosconi 2004	3	1	5	29	0.38 [0.09, 0.76]	0.97 [0.82, 1.00]
Nobili 2008	9	2	2	20	0.82 [0.48, 0.98]	0.91 [0.71, 0.99]
Ossenkoppele 2012a	3	1	1	7	0.75 [0.19, 0.99]	0.88 [0.47, 1.00]
Ossenkoppele 2012b	5	0	1	6	0.83 [0.36, 1.00]	1.00 [0.54, 1.00]
Pardo 2010	2	4	6	6	0.25 [0.03, 0.65]	0.60 [0.26, 0.88]



Forest plot of ^{18} F-FDG PET Conversion from MCI to AD (with Reader I Pardo 2010, Chetelat 2003 temporo-parietal region and Herholz 2011 ADNI study).

Sensibilità tra 25% e 100%
Specificità tra 15% e 100%

Summary ROC plot of ^{18} F-FDG PET Conversion from MCI to AD (with Reader 1 Pardo 2010, Chetelat 2003 temporo-parietal region and Herholz 2011 ADNI study).



From the summary ROC curve
sensitivity 76% (95% CI: 53.8 to 89.7)
at the included study median **specificity of 82%**

Positive likelihood ratio of 4.03 (95% CI: 2.97 to 5.47),
Negative likelihood ratio of 0.34 (95% CI: 0.15 to 0.75)

ADNI study, brain regions choice, reader assessment:
at the median specificity of 82%, the estimated sensitivity was between 74% and 76%.
There was no impact .

Study 2° AIM

Five studies evaluated the accuracy of [1] F-FDG PET for all types of dementia.
sensitivities 46% and 95%
specificities 29% and 100%
NO meta-analysis because of too few studies, and small numbers of participants.

Smailagic N et al. Cochrane Database Syst Rev. 2015

LIMITI PRINCIPALI DEI VARI STUDI

Paziente:

non chiara la **selezione** e la **diagnosi clinica** di AD

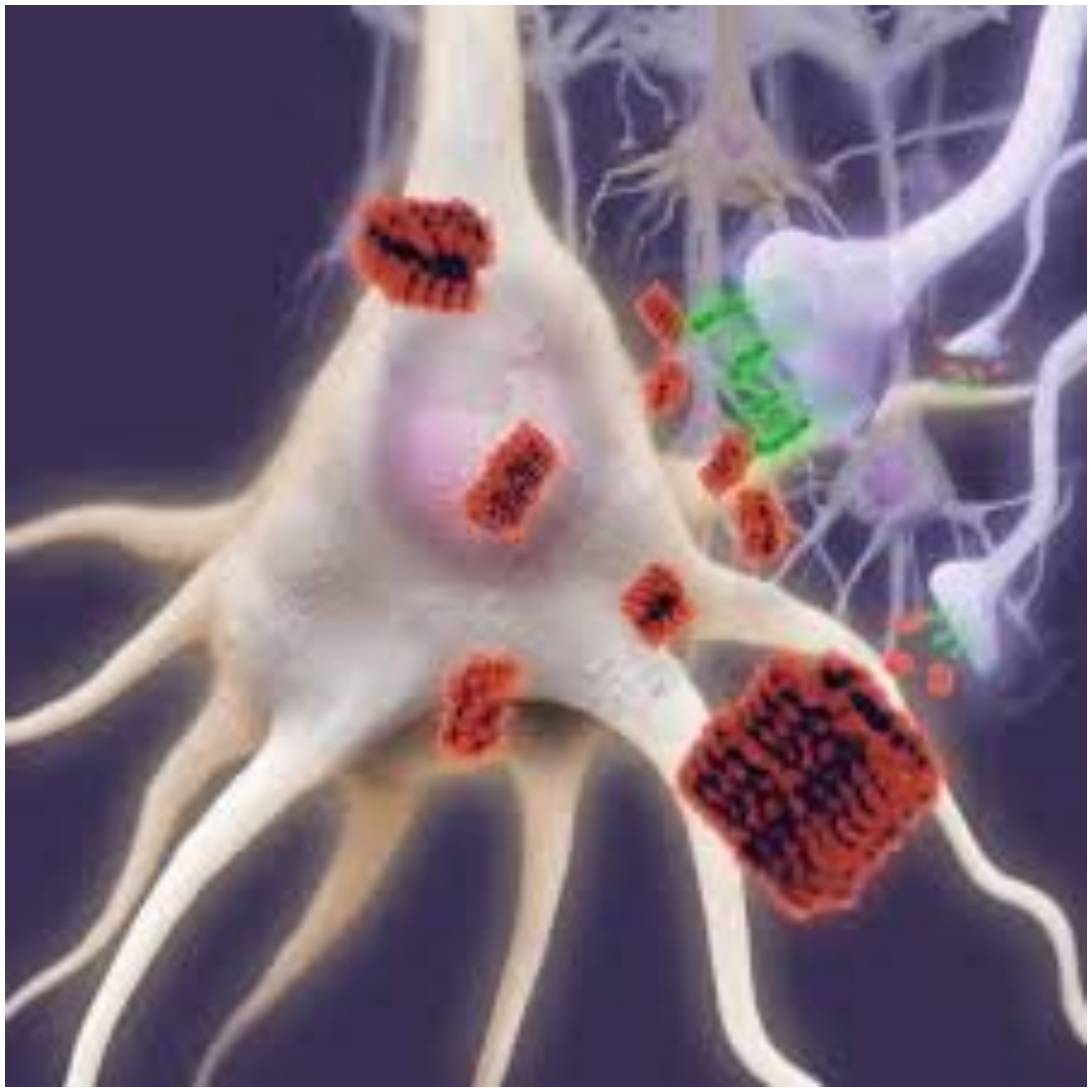
18F-FDG PET

più del 50% degli studi hanno scarsa **qualità metodologica**
non un **cut-off** value ampiamente accettato in MCI
marcata **variazione** dell'accuratezza del test tra gli studi

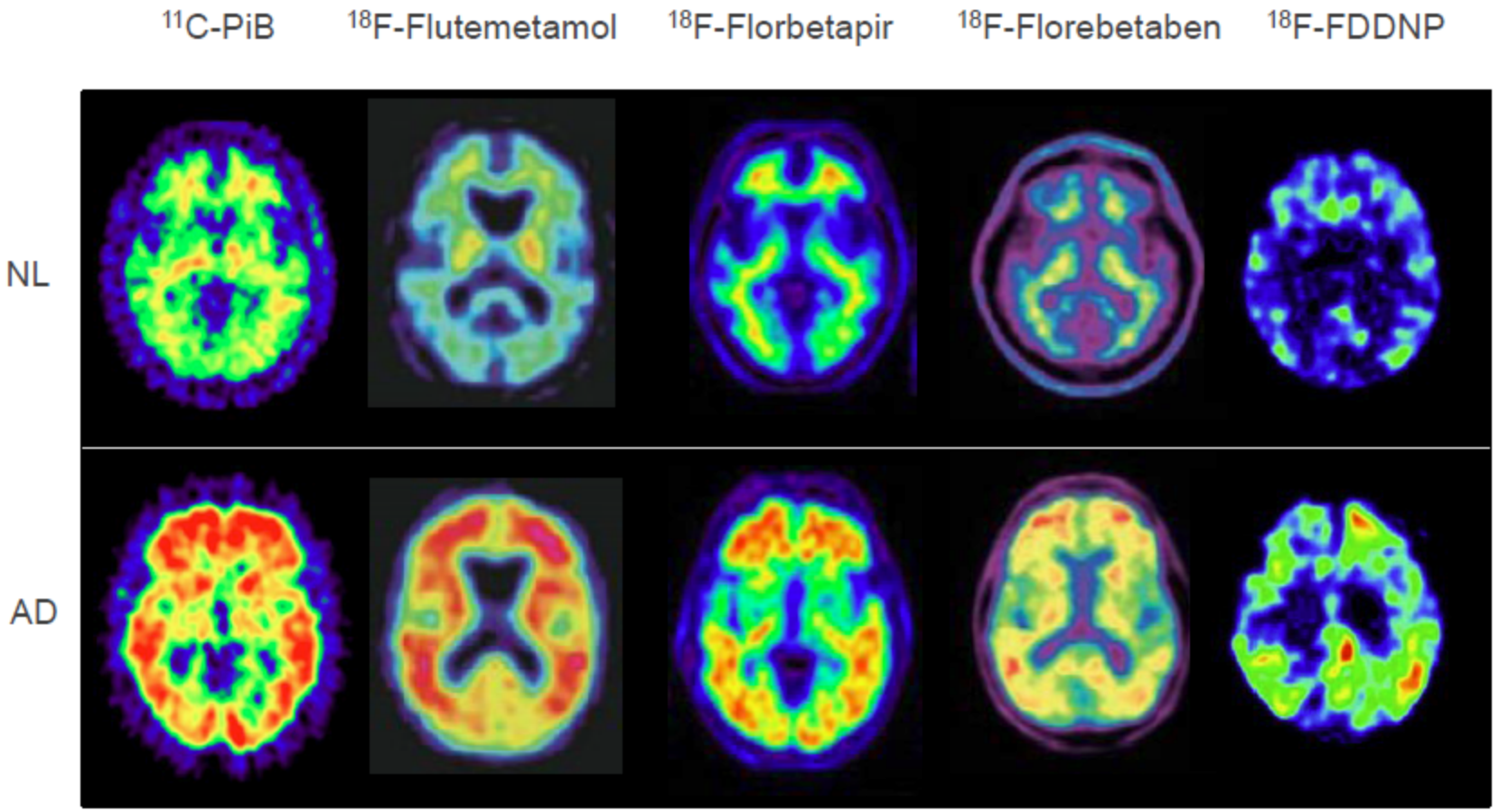
It is difficult to determine to what extent the findings from the meta-analysis can be applied to clinical practice.

Given the considerable **variability of specificity** values and **lack of defined thresholds for** determination of **test positivity** in the included studies,
the current evidence does not support the routine use of ^{18}F-FDG PET scans in clinical practice in people with MCI.

AMILOIDE-PET



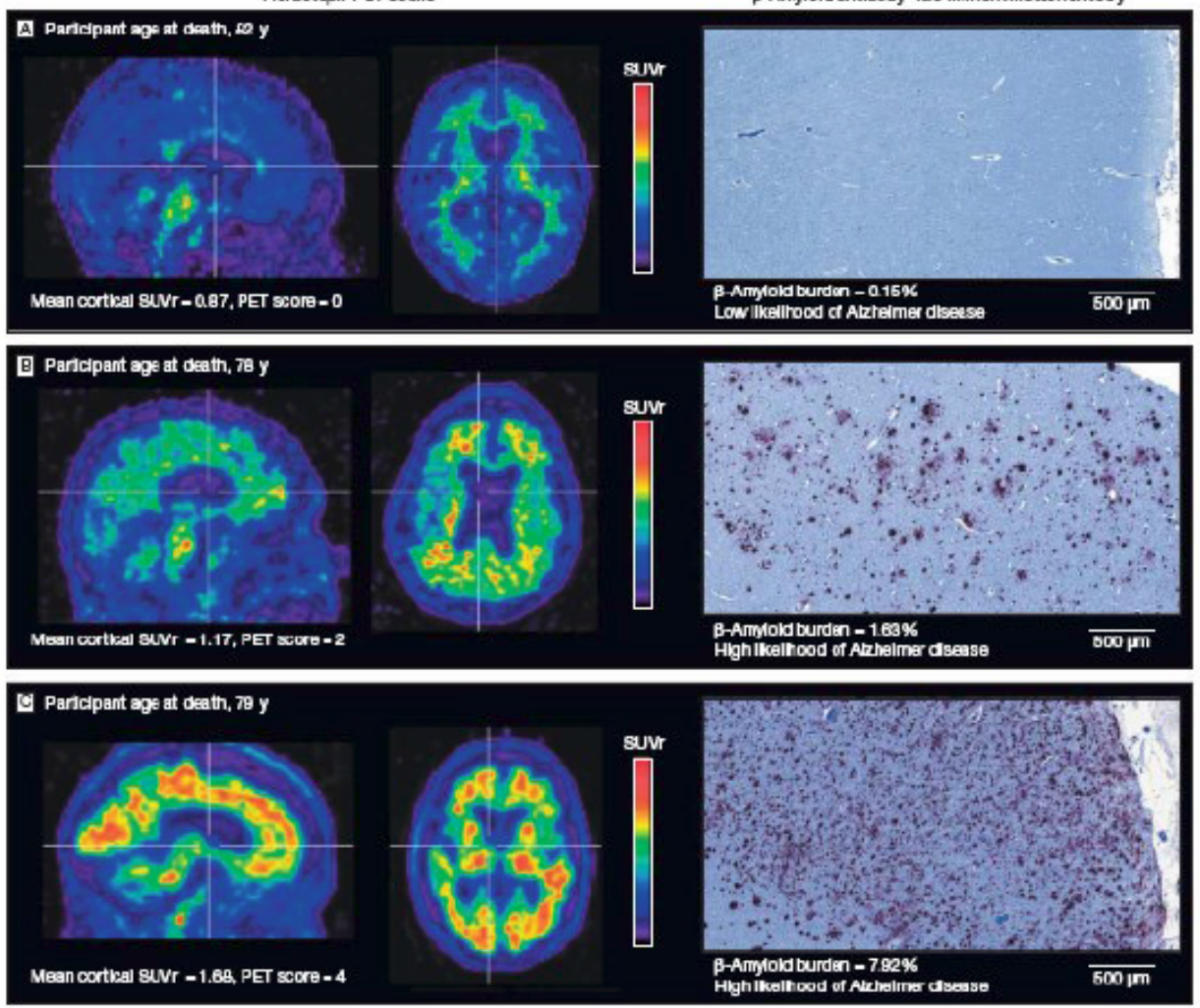
Traccianti PET per amiloide – Confronto AD vs soggetti normali



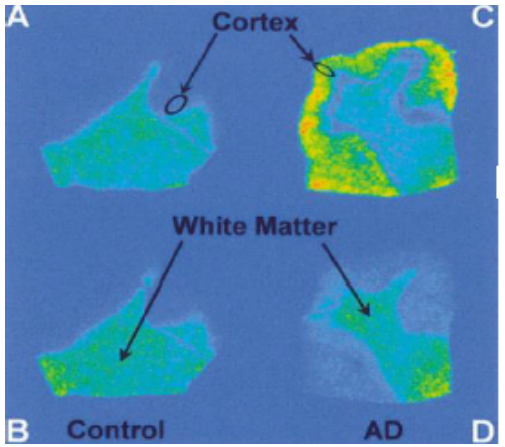
Klunk et al. Ann Neurol 2004; Wong et al. Mol Imaging Biol 2012; Wong et al. J Nucl Med 2010;
Rowe et al. Lancet Neurol 2008; Small et al. NEJM 2006

Traccianti PET per amiloide – Confronto con istopatologia

Figure. Paired Representative Florabelapir-PET Scans and β-Amyloid Antibody 4G8 Immunohistochemistry Photo Micrographs



Sagittal and axial views of positron emission tomographic (PET) scans of representative patients. The vertical bars indicate the range of semiautomated quantitative analysis of the ratio of cortical to cerebellar signal (SUVr) scores. The maximum color (red) corresponds to an SUVr of approximately 2.2. The 4G8 immunohistochemistry shows precuneus gray matter with aggregated β-amyloid (red) using a 3-amino-9-ethylcarbazol chromogen stain and counterstained with acid blue 129 (original magnification ×5).



Imaging in-vitro e in-vivo delle placche Amiloidi con ^{11}C-PIB

Ann Neurol 2004;55:306–319

Post-mortem
Mean: 3 months
Later

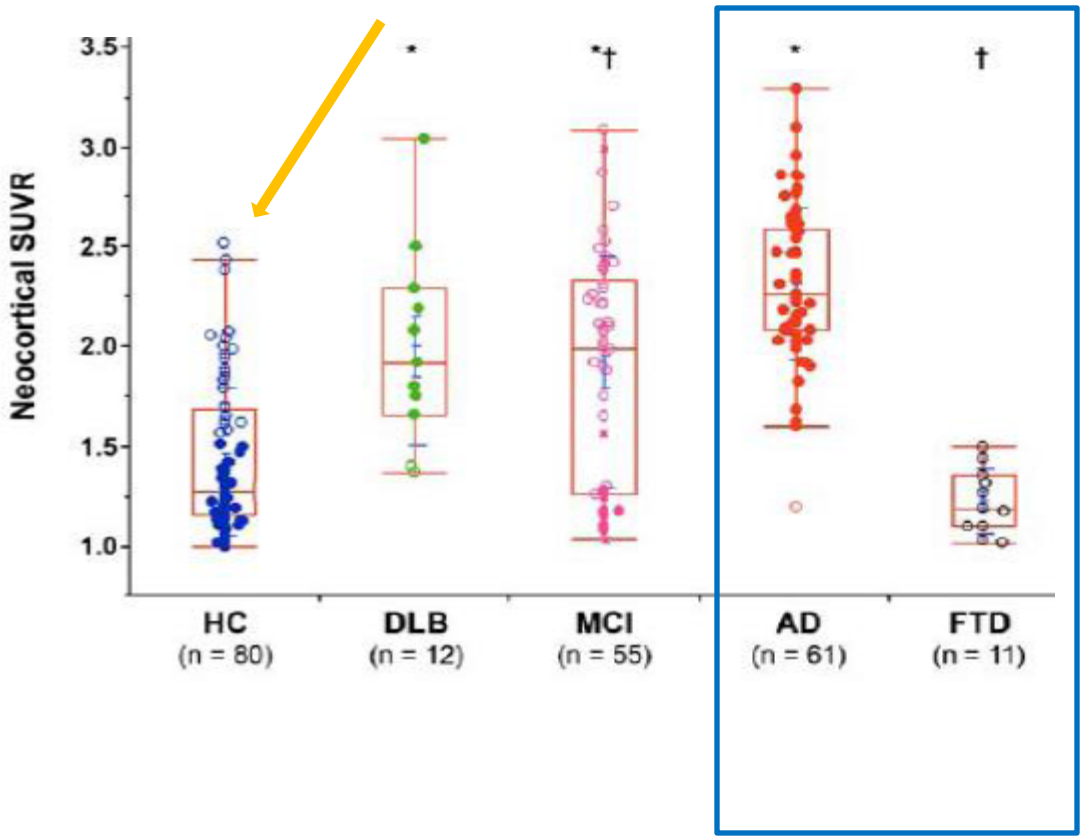
Clark CM et al. JAMA 2011.

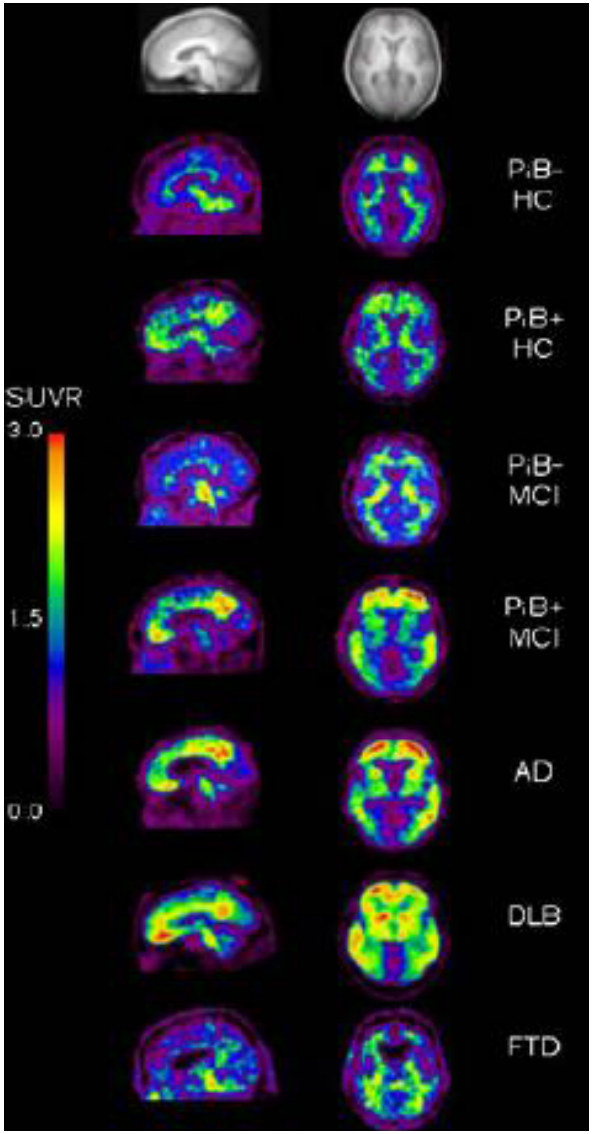
annihilation radiation tomographic.

The ART of Loss: Aβ Imaging in the Evaluation of Alzheimer's Disease and other Dementias

Victor L. Villemagne · Michelle T. Fodero-Tavoletti · Kerryn E. Pike · Roberto Cappai · Colin L. Mas · Christopher C. Rowe

Mol Neurobiol (2008) 38:1–15





It is a powerful tool in the differential diagnosis of AD from fronto-temporal dementia (FTD).

Approximately 30% of asymptomatic controls present cortical (11)C-PiB retention.

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

AIT

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 9 (2013)

Sebbene le placche Aβ sono delle caratteristiche patologiche che definiscono AD, persone anziane normali e pazienti con altre sindromi cliniche hanno elevati livelli di Aβ

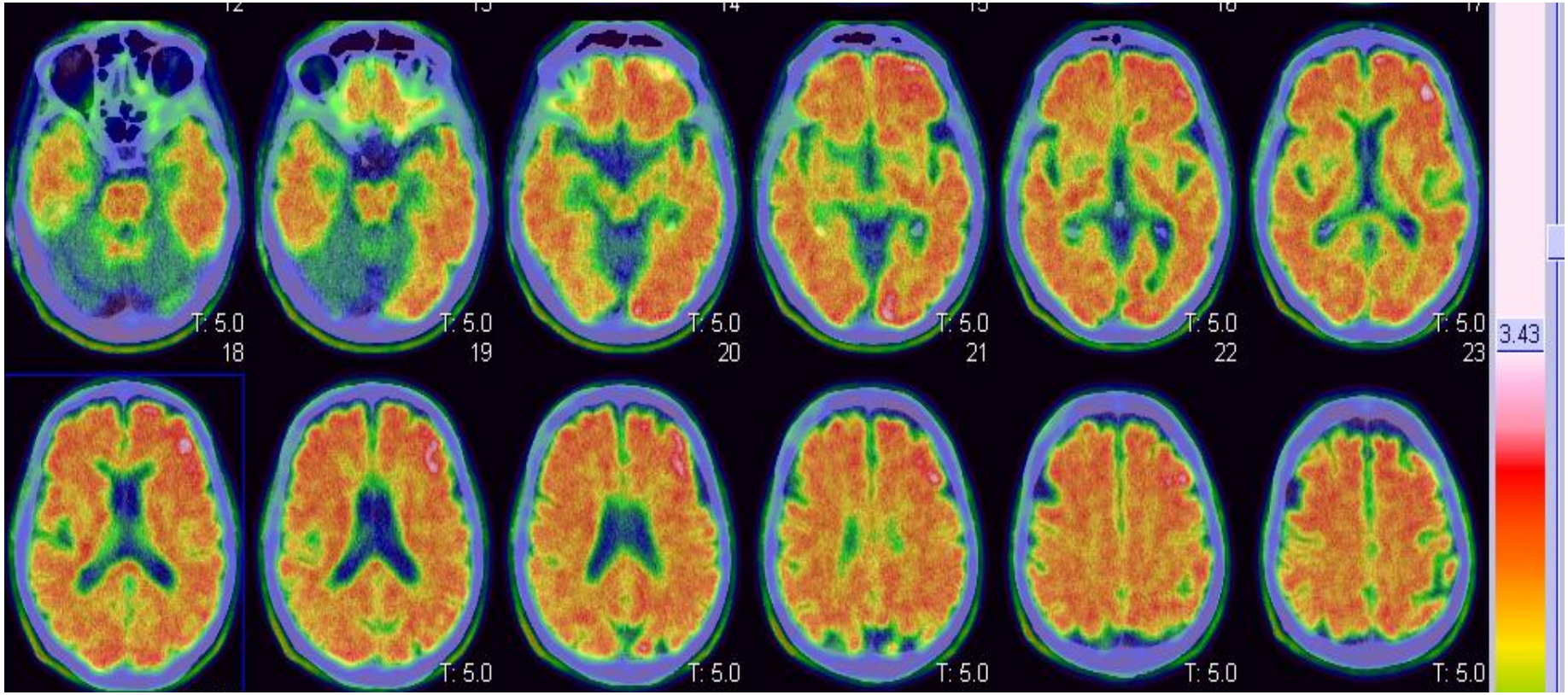
Warning!

Age specific positivity rates for amyloid PET

> 5%	50-60 anni
10%	60-70 anni
25%	70-80 anni
più 50%	80-90 anni

Rowe CC et al. Amyloid imaging results from the Australian Imaging, Biomarkers and Lifestyle (AIBL) study of aging. Neurobiol Aging 2010; 31:1275–83
Morris JC et al. APOE predicts amyloid-beta but not tau Alzheimer pathology in cognitively normal aging. Ann Neurol 2010;67:122–31.

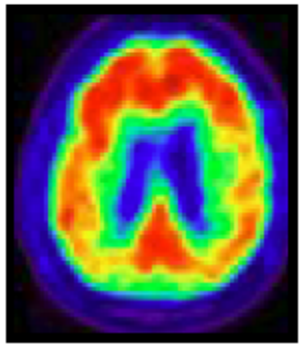
PET positiva = malattia di Alzheimer? NO!



A 65 aa 10-15% di “normali sani” hanno presenza di amiloide
A 85 aa 50% di “normali sani” hanno presenza di amiloide

By U.P. Guerra

Utilizzo clinico dei traccianti PET per amiloide

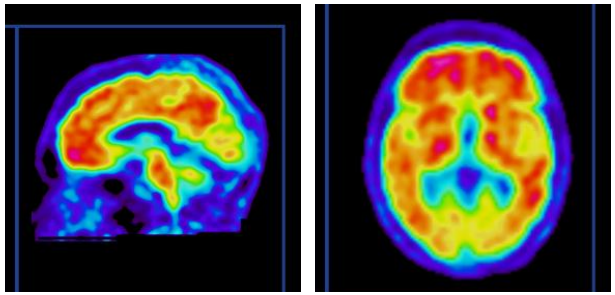


AmyPET +

✗ Diagnosi di AD

✓ Presenza di amiloidosi cerebrale

An amyloid PET report **will not constitute and is not equivalent** to a clinical diagnosis of AD dementia. **Imaging is only one tool**.



Vizamyl EU SmPC, 2014

L'accumulo di amiloide e la neurodegenarazione sono quasi inevitabili con l'età, ma molte persone sono capaci di mantenere una normale funzione cognitiva nonostante queste anormalità all'imaging!

Baseline PiB positive status is associated with a significantly increased risk of cognitive progression in healthy elderly and MCI patients.

K.A. Johnson et al. Appropriate use criteria for amyloid PET. Alzheimer's & Dementia 9 (2013)

None of the MCI Amyloid-negative subjects converted to AD, and thus **Amyloid burden negativity had a 100 % negative predictive value** for progression to AD.

VPN=100%

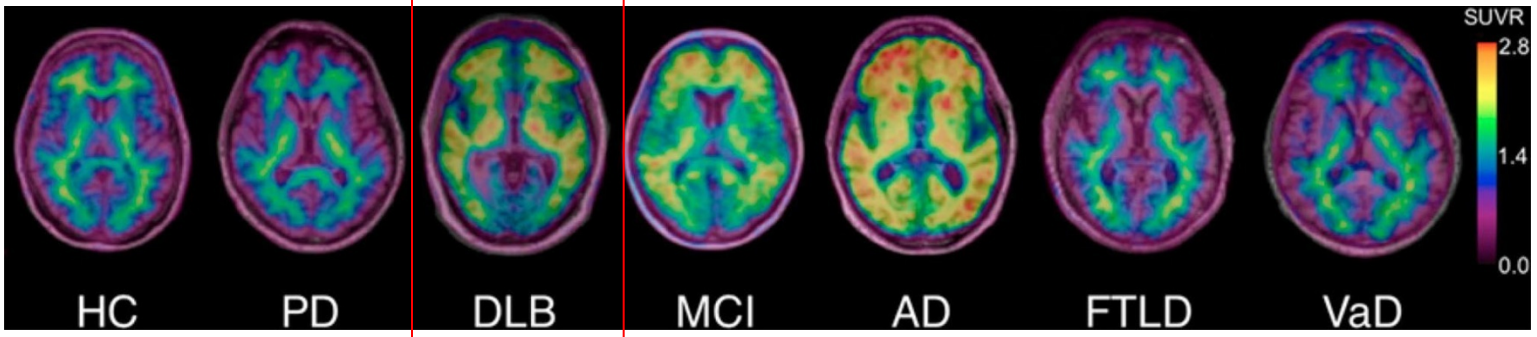
Nordberg, A. et al. A European multicentre PET study of fibrillar amyloid in Alzheimer's disease. Eur. J. Nucl. Med. Mol. Imaging 40, 104–14 (2013).
Forsberg, A. et al. PET imaging of amyloid deposition in patients with mild cognitive impairment. Neurobiol. Aging 29, 1456–65 (2008).

Amyloid PET imaging: applications beyond Alzheimer's disease

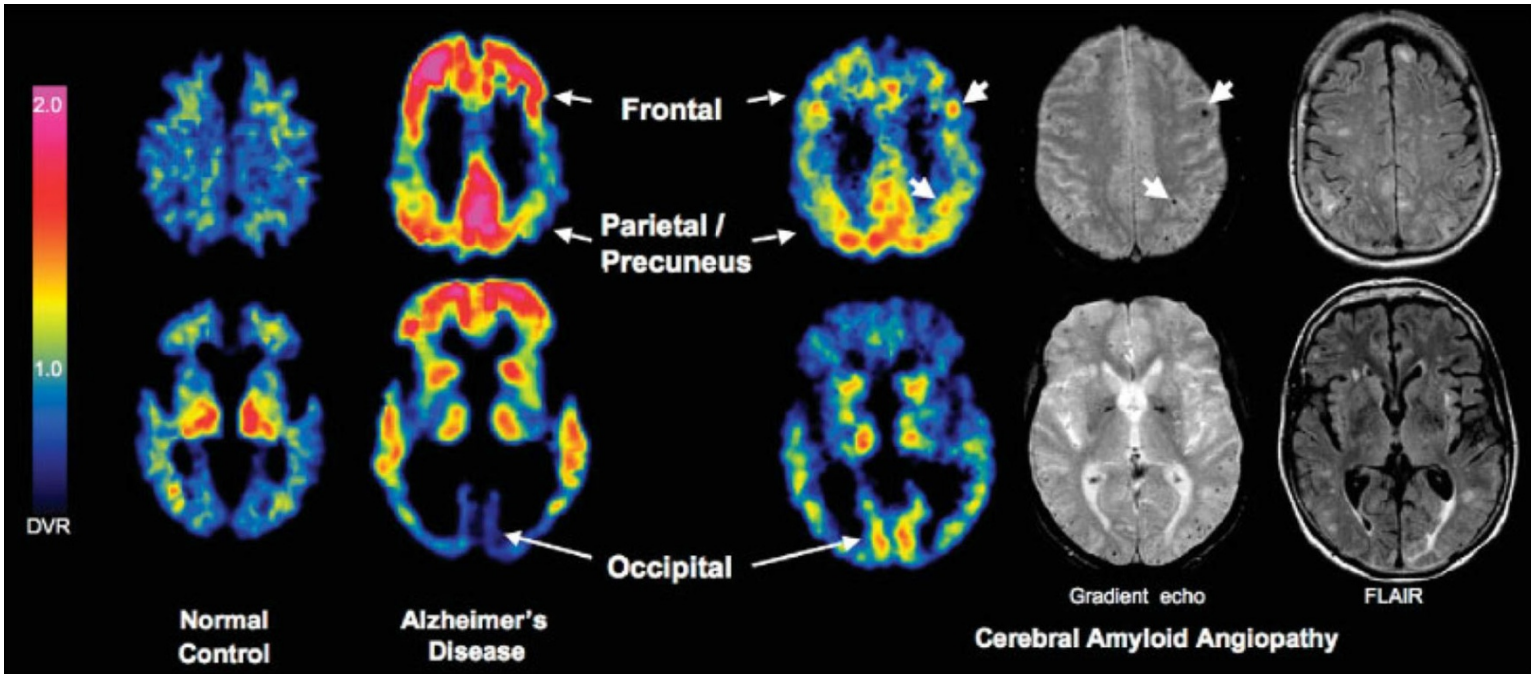
Ana M. Catafau • Santiago Bullich

Clin Transl Imaging (2015) 3:39–55

Warning!



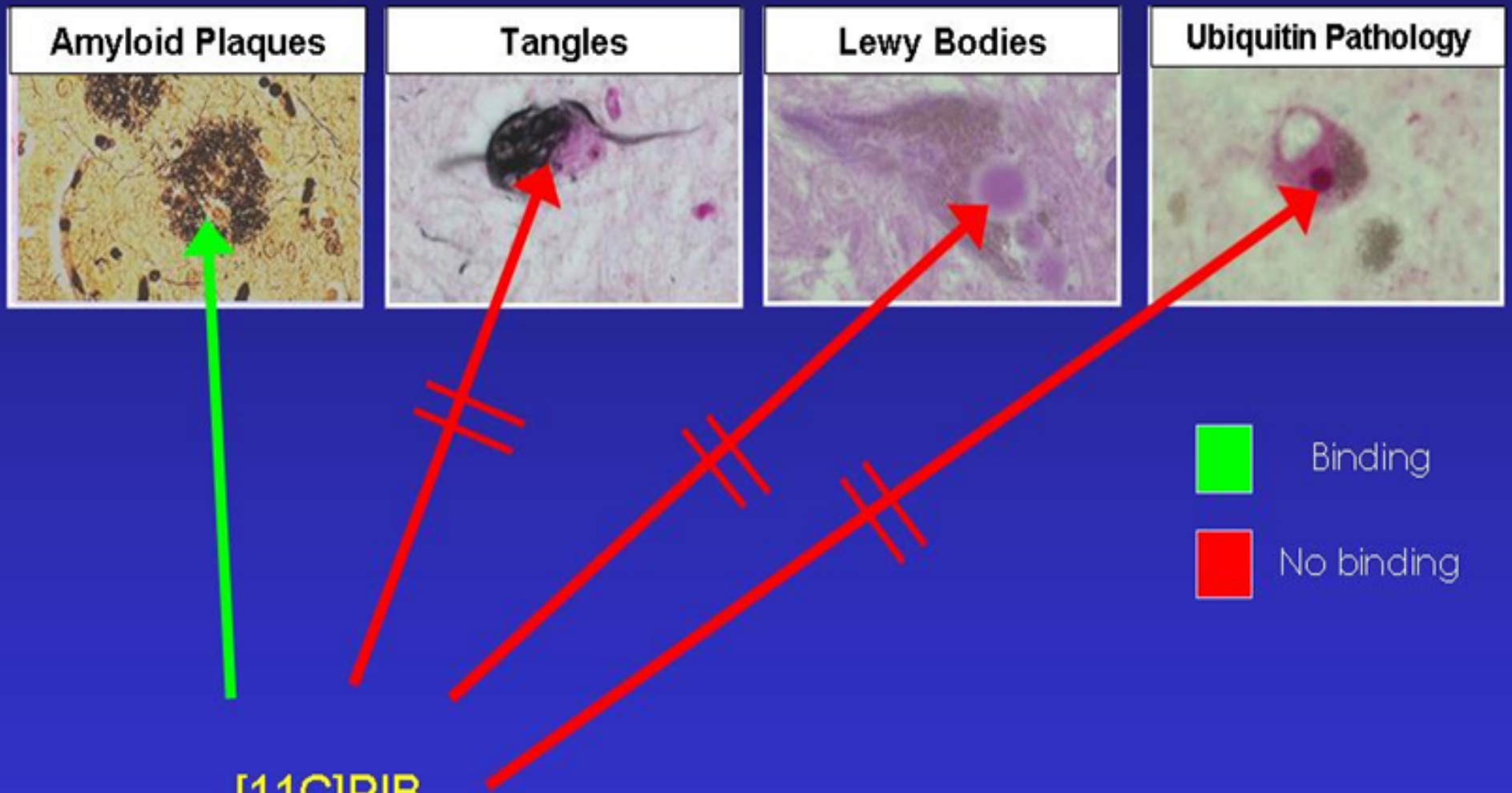
DLB



CAA

"Horizontal" Specificity

between different protein depositions



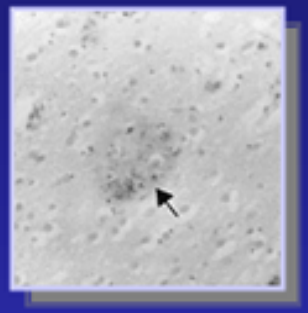
Rowe et al., Klunk et al., Lockhart et al. 2007

No "Vertical" Specificity

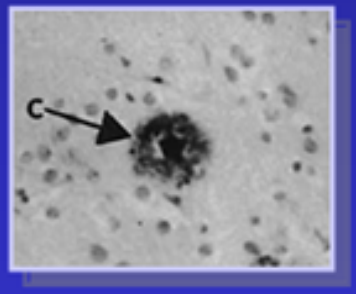
AMYLOID PATHOLOGY

between different types of ß-amyloid depositions

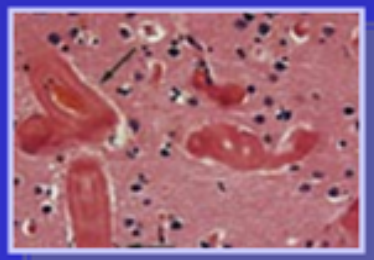
Diffuse plaques



Neuritic plaques



Amyloid angiopathy



[11C]PIB

Binding

Armstrong et al. 1998, Lockhart et al. 2007

Prevalence of Amyloid PET Positivity in Dementia Syndromes:

A Meta-analysis

JAMA. 2015 May 19; 313(19): 1939–1949.

Rik Ossenkoppele et al.

OBJECTIVE— To estimate the **prevalence of amyloid positivity on PET** in a wide **variety of dementia** syndromes.

1359 participants with clinically diagnosed AD
538 participants with clinically non–AD dementia.

1849 healthy as reference groups control (with amyloid PET data)
1369 AD as independent sample (based on autopsy).

The prevalence of amyloid positivity was **not** significantly associated with **sex** and **years of education** in both AD and non–AD dementias

Il rischio di amiloidosi incidentale **aumenta con l'età** e nei soggetti **ApoE Ɛ4**

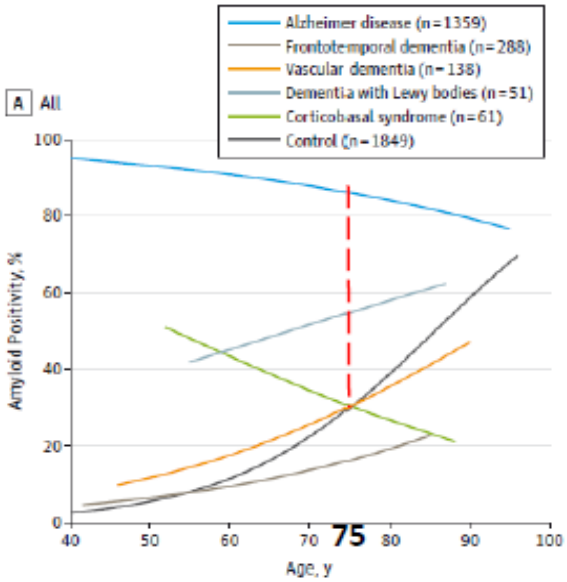
In pts with frontotemporal dementia (12%), vascular dementia (30%), and DLB (51%), the prevalence of amyloid positivity **increased with age**.

In line with recently proposed **appropriate use criteria**, this indicate the potential clinical utility of amyloid imaging for differential diagnosis in **early-onset** dementia

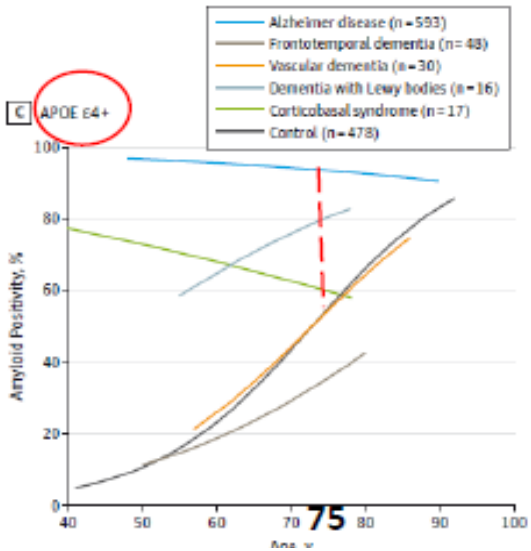
In contrast, the convergence between AD and non–AD dementia participants with age warrants **careful interpretation** of positive amyloid PET scans **in older patients.**

Ossenkoppele et al., JAMA 2015

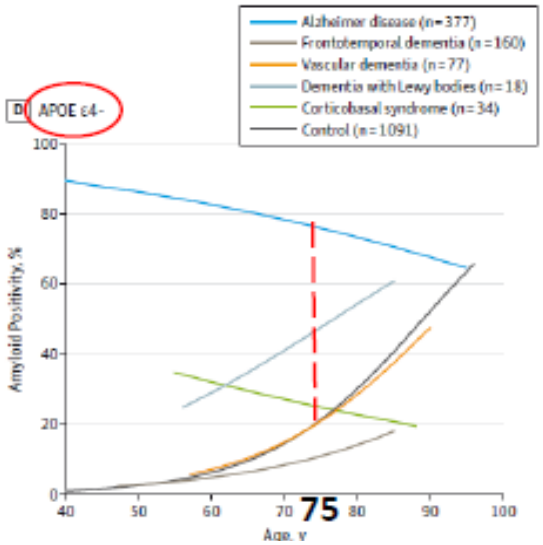
Ossenkoppele et al., JAMA 2015



Tutti: specificità **70%**



ApoE4+:
specificità **45%**



ApoE4-:
specificità **80%**

Amyloid imaging **non sembra giustificabile in APOE ε4 carriers** per **confermare** la diagnosi clinica di AD dementia, perchè la prevalenza della amyloide positività rimane intorno al 90% indipendentemente dall'età.

Rimane la potenziale utilità clinica dell'imaging per **supportare** la diagnosi clinica di AD dementia in **noncarrier APOE ε4** status con età maggiore di 70 anni.

Sebbene non raccomandata nella routine, la conoscenza dello stato APOE può aiutare quando si prenda in considerazione la valutazione del carico amiloideo nella pratica clinica.

^{11}C-PIB-PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI) (Review)

Cochrane Database of Systematic Reviews 2014, Issue 7.

Zhang S, Smailagic N, Hyde C, Noel-Storr AH, Takwoingi Y, McShane R, Feng J

9 studi (247 pts with MCI)

databases to January 2013 (1999 to 2013)

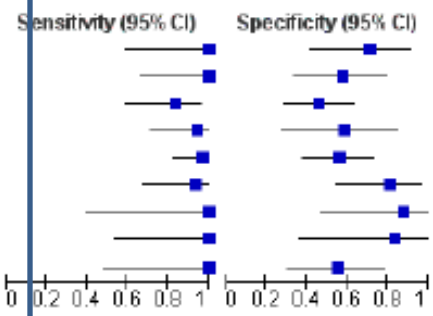
AIM

To determine the **diagnostic accuracy** of the **11C- PIB-PET** scan for detecting participants **with MCI** at baseline who **will clinically convert to Alzheimer's** disease dementia **or other forms** of dementia over a period of time.

274 participants included in the meta-analysis,
112 developed Alzheimer's dementia.
Median proportion converting was 34%.

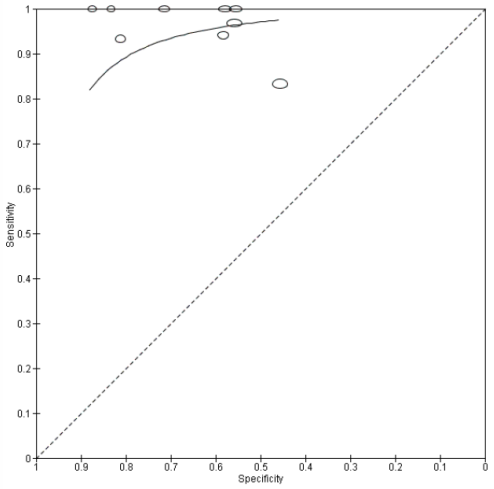
Forest plot of 11C-PIB-PET AD dementia.

Study	TP	FP	FN	TN	Threshold type	Threshold pre-specified	Sensitivity (95% CI)	Specificity (95% CI)
Forsberg 2010	7	4	0	10	quantitative	No	1.00 [0.59, 1.00]	0.71 [0.42, 0.92]
Grimmer 2013	9	8	0	11	quantitative	Yes	1.00 [0.66, 1.00]	0.58 [0.33, 0.80]
Jack 2010	15	19	3	16	quantitative	Yes	0.83 [0.59, 0.96]	0.46 [0.29, 0.63]
Kolvunen 2011	16	5	1	7	quantitative	Yes	0.94 [0.71, 1.00]	0.58 [0.28, 0.85]
Villemagne 2011	30	15	1	19	quantitative	Yes	0.97 [0.83, 1.00]	0.56 [0.38, 0.73]
Okello 2009	14	3	1	13	visual inspection	Yes	0.93 [0.68, 1.00]	0.81 [0.54, 0.96]
Ossenkoppele 2012	4	1	0	7	visual inspection	Not reported	1.00 [0.40, 1.00]	0.88 [0.47, 1.00]
Ossenkoppele 2012a	6	1	0	5	visual inspection	Yes	1.00 [0.54, 1.00]	0.83 [0.36, 1.00]
Wolk 2009	5	8	0	10	visual inspection	Yes	1.00 [0.48, 1.00]	0.56 [0.31, 0.78]



Sensibilità tra 83% e 100%
Specificità tra 46% e 100%

Figure 5. Summary ROC plot of 11C-PIB-PET AD dementia.

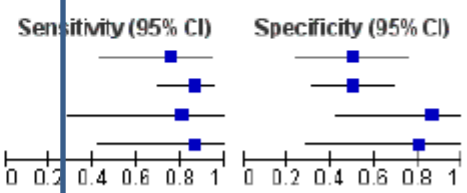


At the median specificity of 58%,
the estimated sensitivity was 96%

4 studi (59 AD , 58 non-AD

Forest plot of 11C-PIB-PET All dementia.

Study	TP	FP	FN	TN	Threshold type	Sensitivity (95% CI)	Specificity (95% CI)
Grimmer 2013	9	8	3	8	quantitative	0.75 [0.43, 0.95]	0.50 [0.25, 0.75]
Villemagne 2011	30	15	5	15	quantitative	0.86 [0.70, 0.95]	0.50 [0.31, 0.69]
Ossenkoppele 2012	4	1	1	6	visual inspection	0.80 [0.28, 0.99]	0.86 [0.42, 1.00]
Ossenkoppele 2012a	6	1	1	4	visual inspection	0.86 [0.42, 1.00]	0.80 [0.28, 0.99]



Sensibilità tra 75% e 86%
Specificità tra 50% e 86%

Potential valuable technique **for prediction of progression** in people with **MCI** and method for clinical practice in the near future.

Tuttavia, data la **eterogenità nella conduzione e interpretazione** del test, la non definita **thresholds** per la determinazione di positività del test e l'inconsistenza della lunghezza del follow-up,
we cannot recommend the routine use of 11C-PIB-PET in clinical practice.

CONCLUSIONI

18F-FDG PET

VANTAGGI

- COSTO LIMITATO

- APPLICABILE COME **BIOMARKER DI NEURODEGENERAZIONE** IN TUTTE LE FORME DI DEFICT COGNITIVO, CON IL QUALE è ALTAMENTE CORRELATO: “ANTIBIOTICO AD AMPIO SPETTRO”

-- LUNGA ESPERIENZA CLINICA (>35aa)

18F-FDG PET

AVVERTIMENTI

-La lettura dell'esame richiede un esperto, meglio se supportato da un metodo di semiquantificazione

-**Non ha specificità neuropatologica**: i quadri topografici possono non corrispondere a quadri patologici definiti.
Es: variante frontale di AD vs bvFTD, DBL vs la variante posteriore di AD, le varie forme di SNAP vs AD/FTD, la demenza semantica Tau o TDP-43 ...

- Il protocollo preparazione paziente/iniezione radiofarmaco è critico, riposo psicosensoriale, farmaci sedativi, controllo glicemia...

Amyloid-PET

VANTAGGI

-NEI casi DUBBi, un esame negativo esclude praticamente la m. Di Alzheimer (**elevato valore predittivo negativo)**

-Indispensabile per la selezione della popolazione per i clinical trials: **“biopsia cereberale in vivo per l’amiloidosi”**

-Markers indispensabile per il monitoraggio dell’efficacia di terapie anti-amiloide

AVVERTIMENTI

-La lettura dell’esame richiede un esperto, meglio se supportato da un metodo di semiquantificazione (medoti ancora instabili)

-La positività dell’esame rivela la amiloidosi cerebrale, non la m. Di Alzheimer

-Problema della amiloidosi incidentale (elevato >75aa): **limitato valore predittivo positivo.**

CONCLUSIONI

Nessuno dei 2 metodi risponde a tutte le domande; una combinazione dei 2 o di uno dei 2 con altri biomarkers può condurre ad una diagnosi ottimizzata e 'personalizzata'.

Ossenkoppele 2012; Zhang 2012; Trzepacz 2014

Il valore di FDG-PET e di amyloid-PET dipende da:

A che domanda vogliamo rispondere???

Diagnosi precoce/conversione a demenza:

FDG più elevata specificità (non di patologia)

Amyloid-PET più elevata sensibilità

Diagnosi differenziale:

Amyloid-PET: AD e DLB vs tutto il resto

FDG diagnosi differenziale all'interno di un gruppo

CONCLUSIONI

GRAZIE

Certamente alleati, perché forniscono **risposte a domande diverse** !

Domanda	FDG-PET	AmyPET
Questo MCI è dovuto ad AD	+	++
Questo paziente è a rischio per patologia AD	+	++
Quanto è grave la malattia di questo paziente con MCI due to AD	++	-
Questo MCI (AD o non-AD) progredirà presto/a medio termine	++	-
Questa demenza è una AD o una FTD	+	++
Questo paziente ha una demenza non-AD; cosa potrebbe avere	++	-
Questa demenza è una AD o una DLB	+	-
Posso selezionare questo paziente per un trial con Ab anti-amiloide	-	++
Sta funzionando questo farmaco neuroprotettivo nell'AD	++	-
Sta funzionando questo farmaco anti-amiloide nell'AD	-	++