

DISORDINI COGNITIVI E DEMENZE:
RECENTI AVANZAMENTI E FRONTIERE
DI RICERCA

Il Disease Management Team del IRCCS Ospedale
Policlinico San Martino

GENOVA

Neuroimaging: Imaging Molecolare

Silvia Morbelli



S.C. Medicina Nucleare

IRCCS Ospedale Policlinico San Martino,

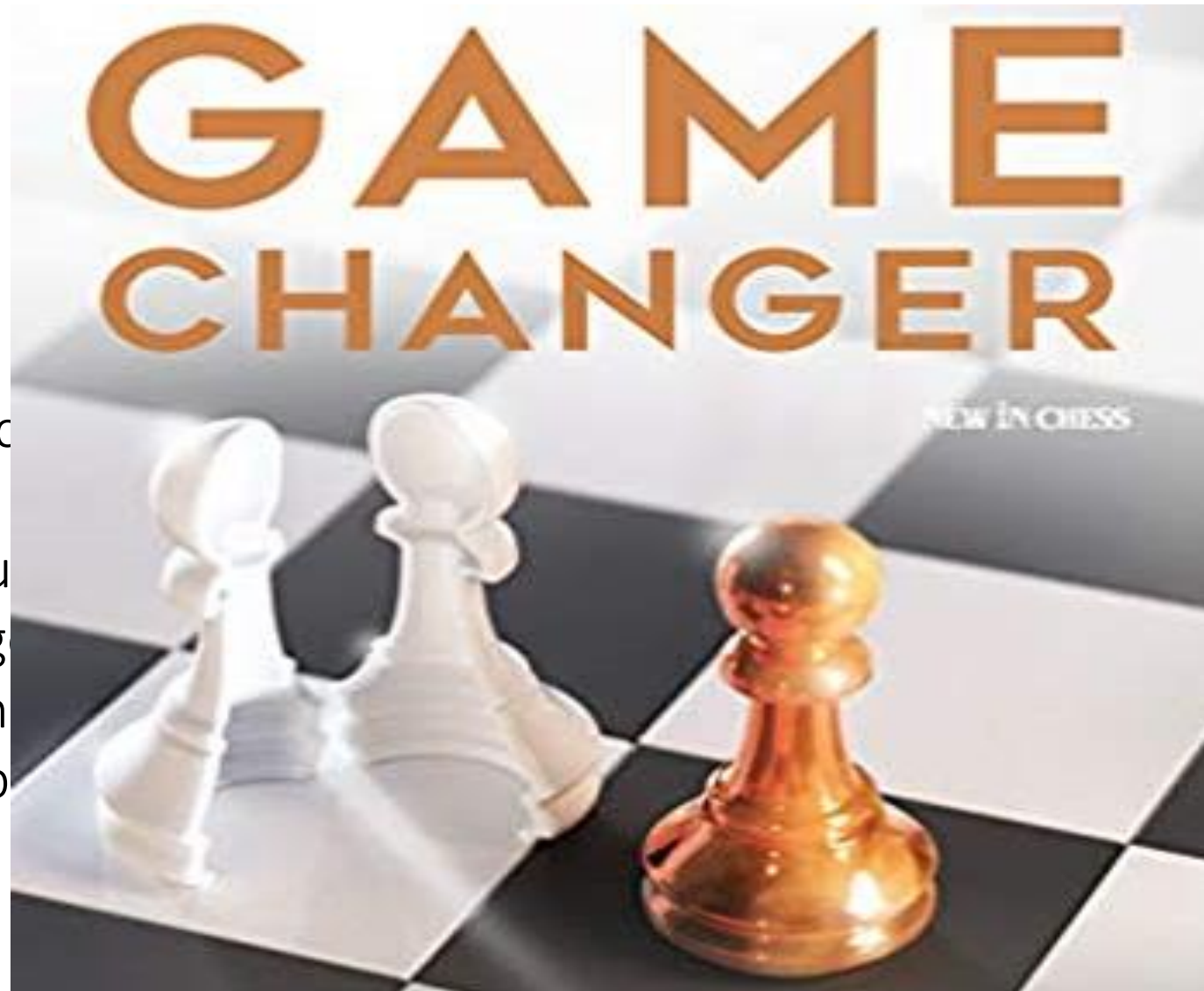
Dipartimento di Scienze della Salute

Universita' di Genova

Avanzamenti e Frontiere di ricerca in ambito PET ed Imaging Molecolare

Tracce

- Neurodegenerative
- Degenerative
- Dancing
- Depression
- ...



BIOGEN PLANS REGULATORY FILING FOR ADUCANUMAB IN ALZHEIMER'S
 DISEASE BASED ON NEW ANALYSIS OF LARGER DATASET FROM PHASE 3
 STUDIES

October 22, 2019 at 6:30 AM EDT

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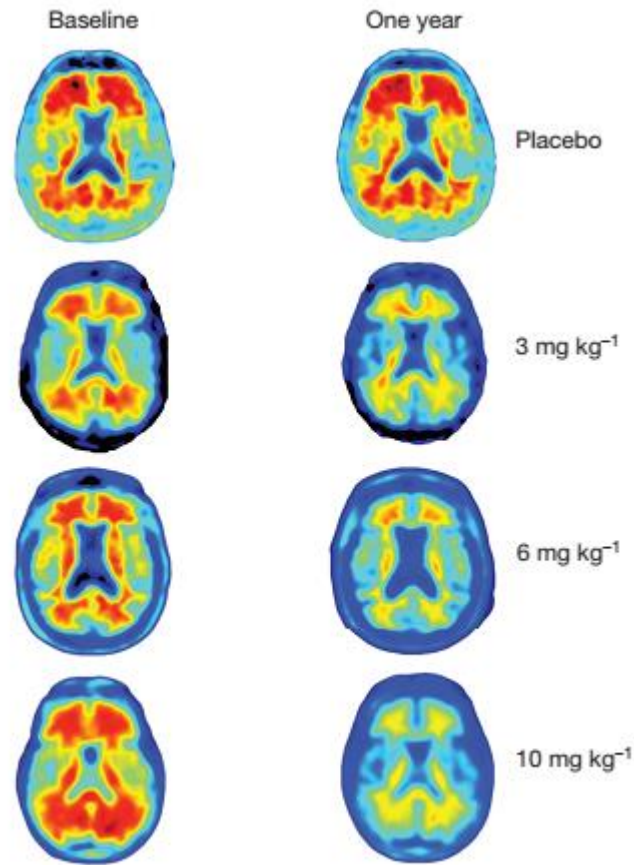
Cosa implica per la ricerca in ambito PET?

- L'amyloid PET come biomarcatore nei trial
- L'amyloid PET come biomarcatore dopo il trial (nella pratica clinica)

The antibody aducanumab reduces $A\beta$ plaques in Alzheimer's disease

Nature volume 537, pages 50–56, 2016

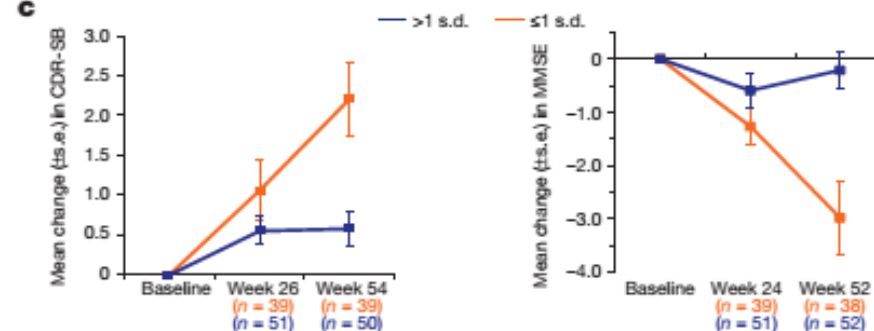
Jeff Sevigny^{1*}, Ping Chiao^{1*}, Thierry Bussière^{1*}, Paul H. Weinreb^{1*}, Leslie Williams¹, Marcel Maier², Robert Dunstan¹, Stephen Salloway³, Tianle Chen¹, Yan Ling¹, John O'Gorman¹, Fang Qian¹, Mahin Arastu¹, Mingwei Li¹, Sowmya Chollate¹, Melanie S. Brennan¹, Omar Quintero-Monzon¹, Robert H. Scannevin¹, H. Moore Arnold¹, Thomas Engber¹, Kenneth Rhodes¹, James Ferrero¹, Yaming Hang¹, Alvydas Mikulskis¹, Jan Grimm², Christoph Hock^{2,4}, Roger M. Nitsch^{2,4§} & Alfred Sandrock^{1§}



“Aducanumab, a human monoclonal antibody that selectively targets aggregated $A\beta$

In a mouse model of AD, aducanumab reduced soluble and insoluble $A\beta$ in a dose-dependent manner

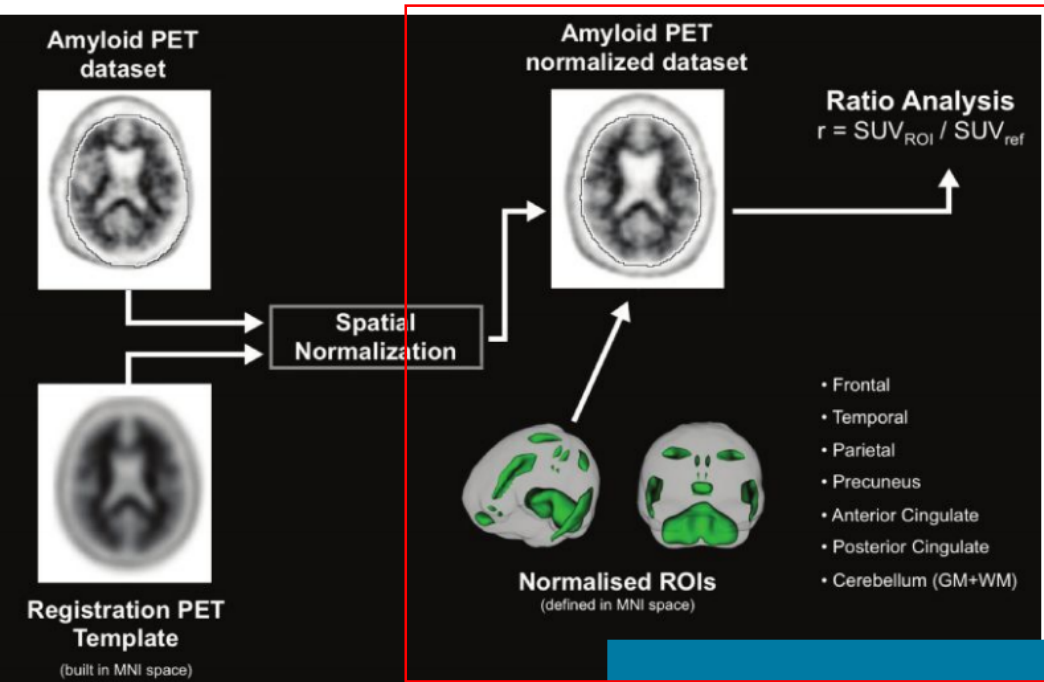
In patients with prodromal or mild AD, one year of monthly intravenous infusions of aducanumab reduces brain $A\beta$ in a dose- and time-dependent manner”



PET results (dal Alz-Forum del 24.10.19)

- Decline of about 0.16 SUVR in those on **low doses** of aducanumab
- 0.24 in the **high-dose** ENGAGE group and 0.27 in the high-dose EMERGE group
- the ENGAGE subgroup with **high exposure** to aducanumab cleared as much amyloid as the EMERGE high-dose group.

SUVratio



- visually inspect image for quality and artifacts
- register on a reference spatial frame (i.e. MNI)
- select reference (cerebellum, brain stem, ...) & uptake ROI (cortical)
- average counts (single/all ROI) and take the ratio
- apply the appropriate cut-off

very common quantification approach

automatic analysis software available

SUVr values/outcome critically depend on ROI definitions and positioning

Optimized classification of ^{18}F -Florbetaben PET scans as positive and negative using an SUVR quantitative approach and comparison to visual assessment



NeuroImage: Clinical 15 (2017) 325–332

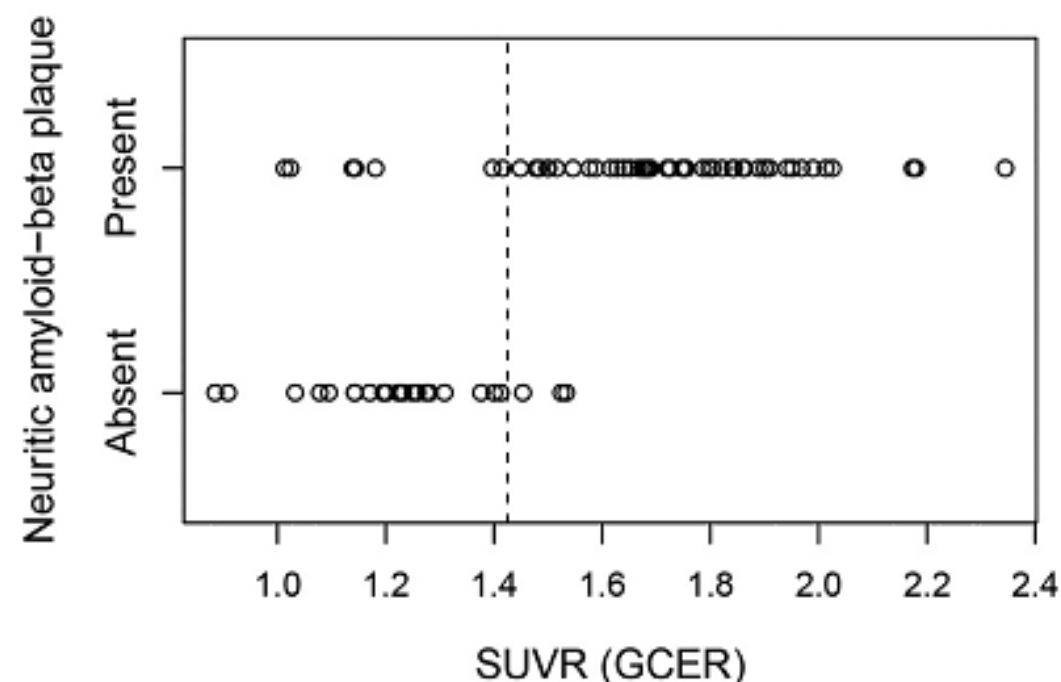
Santiago Bullich^{a,*}, John Seibyl^b, Ana M. Catafau^a, Aleksandar Jovalekic^a, Norman Koglin^a, Henryk Barthel^c, Osama Sabri^c, Susan De Santi^d

^a Piramal Imaging GmbH, Berlin, Germany

^b Molecular Neuroimaging, New Haven, CT, USA

^c Department of Nuclear Medicine, University Hospital Leipzig, Leipzig, Germany

^d Piramal Pharma Inc., Boston, MA, USA

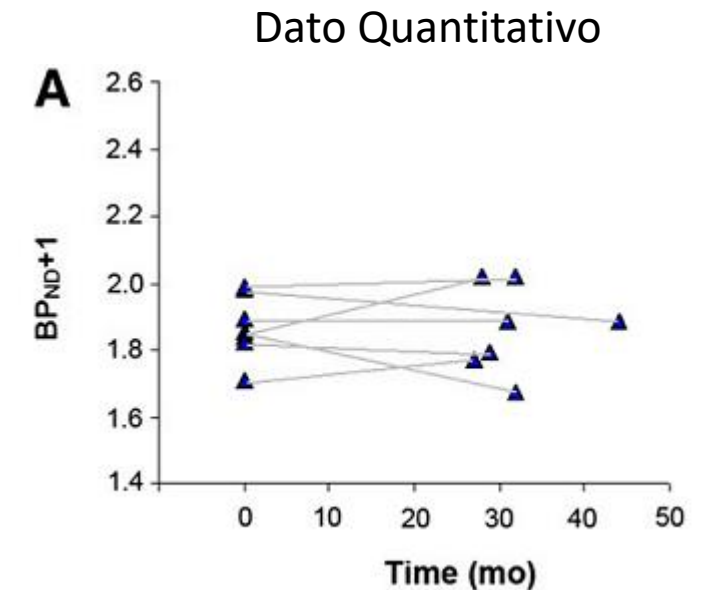
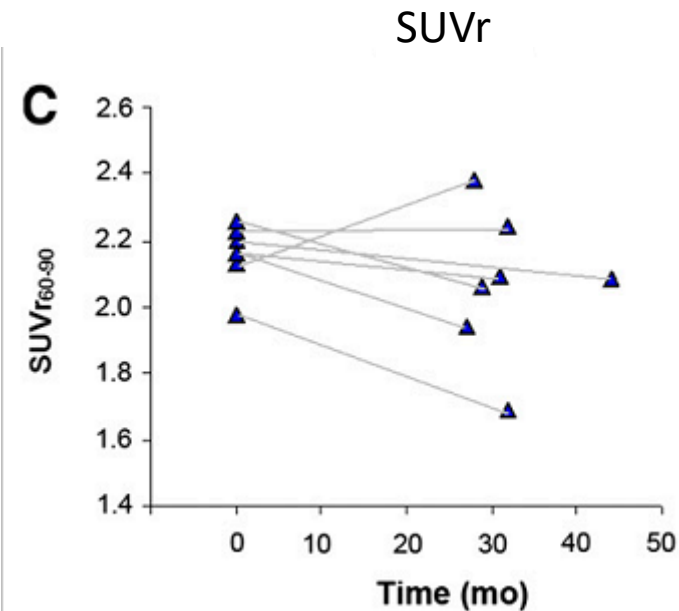
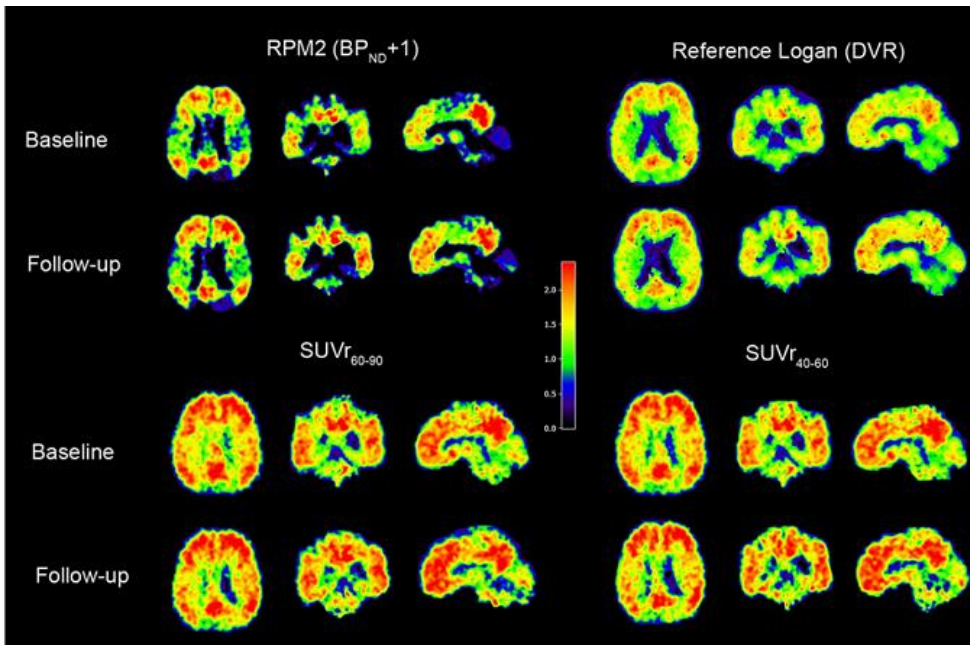


Conclusion: The accurate scan classification obtained in this study supports the use of VA as SoT to generate site-specific SUVR cutoffs. For an elderly end of life population, VA and SUVR cutoff categorization perform similarly in classifying FBB scans as A β -positive or A β -negative. These results emphasize the additional contribution that SUVR cutoff classification may have compared with VA performed by non-expert readers.

Longitudinal Amyloid Imaging Using ^{11}C -PiB: Methodologic Considerations

J Nucl Med 2013; 54:1570–1576
DOI: 10.2967/jnumed.112.113654

Bart N.M. van Berckel¹, Rik Ossenkoppele^{1,2}, Nelleke Tolboom^{1,2}, Maqsood Yaqub¹, Jessica C. Foster-Dingley¹, Albert D. Windhorst¹, Philip Scheltens², Adriaan A. Lammertsma¹, and Ronald Boellaard¹



SUVr is fine for binary classification but it is not robust when used as direct quantifier (exp. in longitudinal studies)

Diagnosi versus Valutazione della risposta alla terapia

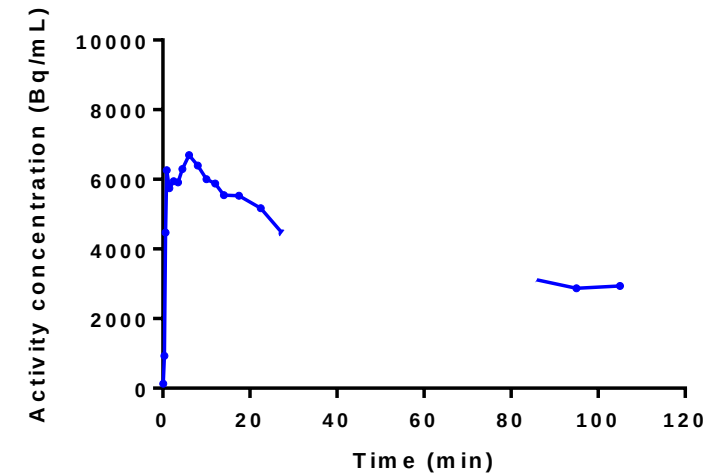
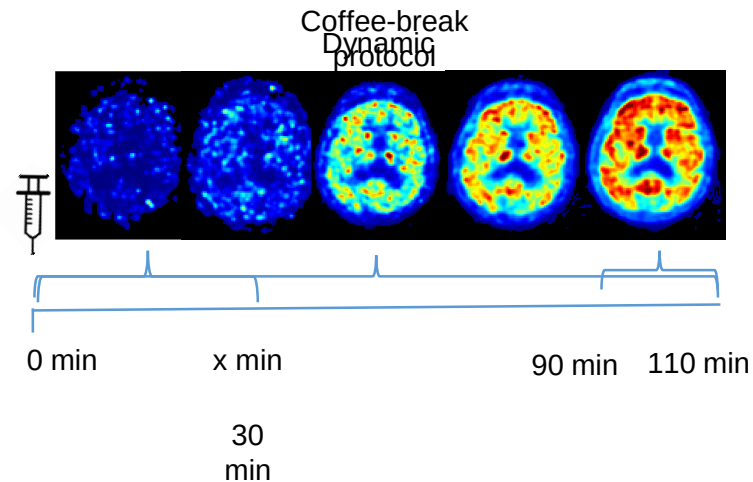
Diagnostic use

- Positive/negative amyloid scan
- Indirect measure of amyloid load



Longitudinal measurements

- Treatment response/ disease progression
- Direct measure of amyloid load



P20: optimized coffee-break protocol for quantitative [18 F] flutemetamol studies
F Heeman, M Yaqub, K Heurling, I Lopes Alves et al Human Amyloid Imaging 2018

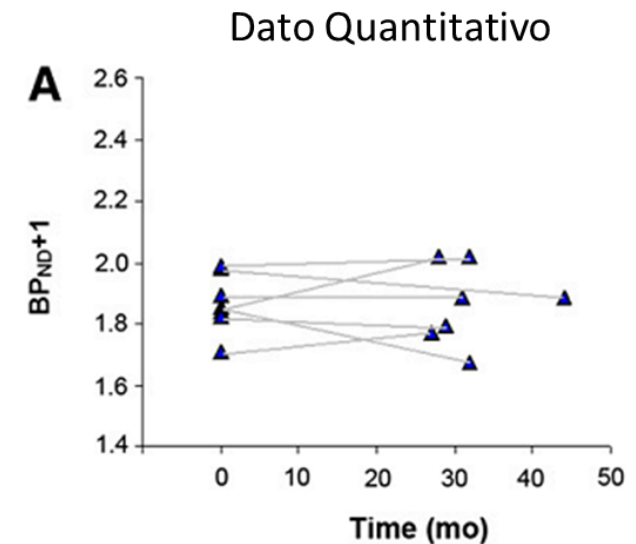
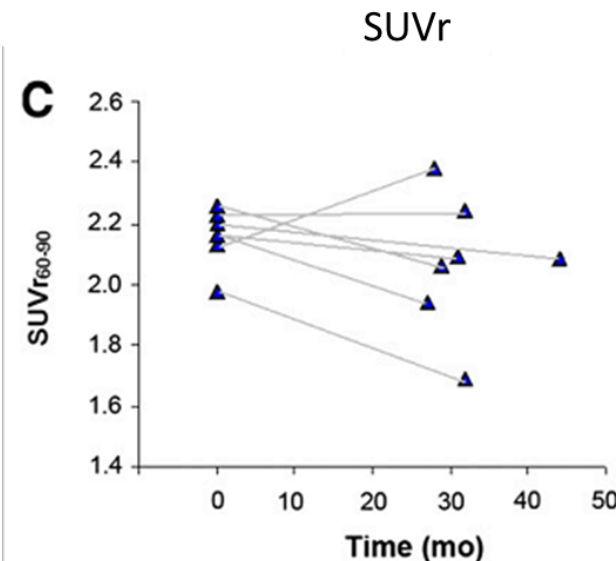
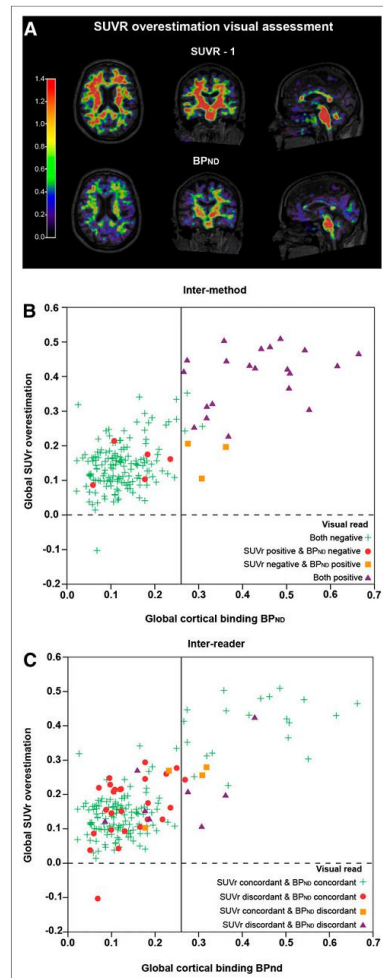
Slides from Amy-PAD study

Assessing Amyloid Pathology in Cognitively Normal Subjects Using ^{18}F -Flutemetamol PET: Comparing Visual Reads and Quantitative Methods

J Nucl Med 2019; 60:541–547
DOI: 10.2967/jnumed.118.211532

Lyduine E. Collij^{*1}, Elles Konijnenberg^{*2}, Juhan Reimand^{1,3,4}, Mara ten Kate², Anouk den Braber^{2,5}, Isadora Lopes Alves¹, Marissa Zwan², Maqsood Yaqub¹, Daniëlle M.E. van Assema⁶, Alle Meije Wink¹, Adriaan A. Lammertsma¹, Philip Scheltens², Pieter Jelle Visser², Frederik Barkhof^{1,7}, and Bart N.M. van Berckel¹

An important factor in considering dynamic PET acquisition is participant burden. In this cohort, 95% of participants indicated they had no objections to undergoing a second dynamic PET scan. The coffee-break protocol used in this study may have facilitated this response and suggests the feasibility of longitudinal dynamic acquisition in cognitively normal elderly persons.



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Cosa implica per la ricerca in ambito PET?

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“The existence of an approved drug to remove amyloid might lead Medicare to approve coverage for amyloid PET scans”

Alz-forum 24 Ottobre 2019

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

Figure 3. Cyclotrons capable of manufacturing amyloid tracers in the United States, as of May 2017



I progetti in corso sono in grado di fornire le risposte nell'eventuale nuovo scenario?

Iniziativa in corso: USA



THE BRAINS BEHIND SAVING YOURS.™

MAJOR NEW RESEARCH STUDY TO DEMONSTRATE VALUE OF PET SCANS IN ALZHEIMER'S DISEASE DIAGNOSIS

*Alzheimer's Association and American College of Radiology Lead Four-Year Trial to
Inform Medicare Coverage of Brain Amyloid Imaging*

“The purpose of the IDEAS Study is to examine how brain imaging, specifically an amyloid PET scan, helps guide doctors in diagnosing and treating Alzheimer’s and other dementias in cases where the cause of cognitive impairment is difficult to diagnose,” said Gil D. Rabinovici, M.D., IDEAS Study Chair and

The IDEAS Study was developed in response to the 2013 CMS National Coverage Decision (NCD) on amyloid PET imaging in dementia and neurodegenerative disease (CAG-00431N) not cover the scans because “the evidence is insufficient to conclude that the use of positron emission tomography (PET) amyloid-beta (A β) imaging is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of ... Medicare beneficiaries with dementia or neurodegenerative disease.”

The IDEAS Study will address two specific aims:

- Assess the impact of amyloid PET on the management of patients meeting Appropriate Use Criteria.
- Assess the impact of amyloid PET over 12 months on major medical outcomes such as hospital admissions and emergency room visits in patients enrolled in the study compared to matched patients not in the study.

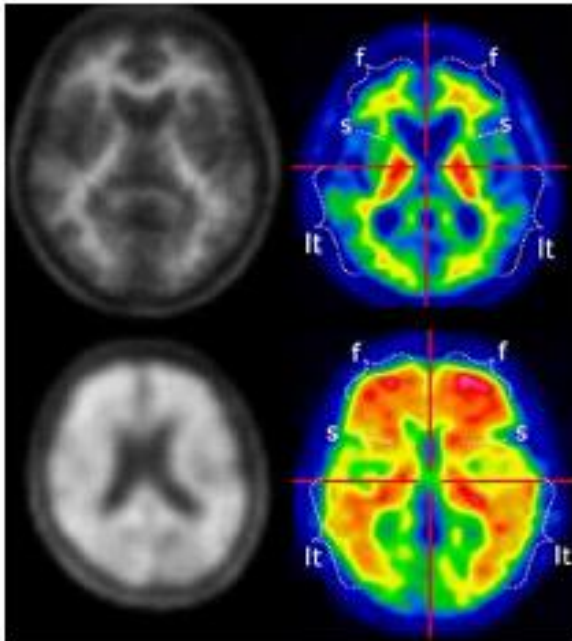
Iniziativa in corso: Europa

Welcome to AMYPAD!

We are a collaborative research initiative aiming to improve the understanding, diagnosis and management of Alzheimer's disease through the utilisation of β -amyloid PET imaging.

The Amyloid imaging to prevent Alzheimer's disease (AMYPAD) initiative aims to:

- improve the diagnostic work-up of people suspected to have Alzheimer's disease and their management (/project/structure/#diagnostic-and-management-study)
- understand the natural history of the disease in a pre-symptomatic stage (/project/structure/#risk-stratification-natural-history-and-enrichment-strategies)
- select people for treatment trials aiming at preventing Alzheimer's disease (/project/structure/#monitoring-treatment-quantifying-patient-specific-efficacy)



Iniziativa in corso: Italia

INTERCEPTOR PROJECT

ON THE EARLY DIAGNOSIS OF THE PRODROMAL STAGE OF ALZHEIMER DISEASE. THE PROGRESSION FROM MILD COGNITIVE IMPAIRMENT (MCI) TO DEMENTIA: THE ROLE OF BIOMARKERS IN THE EARLY INTERCEPTION OF PATIENTS TO WHOM PROVIDE FUTURE DISEASE-MODIFYING DRUGS

Best combination of Biomarkers

**High accuracy (specificity/sensibility), non-invasive,
Highly available on the territory, financially sustainable**

Neuropsychological tests (MMSE e DRF – FCSRT)

MRI with hippocampal volumetry

PET-FDG

CSF for Beta/Tau metabolites

ApoE

EEG x brain connectivity via graph theory

Amyloid PET?

Grazie per l'attenzione ma soprattutto grazie a...



Medicina Nucleare



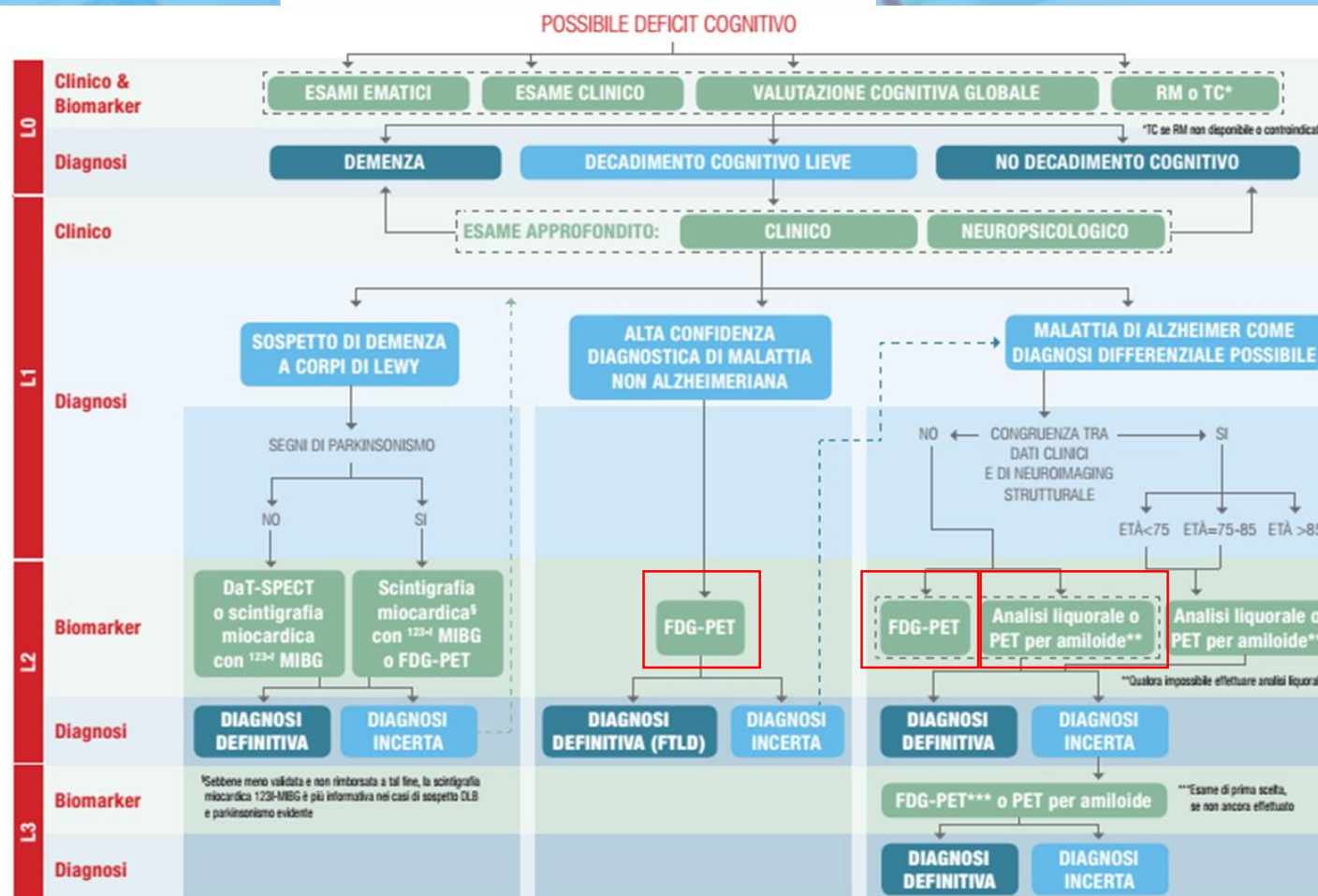
Neurologia

IRCCS Ospedale Policlinico San Martino, Università' di Genova



Iniziative in corso: Italia

**Differenziale
nel Decadimento Cognitivo
Lieve: Raccomandazioni
Consensuali Italiane.**



Amyloid PET per diagnosi

SUVratio

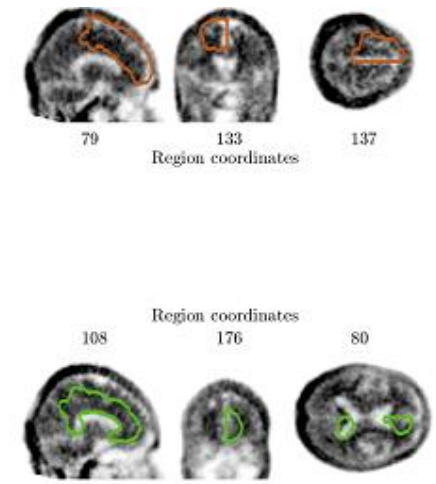
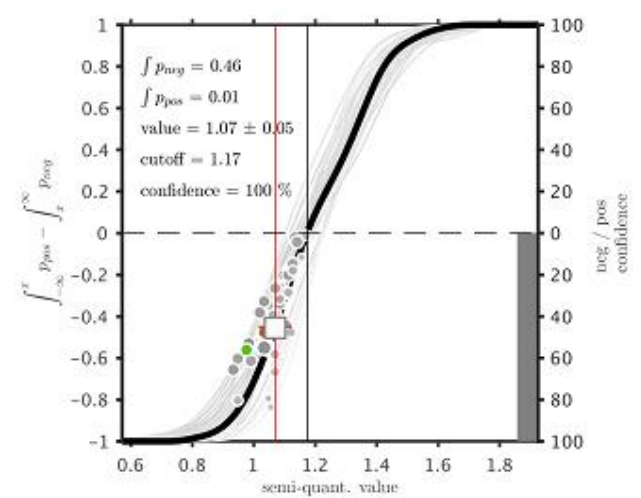
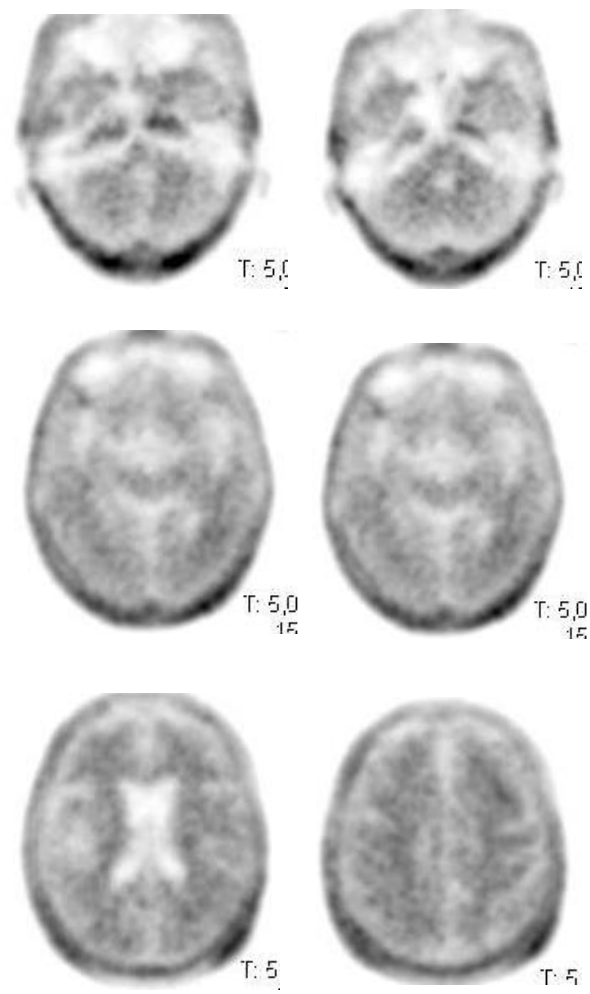


Figure 1: SUVr Regional plot

ELBA SOFTWARE

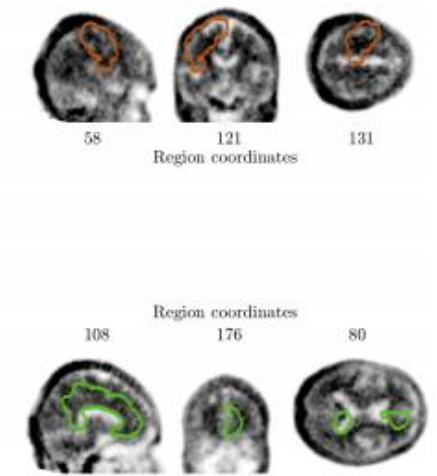
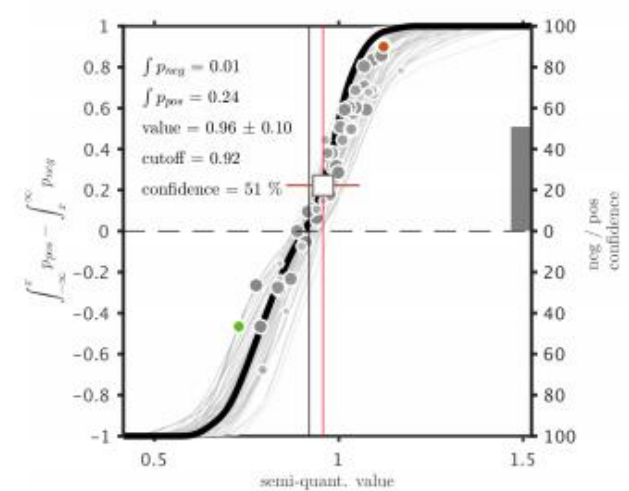


Figure 2: ELBA Regional plot

A kinetics-based approach to amyloid PET semi-quantification

[Authors]

A.Chincarini[1]*, E.Peira [1,4], M.Corosu [1], S.Morbelli [2,3], M. Bauckneht [2,3], S.Capitanio [2,3], M.Pardini [3,4], D.Arnaldi [3,4], C.Vellani [5], D.D'Ambrosio [6], V.Garibotto [7,8], F.Assal [7,8,9], B.Paghera [10], G.Savelli [11] A.Stefanelli [11] U.P. Guerra [11], F. Nobili [3,4]

