Imaging biomarkers in Alzheimer's disease: personalized medicine in neurodegenerative disorders

1 June 2017

V. Garibotto, MD, PD

Nuclear Medicine and Molecular imaging Division

NIMTlab

Hôpitaux Universitaires Genève

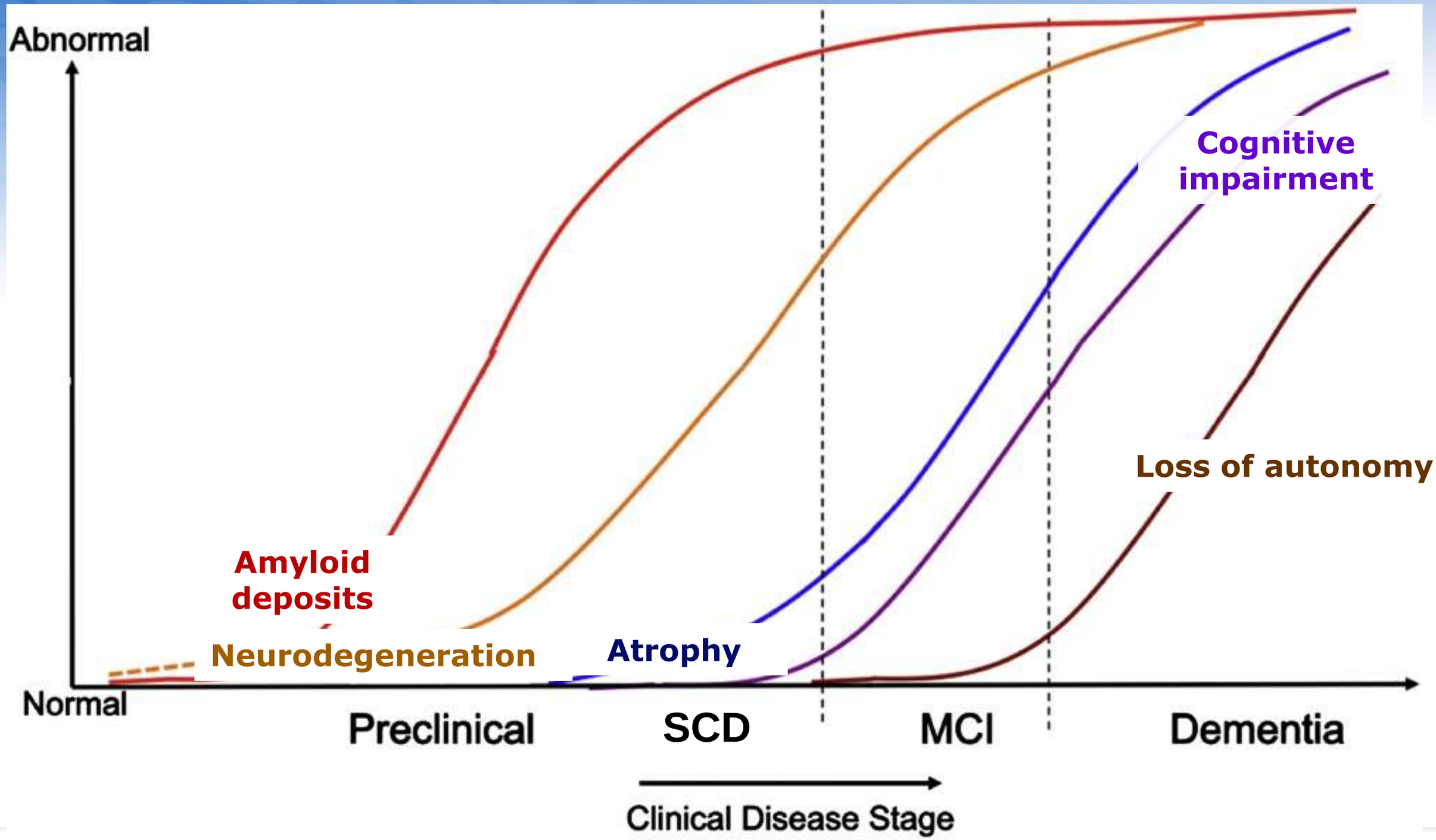
UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Outline

- Biomarkers and imaging in Alzheimer's Disease
  - Evidence from cross-sectional and longitudinal studies
  - Biomarker based diagnosis
  - Use in clinical trials

- Challenges:
  - Clinical validation
  - Standardization
  - Impact on management

Biomarkers in Alzheimer's Disease

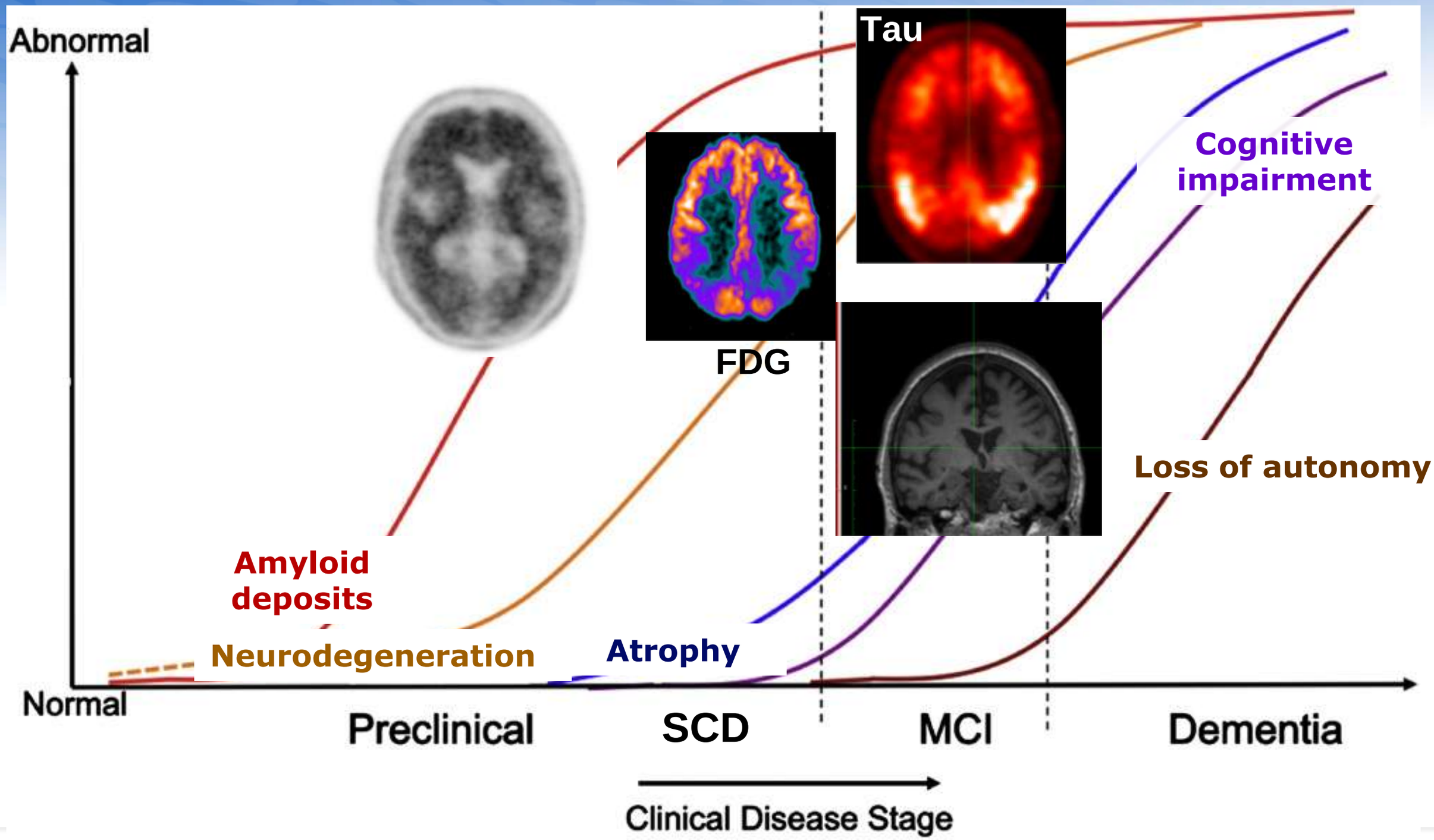


Adapted from Jack et al., 2011

Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Biomarkers in Alzheimer's Disease



Hôpitaux Universitaires Genève

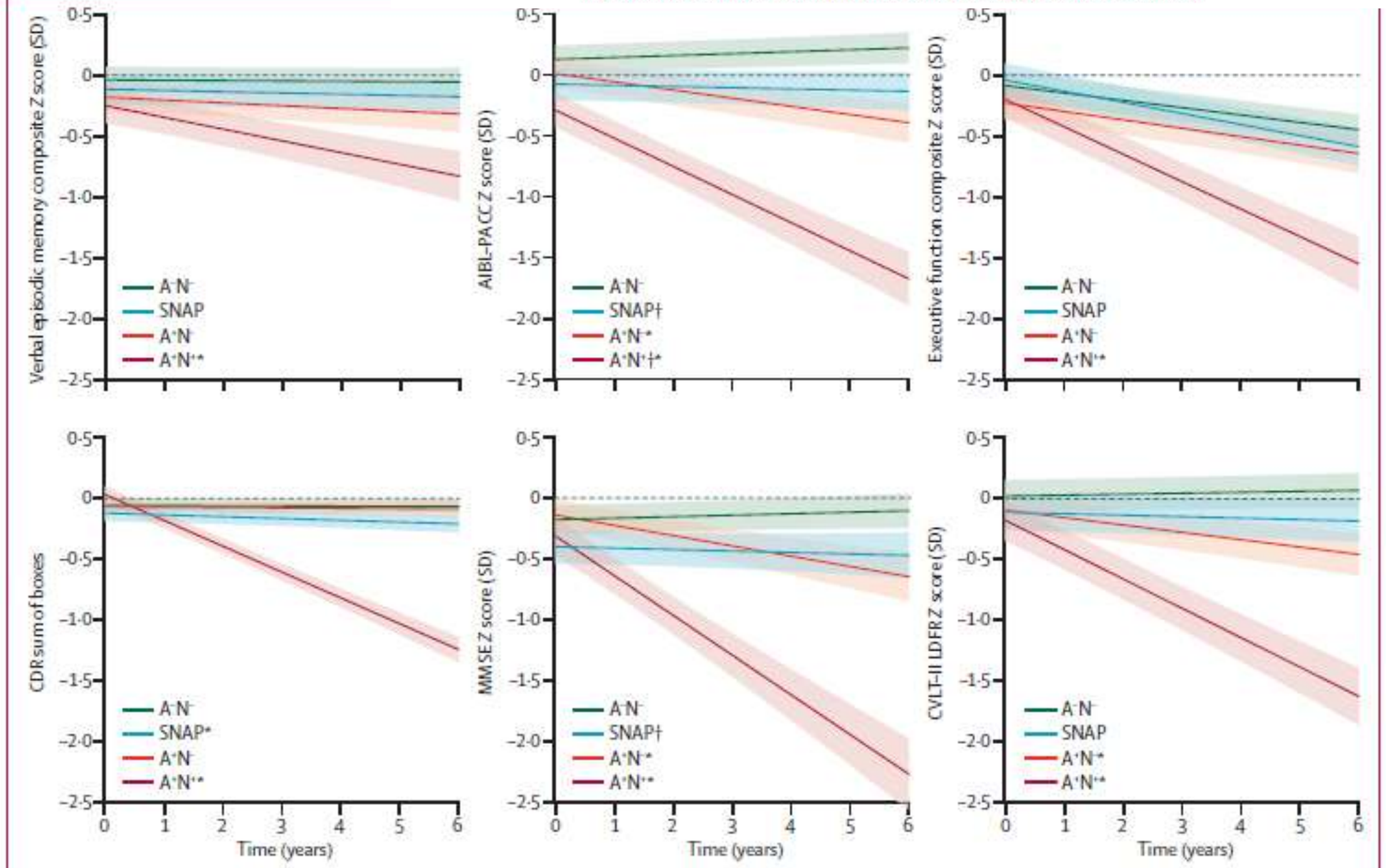
Adapted from Jack et al., 2011

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Lancet Neurol 2016; 15: 1044–53

Clinical and cognitive trajectories in cognitively healthy elderly individuals with suspected non-Alzheimer's disease pathophysiology (SNAP) or Alzheimer's disease pathology: a longitudinal study

Samantha C Burnham, Pierrick Bourgeat, Vincent Doré, Greg Savage, Belinda Brown, Simon Laws, Paul Maruff, Olivier Salvado, David Ames, Ralph N Martins, Colin L Masters, Christopher C Rowe, Victor L Villemagne, for the AIBL Research Group



Clinical diagnosis of Alzheimer's disease:

Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease

Guy McKhann, MD; David Drachman, MD; Marshall Folstein, MD; Robert Katzman, MD; Donald Price, MD; and Emanuel M. Stadlan, MD

July 1984 NEUROLOGY

I. The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

dementia established by clinical examination and documented by the Mini-Mental Test,[1] Blessed Dementia Scale,[2] or some similar examination, and confirmed by neuropsychological tests;

deficits in two or more areas of cognition;

progressive worsening of memory and other cognitive functions;

no disturbance of consciousness;

onset between ages 40 and 90, most often after age 65; and

absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE Alzheimer's disease is supported by:

progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);

impaired activities of daily living and altered patterns of behavior;

family history of similar disorders, particularly if confirmed neuropathologically; and

laboratory results of:

normal lumbar puncture as evaluated by standard techniques,

normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and

evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease, after exclusion of causes of dementia other than Alzheimer's disease, include:

plateaus in the course of progression of the illness;

other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;

seizures in advanced disease; and

CT normal for age.

IV. Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

sudden, apoplectic onset;

focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and

seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of POSSIBLE Alzheimer's disease:

may be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;

may be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be *the* cause of the dementia; and

should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

VI. Criteria for diagnosis of DEFINITE Alzheimer's disease are:

the clinical criteria for probable Alzheimer's disease and

histopathologic evidence obtained from a biopsy or autopsy.

Position Paper

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

Clinical phenotypes
Typical
- Amnestic syndrome of the hippocampal type

Atypical
- Posterior cortical atrophy
- Logopenic variant
- Frontal variant

Preclinical states
Asymptomatic at risk
- No AD phenotype (typical or atypical)

Presymptomatic (autosomal dominant mutation)
- No AD phenotype (typical or atypical)

Required pathophysiological marker
- CSF (low amyloid β_{1-42} and high T-tau or P-tau)

or
- Amyloid PET (high retention of amyloid tracer)

Figure: AD is defined as a clinicobiological entity

J Neuropathol Exp Neurol. 2012 April ; 71(4): 266–273. doi:10.1097/NEN.0b013e31824b211b.

Accuracy of the Clinical Diagnosis of Alzheimer Disease at National Institute on Aging Alzheimer's Disease Centers, 2005–2010

Thomas G. Beach, MD, PhD[1], Sarah E. Monsell, PhD[2], Leslie E. Phillips, PhD[2], and Walter Kukull, PhD[2]

Sensitivity and Specificity of the Clinical Diagnosis of Alzheimer Disease Relative to Stratified Clinical Confidence Levels and Minimum Threshold Levels for Histopathological Severity

Neuropathological AD Definition	Clinically Probable AD N = 526	Clinically Probable or Possible AD N = 648
CERAD NP Freq	N = 327	N = 373
Braak Stage V or VI	Sensitivity 76.6%	Sensitivity 87.3%
N = 427	Specificity 59.5%	Specificity 44.3%
CERAD NP Mod or Freq	N = 366	N = 418
Braak Stage V or VI	Sensitivity = 75.3%	Sensitivity = 85.9%
N = 486	Specificity = 63.0%	Specificity = 47.0%
CERAD NP Freq	N = 370	N = 421
Braak Stage III - VI	Sensitivity = 75.5%	Sensitivity = 85.9%
N = 490	Specificity = 63.6%	Specificity = 47.1%
CERAD NP Mod or Freq	N = 438	N = 511
Braak Stage III-VI	Sensitivity = 70.9%	Sensitivity = 82.7%
N = 618	Specificity = 70.8%	Specificity = 54.5%

Amyloid negative probable AD

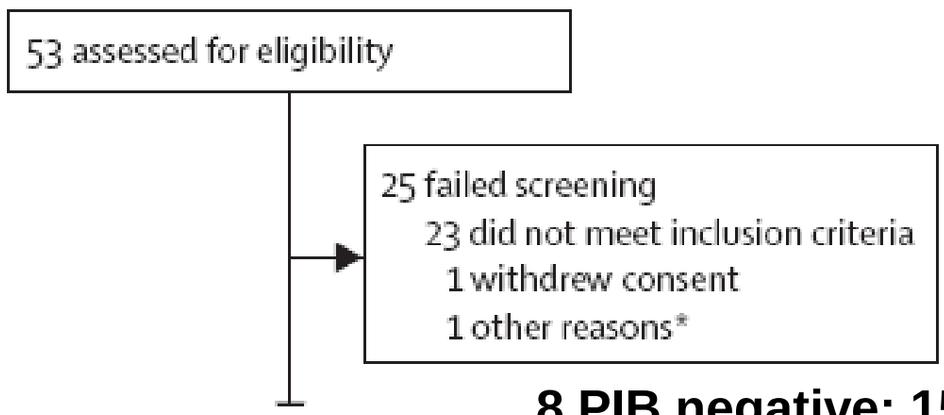
^{11}C-PiB PET assessment of change in fibrillar amyloid-β load in patients with Alzheimer's disease treated with bapineuzumab: a phase 2, double-blind, placebo-controlled, ascending-dose study

Juha O Rinne, David J Brooks, Martin N Rossor, Nick C Fox, Roger Bullock, William E Klunk, Chester A Mathis, Kaj Blennow, Jerome Barakos, Aren A Okello, Sofia Rodriguez Martinez de LIano, Enchi Liu, Martin Koller, Keith M Gregg, Dale Schenk, Ronald Black, Michael Grundman

Summary

Background Carbon-11-labelled Pittsburgh compound B (^{11}C-PiB) PET is a marker of cortical fibrillar amyloid-β load

Lancet Neurol 2010; 9: 363–72

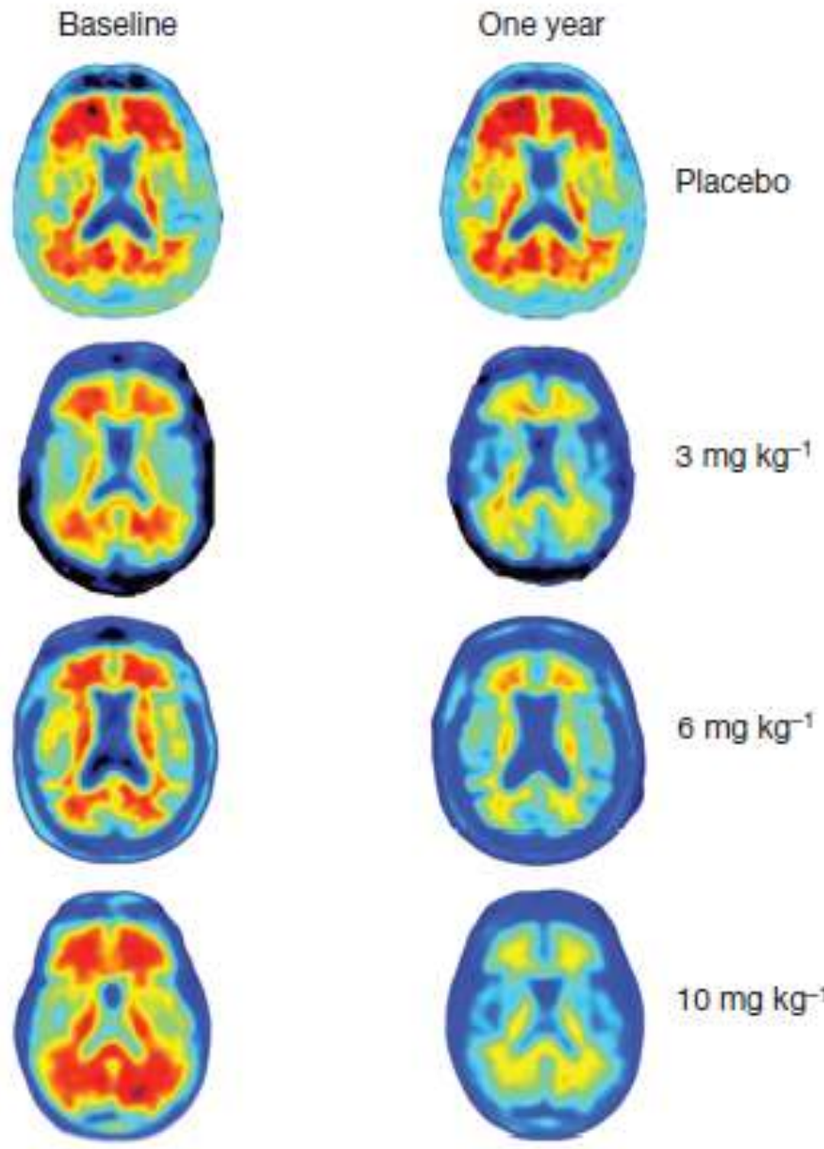


8 PIB negative: 15%

10 to 30% of probable AD are amyloid negative

Amyloid imaging and clinical trials

- Standard for study inclusion
- Tested as treatment biomarker



50 | NATURE | VOL 537 | 1 SEPTEMBER

ARTICLE

The antibody aducanumab r
plaques in Alzheimer's dise

Jeff Sevigny[1]*, Ping Chiao[1]*, Thierry Bussière[1]*, Paul H. Weinreb[1]*, Leslie Williams[1], M
Stephen Salloway[3], Tianle Chen[1], Yan Ling[1], John O'Gorman[1], Fang Qian[1], Mahin Arast
Melanie S. Brennan[1], Omar Quintero-Monzon[1], Robert H. Scannevin[1], H. Moore Arnol
James Ferrero[1], Yaming Hang[1], Alvydas Mikulskis[1], Jan Grimm[2], Christoph Hock[2,4], R

Hôpitaux Universitaires Genève

FACULTÉ DE MÉDECINE

Phases of Bioma
of Cancer Journ

Margaret Sullivan Pepe
Thompson, Mark Thorn

Roadmap to Alzheimer's Biomarkers in the Clinic

The biomarker-based diagnosis of Alzheimer's disease. 2—lessons from oncology

Marina Boccardi [a,b,*], Valentina Gallo [c], Yutaka Yasui [d,e], Paolo Vineis [f], Alessandro Padovani [g], Urs Mosimann [h,i], Panteleimon Giannakopoulos [j], Gabriel Gold [k], Bruno Dubois [l], Clifford R. Jack Jr [m], Bengt Winblad [n], Giovanni B. Frisoni [a,b,o], Emiliano Albanese [p], for the Geneva Task Force for the Roadmap of Alzheimer's Biomarkers [1]

Phase 1—Preclinical Exploratory Studies	Identify and prioritize BM	Same
Phase 2—Clinical Assay Development for Clinical Disease	Ability to distinguish subjects with and without the disease assessing TP and FP rate	Same
Phase 3—Retrospective Longitudinal Repository Studies	Capacity of the biomarker to detect preclinical disease and define criteria for positivity	Use of the biomarker in prospective longitudinal studies in prodromal disease (MCI) GS: progression to dementia at 3 y
Phase 4—Prospective Screening Studies	Impact on diagnosis and treatment of the biomarker-based screening in a relevant population.	Impact on diagnosis and management /treatment of the biomarker based diagnosis in MCI
Phase 5—Disease Control Studies	Impact on disease-associated mortality, morbidity, disability	Same

Clinical validity:
the Geneva Task Force for the Roadmap of Alzheimer's Disease Biomarkers

Biomarker	Phase I	Phase II					Phase III						Phase IV					Phase V
	Pilot Studies	Clinical Assay Development for Clinical Disease					Retrospective Longitudinal Repository Studies						Prospective Diagnostic Studies					Disease Control Studies
	PA	**PA**	**SA1**	**SA2**	**SA3**	**SA4**	**PA 1**	**PA 2**	**SA1**	**SA2**	**SA3**	**SA4**	**PA**	**SA1**	**SA2**	**SA3**	**SA4**	
MRI medial temporal atrophy*																		
^{18}F-fluorodeoxy-glucose PET																		
^{11}C-PIB, ^{18}F amyloid tracers PET																		
CSF (Aβ42, tau, p-tau)																		

Achievement: Full | Partial | Prelim-inary | Not achieved | Not applicable

Frisoni et al., Lancet Neurol, in press; Garibotto et al., NBA, 2017; Chiotis et al., NBA, 2017

Neurobiology of Aging 52 (2017) 214–227

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Roadmap to Alzheimer's Biomarkers in the Clinic

Clinical validity of increased cortical uptake of amyloid ligands on PET as a biomarker for Alzheimer's disease in the context of a structured 5-phase development framework

Konstantinos Chiotis[a], Laure Saint-Aubert[a], Marina Boccardi[b,c], Anton Gietl[d], Agnese Picco[e], Andrea Varrone[f], Valentina Garibotto[g], Karl Herholz[h], Flavio Nobili[e], Agneta Nordberg[a,i,*], for the Geneva Task Force for the Roadmap of Alzheimer's Biomarkers[1]

3—Prospective longitudinal repository studies	Define the ability of amyloid PET imaging to detect the disease in its early phase	Primary 1: To evaluate the capacity of amyloid PET imaging to detect the earliest disease stages	Excellent sensitivity (96%) and moderate specificity (72%) have been reported for amyloid PET imaging discrimination between patients with MCI that remain stable and those with MCI progressing to clinically diagnosed AD dementia.	Fully achieved
		Primary 2: To define criteria for an amyloid PET–positive scan in preparation for phase 4.	Criteria for qualitative assessment are established. Ongoing studies aim to establish standardized quantitative criteria across different centers.	Partly achieved
		Secondary 1: To explore the impact of factors on the discriminatory abilities of amyloid PET imaging before clinical diagnosis.	n/a	Not achieved
		Secondary 2: To compare BM/s with a view to selecting those that are most promising	Direct comparisons of core BM/s indicate that amyloid PET imaging is probably the most sensitive but has only moderate specificity.	Partly achieved
		Secondary 3: To develop algorithms for positivity based on combinations of BM/s.	Combinations of 2 core BM/s indicate that addition of medial temporal atrophy measures or [^{18}F]FDG PET imaging could improve the specificity of amyloid PET imaging.	Partly achieved
		Secondary 4: To determine an amyloid PET testing interval for phase 4 studies if repeated testing is of interest.	Ongoing studies aim to determine whether repeated amyloid PET imaging would be of interest in amyloid-negative patients at baseline.	Preliminary evidence

Neurobiology of Aging 52 (2017) 183–195

Contents lists available at ScienceDirect

Neurobiology of Aging

journal homepage: www.elsevier.com/locate/neuaging

Roadmap to Alzheimer's Biomarkers in the Clinic

Clinical validity of brain fluorodeoxyglucose positron emission tomography as a biomarker for Alzheimer's disease in the context of a structured 5-phase development framework

Valentina Garibotto [a,*], Karl Herholz [b], Marina Boccardi [c,d], Agnese Picco [d,e], Andrea Varrone [f], Agneta Nordberg [g], Flavio Nobili [e], Osman Ratib [a], for the Geneva Task Force for the Roadmap of Alzheimer's Biomarkers

(3) Prospective longitudinal repository studies	Primary 1: to evaluate the capacity of the biomarker to detect the earliest disease stages.	Achieved	Results in MCI show moderate-to-high sensitivity and specificity for progression to AD; i.e., the ability to identify the disease in the earliest stage (prodromal AD) is confirmed.
	Primary 2: to define criteria for a biomarker positive test in preparation for phase 4.	Partly achieved	Quantitative analyses providing a cutoff for test positivity are available and widely tested, but no internationally recognized standard exists yet.
	Secondary 1: to explore the impact of covariates on the discriminatory abilities of the biomarker before clinical diagnosis.	Preliminary evidence	Preliminary data in AD patients on the impact of age at onset on diagnostic performance.
	Secondary 2: to compare markers with a view to selecting those that are most promising.	Partly achieved	Preliminary studies with discordant results (possibly due to the type of analysis used rather than biomarker performance).
	Secondary 3: to develop algorithms for positivity based on combinations of markers.	Partly achieved	Preliminary evidence on association of CSF Aβ42, hippocampal atrophy, and DaTSCAN to FDG PET to increase diagnostic accuracy
	Secondary 4: to determine a biomarker testing interval for phase 4 if repeated testing is of interest.	Preliminary evidence	

Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Standardization

- European Joint Programme of Neurodegenerative Diseases (JPND)
- aim: assessing the current state of neuroimaging biomarker harmonization needs in large scale ND studies

Call for Propos

"Working Groups for Ha
Alignment in Brain Imag
Neurodegener

IMBI: Framework for Innovative Multi-tracer molecular Brain Imaging to enable multi-centre trials and image evaluation in early neurodegenerative diseases

Coordinator: Andreas H. Jacobs, University Muenster, Germany

Co-coordinator: Daniela Perani, IRCCS-San Raffaele, Italy

ND-PETMRI: Development of a Methodological Framework for Integrated PET/MR Imaging of Neurodegeneration

Coordinator: Henryk Barthel, University Leipzig, Germany

Co-coordinator: Thomas Schwarzlmüller, University of Bergen, Norway

PETMETPAT: Harmonisation metabolic FDG brain pattern characteristics

Coordinators: K.L. Leenders and Ronald Boellaard, University Medical Center Groningen, Netherlands

Co-coordinator: José Obeso, Hospitales de Madrid, Spain

SRA-NED: Harmonization of acquisition and processing of Brain Imaging Biomarkers for Neurodegenerative Diseases: A strategic Research Agenda for best-practice guidelines

Coordinator: Giovanni B. Frisoni, University of Geneva, Switzerland

Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

BRAIN IMAGING WORKING GROUPS SUPPORTED BY JPND

SRA-NED

Harmonization of acquisition and processing of brain imaging biomarkers for neuro-degenerative diseases: a strategic research agenda for best-practice guidelines

International survey to identify

1. current barriers for a harmonized use of MRI/PET/EEG
2. community driven solutions to overcome them

http://www.sra-ned.org/

- **Coordinators**
  - Giovanni B. Frisoni
    University of Geneva, Switzerland
  - Jorge Jovicich
    University of Trento, Italy

Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Validation studies ongoing: IDEAS - US

- The Imaging Dementia – Evidence for Amyloid Scanning (IDEAS) Study
  - planned 18 000 scans

- Medicare reimbursement for patients fulfilling appropriate use criteria

- Evaluation of impact on:
  - Management in 3 months:

    ≥ 30% change in medications/planning before and after scanning
  - "hard" health outcomes in 12 months:

    ≥ 10% reduction in hospital admission and ER visits as compared with a matched amyloid PET-naïve cohort

Validation study:

AMYPAD
Amyloid imaging to prevent Alzheimer´s Disease

- A pan-European network led by VUmc, Amsterdam,
- 6000 amyloid PET scans from normal aging, through subjective cognitive impairment (SCI) towards mild cognitive impairment (MCI)
- Longitudinal monitoring, in close collaboration with **EPAD** (ep-ad.org)

Hôpitaux Universitaires Genève

AMYPAD

Amyloid imaging to prevent Alzheimer´s Disease

Diagnostic value:

Usefulness of ß-amyloid imaging in patient management

Diagnostic study

Risk stratification:

Natural history of disease and methods to enrich secondary prevention studies

Prognostic study

Monitoring treatment:

Quantifying patient-specific efficacy

Proof of concept studies

Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Conclusions

- The availability of molecular markers has changed the landscape of AD diagnosis and opened the way for personalized management

- Solid evidence for the diagnostic validity of molecular markers

- Need for standardization of the procedures to define criteria for biomarker positivity

- Evidence for the impact on management will come from large scale ongoing studies

Grazie!!

valentina.garibotto@hcuge.ch

Service de médecine nucléaire et imagerie moléculaire
Hôpitaux Universitaires de Genève
Rue Gabrielle Perret Gentil 4
CH-1205 Genève

Hôpitaux Universitaires Genève

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE