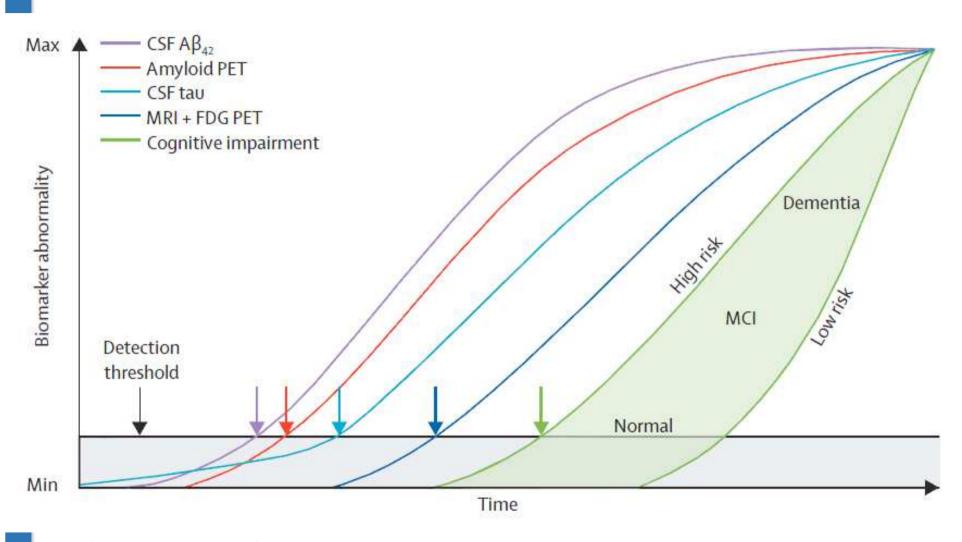


## Validation of biomarkers for Alzheimer's disease

Marina Boccardi LANVIE – Laboratoire du Neuroimagerie du Vieillissement, University of Geneva



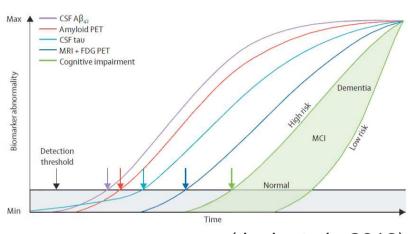
(Jack et al., 2013)



#### Biomarkers role for AD

Formulate positive diagnosis (McKhann et al., 2011; Dubois et al., 2007; 2014)

Move diagnosis backward in the clinical course (MCI stage) (Albert et al., 2011)



(Jack et al., 2013)

Select appropriate patients for clinical trials (Mangialasche et al., 2010)

Monitor the effect of disease-modifying drugs (Sevigny et al, 2016)



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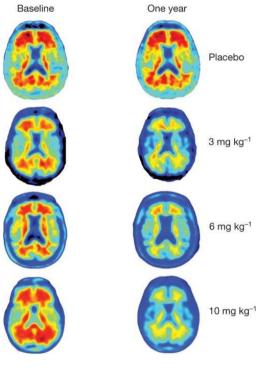


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(Sevigny et al, 2016)

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#### However...

### Use in hybrid research/clinical context + urgent need lead to use before regulators approval

Authorization: 2 positive independent and adequately powered Phase III studies

#### Pre-clinical

Testing of drug in non-farman subjects to gather efficacy, toxicity and pharmacokinetic information

#### Phase 0

Pharmacodynamics and pharmacolumetics particularly oral bioavallability and half-life of the drug

#### Phase I

Testing of drug on healthy volunteers for dose-ranging

#### Phase II

Testing of drug on patients to assess safety and efficacy

#### Phase III

Testing of drug on potents to ossess efficacy, effectiveness and safety

#### Phase IV

Surveillance – watching drug use in public

#### DRUG DEVELOPMENT

#### BIOMARKER DEVELOPMENT

#### ANALYTICAL VALIDITY

The biomarker accurately and reliably measures the analyte of interest in the appropriate patient specimen.

#### CLINICAL VALIDITY

The biomarker accurately and reliably identifies a clinically or biologically defined doorder, or separates one population into two or more groups with distinct clinical or biological outcomes or differences.

#### CLINICAL UTILITY

Evidence that use of the biomarker to guide clinical decisions results in improved measurable clinical outcomes compared with those if the biomarker test results were not applied.

Analytical validity & preliminary clinical validity

Pre-marketing

Post-marketing

#### However...

#### bad biomarker ≈ bad drug

e.g., problems posed by PSA for prostate cancer.

Inconsistent prescription (depending on availability, physician's familiarity with the exam, waiting list...)

Inconsistent refund

Suboptimal use of resources

Drugs to be prescribed based on biomarker-based diagnosis

#### Proposal: the Geneva Biomarker Roadmap Initiative

How to boost development → regulation → rational use?

Define a systematic methodological framework for biomarker validation

Borrow from **oncology** (Pepe et al., 2001)



# IL CERVELLO CHE CAMBIA 7

Sabato 11 novembre 2017

Genova, Aula Magna Clinica Neurologica

# COMMENTARY

# Phases of Biomarker Development for Early Detection of Cancer

Margaret Sullivan Pepe, Ruth Etzioni, Ziding Feng, John D. Potter, Mary Lou Thompson, Mark Thornquist, Marcy Winget, Yutaka Yasui



## 1) INTRODUCTION

Recent developments in such areas of research as geneexpression microarrays, proteomics, and immunology offer new approaches to cancer screening (1). The surge in research to develop cancer-screening biomarkers prompted the establishment of the Early Detection Research Network (EDRN) by the National Cancer Institute (2). The purpose of the EDRN is to coordinate research among biomarker-development laboratories, biomarker-validation laboratories, clinical repositories, and population-screening programs. By coordination of research efforts, the hope is to facilitate collaboration and to promote efficiency and rigor in research.

noninvasively. Biomarkers, however, may be more complicated and/or indirect, involving, for example, measures of immune response to a developing tumor, hormonal changes induced by a tumor, or mass spectrometry profiles of serum protein. In this commentary, we use the term "biomarker" for cancer detection in a broad sense.

Cancer is a diverse disease, and it is unlikely that a single biomarker will detect all cancer of a particular organ with high specificity and sensitivity. Indeed, biomarkers, such as prostate-specific antigen (PSA), that purport to have high sensitivity tend to have low specificity because they do not detect cancer *per se* but rather a more general process. We note that maintaining high specificity (low false-positive rates) is a very high priority for population screening. Even a small false-positive rate translates

Journal of the National Cancer Institute, Vol. 93, No. 14, July 18, 2001

#### The oncology framework- Phases I-II

Phase 1	
Preclinical Exploratory Studies Phase 2	To <b>identify and prioritize leads</b> for potentially useful biomarkers.
Clinical Assay Development for Clinical Disease	To estimate the true and false positive rate or ROC curve and assess its ability to distinguish subjects with and without the disease.
	To <b>optimize procedures for performing the assay</b> and to assess the reproducibility of the assay within and between laboratories.
	To determine the <b>relationship between biomarker measurements made on tumor tissue</b> (phase 1) <b>and</b> the biomarker measurements made <b>on the noninvasive clinical specimen</b> (phase 2).
	To assess factors (e.g. sex, age, etc.), associated with biomarker status or level in control subjects. If such factors affect the biomarker, thresholds for screen positivity may need to be defined separately for screening subpopulations to keep the FPR at a low level for each.
	To assess factors associated with biomarker status or level in cancer case subjects—in particular, disease characteristics such as stage, histology, grade and prognosis.

#### The oncology framework- Phase III

Phase 3	
Retrospective	To evaluate, as a function of time before clinical diagnosis, the capacity
Longitudinal	of the biomarker to detect preclinical disease.
Repository	
Studies	
	To define <b>criteria for a positive screening test</b> in preparation for phase 4.
	To explore the impact of covariates on the discriminatory abilities of
	the biomarker before clinical diagnosis.
	To compare markers with a view to selecting those that are most
	promising.
	To develop algorithms for screen positivity based on combinations of
	markers.
	To determine a screening interval for phase 4 if repeated testing is of
	interest.



#### The oncology framework- Phase IV

Phase 4	
Prospective Screening Studies	to determine the operating characteristics of the biomarker-based <b>screening</b> test in a relevant population by determining the detection rate and the false referral rate.
	To describe the characteristics of <b>tumors</b> detected by the <b>screening</b> test—in particular, with regard to the potential benefit incurred by early detection.
	To assess the practical feasibility of implementing the <b>screening</b> program and compliance of test-positive subjects with work-up and treatment recommendations.
	To make preliminary assessments of the effects of <b>screening</b> on costs and mortality associated with <b>cancer</b> .
	To monitor <b>tumors</b> occurring clinically but not detected by the <b>screening</b> protocol

#### The oncology framework- Phase V

Phase 5	
Cancer	to estimate the <b>reductions in cancer mortality</b> afforded by the screening test
Control	
Studies	
	To obtain information about the costs of screening and treatment and the cost per
	life saved.
	To evaluate compliance with screening and work-up in a diverse range of
	settings.
	To compare different screening protocols and/or to compare different approaches
	to treating screen-detected subjects in regard to effects on mortality and costs.



#### IL CERVELLO CHE CAMBIA 7

Sabato 11 novembre 2017

Genova, Aula Magna Clinica Neurologica

The diagnosis of Alzheimer's disease with biomarkers:
Now despite no cure, or later «only if»?

**International Workshop** 

Geneva, Dec 8-9 2014





#### Principal Investigators







Bengt Winblad

Giovanni B Frisoni

Clifford R Jack Jr

#### Task Force

/centroalzheimer.it/public/MB/BM-Roadmap/The Geneva AD Biomarker Roadmap Task Force.docx



#### Context of use

#### **Purpose**

Determine whether clinical diagnosed MCI in patients accessing memory clinics is due to AD

#### Nature of the disease

Insidious onset due to slowly progressive, well-characterized neurodegenerative processes that begin up to many years before the overt clinical onset of AD.

#### **Population**

the MCI population that is non-proactively screened but who autonomously refers or is referred to a memory clinic or other third-level specialist health service (→ NO screening)



#### Mutatis mutandis

#### Oncology

#### **Dementia**

Tumor tissue

→ Brain tissue

General population

→ MCI

Screening

→ Diagnosis

Cancer mortality

AD-associated mortality, morbidity, disability

Retrospective design →

Prospective design

#### Geneva Biomarker Validation Roadmap

#### Development of AD biomarkers adapted from the framework of Pepe et al. 2001

Phase 1: Rational for the use of the biomarker	Phase 2: Discrimination ability of the biomarker		Phase 3: Detection ability in early phase		Phase 4: Biomarker accuracy in representative MCI patients		Phase 5: Quantify impact of biomarker-based diagnosis on relevant outcomes			
Primary aim	Primary aim	Secondary aims	Primary aims	Secondary aims	Primary aim	Secondary ais	Primary aim	Secondary aims		
Potential leads	Identify discrim- ination accuracy AD/HC	discrim-	discrim-	Assay definition	Assess capacity of	Impact of covariates	Assess true/false	Detect predictive features		Cost/ benefit quantifi- cation
		Ante mortem/ autopsy	earliest (MCI) detection	Compare markers	referral rate in the biomarker-	Practical feasibility	Estimate impact on morbidity &	Compliance in different settings		
Achievement Full Partial		Covariates in HC	Criteria for	Combine markers	diagnosed patients	Estimate impact & costs	disability	Compare different protocols		
Prelim- Not inary achieve	Partial		positivity	Determine testing Interval		Monitor false negatives				



**NPS** 



**CSF** 



**Amyloid-PET** 



**FDG-PET** 



**MTA** 



DA- & NA-ergic imaging

Neurobiol Aging 2017; Issue 52

The Lancet Neurol Policy paper 2017; 16:661-676.

#### Neuropsychology (Gatekeeper) – Validation Status

#### Development of Free and Cued Wordlist Recall adapted from the framework of Pepe et al. 2001

<u> </u>			·					
Phase 1: Rational for the use of Free and Cued Wordlist Recall	Phase 2: Discrimination ability of Free and Cued Wordlist Recall		Phase 3: Detection ability in early phase		Phase 4: Free and Cued Wordlist Recall accuracy in representative MCI patients		Phase 5: Quantify impact of Free and Cued Wordlist Recall-based diagnosis on relevant outcomes	
Primary aim	Primary aim	Secondary aims	Primary aims	Secondary aims	Primary aim	Secondary ais	Primary aim	Secondary aims
Potential leads discrim ination accurace	Identify discrim-	Assay definition	Assess capacity of earliest	Impact of covariates	Assess true/false referral rate	Detect predictive features	Estimate	Cost/ benefit quantifi- cation
	accuracy AD/HC	Ante mortem/ autopsy	(MCI) detection	Compare markers	in Free and Cued Wordlist	Practical feasibility	Estimate impact on morbidity &	Compliance in different settings
Achievement Full Partial		Covariates in HC	Criteria for	Combine markers	Recall diagnosed patients	Estimate impact & costs	disability	Compare different protocols
Prelim- Not inary achiev		Covariates in AD	positivity	Determine testing Interval		Monitor false negatives		

#### Neuropsychology (Gatekeeper) - Research Priorities

Comparing different neuropsychological tests assessing memory function for sensitivity, specificity, positive and negative predictive values

Defining a consensus delayed recall test with multilingual versions and the relative normative populations

Define a consensus algorithm based on neuropsychological tests to access biomarker assessment

Define a consensus neuropsychological test battery required to support a diagnosis of "atypical" (non-memory) AD presentations

Lancet Neurol, 2017;16:661-676.

#### Medial Temporal Atrophy – Validation Status

#### Development of MTA adapted from the framework of Pepe et al. 2001

Phase 1: Rational for the use of MTA		iscrimination of MTA	Phase 3: Detection ability in early phase		Phase 4: MTA accuracy in representative MCI patients		Phase 5: Quantify impact of MTA-based diagnosis on relevant outcomes	
Primary aim	Primary aim	Secondary aims	Primary aims	Secondary aims	Primary aim	Secondary ais	Primary aim	Secondary aims
Potential leads	Identify discrim- ination accuracy AD/HC	definition capacity ion Ante mortem/ (MCI)	Assess capacity of	Impact of covariates	Assess true/false referral rate in MTA	Detect predictive features	Estimate impact on morbidity &	Cost/ benefit quantifi- cation
			(MCI) detection	Compare markers		Practical feasibility		Compliance in different settings
Achievement  Full Partial  Prelim- inary Not achieved applicable		Covariates in HC	Criteria for	Combine markers	diagnosed patients	Estimate impact & costs	disability	Compare different protocols
		Covariates in AD	positivity	Determine testing Interval		Monitor false negatives		

#### Medial Temporal Atrophy – Research Priorities

Phase II Clinical Assay Development for Clinical Disease

SA1 Define a **standard validation procedure for automated segmentation algorithms** based on the harmonized manual segmentation protocol

Assess reproducibility between different algorithms

Phase III Prospective Longitudinal Repository Studies

PA1 Assess accuracy of prediction of MCI progression to AD in clinical samples with adequate follow-up

PA2 Define the **threshold** for hippocampal atrophy taking into account the effect of covariates

SA1 Explore the impact of covariates on the discriminatory abilities of hippocampal volumetry in detecting MCI due to AD

Lancet Neurol, 2017;16:661-676.

#### Amyloid Imaging - Validation Status

#### Development of amyloid PET adapted from the framework of Pepe et al. 2001

Phase 1: Rational for the use of amyloid PET	If for the Phase 2: Discrimination ability of amyloid PET		Phase 3: Detection ability in early phase		Phase 4: Amyloid PET accuracy in representative MCI patients		Phase 5: Quantify impact of amyloid PET-based diagnosis on relevant outcomes	
Primary aim	Primary aim	Secondary aims	Primary aims	Secondary aims	Primary aim	Secondary ais	Primary aim	Secondary aims
Potential leads ination	discrim-	Assay definition	Assess capacity of	Impact of covariates	Assess true/false referral rate in amyloid PET	Detect predictive features	Estimate impact on morbidity &	Cost/ benefit quantifi- cation
	accuracy	Ante mortem/ autopsy	earliest (MCI) detection	Compare markers		Practical feasibility		Compliance in different settings
Achievement Full Partial		Covariates in HC	Criteria for	Combine markers	diagnosed patients	Estimate impact & costs	disability	Compare different protocols
Prelim-inary	Not achieved	Covariates in AD	positivity	Determine testing Interval		Monitor false negatives		

#### Amyloid Imaging – Research Priorities

Phase II Clinical Assay Development for Clinical Disease

SA1 Assess on the same population comparability and reproducibility of ligands, operating procedures, and readout methods.

SA3 Assess the impact of covariates (gender, education, levels of cognitive activity) on ligands uptake and define whether and how they should affect the definition of positivity. SA4 Assess the effect of disease characteristics (stage, genotype, disease onset, clinical manifestation) and other covariates in patients on levels of uptake, to quantify the informative value of amyloid imaging in patients

Phase III Prospective Longitudinal Repository Studies

PA1 Discrimination ability of MCI due to AD may provide more stable results if re-run after definition of one standard procedure

PA2 Progress the definition of positivity mainly by **standardizing the reading criteria** SA1 Collect evidence on the impact of covariates on the discriminatory abilities of the biomarker

SA2 Compare the predictive performance of amyloid imaging versus other biomarkers (particularly CSF A 42, assessed with the new standard)

SA3 Develop sensitive **algorithms** for positivity based on combinations of amyloid imaging and other markers

SA4 Investigate the meaning of intermediate levels of uptake (quantitative assessment) or dubious cases (visual assessment) and define whether **repeated testing** may be useful, at which time interval, and for which patients

#### Cerebrospinal Fluid Abeta & Tau – Validation Status

#### Development of CSF biomarkers adapted from the framework of Pepe et al. 2001

Phase 1: Rational for the use of CSF biomarkers		Phase 2: Discrimination ability of CSF biomarkers		Phase 3: Detection ability in early phase		Phase 4: CSF biomarkers accuracy in representative MCI patients		Phase 5: Quantify impact of CSF biomarkers-based diagnosis on relevant outcomes	
Primary aim	Primary aim	Secondary aims	Primary aims	Secondary aims	Primary aim	Secondary ais	Primary aim	Secondary aims	
Potential leads	Identify discrim- ination	discrim- definition	Assess capacity of earliest	Impact of covariates	Assess true/false referral rate in CSF biomarkers	Detect predictive features	Estimate	Cost/ benefit quantifi- cation	
	accuracy AD/HC	Ante mortem/ autopsy	Ante (MCI)	Compare markers		Practical feasibility	impact on morbidity &	Compliance in different settings	
Achievement  Full Partial  Preliminary  Not achieved		Covariates in HC	Criteria for	Combine markers	diagnosed patients	Estimate impact & costs	disability	Compare different protocols	
		Covariates in AD	positivity	Determine testing Interval		Monitor false negatives			

#### Cerebrospinal Fluid Abeta & Tau – Research Priorities

Phase II Clinical Assay Development for Clinical Disease

Develop&implement optimized protocol for standardized pre-analytical handling of CSF samples. Validate **novel fully automated immunoassays**, using Certified Reference Materials (CRM).

SA3 Determine the effects of non-AD brain pathologies on the CSF levels of different variants of Aβ and tau.

SA4 Assess the effects of disease characteristics (stage, genotype, disease onset, clinical manifestation) and other covariates on the levels of CSF biomarkers.

Phase III Prospective Longitudinal Repository Studies

PA2 Define cut off values for all CSF biomarkers (or CSF biomarker ratios) using the optimized protocol for standardized pre-analytical handling of CSF samples. This needs to be done for each new fully automated immunoassay using a suitable reference (e.g. pathology or amyloid PET).

SA2 Determine the optimal combination of different CSF biomarkers for detection of MCI due to AD when using the optimized protocol for standardized pre-analytical handling of CSF samples in combination with novel fully automated immunoassays and Certified Reference Materials (CRM).

SA3 Develop optimal algorithms combining CSF biomarkers with other measures, including MRI and cognitive tests.

SA4 Determine the intra-individual changes of CSF biomarkers over time during prodromal stages of AD when using the optimized protocol for standardized pre-analytical handling of CSF samples in combination with novel fully automated immunoassays and Certified Reference Materials (CRM).

Lancet Neurol, 2017;16:661-676.

#### FDG-PET – Validation Status

#### Development of 18F-FDGPET adapted from the framework of Pepe et al. 2001

Phase 1: Rational for the use of 18F-FDGPET	Phase 2: Discrimination ability of 18F-FDGPET		Phase 3: Detection ability in early phase		Phase 4: 18F-FDGPET accuracy in representative MCI patients		Phase 5: Quantify impact of 18F-FDGPET-based diagnosis on relevant outcomes	
Primary aim	Primary aim	Secondary aims	Primary aims	Secondary aims	Primary aim	Secondary ais	Primary aim	Secondary aims
Potential leads	Identify discrim- ination	Assay definition	Assess capacity of earliest (MCI) detection	Impact of covariates	Assess true/false referral rate in 18F- FDGPET	Detect predictive features	Estimate	Cost/ benefit quantifi- cation
Potential leads	accuracy AD/HC	Ante mortem/ autopsy		Compare markers		Practical feasibility	impact on morbidity &	Compliance in different settings
Achievement  Full Partial  Preliminary  Not achieved		Covariates in HC	Criteria for	Combine markers	diagnosed patients	Estimate impact & costs	disability	Compare different protocols
		Covariates in AD	positivity	Determine testing Interval		Monitor false negatives		

#### FDG-PET – Research Priorities

Phase II Clinical Assay Development for Clinical Disease
SA4 Assess the **effect of covariates** and disease
characteristics (stage, onset of disease, clinical presentation, reserve capacity, comorbidities, genotype) on levels and distribution of cerebral glucose hypometabolism and on normality thresholds.

Phase III Prospective Longitudinal Repository Studies

PA1 Assessment of the accuracy of FDG-PET in prodromal AD detection may need to be re-assessed after completion of SA4, to investigate possibly better performance

PA2 Harmonize reading criteria and determine a standard threshold for hypometabolism; validate the reading procedures for reproducibility

Lancet Neurol, 2017;16:661-676.

#### Biomarkers for LBD – Validation Status

#### Development of 123I-ioflupane SPECT adapted from the framework of Pepe et al. 2001

Phase 1: Rational for the use of 123I-ioflupane SPECT		ase 2: Discrimination ability of 123I-ioflupane SPECT		Phase 3: Detection ability in early phase		Phase 4: 123I-ioflupane SPECT accuracy in representative MCI patients		Phase 5: Quantify impact of 123I-ioflupane SPECT-based diagnosis on relevant outcomes	
Primary aim	Primary aim	Secondary aims	Primary aims	Secondary aims	Primary aim	Secondary ais	Primary aim	Secondary aims	
Potential leads	Identify discrim- ination accuracy AD/HC	Assay definition	Assess capacity of earliest	Impact of covariates	Assess true/false referral rate in 123I- ioflupane	Detect predictive features	Fatimata	Cost/ benefit quantifi-cation	
		Ante mortem/ autopsy	(MCI) detection	Compare markers		Practical feasibility	Estimate impact on morbidity &	Compliance in different settings	
Achievement Full Partial		Covariates in HC	Criteria for	Combine markers	SPECT diagnosed patients	Estimate impact & costs	disability	Compare different protocols	
Prelim- inary achiev	Not	Covariates in AD	positivity	Determine testing Interval		Monitor false negatives			

#### Biomarkers for LBD – Validation Status

#### Development of 123I-MIBG SPECT adapted from the framework of Pepe et al. 2001

Phase 1: Rational for the use of 123I- MIBG SPECT	Phase 2: Discrimination ability of 123I-MIBG SPECT		Phase 3: Detection ability in early phase		Phase 4: 123I-MIBG SPECT accuracy in representative MCI patients		Phase 5: Quantify impact of 123I-MIBG SPECT-based diagnosis on relevant outcomes			
Primary aim	Primary aim	Secondary aims	Primary aims	Secondary aims	Primary aim	Secondary ais	Primary aim	Secondary aims		
Potential leads Potential leads AD/HC	discrim-	Assay definition	Assess capacity of	Impact of covariates	Assess true/false	Detect predictive features	Estimate	Cost/ benefit quantifi- cation		
	accuracy	Ante mortem/ autopsy	earliest (MCI) detection	Compare markers	referral rate in 123I- MIBG	Practical feasibility	Practical impact on feasibility morbidity &	Compliance in different settings		
Achievement Full Partial Preliminary Not applicable		Covariates in HC	Criteria for	Combine markers	SPECT diagnosed patients	Estimate impact & costs	disability	Compare different protocols		
		Covariates in AD	positivity	Determine testing Interval		Monitor false negatives				

#### Biomarkers for LBD – Research Priorities

Phase II Clinical Assay Development for Clinical Disease

SA2 Investigate the relationship between DaT SPECT and the degeneration of the nigrostriatal dopaminergic system postmortem in the same sample.

Phase III Prospective Longitudinal Repository Studies

PA1 Evaluate the capacity of DaT SPECT to **discriminate DLB at the MCI stage**, in samples with availability of reference standard (at least clinical diagnosis at follow up)

PA2 Define criteria for positivity, based on the discrimination ability demonstrated in PA1

SA1 Explore the impact of covariates on the discriminatory abilities of the biomarker in MCI samples, and versus a reference standard (at least diagnosis at follow up)

SA2 Compare the performance of DaT SPECT with AD biomarkers in MCI samples

SA3 Develop an **algorithm** entering DaT SPECT in the diagnostic work-up in optimal combination with other biomarkers. Lancet Neurol, 2017;16:661-676.

#### Discussion

Current state of development and validation of biomarkers for the early and differential diagnosis of Alzheimer's disease. PA: primary aim. SA: secondary aim. Green: fully achieved; yellow: partly achieved; orange: preliminary evidence; red: not achieved; white: not applicable.

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
	PA	PA	SA1	SA2	SA3	SA4	PA1	PA2	SA1	SA2	SA3	SA4	PA	SA1	SA2	SA3	SA4	Studies
MR medial temporal atrophy																		
<sup>18</sup> F-fluorodeoxy-glucose PET																		
<sup>11</sup> C-PIB, <sup>18</sup> F amyloid ligands PET																		
CSF (Aβ42, tau, p-tau)																		
<sup>123</sup> l-ioflupane SPECT																		
<sup>123</sup> I-MIBG SPECT																		

Achievement



Partial

Preliminary



Not Achieved

#### Discussion

- -Gaps → research priorities identified
- -Biomarkers should be used in qualified memory clinics
- -Need of clinical guidelines: available for SINGLE biomarker
- -Patients should be informed about the "research" use of biomarkers
- -Roadmap may be used by researchers and funders



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