IL CERVELLO CHE CAMBIA 7
Sabato 11 novembre 2017
Genova, Aula Magna Clinica Neurologica

# Validation of biomarkers for Alzheimer's disease

Marina Boccardi
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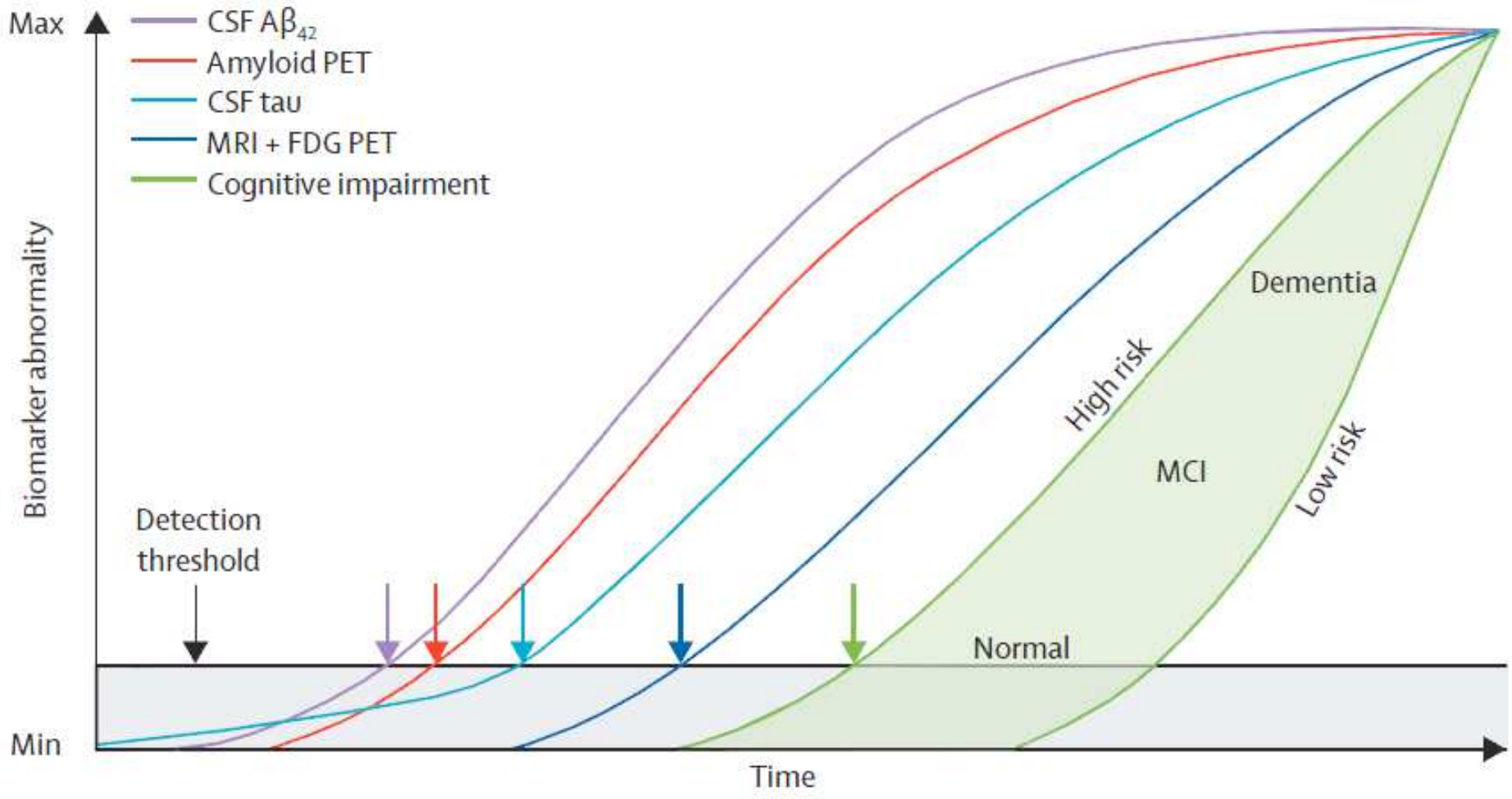
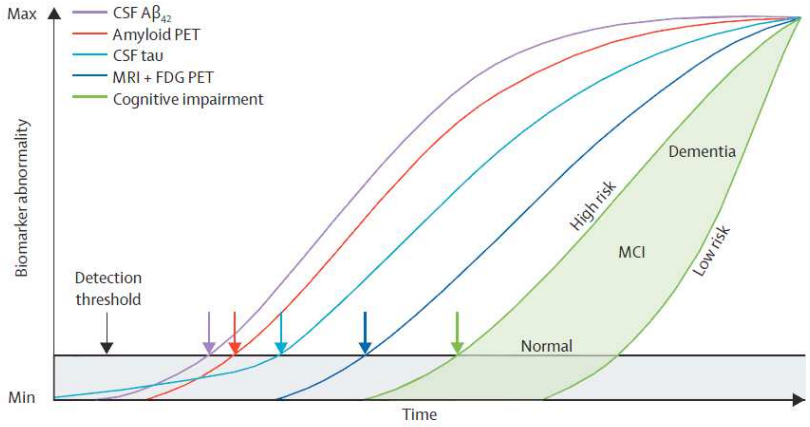



(Jack et al., 2013)

# 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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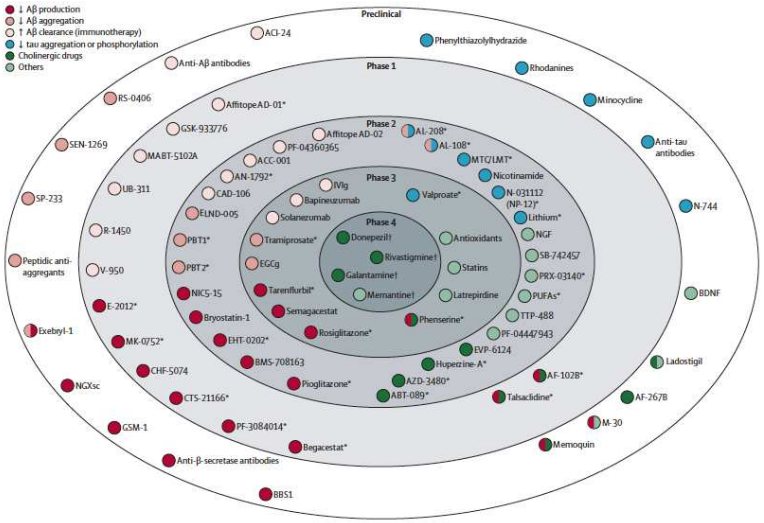


(Mangialasche et al., 2010)

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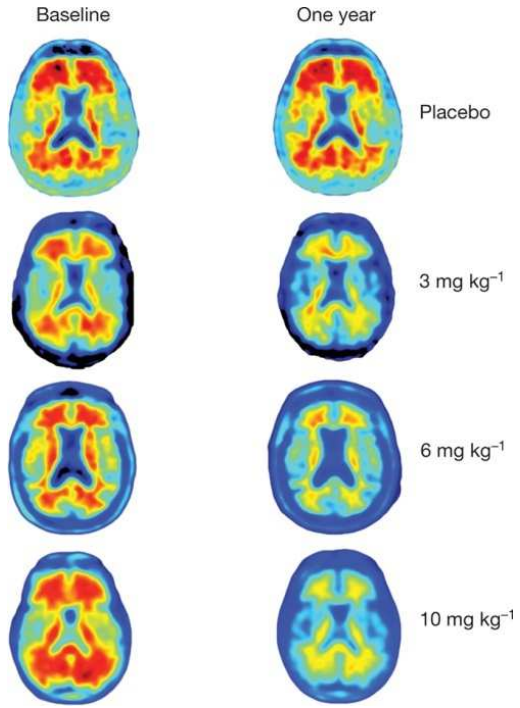
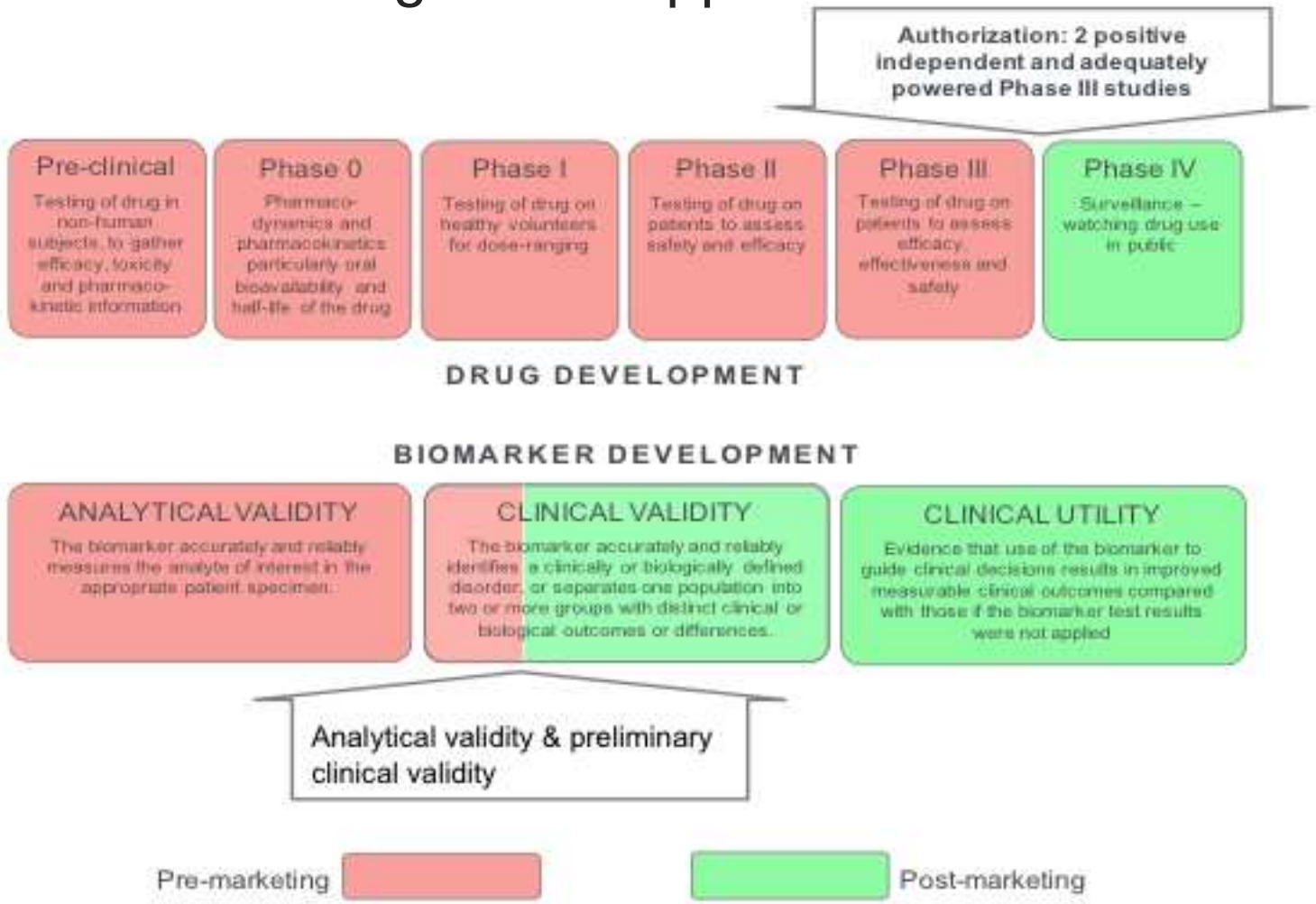



(Sevigny et al, 2016)

# However..

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



# 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)

# 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 gene-expression 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** | To **identify and prioritize leads** for potentially useful biomarkers. |
| **Phase 2** | |
| **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 **optimize procedures for performing the assay** and to assess the reproducibility of the assay within and between laboratories. |
| | To determine the **relationship between biomarker measurements made on tumor tissue** (phase 1) **and** the biomarker measurements made **on the noninvasive clinical specimen** (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 Longitudinal Repository Studies** | To evaluate, as a function of time before clinical diagnosis, the **capacity of the biomarker to detect preclinical disease**. |
| | To define **criteria for a positive screening test** 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 **screening** test in a relevant population by determining the detection rate and the false referral rate. |
| | To describe the characteristics of **tumors** detected by the **screening** test—in particular, with regard to the potential benefit incurred by early detection. |
| | To assess the practical feasibility of implementing the **screening** program and compliance of test-positive subjects with work-up and treatment recommendations. |
| | To make preliminary assessments of the effects of **screening** on costs and mortality associated with **cancer**. |
| | To monitor **tumors** occurring clinically but not detected by the **screening** protocol |

# The oncology framework- Phase V

| | |
|---|---|
| **Phase 5** | |
| **Cancer Control Studies** | to estimate the **reductions in cancer mortality** afforded by the screening test |
| | 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. |

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# The diagnosis of Alzheimer's disease with biomarkers:

## Now despite no cure, or later «only if»?

**International Workshop**

Geneva, Dec 8-9 2014

HUG
Hôpitaux Universitaires de Genève

# 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

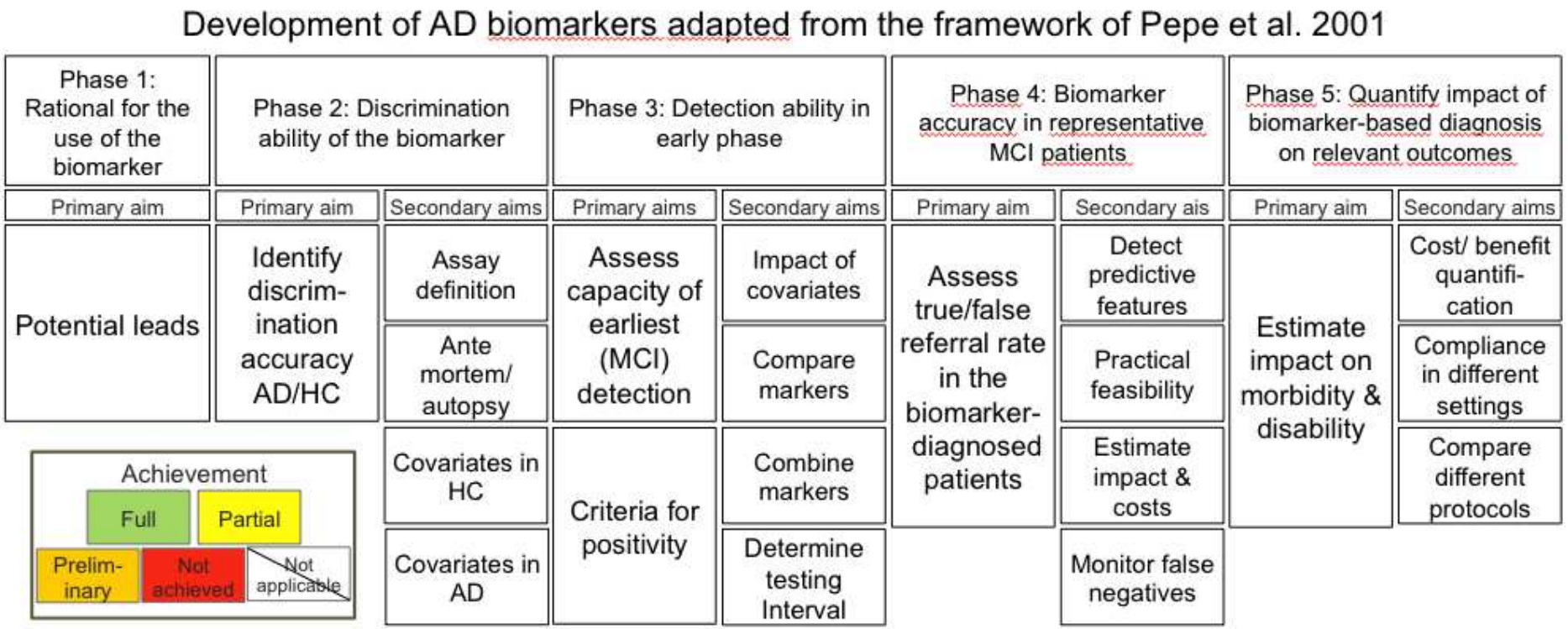
**Nature of the disease**
Insidious onset due to slowly progressive, well-characterized neurodegenerative processes that begin up to many years before the overt clinical onset of AD.

**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 |

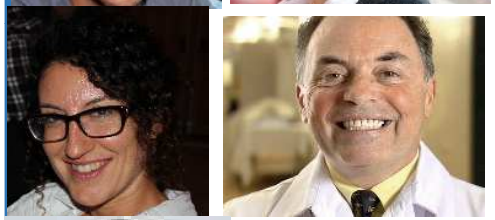
# *Geneva Biomarker Validation Roadmap*



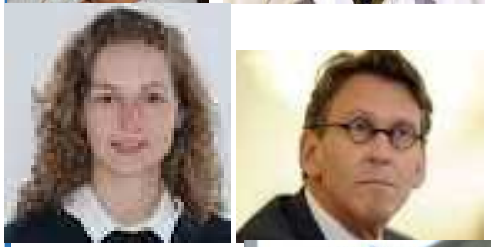
NPS

CSF

Amyloid-PET



FDG-PET



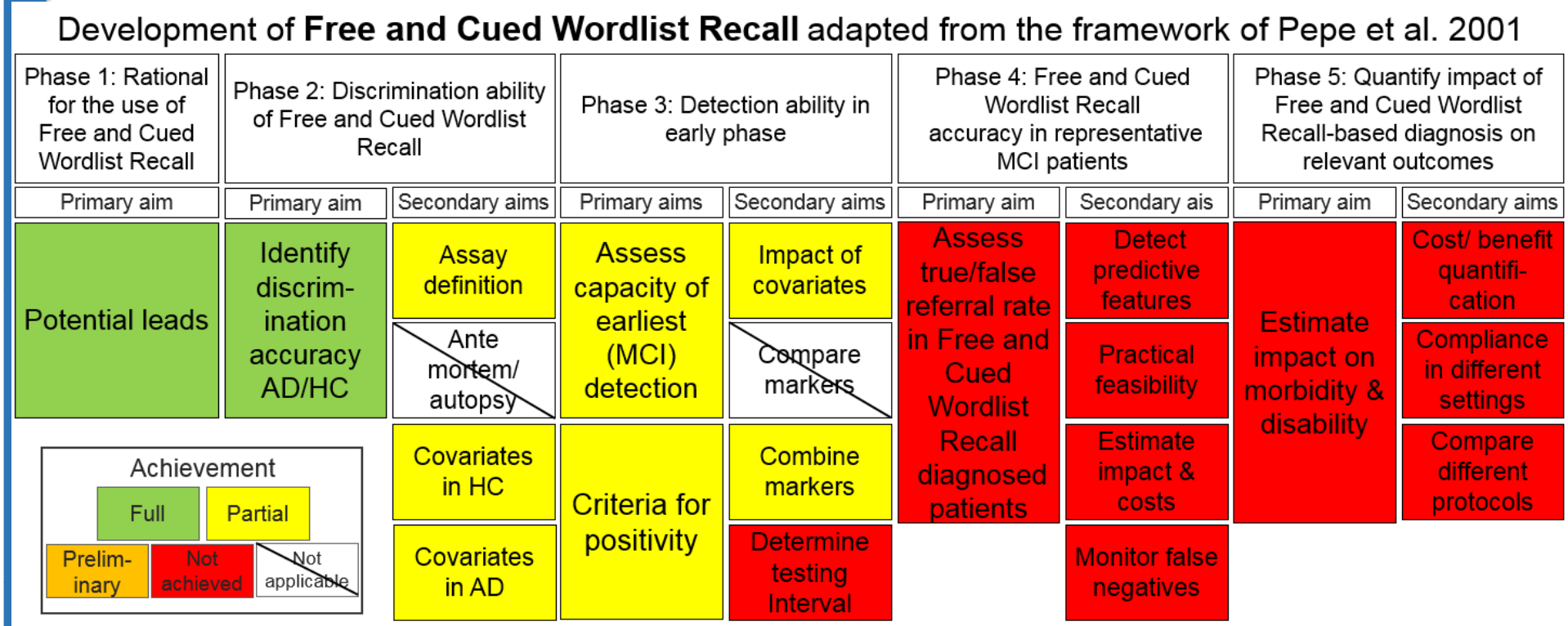
MTA

DA- & NA-ergic imaging

Neurobiol Aging 2017; Issue 52

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

# *Neuropsychology (Gatekeeper) – Validation Status*




Cerami et al., Neurobiology of Aging, 2017

# Neuropsychology (Gatekeeper) - Research Priorities

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

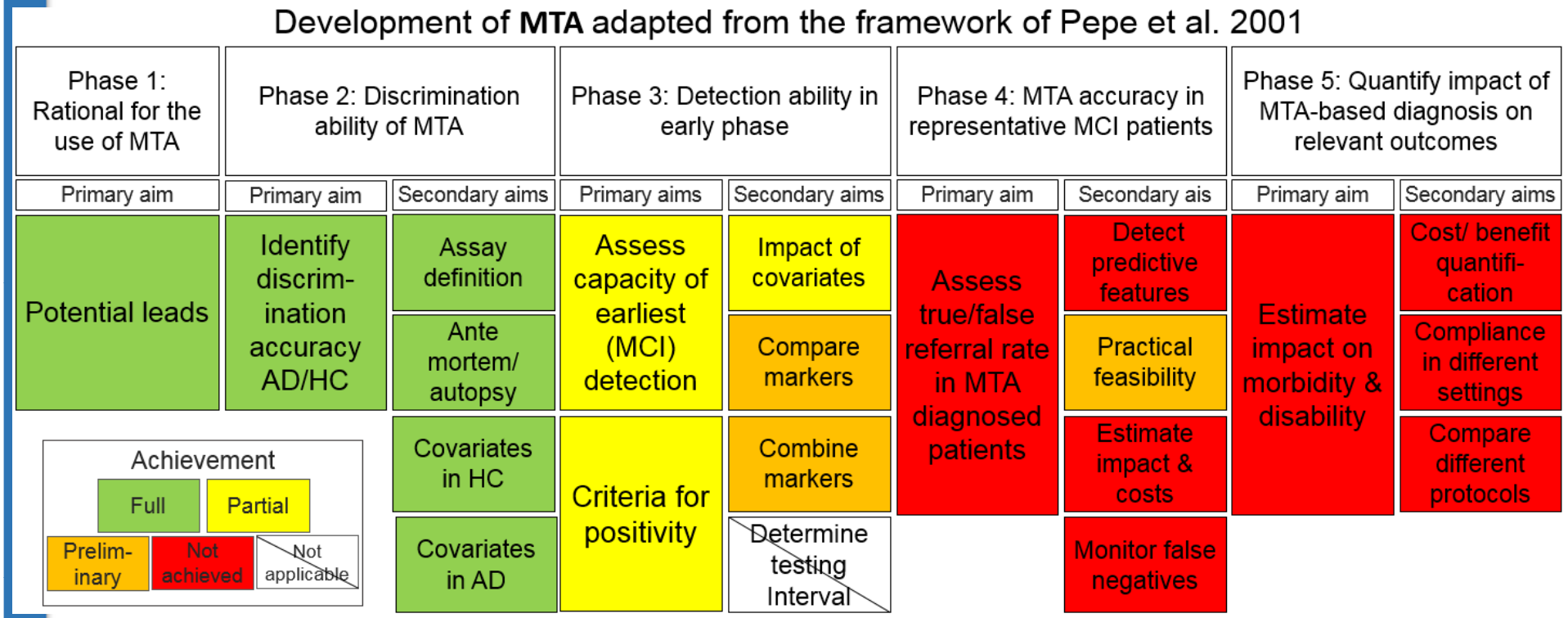
Defining a **consensus delayed recall test with multilingual versions and the relative normative populations**

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*




ten Kate et al., Neurobiology of Aging, 2017

# *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*

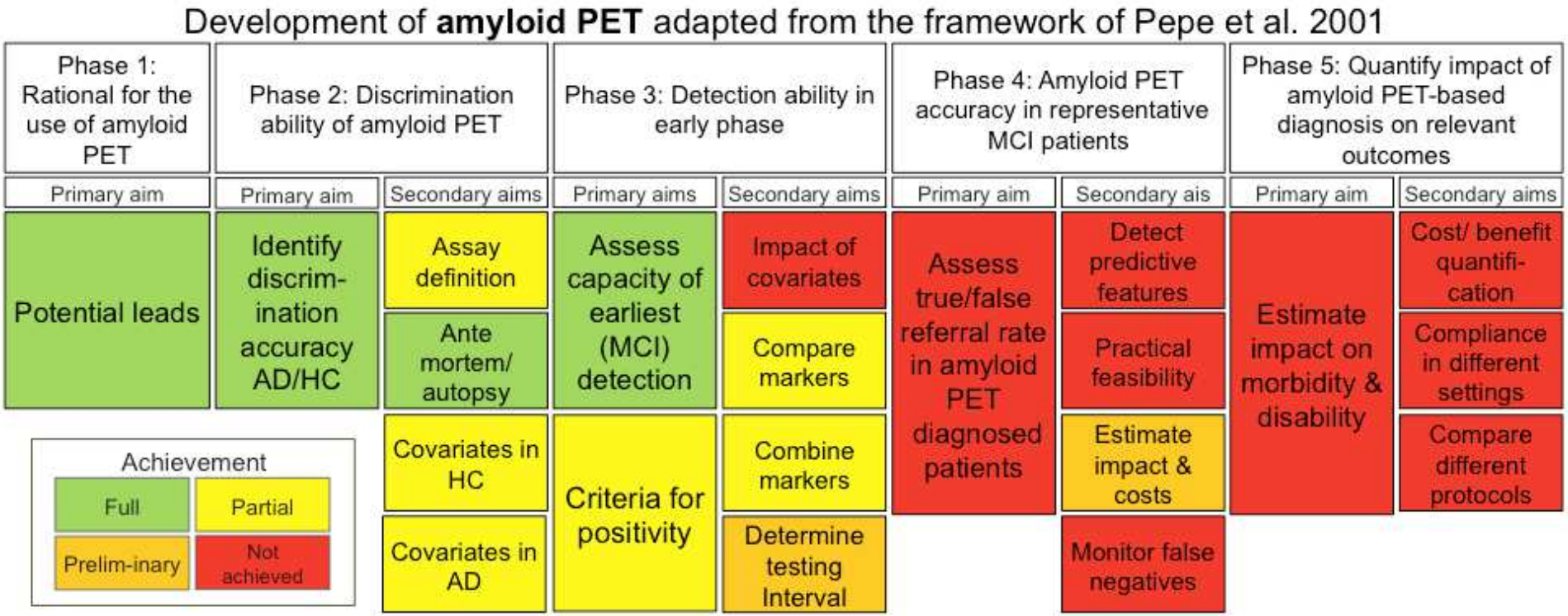
PA1 Assess accuracy of prediction of MCI progression to AD in clinical samples with adequate follow-up

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*




Chiotis et al., Neurobiology of Aging, 2017

# *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

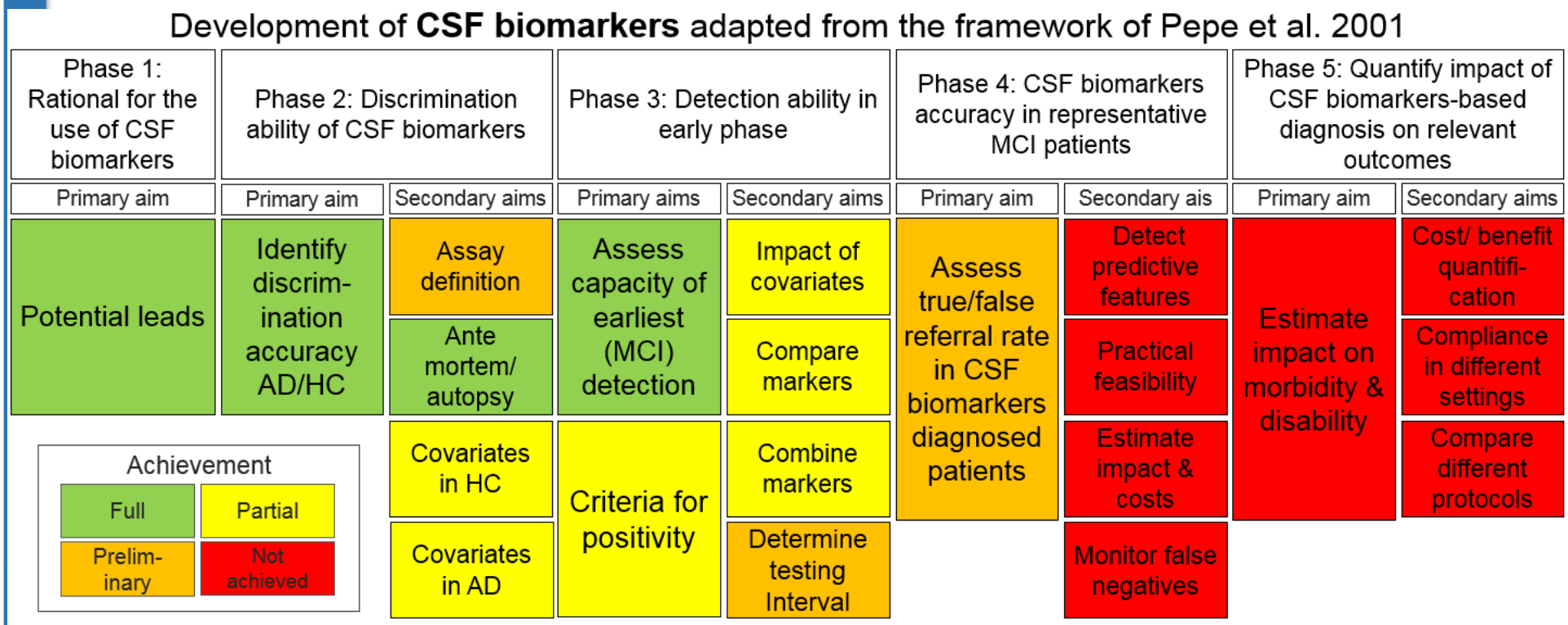
SA2 Compare the predictive performance of amyloid imaging versus other biomarkers (particularly CSF A□42, assessed with the new standard)

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

Lancet Neurol, 2017;16:661-676.

# *Cerebrospinal Fluid Abeta & Tau – Validation Status*




Mattsson et al., Neurobiology of Aging, 2017

# *Cerebrospinal Fluid Abeta & Tau – Research Priorities*

*Phase II Clinical Assay Development for Clinical Disease*

SA1 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).

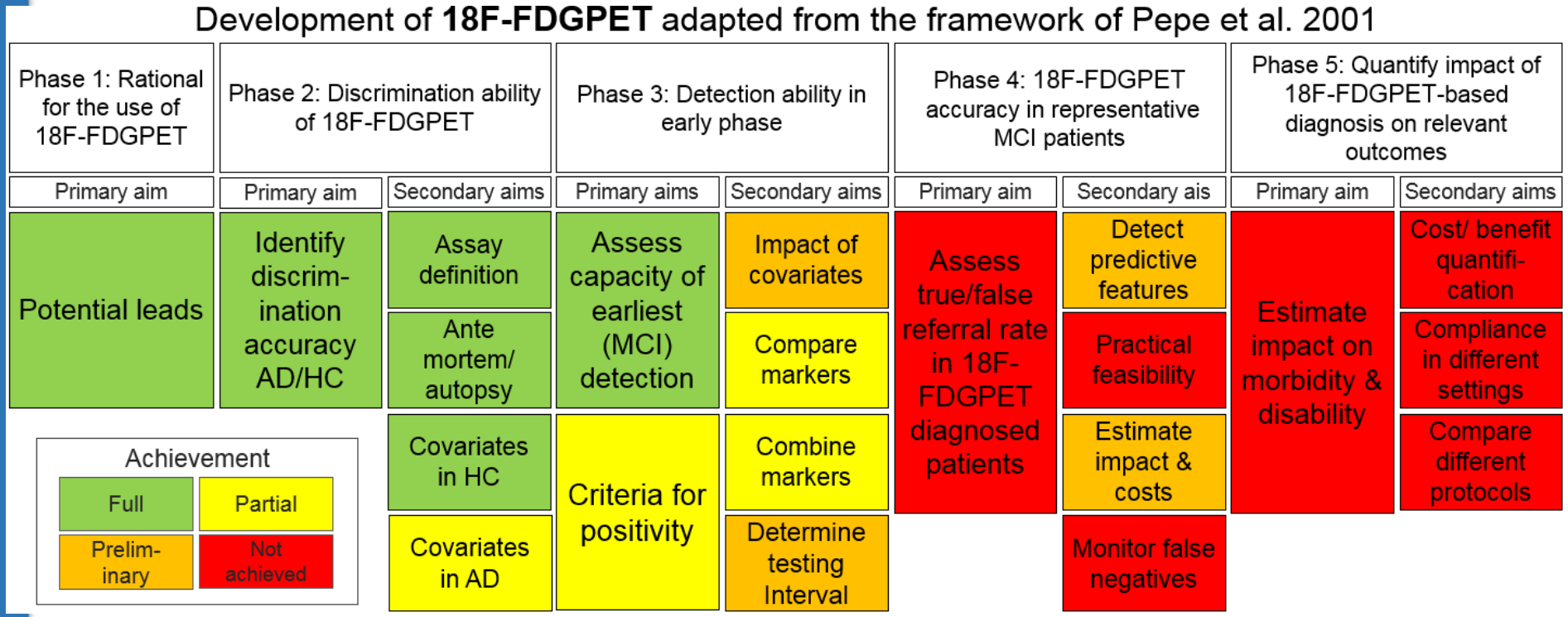
SA2 Determine the optimal combination of different CSF biomarkers for detection of MCI due to AD when using the optimized protocol for standardized pre-analytical handling of CSF samples in combination with novel fully automated immunoassays and Certified Reference Materials (CRM).

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*




Garibotto et al., Neurobiology of Aging, 2017

# *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.

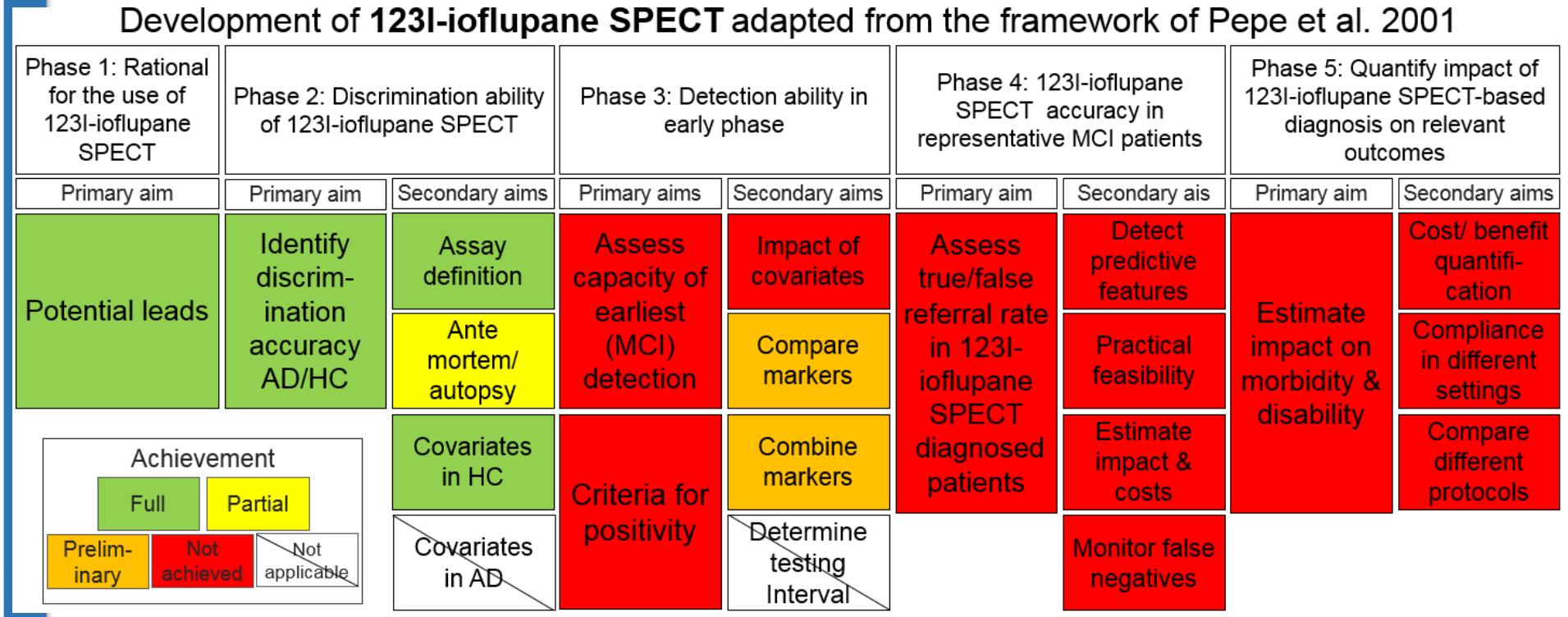
*Phase III* *Prospective Longitudinal Repository Studies*

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

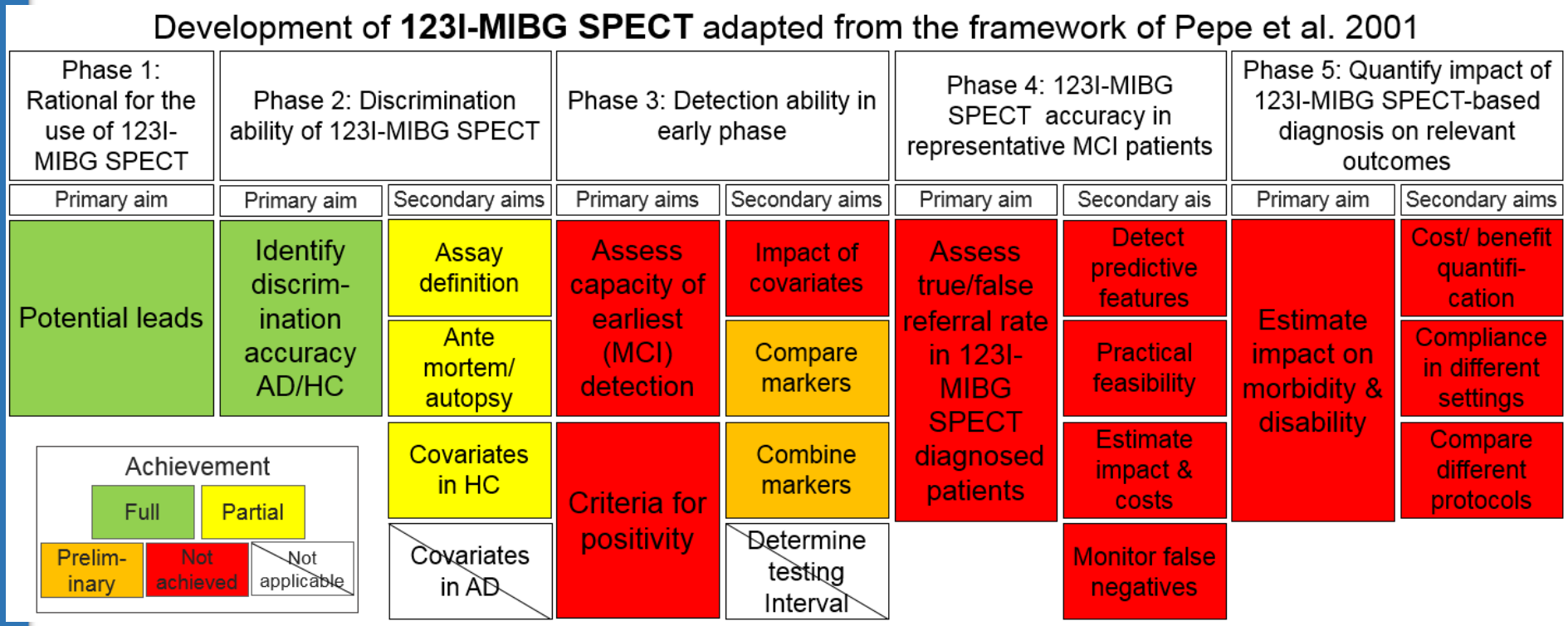
Lancet Neurol, 2017;16:661-676.

# *Biomarkers for LBD – Validation Status*




Sonni et al., Neurobiology of Aging, 2017

# *Biomarkers for LBD – Validation Status*




Sonni et al., Neurobiology of Aging, 2017

# *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 Studies |
| | **PA** | **PA** | **SA1** | **SA2** | **SA3** | **SA4** | **PA1** | **PA2** | **SA1** | **SA2** | **SA3** | **SA4** | **PA** | **SA1** | **SA2** | **SA3** | **SA4** | |
| MR medial temporal atrophy | | | | | | | | | | | | | | | | | | |
| $^{18}$F-fluorodeoxy-glucose PET | | | | | | | | | | | | | | | | | | |
| $^{11}$C-PIB, $^{18}$F amyloid ligands PET | | | | | | | | | | | | | | | | | | |
| CSF (Aβ42, tau, p-tau) | | | | | | | | | | | | | | | | | | |
| $^{123}$I-ioflupane SPECT | | | | | | | | | | | | | | | | | | |
| $^{123}$I-MIBG SPECT | | | | | | | | | | | | | | | | | | |

Achievement — Full — 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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