BfArM
Bundesinstitut für Arzneimittel und Medizinprodukte

What is required to accept a biomarker as primary outcome measure – an EU regulatory perspective

Dr. Karl Broich

Deputy Head of Agency

Federal Institute for Drugs and Medical Devices (BfArM)

Kurt-Georg-Kiesinger-Allee 38, D-53175 Bonn

Germany

Co-Chair, CNS-WP at EMA, London, UK

BfArM

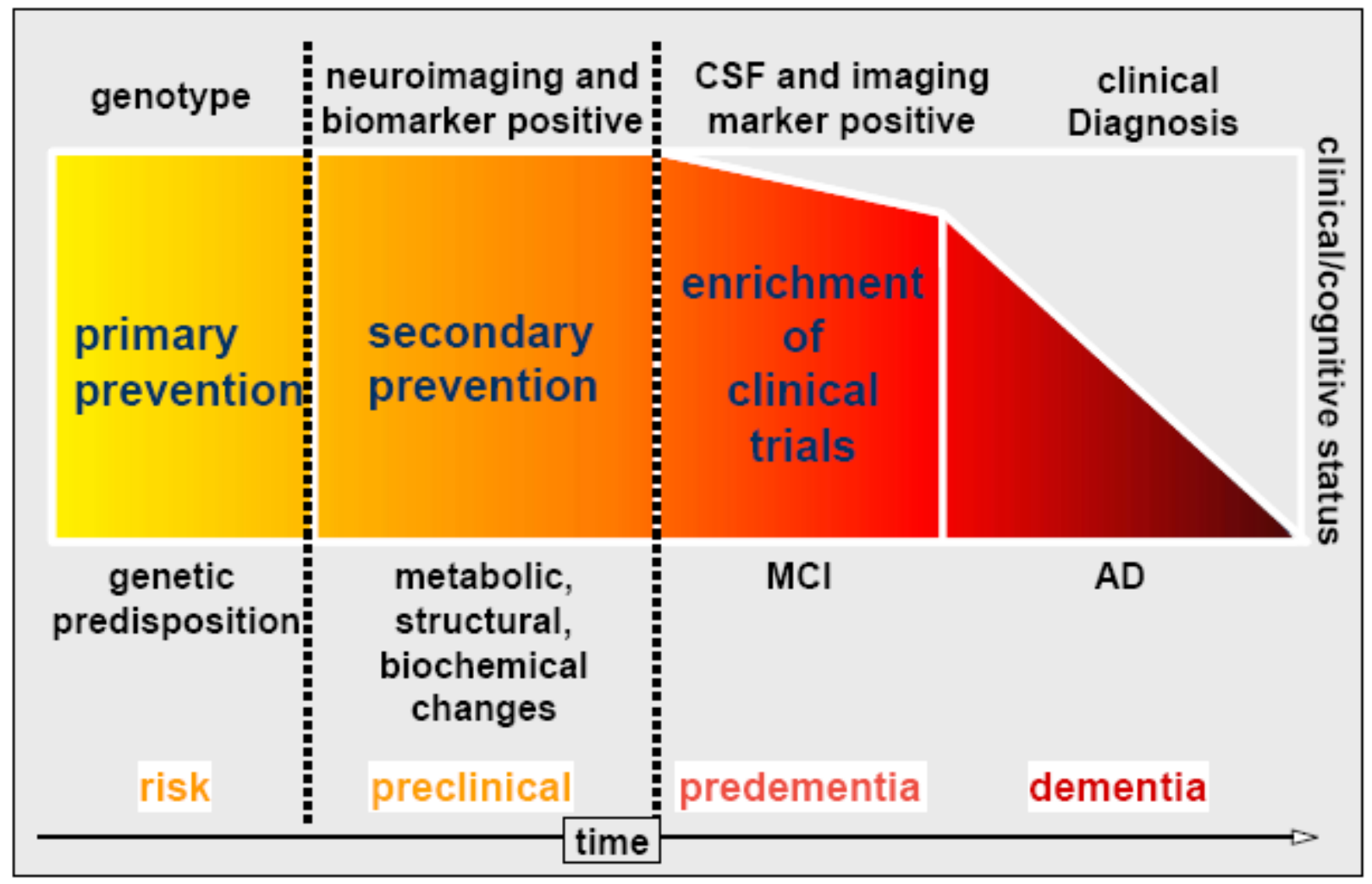
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

ISCTM Meeting, Washington,DC; Feb. 2011

Disclaimer

- **Personal views are presented**
- **Expressions cannot be regarded as official positions of EMEA or BfArM**
- **Based on NfG on development of medicinal products for the treatment of Alzheimer‘s Disease and other dementias**
- **Based on NfG on the qualification of new methodologies published for consultation EMEA/CHMP/SAWP/72894/ 2008**

How early is early?



ISCTM Meeting, Washington,DC; Feb. 2011

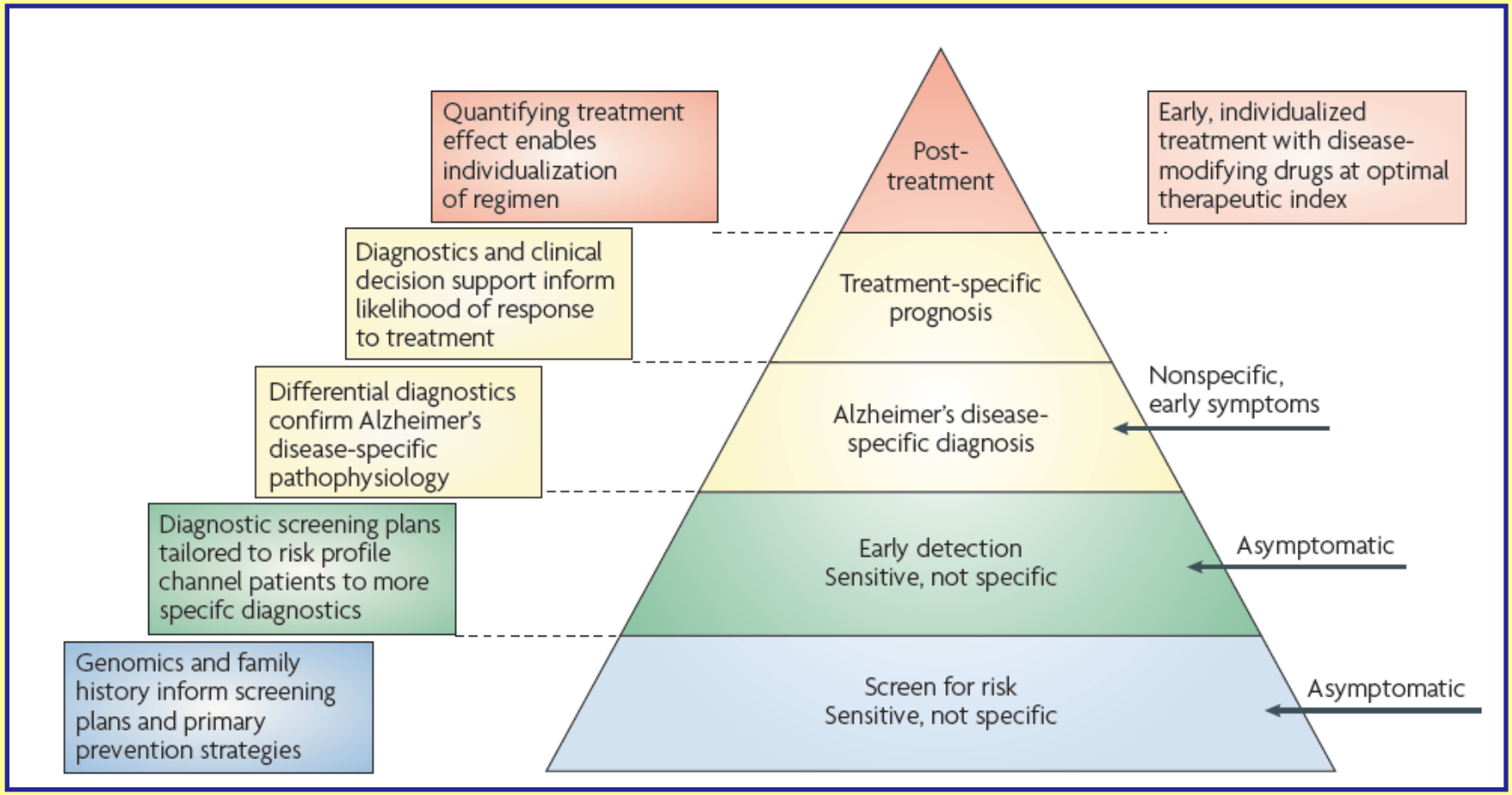
Issues with Trials in Early Phases

- **Clinical Endpoints of interest may be difficult to use**
  - **Long follow-up measurement**
  - **Expensive measurements**
  - **Rare events**
  - **High drop-out rates**
  - **…..**

Biomarkers the way out?

- **Surrogate (replacement) Endpoint**
  - **Easier/quicker to measure**
  - **Reduce trial duration, size and expenditures**
  - **Should be measured accurately and reproducible**
  - **Change in proportion to what it represents**

Biomarkers in DAT



From: Hampel H, Frank R, Broich K et al. NRDD, 2010, 9: 560-574

Biomarkers can be used as tools to

- Understand the biology of a disease
- Understand the effects of medicinal products
- Provide information on sub-populations of patients that might respond to treatment or be susceptible to side effects (individualized medicine)
- Developing better diagnostics and medicinal products
- Improve methodology of clinical trials

How to validate a „Surrogate Endpoint“

Bucher HC et al., JAMA (1999) 282, 771-778

(1) **Plausible connection between basic science and clinical trials**

(2) **Is there a strong, independent, consistent association between surrogate endpoint and clinical outcome (necessary, not sufficient)**

(3) **Evidence from randomized trials that improvements in the surrogate endpoint leads consistently to improvement of the target outcome**

(4) **Large, precise, and lasting treatment effects**

(5) **Are the likely benefits worth the potential harms and costs**

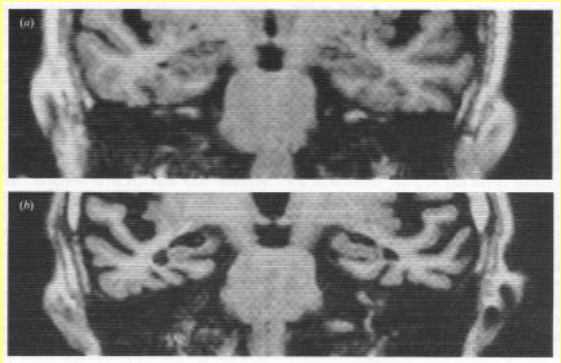
Examples of Proposed Surrogate Endpoints

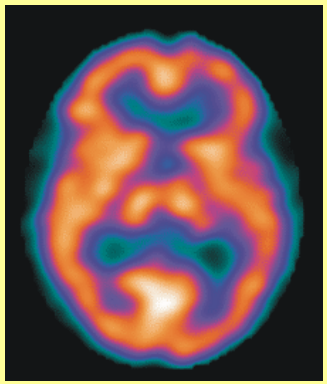
Surrogate Endpoint	Clinical Outcome
Serum Lipid Levels ↓	Cardiovascular Mortality ↓
Blood pressure ↓	Cardiovascular Mortality ↓
Tumor volume ↓	Survivalrate/-time ↑
Bone Mineral Density ↑	Fracture rate ↓
CD4 cell count ↑	Mortality ↓
Intraocular pressure ↓	Risk of Glaucoma ↓
Class 1C Antiarrhythmics VES after Myocardial Inf.	Cardiovascular Mortality ↑
Vaccine Trial AN 1792: MR	Brain Atrophy ↑

ISCTM Meeting, Washington,DC; Feb. 2011

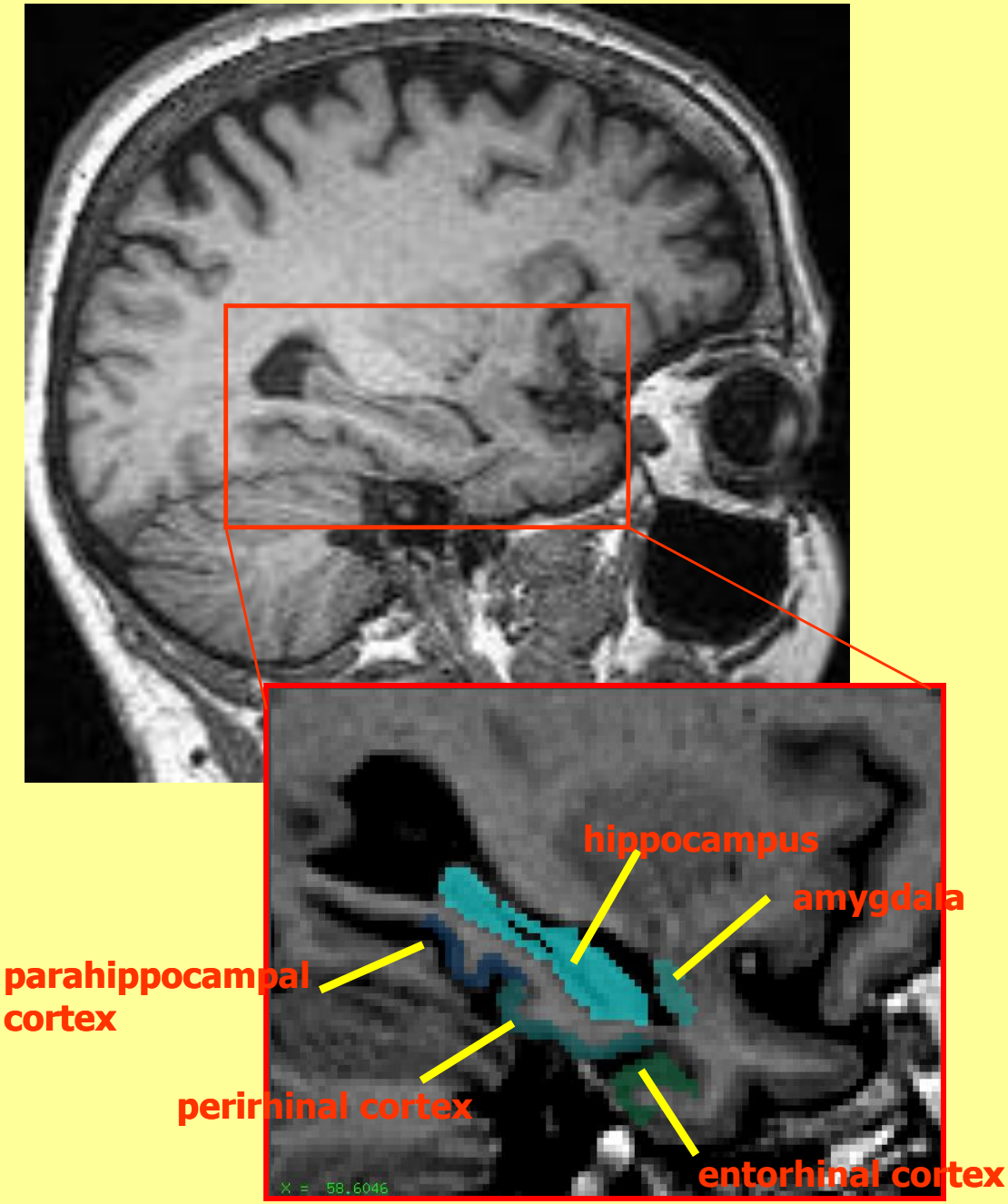
Surrogate Endpoints: Neuroimaging

- Structural MRI
  - Hippocampus
  - Entorhinal cortex
- Functional Imaging
  - PET/SPECT
  - MRS
  - fMRI

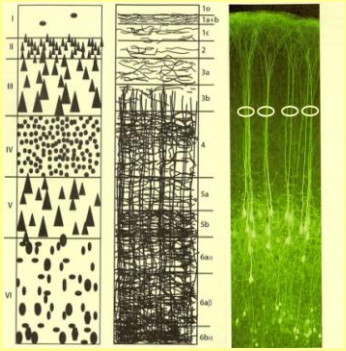


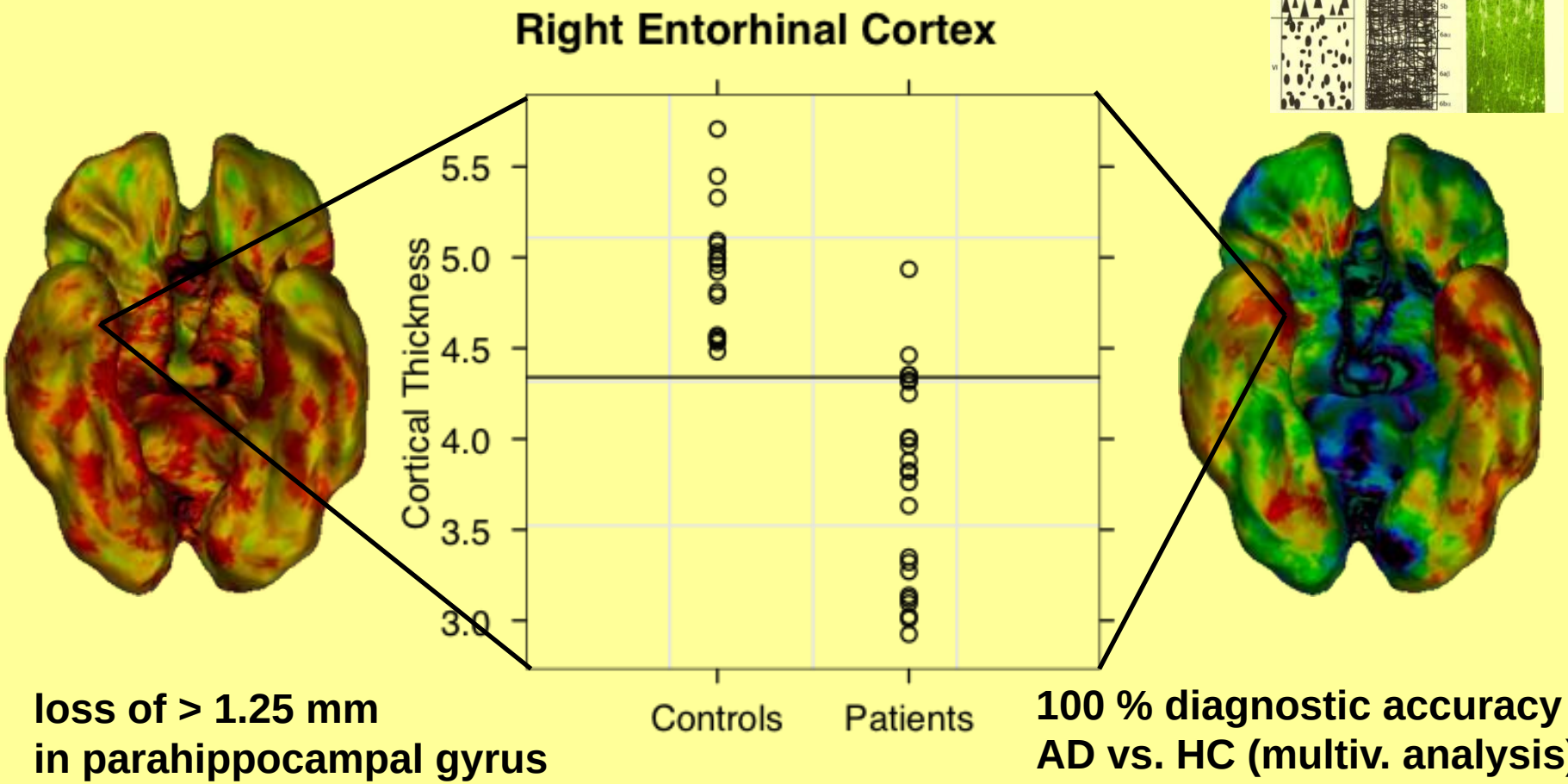


- Links need to be established:
  - Imaging tool and desired clinical outcome
  - Imaging tool and disease modification


hippocampus
amygdala
parahippocampal
cortex
perirhinal cortex
entorhinal cortex
X = 58.6046

Quantitative analysis of cortical thickness in MCI





loss of > 1.25 mm in parahippocampal gyrus

100 % diagnostic accuracy AD vs. HC (multiv. analysis)

Lerch et al. (2005) Cerebral Cortex; Lerch et al. (2007) Neurobiol Aging

Imaging of Amyloid Load by PET

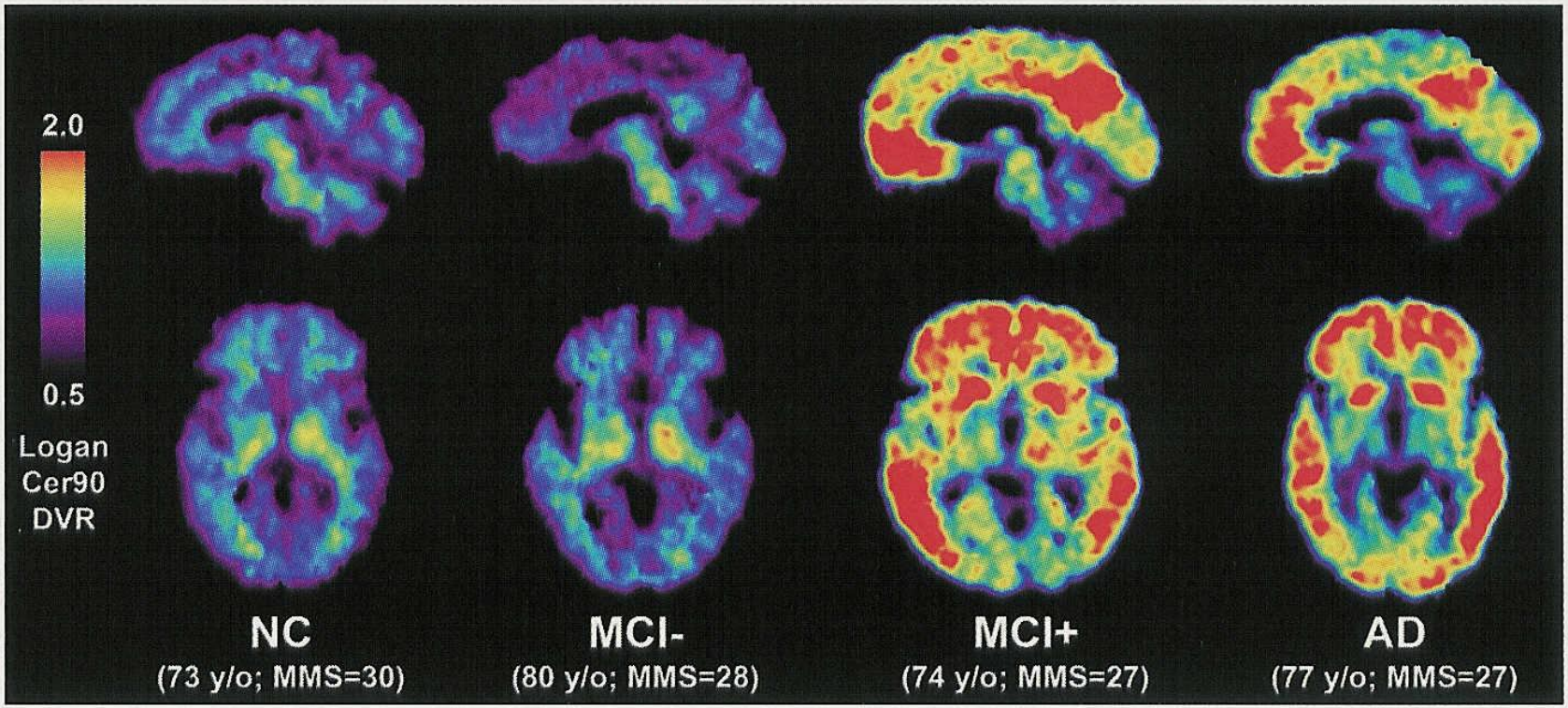


Figure 1 PET images produced using Pittsburgh Compound-B (PIB) shown in sagittal (top) and transaxial (bottom) views. Shown from left to right are a cognitively normal control (NC), an MCI subject with no evidence of amyloid deposition (MCI–), an MCI subject with heavy amyloid deposition (MCI+), and a case with mild Alzheimer disease (AD). *Courtesy University of Pittsburgh Amyloid Imaging Group.*

from: Blennow & Zetterberg:, Nature Medicine 2006, 12, 753-754

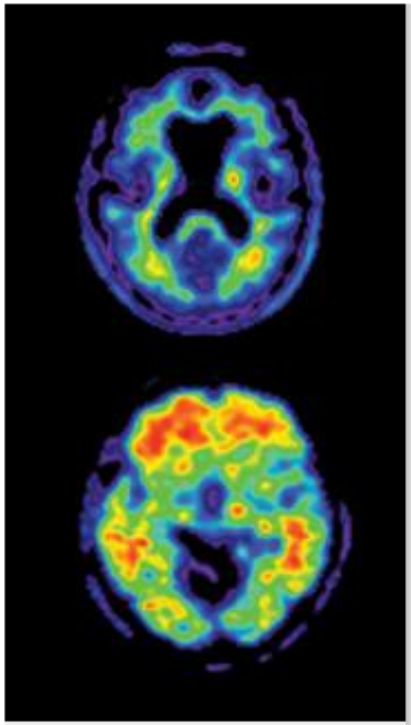
Alzheimer's-disease probe nears approval

Imaging technique could help to resolve questions about brain plaques associated with the condition.

Heidi Ledford

An imaging agent that reveals a signature of Alzheimer's disease in the brain — given conditional support last week by advisers to the US Food and Drug Administration (FDA) — is likely to be more valuable to scientists than to patients.

The agent, called florbetapir (Amyvid), enables physicians to determine whether Alzheimer's disease is the cause of a patient's dementia. In the future, it may also help them to catch the disease before obvious symptoms appear, a hope that has sparked fresh debate about the value of early diagnosis for a devastating, untreatable disease. The panel of advisers — whose guidance is usually, but not always, followed by the FDA — also stated that the test should not be given final approval until its developers demonstrate that clinicians can uniformly interpret its results.



Florbetapir reveals amyloid plaque build-up (red) in the brain of someone with Alzheimer's disease (bottom), which is absent in a healthy brain (top).

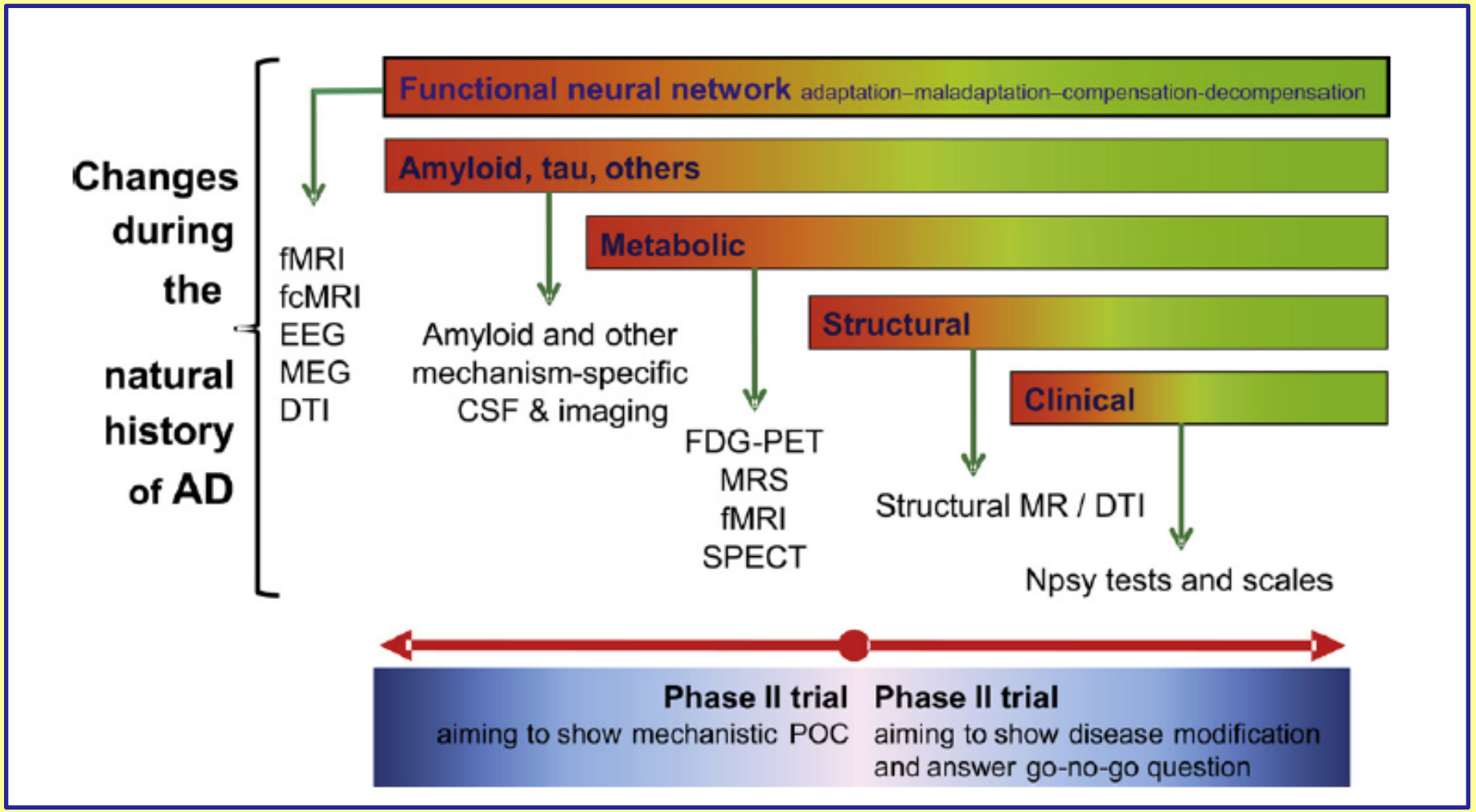
nature news

Published online 25 January 2011 |

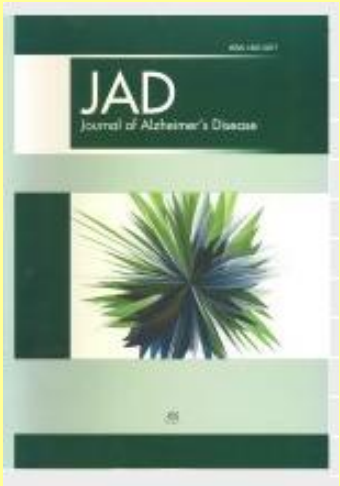
***Nature* 469**, 458 (2011)

ISCTM Meeting, Washington,DC; Feb. 2011

Imaging Markers in Phase II Trials



From: Hampel et al. Progress in Neurobiol. 2011 in press



CSF-Biomarkers as Predictors for Conversion from Mild Cognitive Impairment to Alzheimer-Type Dementia: *Implications for Trial Design*

Authors

Ineke A. van Rossum[1], Stephanie Vos[2], Ron Handels[2], Pieter Jelle Visser[1, 2]

[1]Alzheimer Centre, Department of Neurology, VU University Medical Centre, Amsterdam, The Netherlands
[2]Alzheimer Centre, School for Mental Health and Neuroscience (MHeNS), University Medical Centre, Maastricht, The Netherlands

Abstract

Disease modifying drugs for Alzheimer's disease (AD) are likely to be most effective when given in non-demented subjects. In this review we summarized biomarkers in cerebrospinal fluid (CSF) and blood that can predict AD-type dementia in subjects with mild cognitive impairment (MCI). In addition, we investigated whether these markers could reduce sample size and costs if used to select subjects for trials on the prevention of AD in subjects with MCI. A meta-analysis of markers that had been investigated in multiple studies showed that the combination of amyloid-β ($A\beta_{1-42}$ and tau in CSF had the best predictive accuracy for AD (odds ratio (OR) 18.1, 95% confidence interval (CI) 9.6–32.4). $A\beta_{1-42}$, total tau, and phosphorylated tau in CSF also predicted conversion, but with lower accuracy (OR 7.5 to 8.1). Plasma levels of $A\beta_{1-40}$, $A\beta_{1-42}$, the ratio $A\beta_{1-42}/A\beta_{1-40}$ and homocysteine did not predict outcome. In a fictive trial design, the use of the combination of $A\beta_{1-42}$ and tau in CSF in the selection of subjects could reduce sample size by 67% and trial costs by 60% compared to a trial in which unselected subjects with MCI would be enrolled. In conclusion, the combination of $A\beta_{1-42}$ and tau in CSF is useful to select subjects for trials that aim to slow down the progression from MCI to AD-type dementia.

Keywords

Alzheimer's disease, biomarkers, blood, cerebrospinal fluid, cost-benefit, decision analysis, mild cognitive impairment

ISCTM Meeting, Washington,DC; Feb. 2011

Regulatory view: still no sufficiently validated surrogates for phase III pivotal studies in patients with Alzheimer's disease available!

- **Cerebrospinal fluid markers (e.g. phospho-τ ⬆ and β-Amyloid I-42 ⬇)**
  - helpful as trait markers with high sensitivity and specificity
  - yet no value as state markers
- **Brain imaging (e.g. MRI of medial temporal lobe)**
  - helpful as trait markers for enrichment of populations at risk
  - serial MRI helpful as state marker
  - can be used as endpoint in dose finding
  - proof of concept studies
  - as secondary endpoint in pivotal studies
- **Brain imaging (e.g. PET-amyloid imaging or regional glucose metabolism)**
  - helpful as trait marker
  - yet no value as state marker

„Disease Modification“

For regulatory purposes a disease modifying effect will be considered when the pharmacologic treatment **delays the underlying pathological or pathophysiological disease processes and when this is accompanied by an improvement of clinical signs and symptoms of the dementing condition**. Consequently a true disease modifying effect cannot be established solely based on clinical outcome data, such a clinical effect must be accompanied by strong supportive evidence from a biomarker programme.

ISCTM Meeting, Washington,DC; Feb. 2011

„Two step approach“

If in a **first step delay in the natural course of progression of the disease based on clinical signs and symptoms** of the dementing condition can be established, this may be acceptable for a limited claim, e.g. delay of disability. If these results are supported by a **convincing package of biological and/or neuroimaging data**, e.g. showing delay in the progression of brain atrophy, a full claim for disease modification could be considered.

Early Involvement of SAWP at EMA – What will be offered?

- **CHMP Qualification Opinion** on the acceptability of a specific use of the proposed method (e.g. use of a biomarker) in a research and development (R&D) context (non-clinical or clinical studies), based on the assessment of submitted data.

- **CHMP Qualification Advice on future protocols and methods for further method development towards qualification**, based on the evaluation of the scientific rationale and on preliminary data submitted.