BfArM
Bundesinstitut für Arzneimittel und Medizinprodukte

Prodromal Alzheimer's Disease- EU Regulatory Point of View

Dr. Karl Broich

Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM)
Kurt-Georg-Kiesinger-Allee 38, D-53175 Bonn
Germany

EWP – CNS Drafting Group

ISCTM Winter Meeting, Washington, Feb. 2010.

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

Revision of the NfG „AD and other dementias“

- addresses different types of dementia
- differences in severity
  - MCI/preclinical/prodromal/very mild DAT
  - mild
  - moderate
  - severe
- disease modification
- discussion on biomarkers for diagnostic purposes and as surrogate endpoints
- discussion on adequate study designs

Possible Cornerstones in the Treatment of Patients with Dementia

- **NfG on Medicinal Products for Treatment of Alzheimer‘s Disease**
  - **Symptomatic Improvement**
  - **Slowing or arrest of progression**
  - **Primary prevention**

NEW: http://www.emea.europa.eu

Alzheimer's Disease: Efficacy (Symptomatic Improvement)

- 2 primary Endpoints
  - mandatory: **cognitive** domain
    functional domain
  - both endpoints should show significant differences
- Response criteria for clinical relevance:
  proportion of patients with meaningful benefit ?
- Duration of treatment: at least 6 months
- secondary endpoints
  - global domain
  - additional symptoms

Revision of Diagnostic Criteria

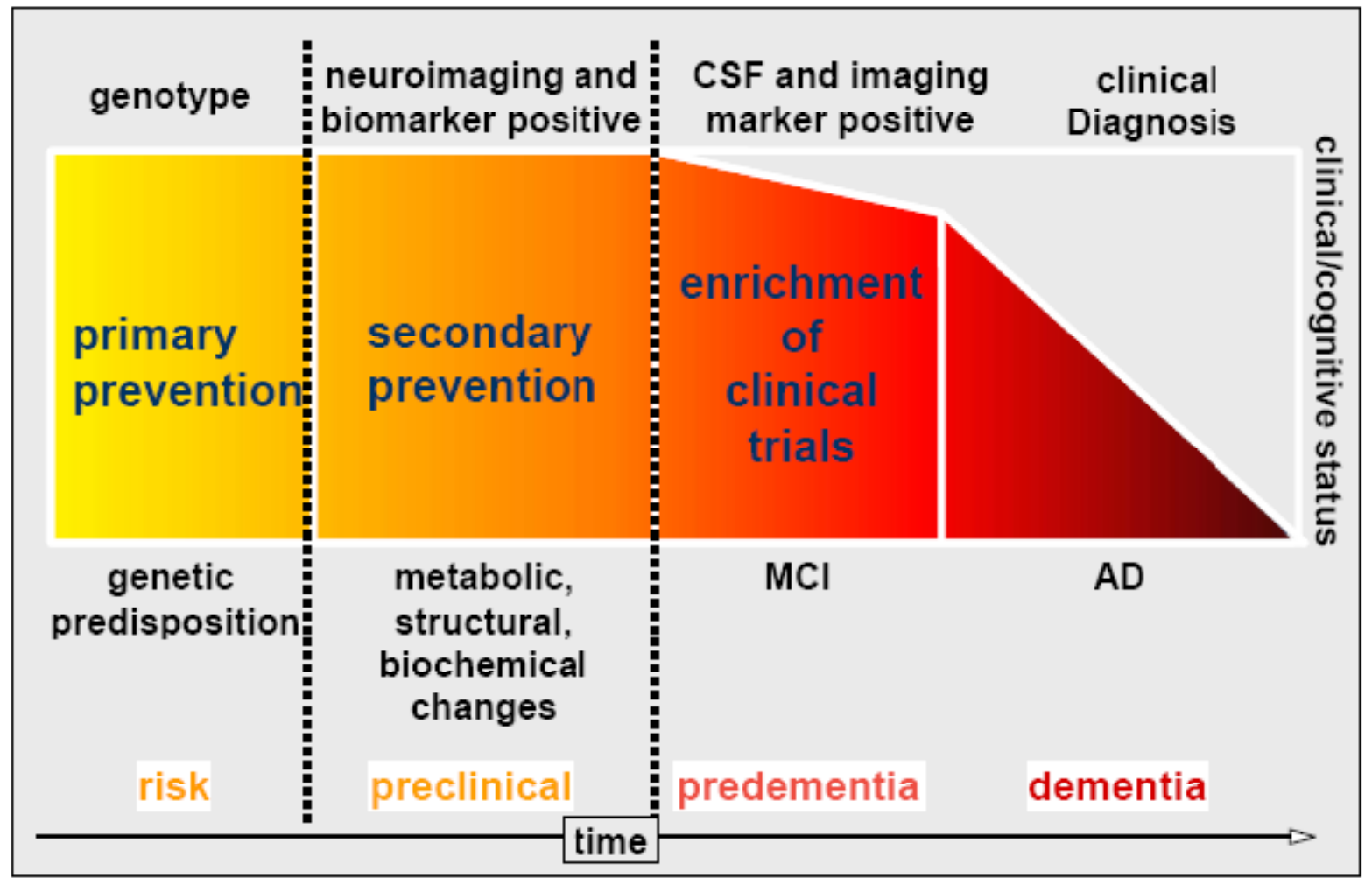
Dubois B, Feldman HH, Jucova C et al. 2007

- **Core diagnostic Criterion:**
  Early and significant episodic memory impairment

- **At least one supportive criterion of**
  - **MTL atrophy shown with MRI**
  - **Abnormal CSF (amyloid-ß, tau, phospho-tau)**
  - **Specific pattern shown with PET**
  - **Proven DAT mutation**

- **Validation studies necessary !!!**

How early is early?

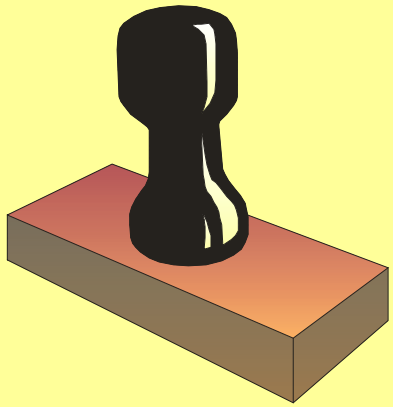


From: Hampel & Broich 2009

„Ideal Medicinal Product“

- *Efficacious* in clinical trials, generalisable to the community
- *Safe* (*acceptable side effect profile* without serious risk)

- Approval in case of positive benefit-risk assessment



Alzheimer's Disease: Efficacy (Disease Modification)

- 2 primary Endpoints
  - mandatory: **cognitive** domain
    functional domain
  - both endpoints should show significant differences
- Response criteria for clinical relevance: proportion of patients with meaningful benefit ?
- Duration of treatment: 18 months (?)
- secondary endpoints
  - global domain
  - Biomarkers
    - **e.g. serial volumetric MRI**
    - **e.g. Amyloid-Imaging**
  - Quality of Life
  - additional symptoms

„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 Winter Meeting, Washington, Feb. 2010.

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 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

ISCTM Winter Meeting, Washington, Feb. 2010.

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 Winter Meeting, Washington, Feb. 2010.

Amyloid Hypothesis

Changes in Aβ metabolism

↓

Oligomerization of Aβ42 and initial (diffuse) Aβ42 deposits

↓

Inflammatory responses and Aβ plaque formation

↓

Progressive synaptic/neuronal injury

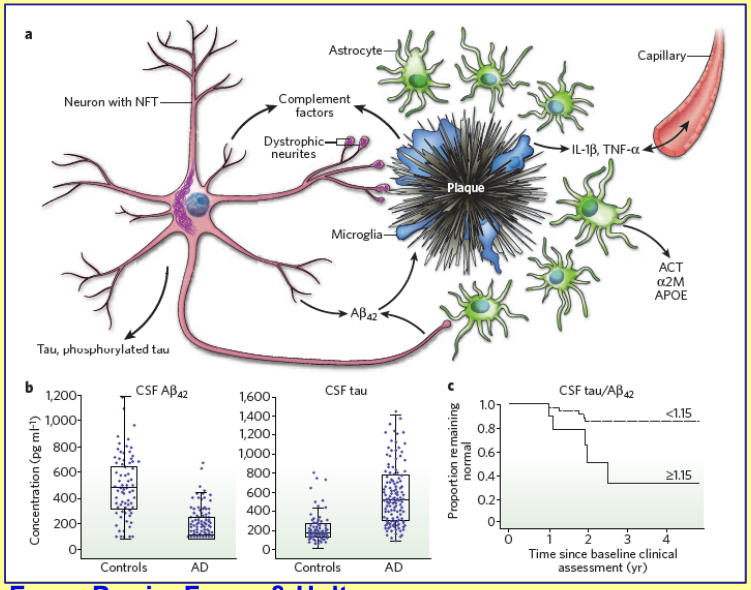
↓

Aberrant oligomerization and Hyperphosphorylation of tau

↓

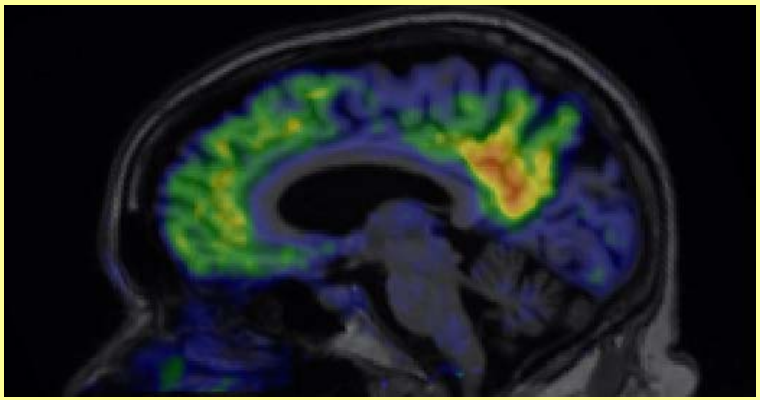
Dementia with plaque and tangle morphology

Modified from: Haass 2007



From: Perrin, Fagen & Holtzman

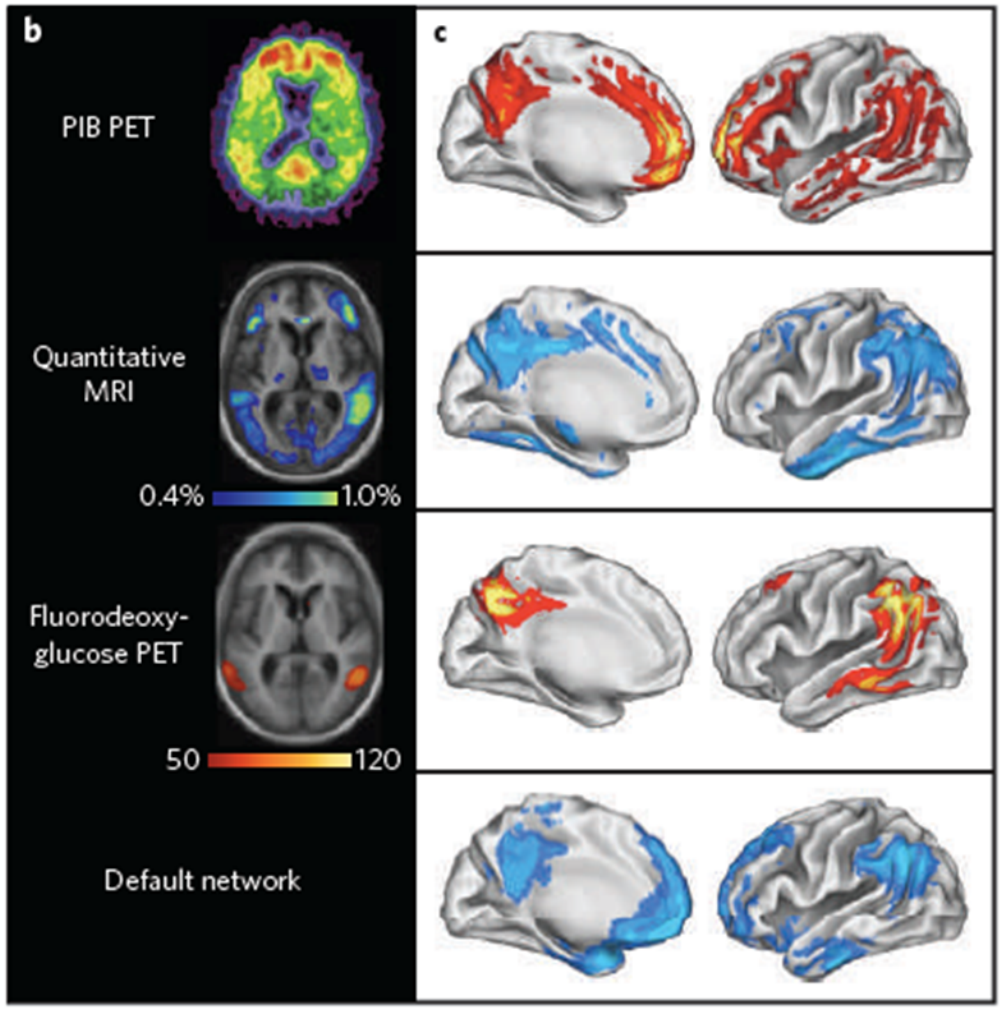
NATURE|Vol 461|15 October 2009|doi:10.1038/nature08538



Amyloid - Imaging

ISCTM Winter Meeting, Washington, Feb. 2010.

One or combination ?



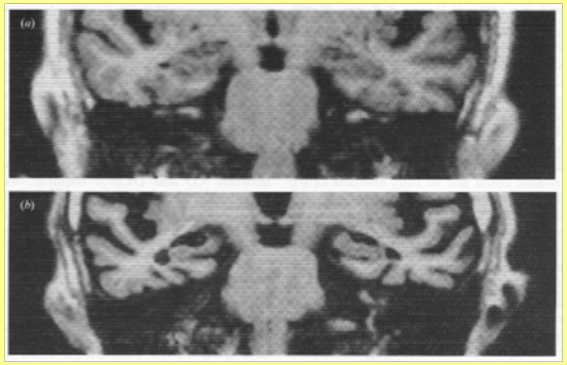
Specificity
Sensitivity
Predictive Values

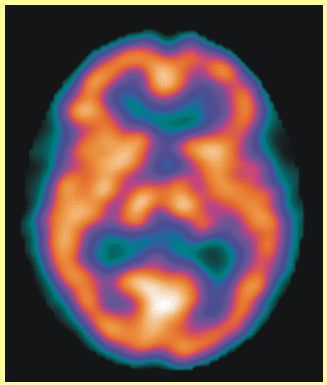
From: Perrin, Fagen & Holtzman

NATURE|Vol 461|15 October 2009|doi:10.1038/nature08538

Surrogate Endpoints: Neuroimaging

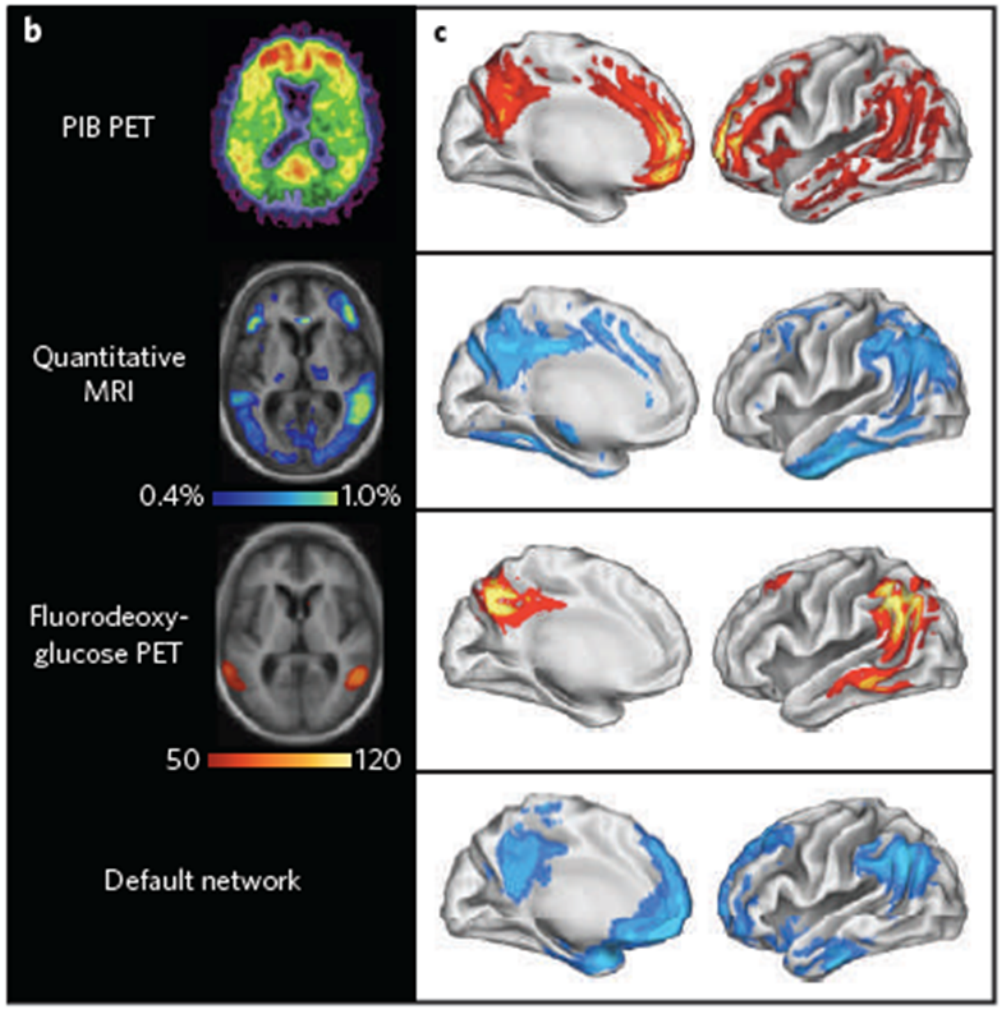
- Structural MRI
  - Hippocampus
  - Entorhinal cortex
- Functional Imaging
  - PET/SPECT
  - MRS
  - fMRI





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

Possible Surrogate Marker?



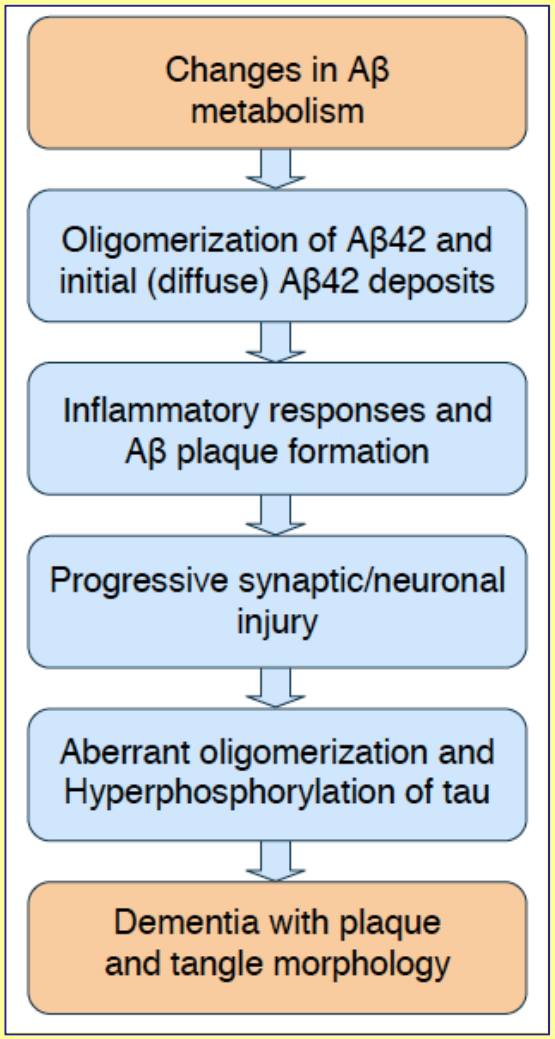
Sensitivity to change

Relation to / prediction of clinical outcome

From: Perrin, Fagen & Holtzman

NATURE|Vol 461|15 October 2009|doi:10.1038/nature08538

Amyloid Hypothesis



Modified from: Haass 2007

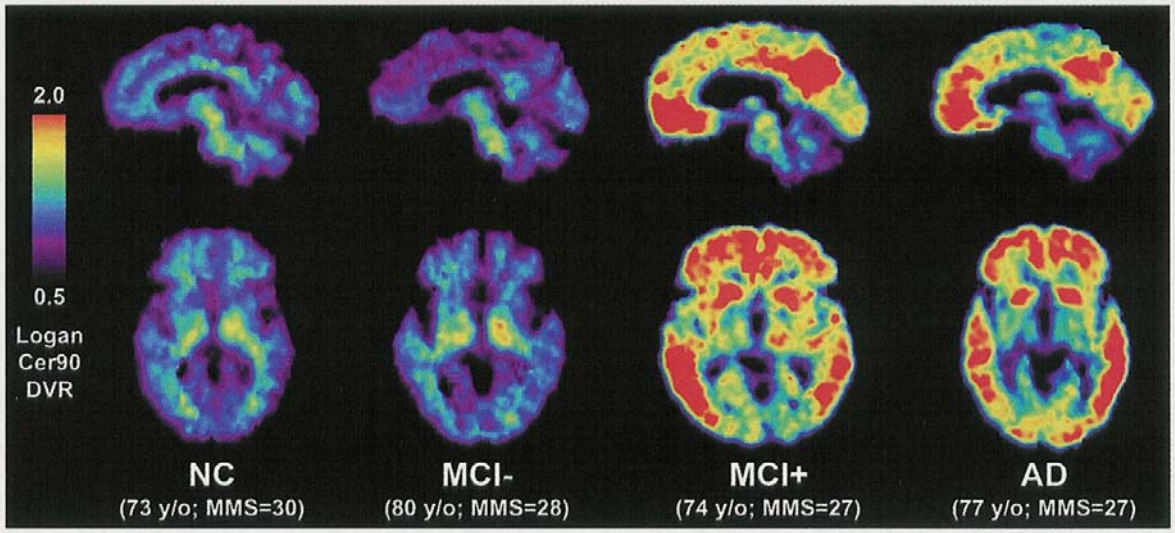


Figure 1 PET images produced using Pittsburgh Compound-B (PIB) shown in sagittal (top) and transaxial (bottom) views. Shown from left to right are a cognitively normal control (NC), an MCI subject with no evidence of amyloid deposition (MCI–), an MCI subject with heavy amyloid deposition (MCI+), and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

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

„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.

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

Early Involvement of SAWP – 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.