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Bundesinstitut für Arzneimittel und Medizinprodukte

Identifying and Meeting Regulatory Challenges for Indications in Personalized Medicine

Dr. Karl Broich

Federal Institute of Drugs and Medical Devices (BfArM)
Kurt-Georg-Kiesinger-Allee 38, D-53175 Bonn
Germany

German Alternate, CHMP

BfArM

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Disclaimer

- Personal views are presented
- Expressions cannot be regarded as official positions of EMEA or BfArM
- Based on NfG on the qualification of new methodologies published for consultation EMEA/CHMP/SAWP/72894/2008
- Based on NfG on genomic biomarkers related to drug response: context, structure and format of qualification submissions

  EMEA/CHMP/ICH/380636/2009

Many Definitions

- Pharmacogenetics
- Pharmacogenomics
- Personalized Medicine
- Personalized Prescription
- Biomarker
- Qualification
- Validation
- Surrogacy

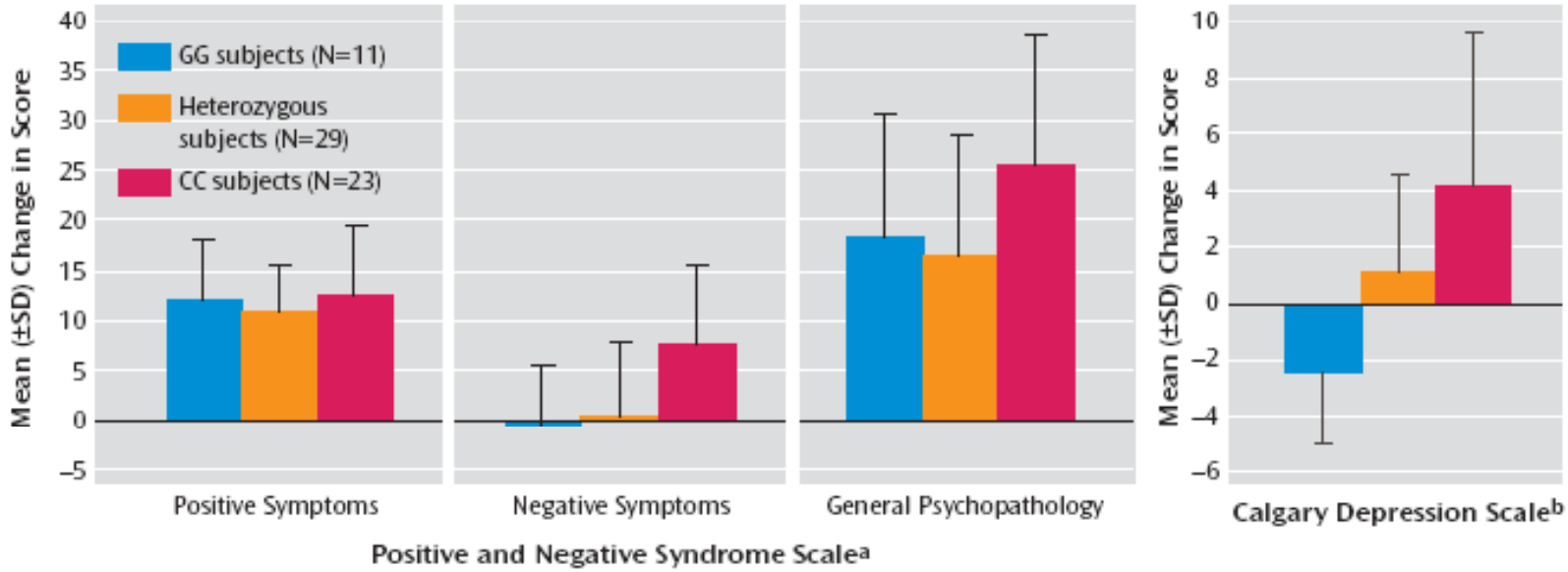
Consideration of genetic, environmental and personal variables

- Safety and efficacy
- Pharmacokinetics and pharmacodynamics
- Therapeutic window
- Idiosyncratic and dose-related adverse drug reactions

5-HT1A-receptor and antipsychotic response

Reynolds GP et al, Am J Psychiatry 2006, 163:1826-1829

FIGURE 1. Influence of 5-HT$_{1A}$ Receptor −1019C/G Polymorphism on the Effect of 3 Months of Antipsychotic Drug Treatment of First-Episode Psychosis on Symptom Changes



[a] Significant effect of genotype on changes in negative subscale score ($F=8.00$, $df=2, 60$, $p=0.001$; $R^2=0.211$) and in general psychopathology subscale score ($F=3.55$, $df=2, 60$, $p<0.05$; $R^2=0.106$), but not in positive subscale score ($F=0.51$, $df=2, 60$, $p>0.1$).

[b] Significant effect of genotype on change in score ($F=9.85$, $df=2, 60$, $p<0.001$; $R^2=0.247$). Positive values indicate improvements in symptoms.

5-HT1A-receptor and antipsychotic response

Wang et al, J Psychypharmacol 2008, 22: 904-909

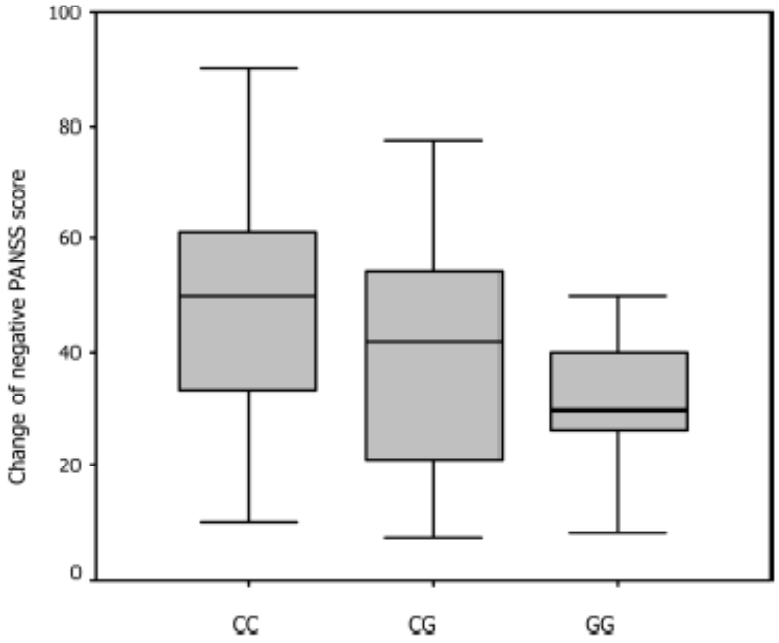


Figure 1 Association between 5-HT_1A genotypes and changes in negative PANSS scores. $P = 0.019$

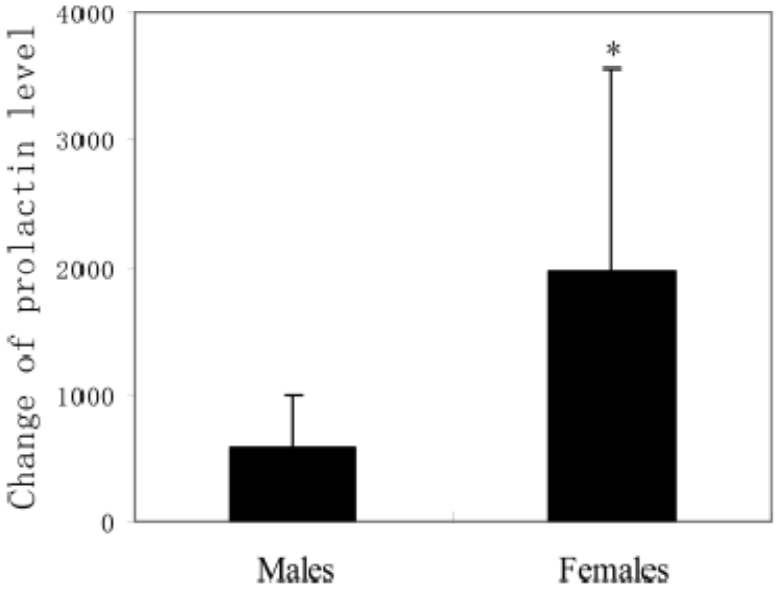


Figure 2 Changes in prolactin levels in males and females
$^*P < 0.001$

Pharmacogenomic tests

- AmpliChip CYP450 test
- Luminex tag-it mutation detection kit
- LGC clozapine response test
- PGx predict: Clozapine
- Phyzio type system

Pharmacogenomics: Safety

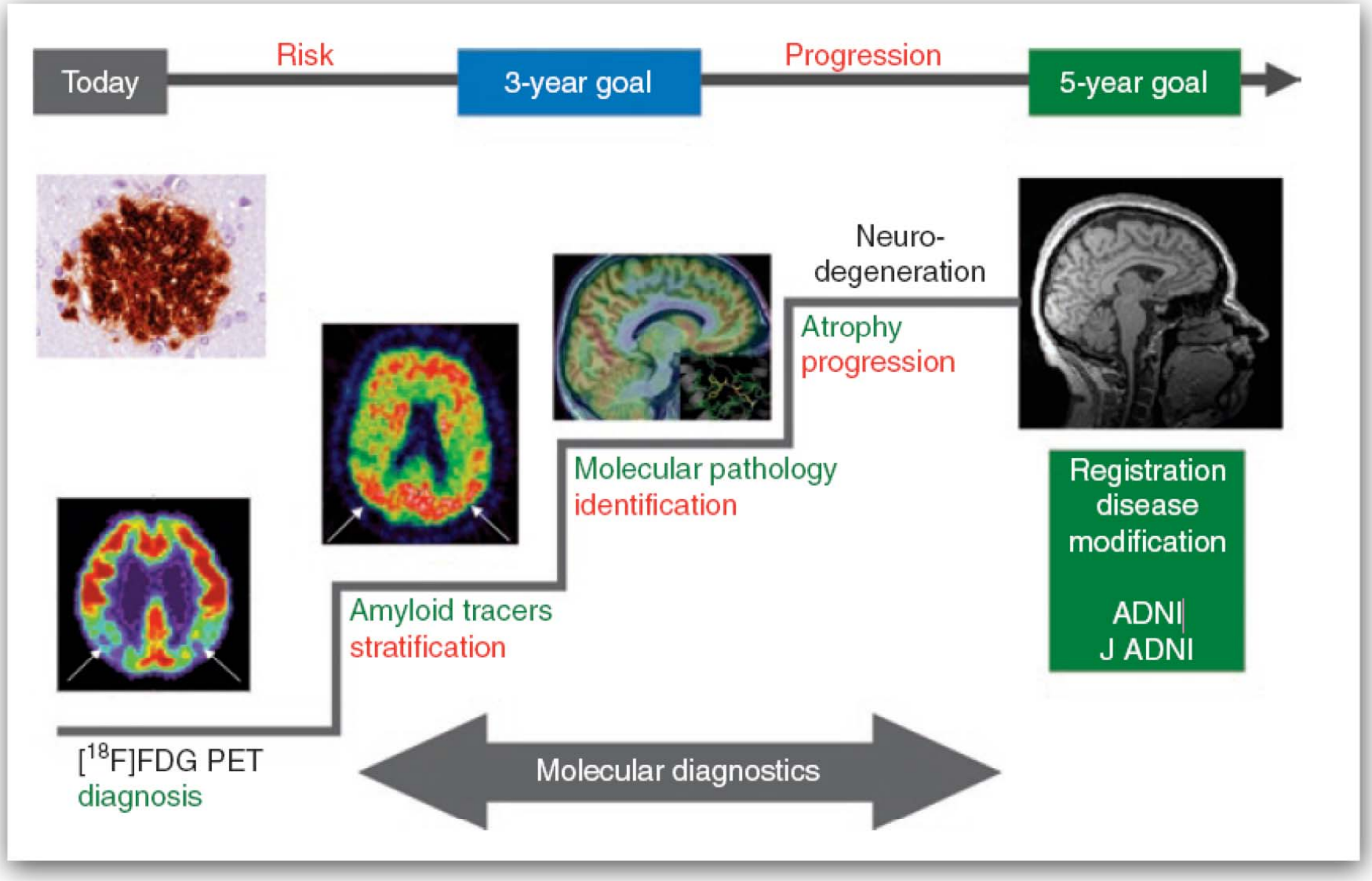
Pharmacogenomics. 2008 October ; 9(10): 1543–1546. doi:10.2217/14622416.9.10.1543.

Carbamazepine, *HLA-B*1502* and risk of Stevens–Johnson syndrome and toxic epidermal necrolysis: US FDA recommendations

P Brent Ferrell Jr[1] and **Howard L McLeod**[1,2,†]

1*University of North Carolina, Institute for Pharmacogenomics and Individualized Therapy, UNC Schools of Pharmacy and Medicine, and the Lineberger Comprehensive Cancer Center, USA*

2*University of North Carolina, Campus Box #7360, Chapel Hill, NC 27599–7360, USA Tel.: +1 919 966 0512; Fax: +1 919 966 0644; E-mail: hmcleod@email.unc.edu*


Today
Risk
3-year goal
Progression
5-year goal
Neuro-
degeneration
Atrophy
progression
Molecular pathology
identification
Amyloid tracers
stratification
[18F]FDG PET
diagnosis
Molecular diagnostics
Registration
disease
modification
ADNI
J ADNI

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

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

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 !!!**

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

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)

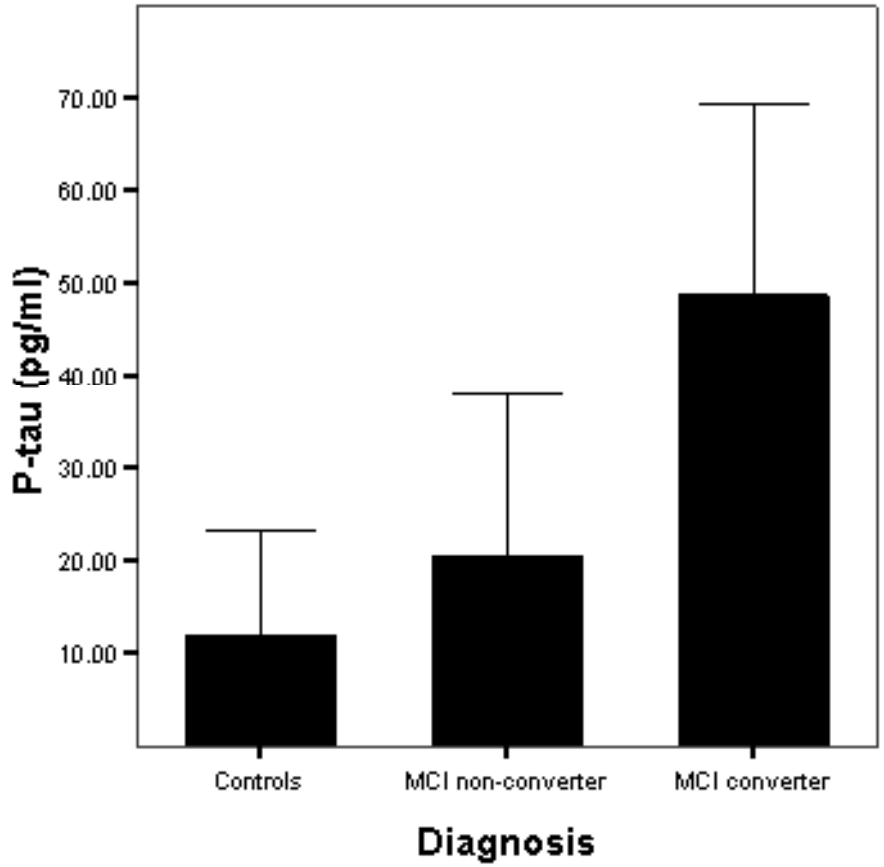
(3) Evidence from randomized trials that improvements in the surrogate endpoint leads consistently to improvement of the target outcome

(4) Large, precise, and lasting treatment effects

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

phospho-tau and MCI

4 centers, n: 144 - 56 HC, 88 MCI (43 conv / 45 non-conv)



from:

Ewers M et al.

Neurology, 69, 2205-2212 (2007)

A priori cut off point:

27,32pg/ml

Centers: München, Heidelberg, Amsterdam, Pitea

Imaging of Amyloid Load by PET

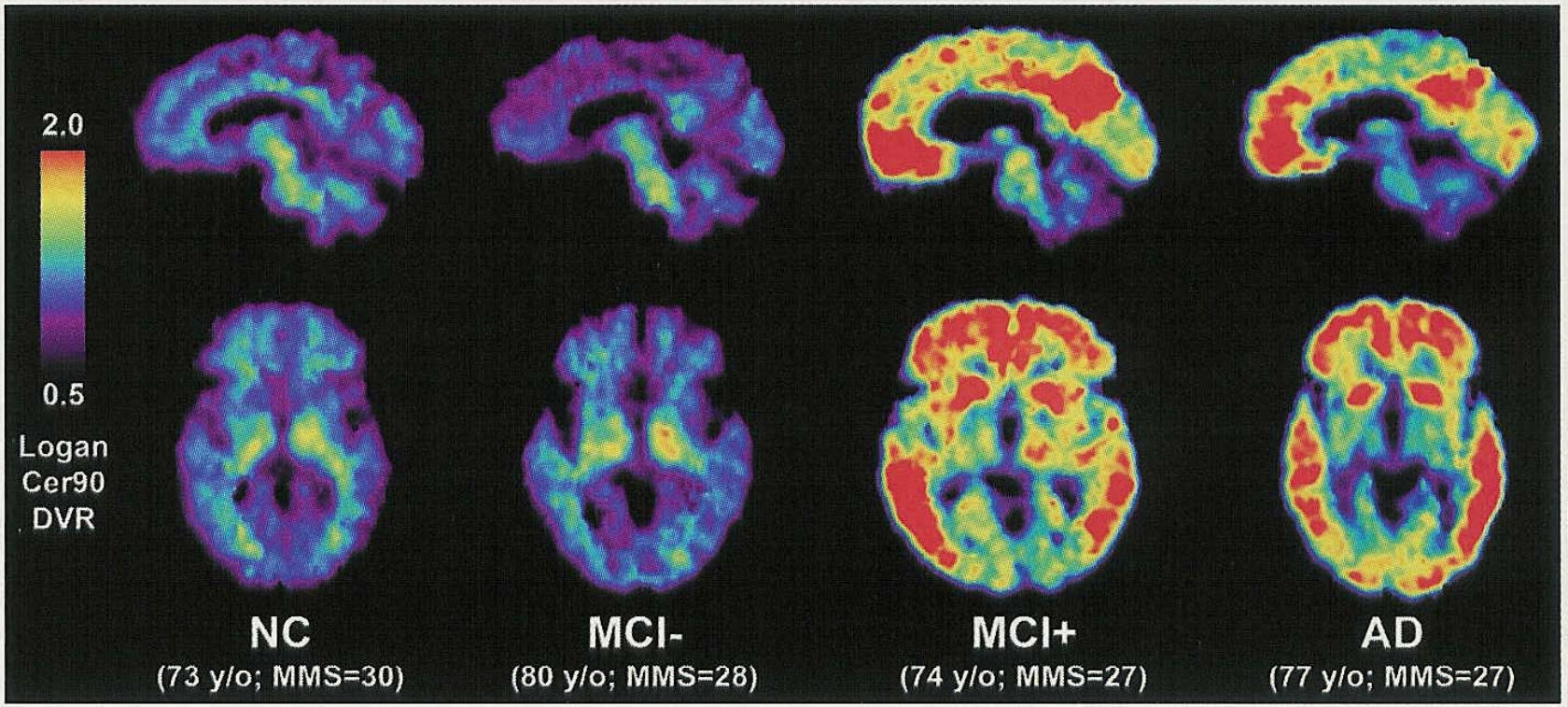


Figure 1 PET images produced using Pittsburgh Compound-B (PIB) shown in sagittal (top) and transaxial (bottom) views. Shown from left to right are a cognitively normal control (NC), an MCI subject with no evidence of amyloid deposition (MCI–), an MCI subject with heavy amyloid deposition (MCI+), and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

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

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

EMEA-Guidance Documents

- NfG on the qualification of new methodologies published for consultation EMEA/CHMP/SAWP/72894/2008

- NfG on genomic biomarkers related to drug response: context, structure and format of qualification submissions

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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.

Who will be the Qualification team?

- One Coordinator (SAWP or CHMP member)
- Minimum 4 experts (not bound to Coordinator country)
- One EMEA Scientific Administrator

Which other regulatory agencies?

- Applicants are encouraged to apply in parallel to the EMEA and FDA. The confidentiality agreement between the FDA and EMEA makes it possible to have the procedure ongoing at the same time in both agencies.
- The agencies will communicate the assessment and meet with the Applicant together.
- The same conclusion to the advice is envisaged.

What is new / What is the ultimate goal?

- SAWP / CHMP early involvement on the design of the strategy towards qualification of novel methodologies
- SAWP / CHMP commitment to evaluate the data obtained from the agreed studies and to provide a Qualification Opinion regarding the use of the method in R&D
- Goal: speed up drug development, contribute to public health