# The Role of Biomarkers in Clinical Trials in Early AD

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# Challenges of AD Clinical Trials

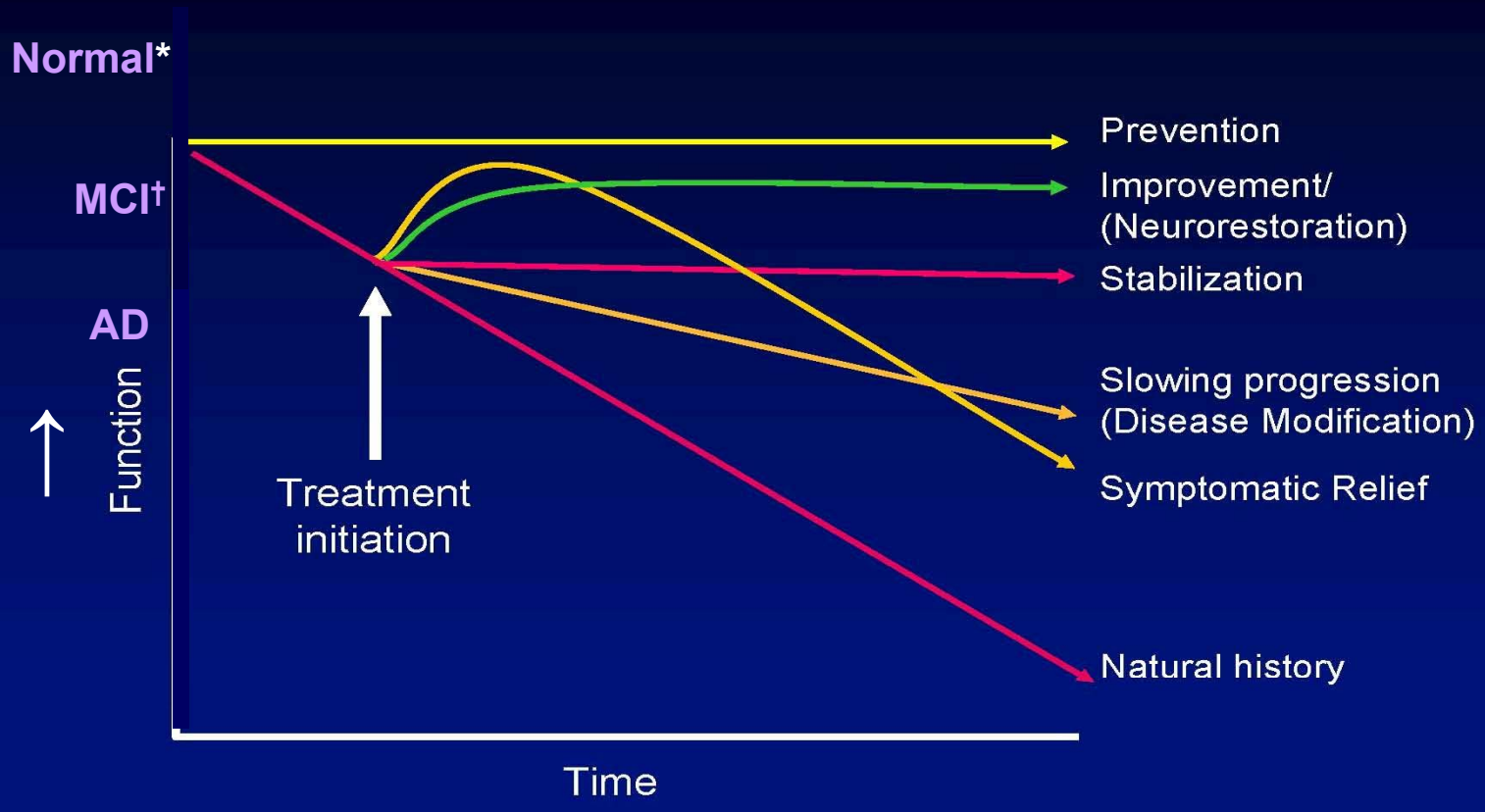
- Large numbers of patients required
  - Necessitates large number of sites and geographies
- Long in duration
- Changing population (progressive disease)
- Diagnosis is purely clinical
- Measures are:
  - Clinical assessments
  - Psychometric instruments
- Extremely difficult to conduct in Early AD

# Example of AD Clinical Trial:
## Bapineuzumab in Patients With Mild to Moderate AD

- **Inclusion Criteria:**
  - Diagnosis of probable AD
  - Mini-Mental Status Exam score of 16-26 inclusive
- **Primary Outcome Measures:** Cognitive and Functional
- **Secondary Outcome Measures:** Cognitive and Global
- **Study duration:** 18 months
- **N=1250**
- **Study sites**: Approximately 230 study sites in the US and Canada and up to 35 sites outside of North America will be involved.

www.clinicaltrials.gov/ct2/show/NCT00574132

# Possible Outcomes of Therapeutic Intervention




*Rachel J. Schindler, MD*
*Pfizer, 2004*


*Cognitive impairments detectable, selected biomarkers abnormal, but MMSE remains within normal limits
†MMSE between 26 and 28

# Proposed Research Diagnostic Criteria for Probable AD

## *Making the Diagnosis of AD Earlier*

### Traditional Criteria

- Objective deficit in two or more domains of cognition, one of which is memory
- Impaired cognitive domains must interfere with social function or activities of daily living (ADL)
- Dementia established by clinical and NP exam
- Absence of other diseases which could cause dementia

### Dubois Research Criteria

- Presence of an early and significant episodic memory impairment
- Presence of *at least one* of the following:
  - Medial Temporal Lobe Atrophy
  - Abnormal CSF ($\downarrow A\beta_{42}$, $\uparrow$pTau)
  - $\downarrow$ FDG-PET, $\uparrow$ Brain Amyloid
  - AD Autosomal Dominant Mutation*

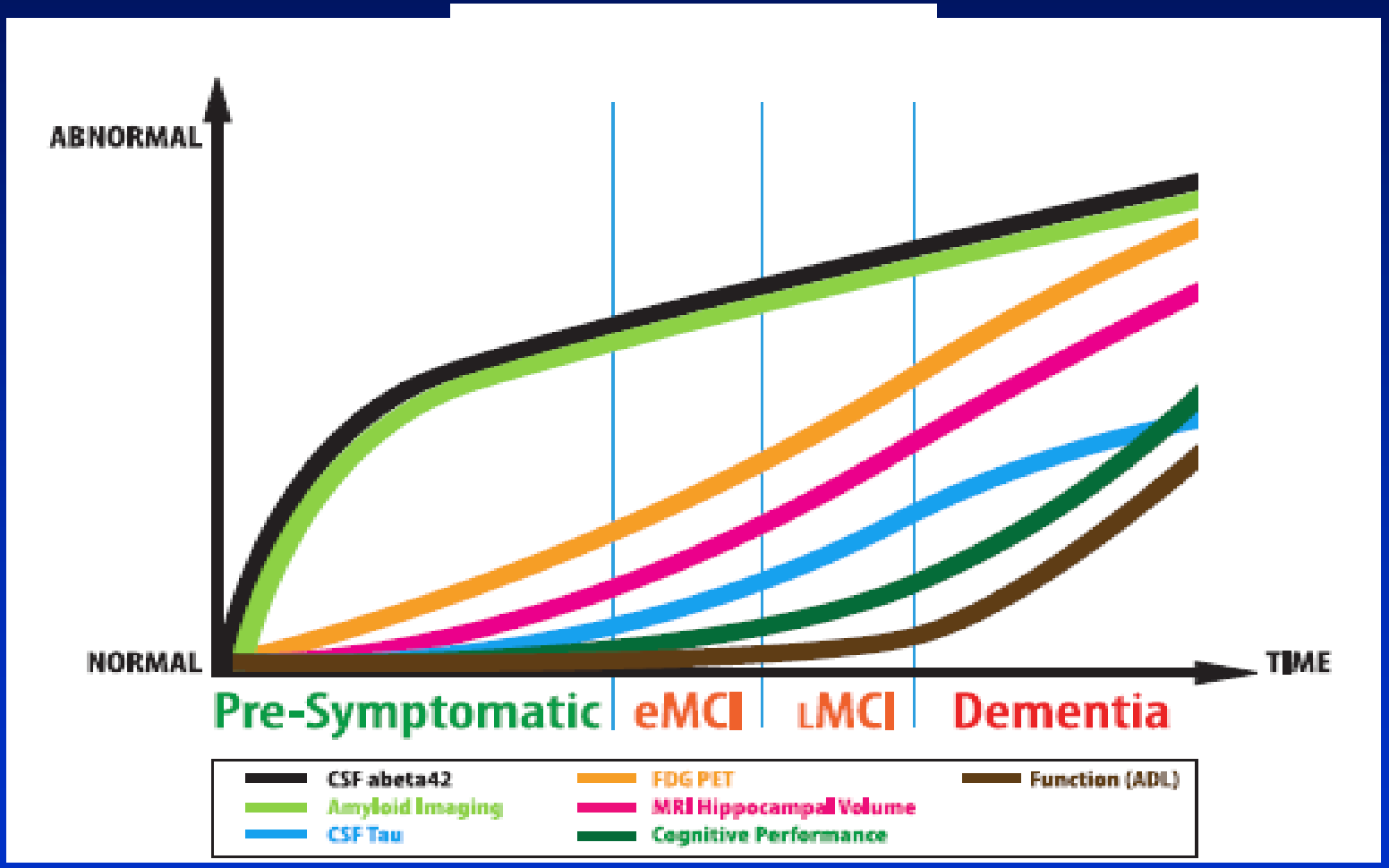
*Applies to Early Onset, Familial AD

Dubois B. et al., Lancet Neurol. 2007 Aug;6(8):734-46.

# Major Studies on Biomarkers

| | Alzheimer's Disease Neuroimaging Initiative (ADNI) | Australian Imaging Biomarkers and Lifestyle Flagship Study of Aging | AddNeuroMed |
|---|---|---|---|
| **Start date** | 10-01-2004 | 11-14-2006 | Concept: 2004<br>Clinical: 2006 |
| **End date** | ADNI II ongoing | ongoing | Phase I: 2009<br>Data analysis ongoing |
| **Subjects** | HC- 200<br>MCI-400<br>AD- 200 | HC- 768<br>MCI- 133<br>AD- 211 | Varies by study<br>6 sites |
| **Markers studied** | MRI, PET, CSF | MRI, PET, CSF | Urine, blood, MRI |
| **Citation** | http://www.adni-info.org/ | http://www.aibl.csiro.au/ | http://www.innomed-addneuromed.com/ |

# Progression of AD Biomarkers and AD Symptoms




Jack CR Jr, et al. Lancet Neurol. 2010;9(1):119-28.

# Use of Biomarkers in AD Clinical Research

- **Inclusion/exclusion criteria (patient identification and selection)**
- **Stratification**
- **Enrichment**
- **Proof of mechanism**
- **Monitoring of therapeutic response**
  - Early sign of efficacy
  - Lack of response
  - Early relapse
- **Surrogate marker**

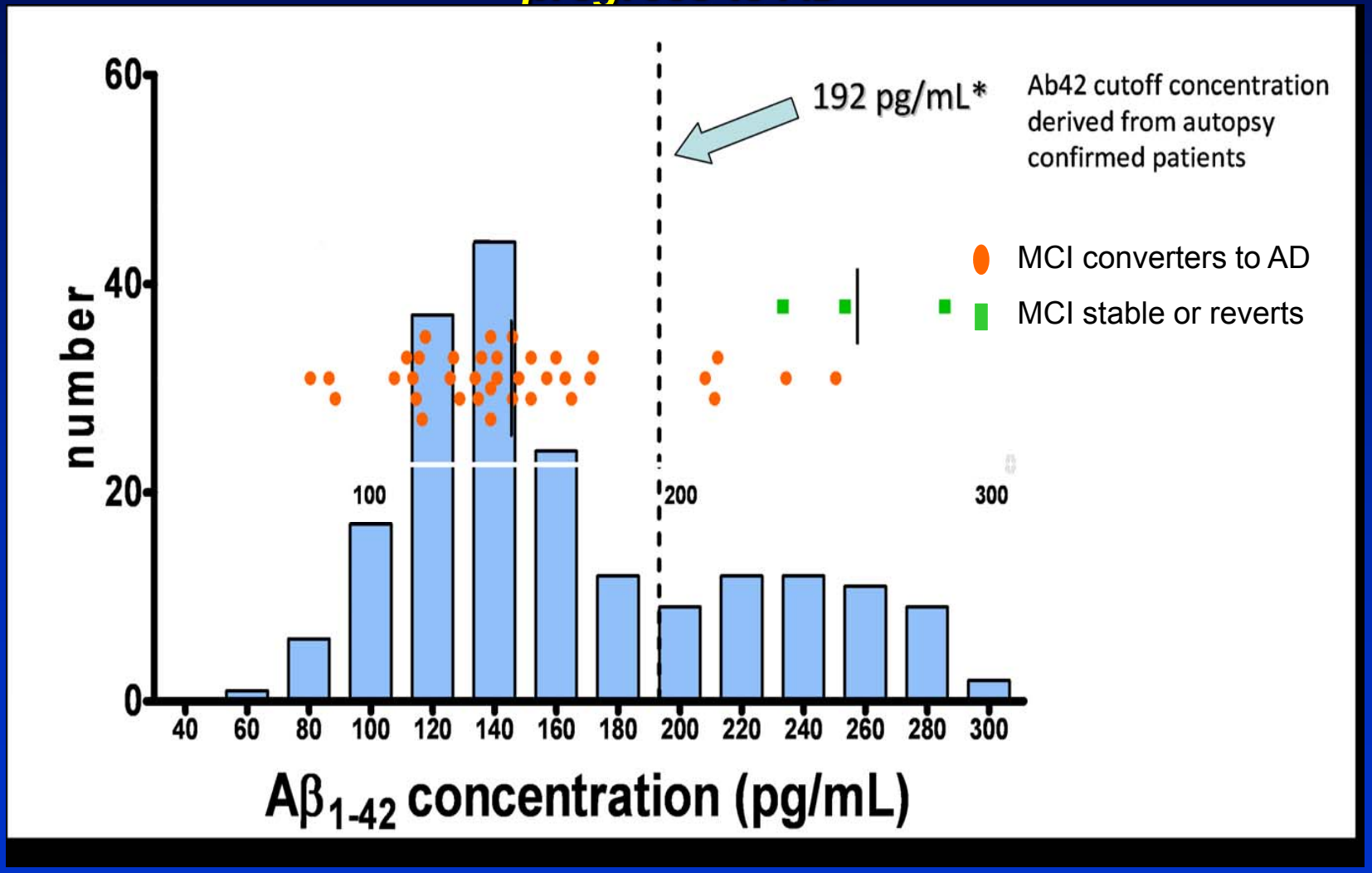
# CSF Biomarkers: Aß$_{1-42}$

- **Amyloid precursor protein (APP)**
  - Nonamyloidogenic pathway cleaved at the α-site
- Amyloidogenic pathway cleaved at the β-site
  - Digestion by γ–secretase → Aβ peptides
- Aβ peptides
  - Many length variations
  - The 42 residues long Aβ isoform (Aβ42) forms oligomers and fibrils that accumulate in extracellular plaques.
  - Deposition of $A\beta_{42}$ in plaques ⇒ decrease in CSF Aβ42 levels seen in AD.

Mattson N et al. Ann. N.Y. Acad. Sci. 1180: 28–35 (2009).

# Using an $A\beta_{1-42}$ Cut-Off of 190 pg/ml for Clinical Trial Enrichment

***Pre-demented patients with low $A\beta_{1-42}$ are much more likely to progress to AD***




Adapted from Shaw et al., . *Ann. Neurol.* 2009;18:403-413

# CSF Biomarkers: T-tau and P-tau

- Neurofibrillary tangles (NT) composed of phosphorylated tau (p-$Tau_{181 \text{ or } 231}$) aggregates: A major hallmark of AD
- Tau supports cytoskeleton function by stabilizing microtubules
  - Total tau (t-Tau) levels elevated in setting of axonal injury
  - Phosphorylation diminishes tau functionality → increased cytoskeleton flexibility → loss of axonal integrity
  - CSF levels of p-$Tau_{231}$ correlate best with NT pathology
  - Ratio of CSF t-Tau to p-Tau differentiates AD from other neruodegenerative diseases (e.g. FTD, CJD)
- **Not elevated until much later in presymptomatic AD than beta amyloid**

Mattson N et al. Ann. N.Y. Acad. Sci. 1180: 28–35 (2009).

# Using CSF Biomarkers to Predict Progression from MCI to AD*

| Measure | Cutoff Value | Sensitivity/ Specificity | Hazard Ratio† |
|---|---|---|---|
| **T-Tau** $A\beta_{1-42}$ | >350 ng/L <530 ng/L | 95% / 83% | 17.7 (p<0.0001) |
| **P-Tau$_{181}$** $A\beta_{1-42}$ | >60 ng/L <530 ng/L | 95% / 81% | 16.8 (p<0.0001) |
| **T-Tau** $A\beta_{1-42}$ **/ P-Tau$_{181}$** | >350 ng/L <6.5 | 95% / 87% | 19.8 (p<0.0001) |

*4-6 year follow up

†Adjusted for age, sex, ApoE4, and educational level

Hansson O et.al., *Lancet Neurol* 2006;5:228–34

# Volumetric MRI

- Serial volumetric MR images
  - Regional (hippocampal and entorhinal cortex) and whole brain volume change are validated markers of disease progression (Percent [%] atrophy per year)
    - **Regional** best for *early* progression
      - AD: 3.0 – 6.0 versus Control: 0.3 – 2.2
    - **Whole brain** better for progression *after onset* of clinical AD
      - AD: 1.4 – 2.2 versus Control: up to 0.7
- Best validated marker for disease progression

Frisoni GB et al., *Nat. Rev. Neurol.* 6, 67–77 (2010)

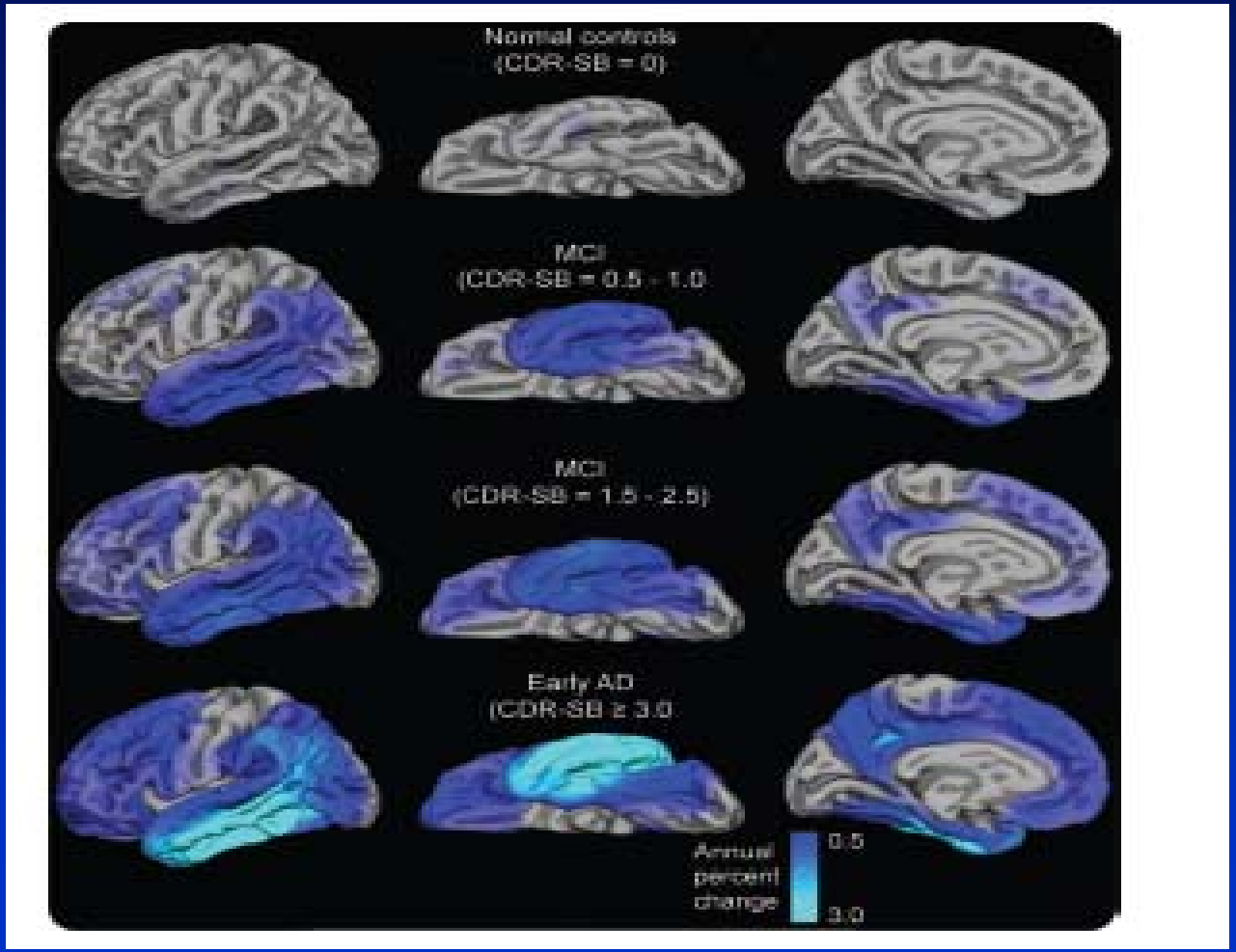
# Annual Atrophy Rates During Progressive Stages of AD

**Normal controls**

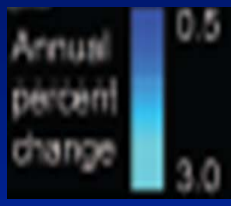
**Early MCI**

**Late MCI**

**Mild AD**




**Legend**




Neurology® 2009;73:457-465

McDonald CR, et al. Neurology. 2009 Aug 11;73(6):457-65.

# Functional Imaging I: FDG-PET

- **Positron Emission Tomography (PET): enables functional processes to be assessed in living patients**
- **Metabolic function (glucose metabolism) can be quantified and imaged in three dimensions**
  - The glucose analog 2-[18F]-fluoro-2-deoxy-d-glucose (18F-FDG) is the standard tracer
  - 18F-FDG-PET studies have predicted which healthy elderly individuals developed MCI and which patients with MCI converted to AD
    - Medial temporal glucose hypometabolism predicted MCI
    - Hypometabolism in posterior cingulate cortex was the earliest and most sensitive marker for predicting the conversion of MCI to AD.

Nordberg A et al., *Nat. Rev. Neurol.* 6, 78–87 (2010)

# Functional Imaging II: Amyloid PET

- **Several PET tracers have been developed that enable *in vivo* imaging of brain amyloid**
  - 11C-PIB and other C-based compounds
  - 18F (FDDNP, BAY94-9172, AV-45, Flumetamol, others)
    - F-based compounds more stable and do not require on site synthesis and use
- **PET amyloid tracers label fibrillar Aβ**
  - Associated with plaque formation
  - Not agreed whether this is most important for AD
- **Threshold reached at around onset of clinical AD**
- **Present in many older adults (>80 years) without AD**
- **Earliest marker of AD pathology (along with CSF Aβ)**
  - Predictive of transition (especially for age < 65) from:
    - Normal to MCI
    - MCI to AD

Nordberg A et al., *Nat. Rev. Neurol.* 6, 78–87 (2010)

# Summary: Biomarkers in Early AD

- There is a correlation between structural and functional imaging and biochemical biomarkers and degree of cognitive impairment.
- Changes occur *before* the diagnosis of dementia
- Use of biomarkers makes possible the conduct of clinical trials in Early AD, *before* the onset of dementia, when many therapeutic agents in development may have their greatest effect.

# Trial Design: Factors Affecting Sample Size

- **Primary outcome measure**
  (single or composite; reliability and validity)
- **Rate of decline in untreated population**
- **Magnitude of treatment effect**
- **Dropout and withdrawal,**
  especially in long trials where disease is progressive and extrapolation may be necessary
- **Interim analyses and their frequency**
- **Analytic methods addressing**:
  - dropout effect (e.g., LOCF, Mixed-effect Model Repeated Measures)
  - variability (e.g. inclusion of baseline covariates)

# Effect on Sample Size of Using Biomarkers in Clinical Trials

| Study Population | Covariates | Primary Outcome* | Sample Size Calculation |
|---|---|---|---|
| ADNI MCI cohort | None | CDR-SB + ADAScog12 | 40% effect, N=334<br>30% effect, N=593 |
| CSF $A\beta_{1-42}$ <193pg/ml | None | CDR-SB + ADAScog12 | 40% effect, N=212<br>30% effect, N=376 |
| CSF $A\beta_{1-42}$ <193pg/ml | vMRI | CDR-SB + ADAScog12 | 40% effect, N=182<br>30% effect, N=324 |
| CSF $A\beta_{1-42}$ <193pg/ml | vMRI | CDR-SB | 40% effect, N=87<br>30% effect, N=154 |

ADNI data, Aisen P et al. 2009

* Analysis performed using linear mixed effects modeling

# Early AD Trial Designs

| | Mild AD | Early AD | Very Early AD |
|---|---|---|---|
| **Cognitive Status** | Mild dementia | Mild cognitive impairment | Cognitively normal |
| **Clinical Dementia Rating global score** | 0.5-1 | 0.5 | 0 |
| **MMSE range** | 16-26 | 25-30 | 28-30 |
| **Biomarker for subject selection** | none | Amyloid imaging and/or CSF abeta42 | Amyloid imaging and/or CSF abeta42 |
| **Biomarker for subject stratification** | None or APOE genotype | APOE genotype | APOE genotype |
| **Primary cognitive outcome measure** | ADAScog11 | ADAScog12 (includes delayed recall) | Sensitive memory and/or exec. function measure |
| **Primary global/functional outcome measure** | CDR-SB | CDR-SB | none |
| **Analysis covariates** | Baseline cognition and regional brain volume | Baseline cognition and regional brain volume | Regional brain volume |
| **Biomarker outcome** | Regional brain atrophy | Regional brain atrophy | Regional brain atrophy and/or amyloid measure (as surrogate endpoint) |
| **Duration of treatment** | 18 months | 24 months | 24-36 months |
| **Primary analysis** | Change score or slope of co-primaries: ADAScog11, CDR-SB | Change score or slope of co-primaries: ADAScog12, CDR-SB | Regional brain atrophy rate and cognitive decline |

Slide Courtesy
Paul Aisen

# Future Directions for Biomarker Research

- Importance of clinical trials to gather the data needed to validate candidate markers
- Comparative value of different imaging methods (atrophy, amyloid deposition, metabolism)
- Comparative value of different biochemical biomarkers (CSF and possible plasma) at different stages
- Long-term follow-up of individual biomarkers to understand their natural history
- Cross-sectional correlation of biomarkers with clinical state to gain further insight into which markers may be most valuable in different populations, stages, and settings

# Conclusions: The Promise of Biomarkers in AD Clinical Trials

- Reduce sample size through identification of subjects
- Reduce trial duration
- Demonstrate mechanism of action
- Monitor the effects of the therapeutic intervention
- Serve as primary outcome measures, in addition to or in place of cognitive and functional measures
- Study patients with Early AD when pharmacotherapy may make the greatest difference