# Changing diagnostic criteria for AD - Impact on Clinical trials

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# DISCLOSURE

1) Consultancy:
**Affiris, Eli Lilly, Roche**

2) Funding for my Institution:
**Pfizer, Roche**

# IWG-1 criteria (2007-2010)

**First introduction of different AD clinical stages**

- ❑ prodromal stage
- ❑ dementia stage

**First introduction of different AD preclinical states**

- ❑ asymptomatic at risk (biomarker positive)
- ❑ presymptomatic (mutation carriers)

**First introduction of different forms of AD**

- ❑ typical
- ❑ atypical

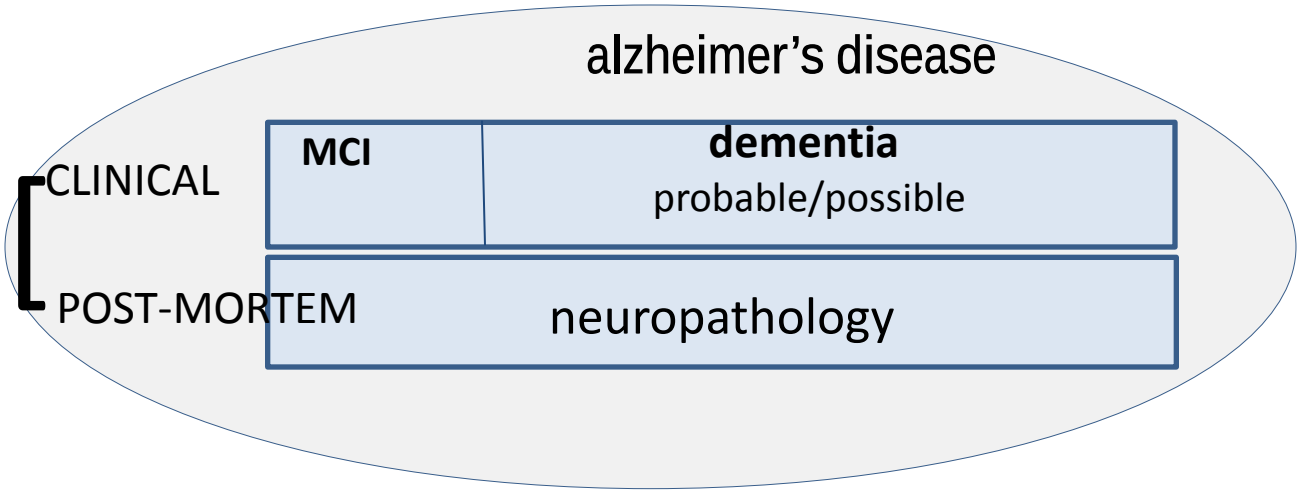
**One disease: one set of criteria**

**AD: a clinico-biological entity**

# The conceptual shift

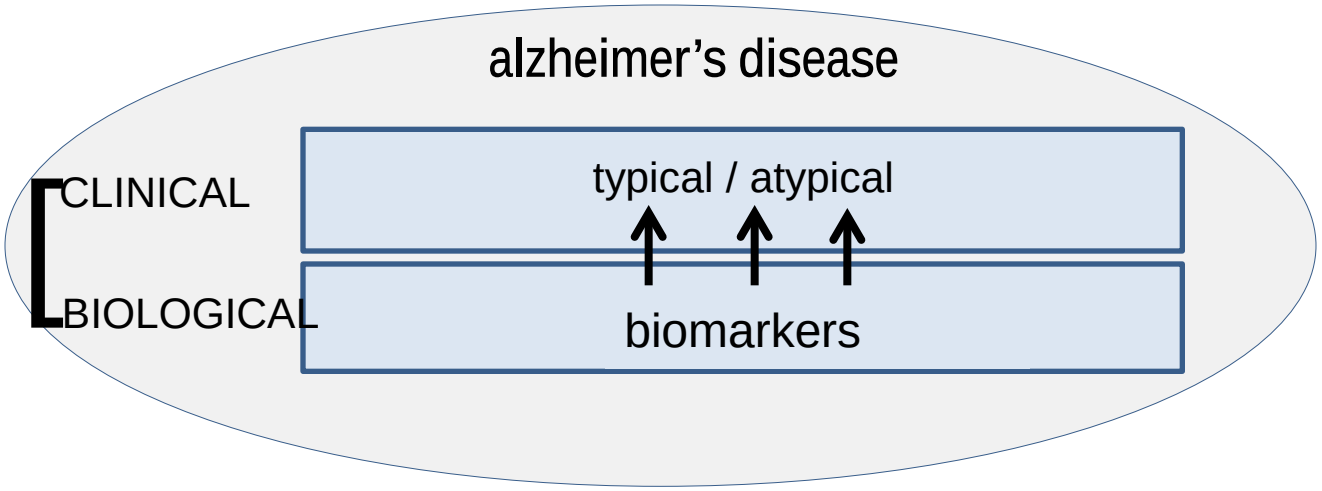
**1984**
NINCDS-ADRDA

**clinical pathological entity**

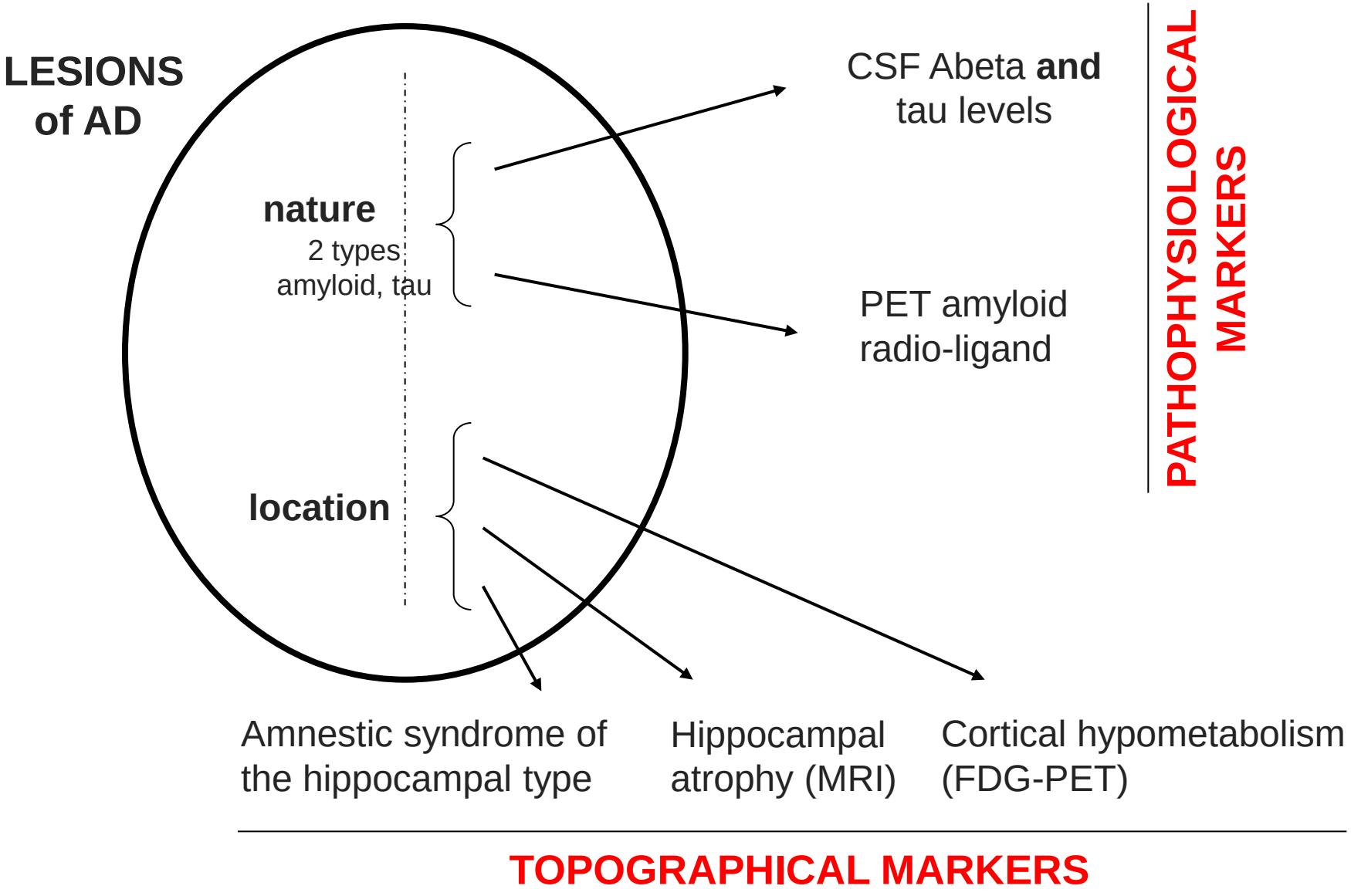



**2007**
IWG

**clinical biological entity**



# The different biomarkers of AD



# The 2 types of biomarkers *(LN, 2014)*

**Diagnostic markers**

- Pathophysiological markers
- Reflect in-vivo pathology (amyloid and tau changes)
- Are present at all stages of the disease
- Observable even in the asymptomatic state
- Might not be correlated with clinical severity
- Indicated for inclusion in protocols of clinical trials

**Progression markers**

- Topographical or downstream markers
- Poor disease specificity
- Indicate clinical severity (staging marker)
- Might not be present in early stages
- Quantify time to disease milestones
- Indicated for disease progression

**Lancet Neurology, June 2014**

# The « IWG-2 criteria »

*Lancet Neurol, 2014*

**A simplified algorithm is proposed:**

In any condition and at any stage of the disease,
the diagnosis of AD relies on the presence of a pathophysiological marker.

***Typical***
- Amnestic syndrome of the Hipp. type

***Atypical***
- Posterior cortical atrophy
- Logopenic variant
- Frontal variant

***Asymptomatic at risk***
- No AD phenotype (typical or atypical)

***Presymptomatic*** (AD mutation)
No AD phenotype (typical or atypical)

- **CSF** (low β1–42 **and** high T or P-tau)

**OR**

- **Amyloid PET** (high retention of tracer)

# IWG-2 criteria for typical AD, at any stage
# For instance, for prodromal AD

**CLINICO - BIOLOGICAL ENTITY**

- ❑ Amnestic syndrome of the hippocampal type
- ❑ Isolated or associated with other cognitive or behavioral changes

- CSF (low β1–42 and high T or P-tau)

**OR**

- Amyloid PET (+)

2011

# (3) NIA/AD diagnostic Criteria

**The NIA/AA criteria acknowledge that :**

- brain changes can occur long before dementia symptoms
- disease biomarkers might be useful for the diagnosis

**3 recognized stages with 3 different diagnostic algorithms**

- AD dementia stage (10 categories)
- MCI stage (4 categories)
- preclinical stage (3 categories)

**2 types of MCI criteria :**

- for clinical setting
- for research purposes that are based on the use of biomarkers:

| Cognition | Likelihood of AD | Biomarker Evidence |
|---|---|---|
| MCI | High likelihood | (+) amyloid-β biomarker **AND** (+) neuronal injury biomarker* |
| MCI | Intermediate likelihood | (+) amyloid-β biomarker **OR** (+) neuronal injury biomarker* |
| MCI | Uninformative situation | Biomarkers fall in ambiguous ranges, conflict, not obtained |
| MCI | Unlikely due to AD | Demonstrated absence of AD-type molecular marker and possible presence of marker suggestive of non-AD disorder |

# Prodromal versus MCI due to AD

| Characteristics | IWG-2 | NIA/AA |
|---|---|---|
| Pathophysiological markers only | YES | |
| At least, amyloid marker necessary | YES | |
| Specific clinical phenotype required | YES | |
| Integration within a continuum | YES | |
| Different levels of likelyhood | NO | |
| Only clinical | NO | |

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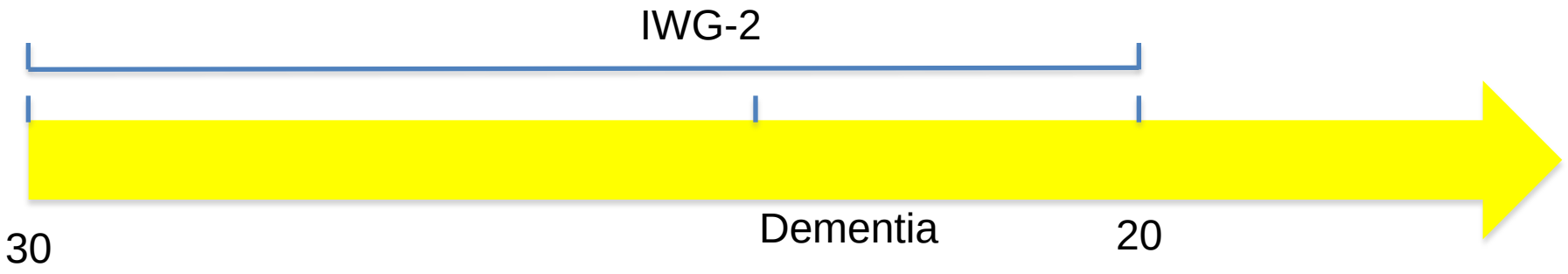
# « Early AD »: the right target

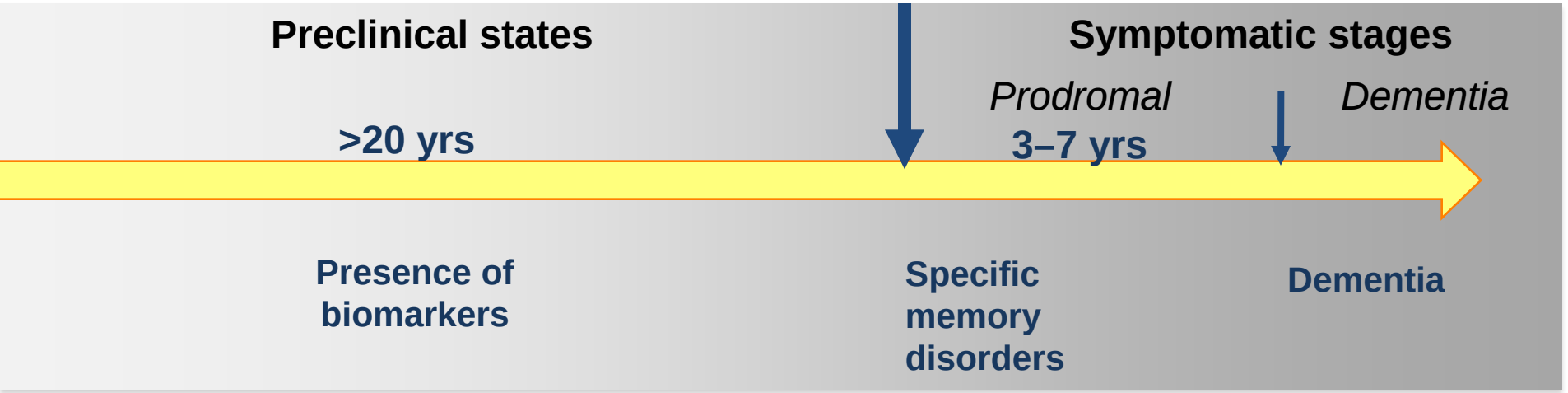
- This includes ‘Prodromal + Mild AD dementia’
- IWG-2 criteria with MMS ≥ 20




**Advantages:**

- Focus on early stage of AD
- One disease = One set of criteria
- Possibility for a secondary stratification

# The preclinical states of AD




## Who are they?

***Presymptomatic AD***

= with autosomal dominant monogenic AD mutation:
they will develop AD

***Asymptomatic at risk for AD (AR-AD)***

= with a positive pathological marker (brain or CSF):
they will or will not develop AD

*Dubois et al, Lancet Neurology, 2010*

# IWG-2 criteria for asymptomatic at risk

**<u>Absence of specific</u> clinical phenotype of AD** (both are required):

- ❑ Absence of amnestic syndrome of the hippocampal type
- ❑ Absence of any clinical phenotype of atypical AD

- **CSF** (low β1–42 and high T or P-tau)

**OR**

- **Amyloid PET (+)**

# Should we treat subjects at preclinical states?

- Drugs
  - Yes, if drugs decrease AD brain lesions
  - Yes, if drugs have no side effects in the long term
- Design
  - Yes, if we know how to assess the clinical efficacy at preclinical stages
- Subjects
  - Yes, if we can ascertain that they all will further develop Alzheimer's disease

# Unresolved Issues about AR-AD

1) Will they **all** convert to AD? Ethical issues:
- What should we **disclose** about their status and their risk?
- Can we treat someone against a disease that he/she will never develop?

2) **When** will they convert to AD? Therapeutic issues:
- Duration of the study?
- Factors to be controlled: age? APOE status? amyloid burden? cognitive reserve? education? preventive genetic/epigenetic factors?…

⇒ A need to better know the natural history of AD

⇒ A need to identify markers of a further conversion

# IWG-2 criteria for presymptomatic AD

**Absence of <u>specific clinical phenotype of AD</u>**
(both are required):

- ❑ Absence of amnestic syndrome of the hippocampal type
- ❑ Absence of any clinical phenotype of atypical AD

Proven AD autosomal dominant mutation for AD

# Added-value of the IWG-2 criteria

- They focus on the **entire continuum** of AD including the preclinical states;
- They utilize a **single diagnostic framework** for the entire range of clinical severity
- They integrate **pathophysiological** biomarkers into all phases of the diagnostic approach to improve on the diagnostic specificity
- AD diagnosis is now based **at least** on the presence of brain amyloidosis
- They integrate causative **mutations** into diagnosis
- They are **simple** to apply
- They can be used for inclusion of patients with **« early AD »**, an important target for clinical trials

# Limitations

- The willingness of individuals to undergo **lumbar puncture**
- The criteria mainly apply for research, memory clinics and **expert centers**
- There are **ethical and practical concerns** about disclosure of biomarker status in asymptomatic or very early symptomatic individuals
- **Norms** are needed for biomarkers
- Norms are needed for episodic memory tests that can be applied for a wide range of age, education, culture
- This requires a coordinated international effort

# We gratefully acknowledge the IWG participants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