"The added value of the IWG-2 diagnostic criteria for Alzheimer's' disease"

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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

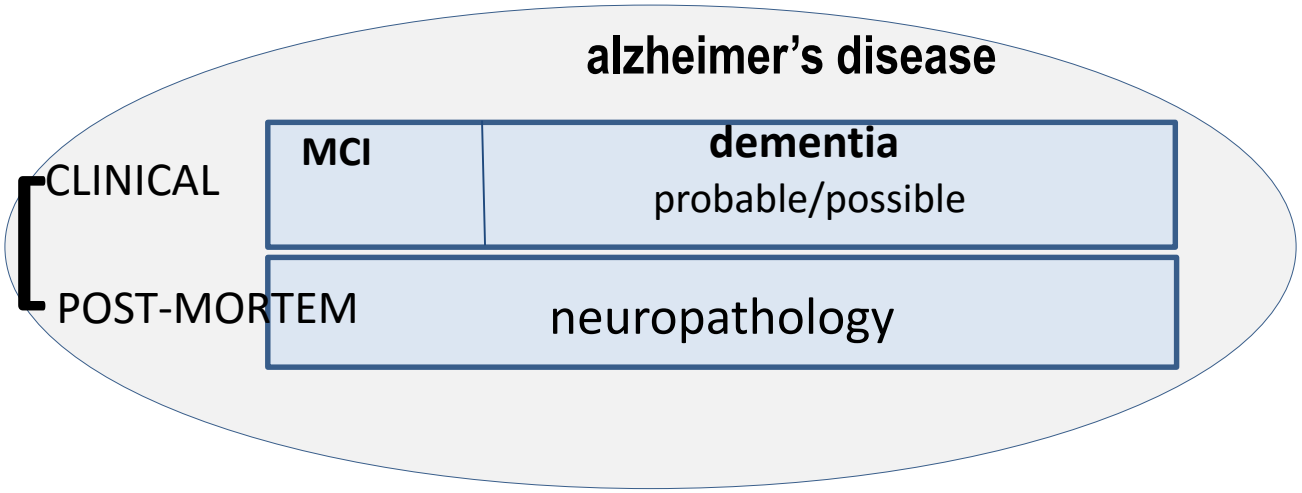
One disease: one set of criteria

AD: a clinico-biological entity

The conceptual shift

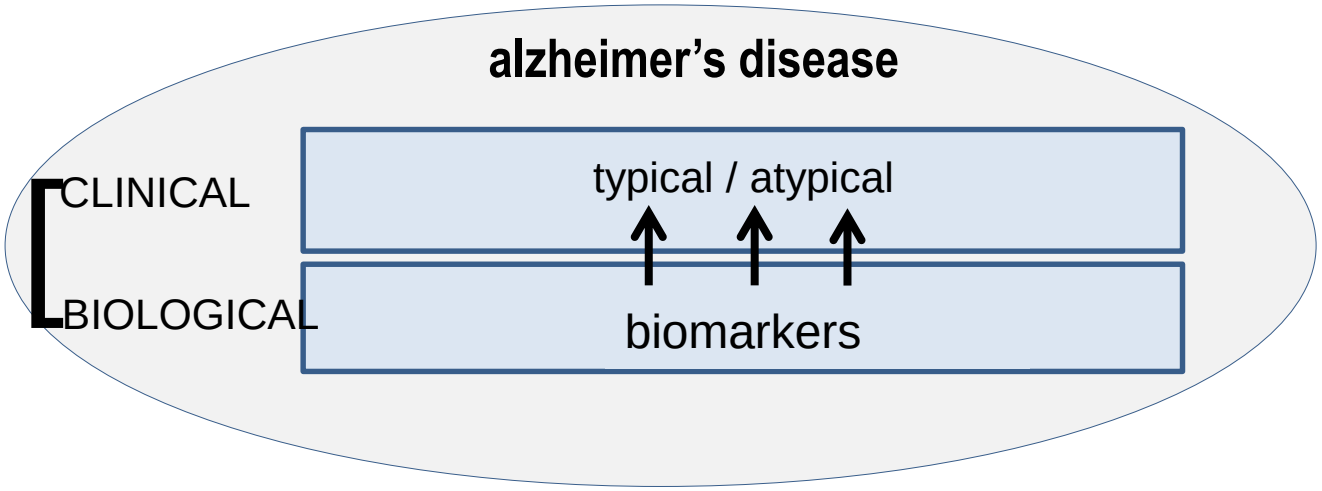
1984
NINCDS-ADRDA

clinical pathological entity

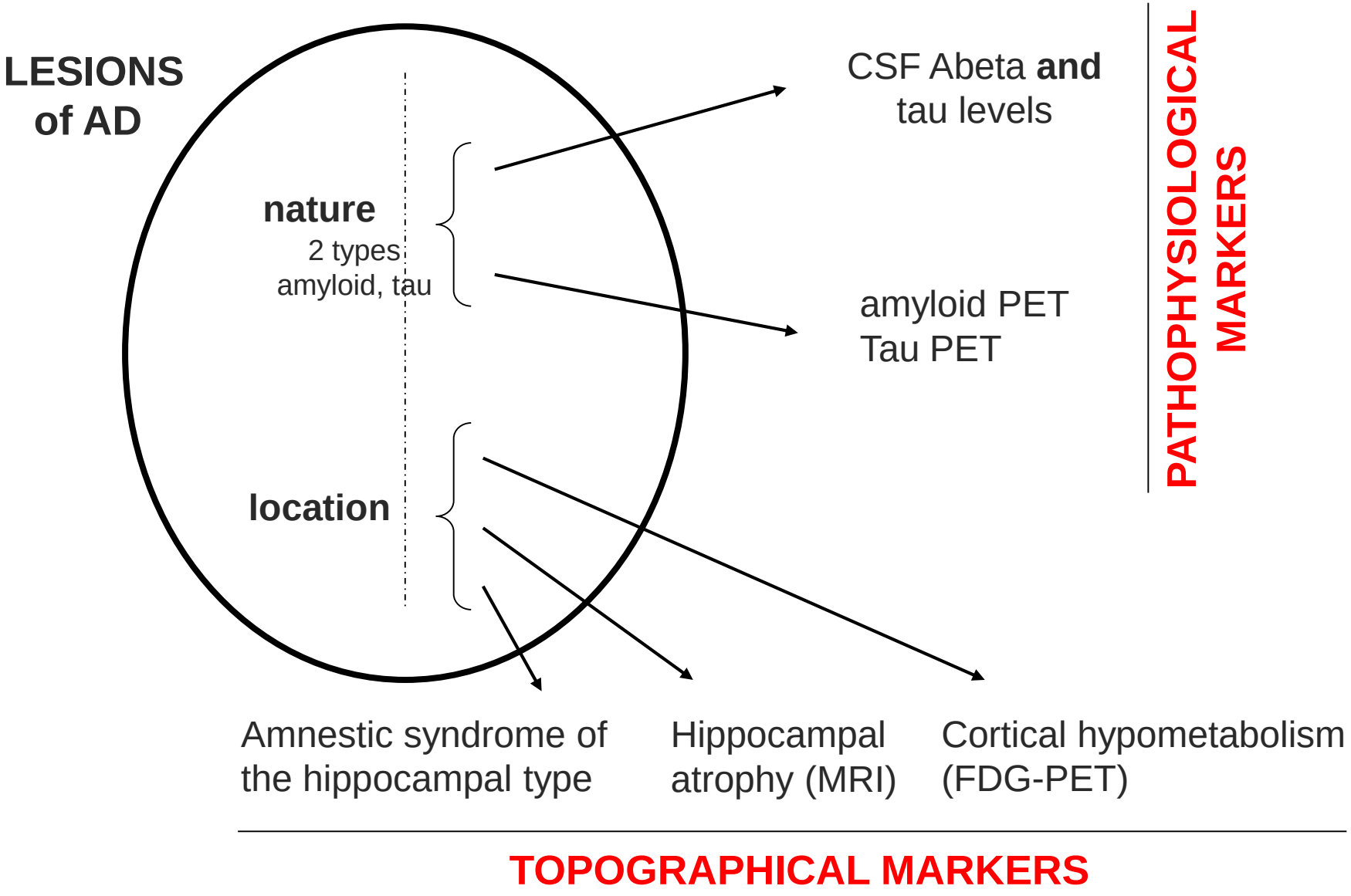


2007
IWG

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

IWG-2 criteria for typical AD, at any stage

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:

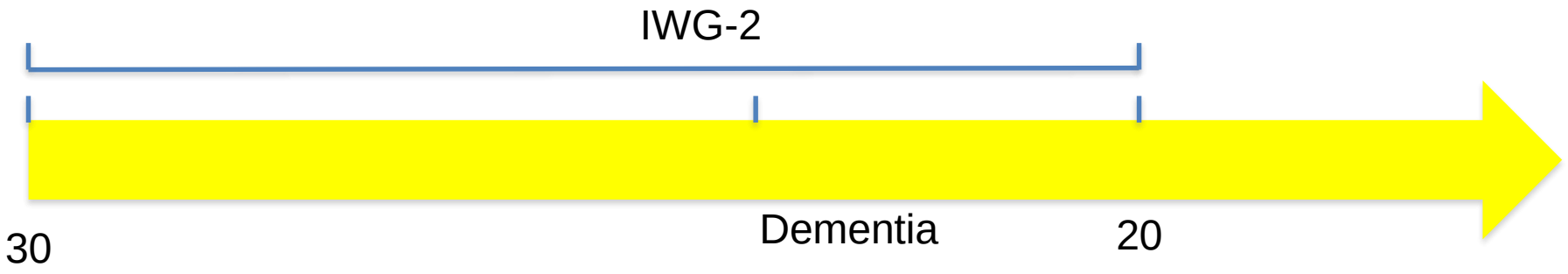
Cognition	Likelihood of AD	Biomarker Evidence
MCI	High likelihood	(+) amyloid-β biomarker **AND** (+) neuronal injury biomarker*
MCI	Intermediate likelihood	(+) amyloid-β biomarker **OR** (+) neuronal injury biomarker*
MCI	Uninformative situation	Biomarkers fall in ambiguous ranges, conflict, not obtained
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	NO
At least, amyloid marker necessary	YES	NO
Specific clinical phenotype required	YES	NO
Integration within a continuum	YES	NO
Different levels of likelihood	NO	YES
Only clinical	NO	YES

« Early AD »: the right target

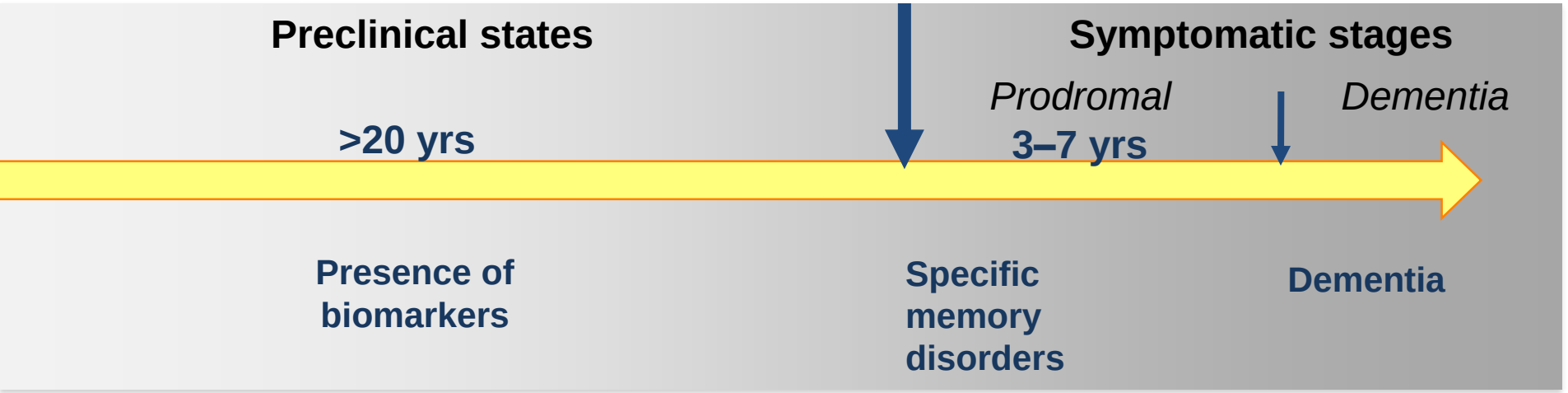
- This includes ‘Prodromal + Mild AD dementia’
- IWG-2 criteria with MMS ≥ 20



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

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 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 (+)**

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

Update: The new lexicon (1)

(Dubois et al, Lancet Neurology 2010)

AD: starts with the first specific symptoms and encompasses both the prodromal and dementia phases

AD dementia: phase of AD with an impact on ADL

Prodromal AD: the early symptomatic, predementia phase of AD

Typical AD: common clinical phenotype of AD, characterized by an early amnestic syndrome of the hippocampal type

Atypical AD: less common but well characterized clinical phenotypes: logopenic aphasia, posterior cortical atrophy, frontal variant of AD. The diagnosis of AD needs in vivo evidence of pathophysiological markers

Mixed AD: patients who fulfill the criteria for AD with clinical and biomarkers evidence of other co-morbid disorders

Update: The new lexicon (2)

Preclinical stages of AD

Asymptomatic at risk: cognitively normal individuals with in vivo pathophysiological biomarkers of AD

Presymptomatic AD: cognitively normal individuals with a proven autosomal dominant mutation

Alzheimer's pathology: neurobiological changes responsible for AD

Pathophysiological markers: in vivo biological changes that reflect the underlying AD pathology (CSF Abeta and tau; PET-amyloid).

They are markers of diagnosis, more targeted at identifying AD.

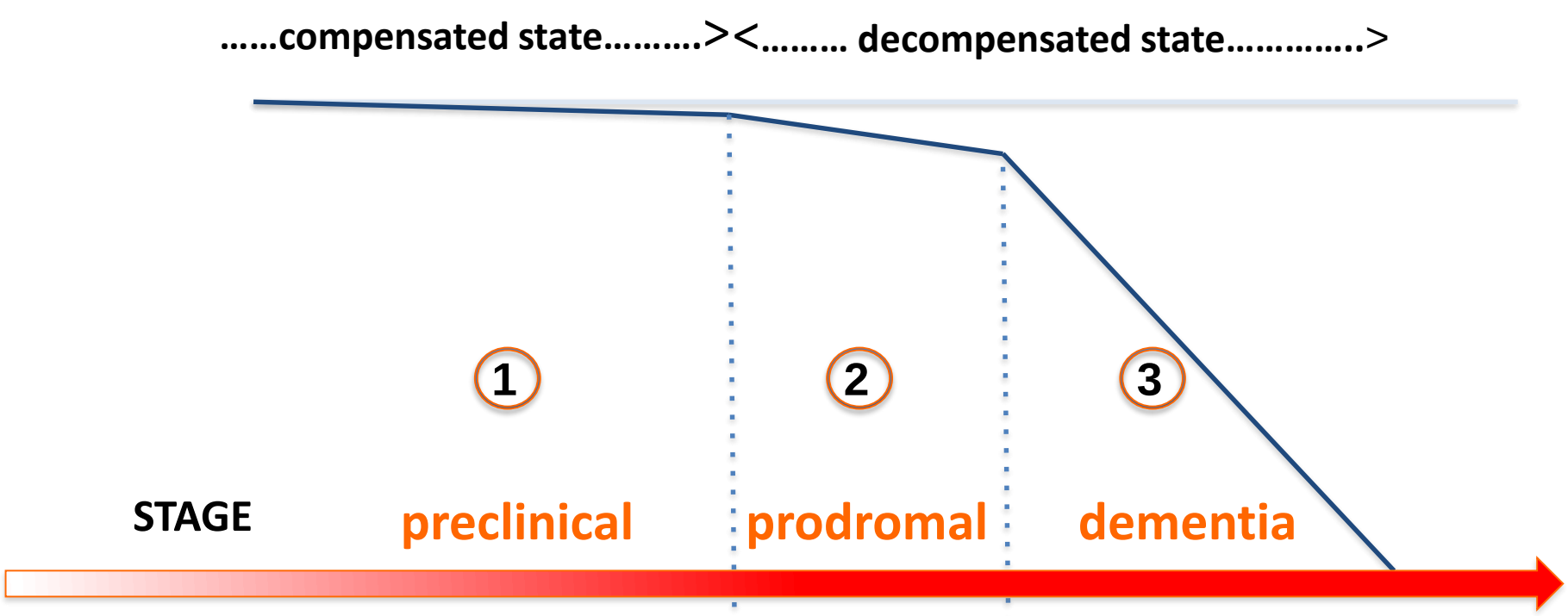
Topographical biomarkers: downstream markers of neurodegeneration: can be structural (atrophy/MRI) or metabolic (hypometabolism/FDG-PET).

They are markers of progression, more targeted at assessing changes over time and predicting outcomes.

What's next?

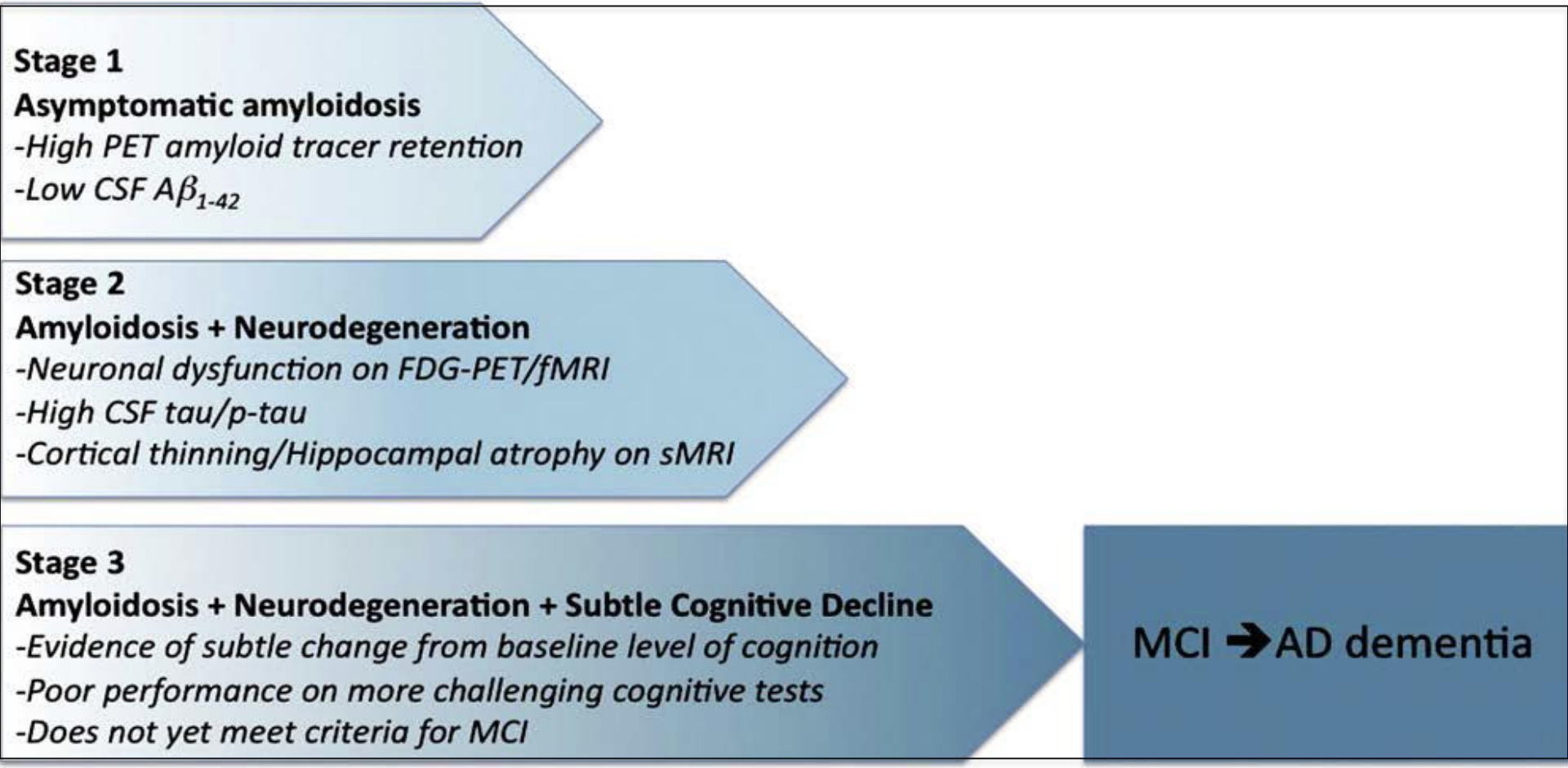
- The preclinical states of AD

AD = a continuum with different stages



NIA-AA: Preclinical AD

Sperling et al, 2011



POSITION PAPER

PART is part of Alzheimer disease

Charles Duyckaerts · Heiko Braak · Jean-Pierre Brion · Luc Buée · Kelly Del Tredici · Michel Goedert · Glenda Halliday · Manuela Neumann · Maria Grazia Spillantini · Markus Tolnay · Toshiki Uchihara

« Entorhinal-hippocampal tau pathology is an invariant feature of AD and is always associated with its development ».

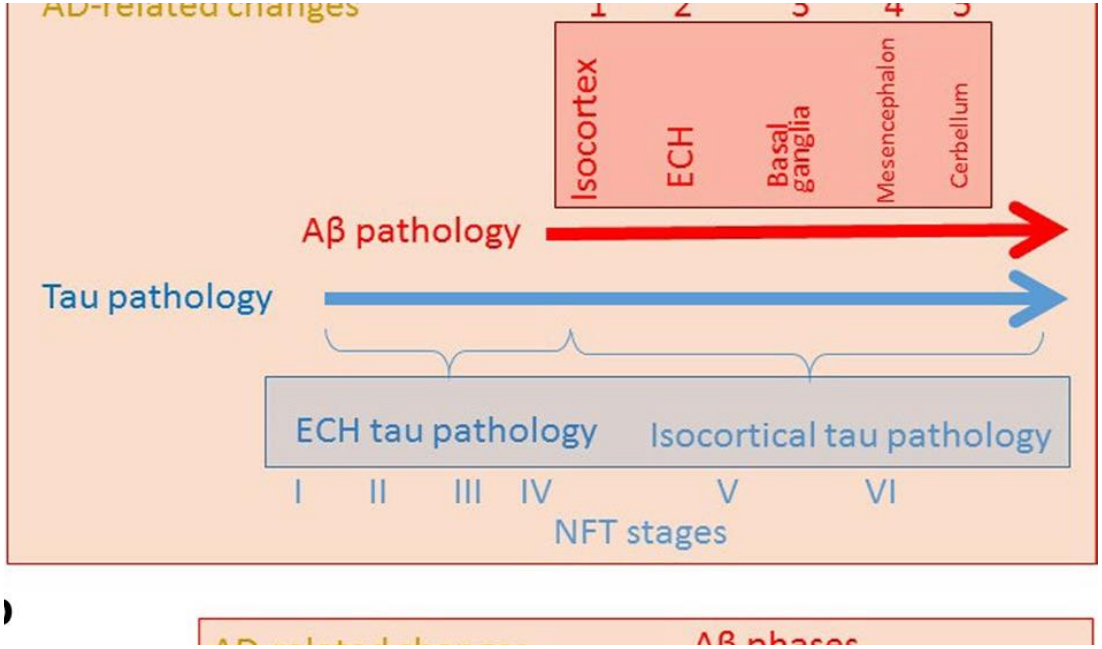


Fig. 1 Relationship between the development of tau pathology and Aβ deposition. **a** Tau pathology in the entorhinal cortex and hippocampus (ECH) belongs to the AD continuum. It is complemented over time by Aβ deposition that occurs in an ordered manner

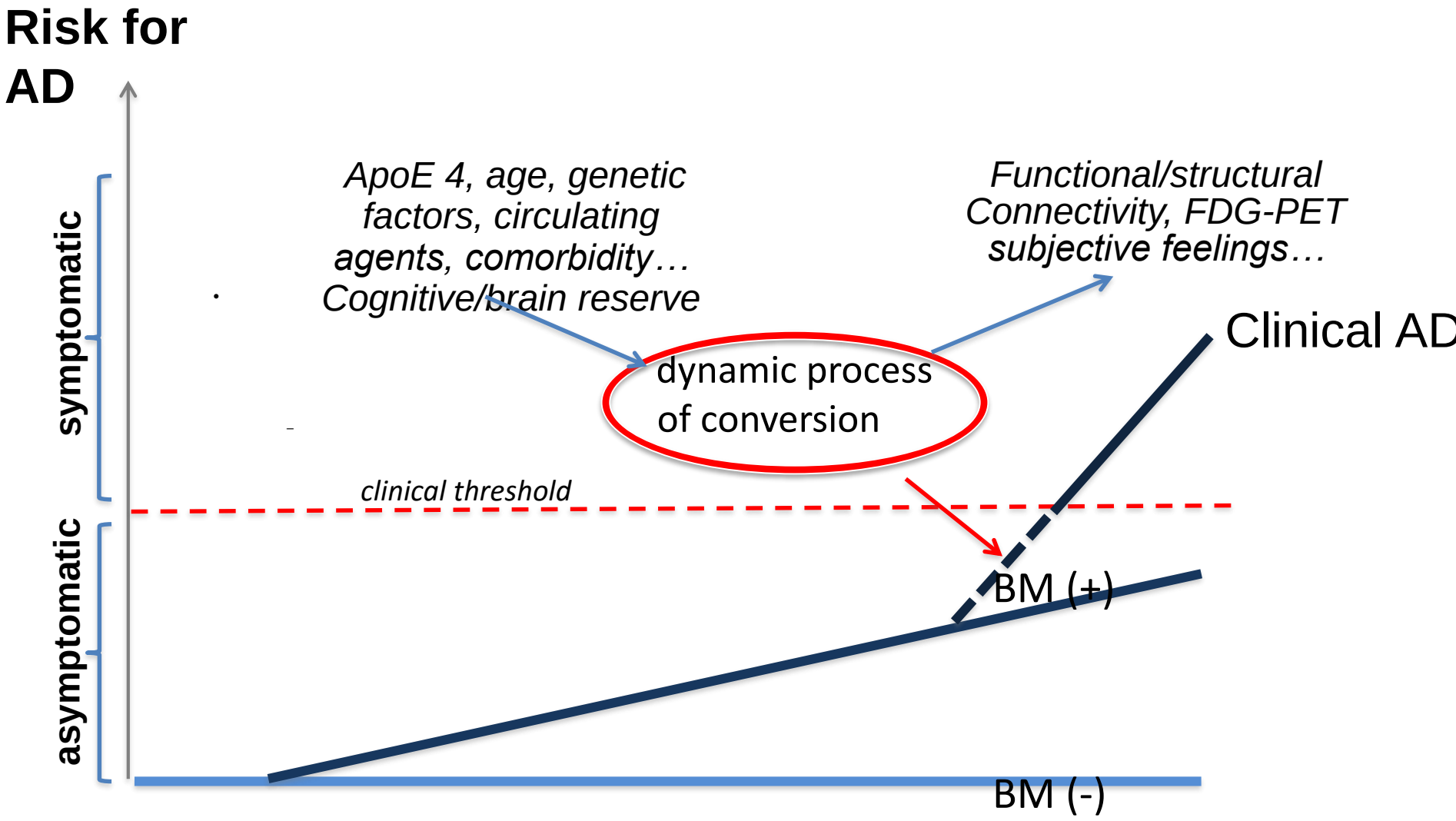
Unresolved issues about preclinical states of AR-AD

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?…

⇒ to better know the natural history of AD
⇒ identify predictive markers of a further conversion
⇒ identify the risk/preventive factors of a clinical disease

The risk for AD - Hypothetical model



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