LIQUOR

CONVEGNO SIN REGIONE LAZIO APPROCCIO DIAGNOSTICO E TERAPEUTICO ALLE MALATTIE RESPONSABILI DI DECADIMENTO COGNITIVO

ALESSANDRO MARTORANA-UOSD CENTRO DEMENZE
PTV UNIVERSITA' DI ROMA TOR VERGATA

ROMA, 22 NOVEMBRE 2019

PREMISES

- Biomarkers hold promise for enabling more effective drug development in AD and establishing a more personalized medicine approach.
- they may soon become essential in staging, tracking, and providing a more quantitative categorization of the disease, as well as for documenting the effect of potential therapeutics.

Draft guidance from FDA, EMA and CHMP

PROS AND CONS FOR CSF SAMPLING

- CSF represents a logical source for developing viable biomarkers in AD given its direct interaction with the extracellular space in the brain, thus potentially reflecting the associated pathophysiological alterations.
- The overall safety record of lumbar puncture is strongly supported by extensive meta-analyses.
- However, fluid biomarkers are unable to reflect brain regional patho-geographies, which may be particularly important during early AD.

PROS AND CONS FOR CSF SAMPLING

- the relative invasiveness of CSF collection by lumbar puncture
- limited access and acceptability in some countries
- the inability to collect samples from large populations especially if serial measures are needed
- concerns over slowing for subject recruitment into clinical trials
- educational gaps on the safety of lumbar puncture
- development and validation of CSF assays and clinical utility.

Amyloid cascade hypothesis

Missense mutations in *APP*, *PS1*, or *PS2* genes

↓

Increased Aβ42 production and accumulation

↓

Aβ42 oligomerization and deposition as diffuse plaques

↓

Subtle effects of Aβ oligomers on synapses

↓

Microglial and astrocytic activation (complement factors, cytokines, etc.)

↓

Progressive synaptic and neuritic injury

↓

Altered neuronal ionic homeostasis; oxidative injury

↓

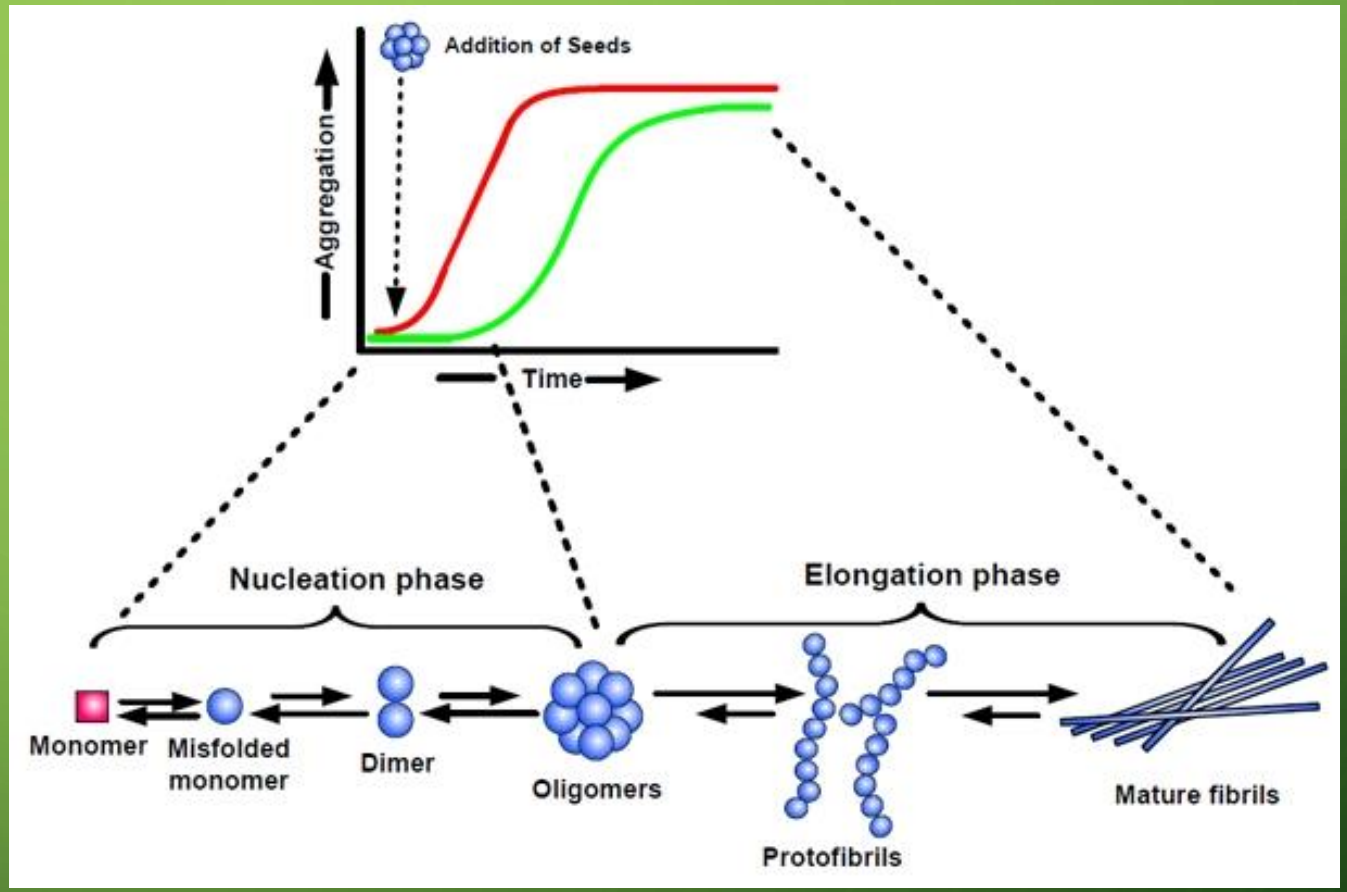
Altered kinase/phosphatase activities ➤ tangles

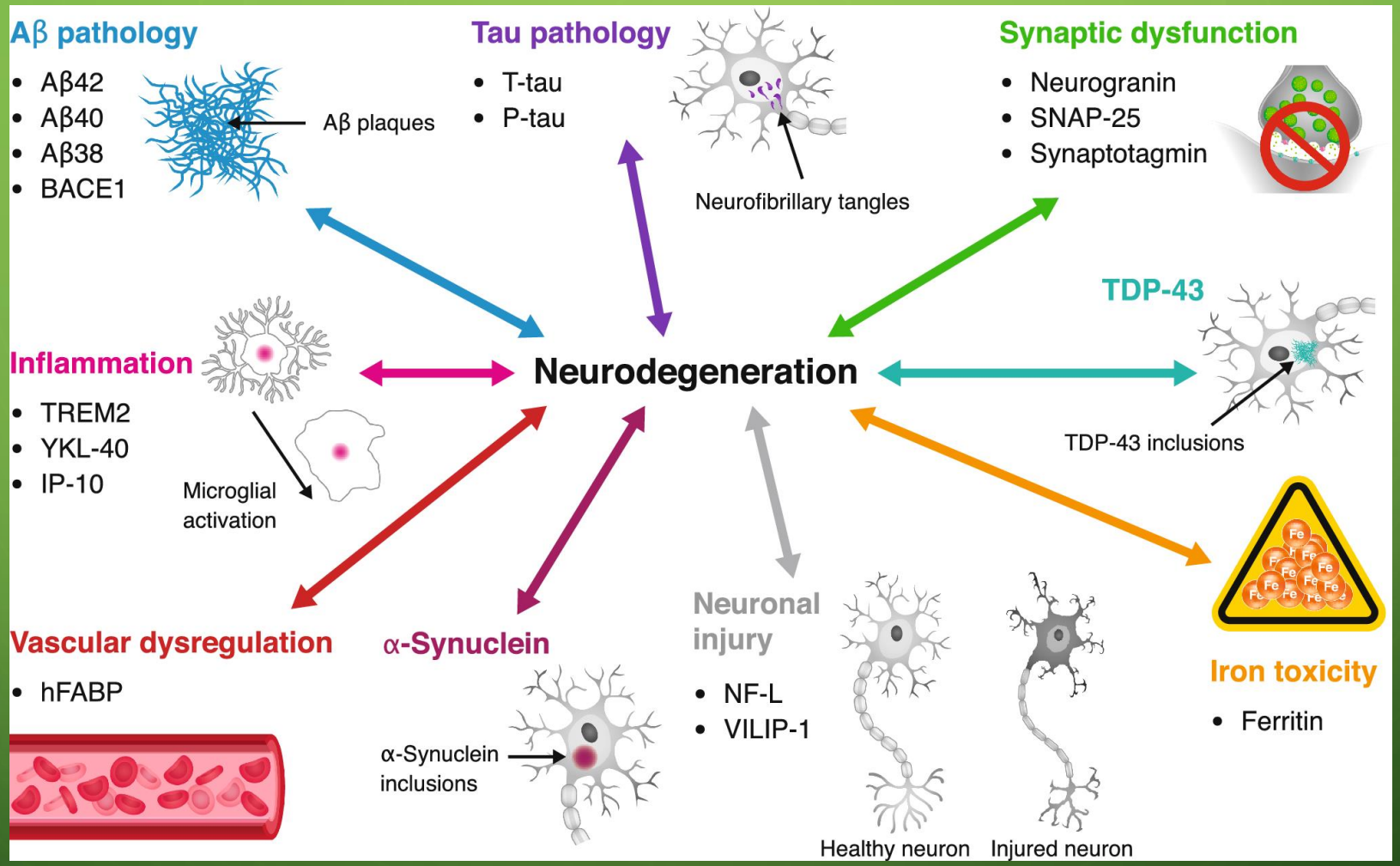
↓

Widespread neuronal/neuritic dysfunction and cell death with transmitter deficits

↓

Dementia




Aβ pathology
• Aβ42
• Aβ40
• Aβ38
• BACE1
Aβ plaques
Tau pathology
• T-tau
• P-tau
Neurofibrillary tangles
Synaptic dysfunction
• Neurogranin
• SNAP-25
• Synaptotagmin
TDP-43
TDP-43 inclusions
Inflammation
• TREM2
• YKL-40
• IP-10
Microglial activation
Neurodegeneration
Vascular dysregulation
• hFABP
α-Synuclein
α-Synuclein inclusions
Neuronal injury
• NF-L
• VILIP-1
Healthy neuron
Injured neuron
Iron toxicity
• Ferritin

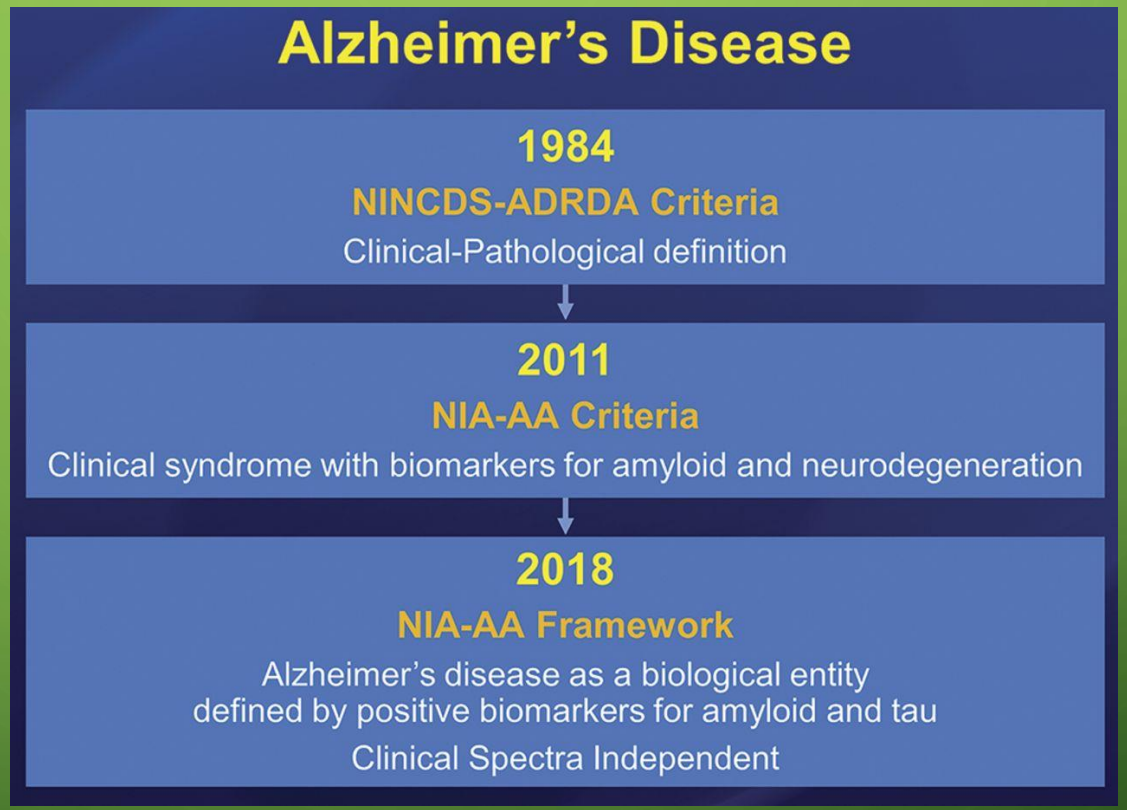
NOT NECESSARILY ALZHEIMER'S

- It is now well established that the prototypical multidomain amnestic dementia phenotype historically used to define probable AD does not "rule in" AD pathologic change (which implies change from normal) at autopsy and the absence of the syndrome does not "rule out" AD pathologic change.
- From 15% to 40% of individuals clinically diagnosed as AD dementia by experts do not display AD neuropathologic changes at autopsy, and a similar proportion has normal amyloid PET or CSF Aβ42 studies.
- Thus, the multidomain amnestic dementia phenotype is not specific; it can be the product of other diseases as well as AD.
- Non amnestic clinical presentations, that is, language, visuospatial, and executive disorders, may also be due to AD.
- In addition, AD neuropathologic changes are often present without signs or symptoms, especially in older persons

AND….

- 30 to 40 % of cognitively unimpaired elderly persons have AD neuropathologic changes at autopsy and a similar proportion has abnormal amyloid biomarkers.
- The fact that an amnestic multidomain dementia is neither sensitive nor specific for AD neuropathologic change suggests that cognitive symptoms are not an ideal way to define AD
- Defining AD by biomarkers indicative of neuropathologic change independent from clinical symptoms represents a profound shift in thinking.
- For many years, AD was conceived as a clinical-pathological construct; it was assumed that if an individual had typical amnestic multidomain symptoms, they would have AD neuropathologic changes at autopsy and if symptoms were absent, they would not have AD at autopsy.
- Symptoms/signs defined the presence of the disease in living persons, and therefore, the concepts of symptoms and disease became interchangeable.

CAN WE CHANGE THE VIEW?



UNDERSTANDING THE DISEASE CONTINUUM

- Based on currently available information, AD is best conceptualized as a biological and clinical continuum covering both the preclinical (clinically asymptomatic individuals with evidence of AD pathology) and clinical (symptomatic) phases of AD.
- In the broadest sense, a continuum is defined as a seamless sequence in which adjacent elements (severities) are not perceptibly different from each other, although the extremes are distinct.

Aisner et al., 2017 BMC Neurology

UNDERSTANDING THE DISEASE CONTINUUM

- In AD, this equates to disease progression from an asymptomatic phase to the symptomatic phase, during which biomarker changes continue and symptoms of cognitive and then functional impairment become increasingly evident, with the eventual loss of independence and death.
- These changes in the individual components of the continuum occur in a sequential but overlapping manner accumulation of Aβ strongly implicates this molecule as a pathological driver in AD, but there is controversy over whether Aβ accumulation alone indicates inevitable progression to AD
- Tau pathology has been suggested as a facilitator of the downstream effects of amyloid.

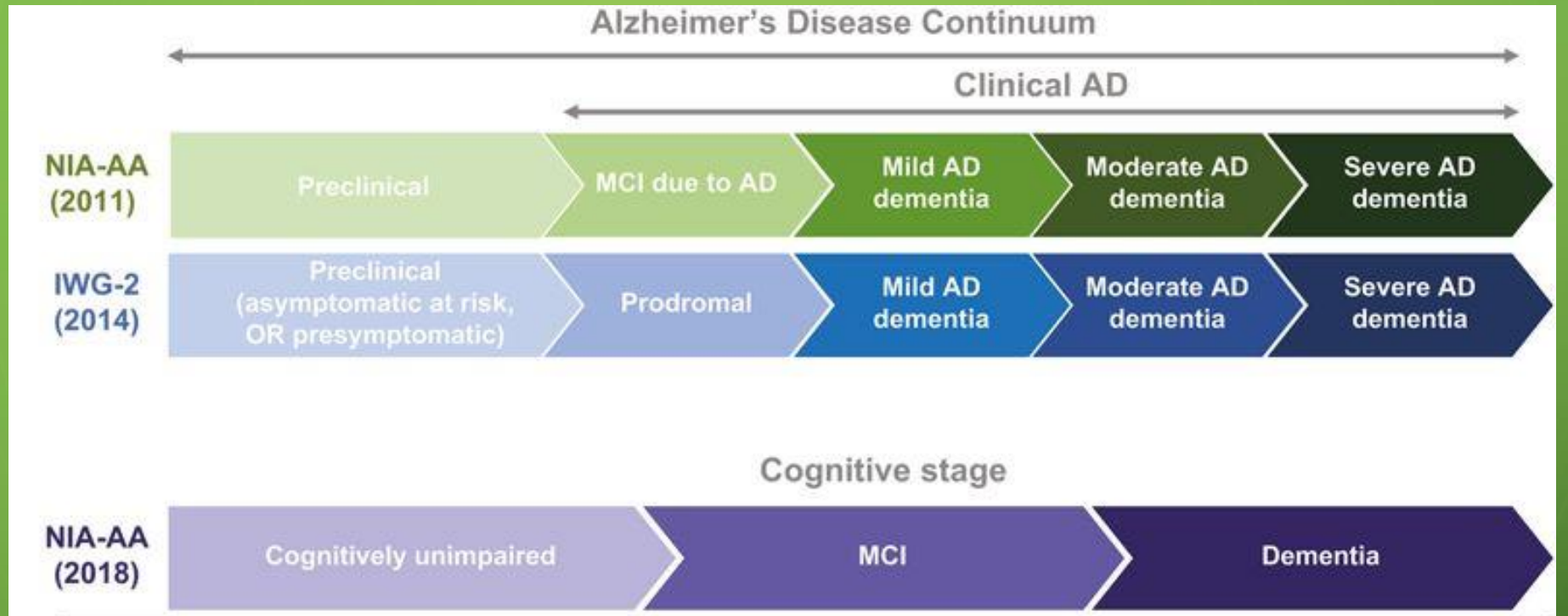
see Aisner et al., 2017; Mucke et al., 2010

ROLE OF BIOMARKER ASSESSMENT

- A diagnosis should be based on both the presence and absence of biomarkers in three categories (amyloid, tau, and neurodegeneration (A/T/N).
- diagnosis is based on both Aβ and tau pathology.
- Using these criteria, the authors went further to differentiate between a "state " and a " stage" .

In simple terms, a state is considered asymptomatic at risk of AD (cognitively normal and amyloid or tau positive but not both) or AD (amyloid and tau positive), while a stage refers to the degree of disease progression within a given state (e.g., clinical AD, preclinical AD, MCI due to AD or prodromal AD, dementia due to AD).

Jack et al., 2017 Neurology



Cognitive stage

NIA-AA (2018)	Cognitively unimpaired	MCI	Dementia

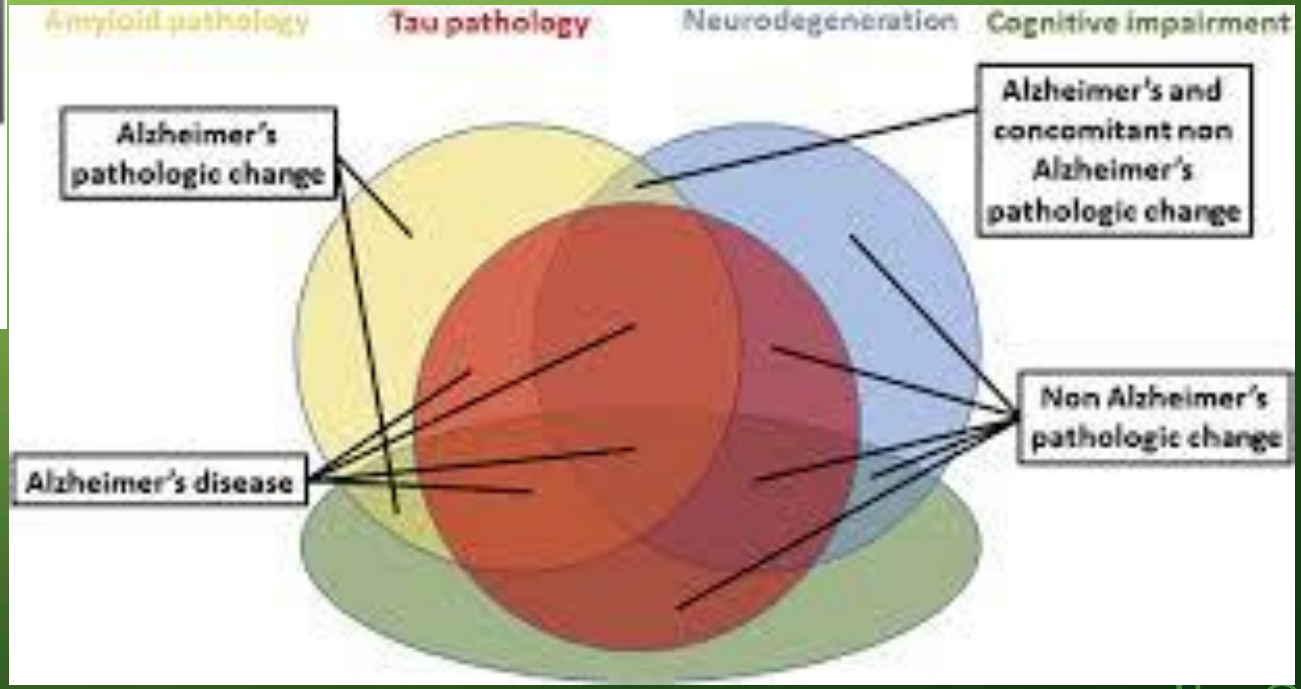
Biomarker category			
A-T-(N)-	Normal AD biomarkers, cognitively unimpaired	Normal AD biomarkers with MCI	Normal AD biomarkers with dementia
A+T-(N)-	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
A+T+(N)-	Preclinical Alzheimer's disease	Alzheimer's disease with MCI (prodromal AD)	Alzheimer's disease with dementia
A+T+(N)+			
A+T-(N)+	Alzheimer's and concomitant suspected non-Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non-Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non-Alzheimer's pathologic change with dementia
A-T+(N)-	Non-Alzheimer's pathologic change, cognitively unimpaired	Non-Alzheimer's pathologic change with MCI	Non-Alzheimer's pathologic change with dementia
A-T-(N)+			
A-T+(N)+			

		Syndromal Cognitive Stage		
		Cognitively unimpaired	**MCI**	**dementia**
Biomarker Profile	$A^- T^- (N)^-$	normal AD biomarkers, cognitively unimpaired	normal AD biomarkers with MCI	normal AD biomarkers with dementia
	$A^+ T^- (N)^-$	Preclinical Alzheimer's pathologic change	Alzheimer's pathologic change with MCI	Alzheimer's pathologic change with dementia
	$A^+ T^- (N)^+$	Alzheimer's and concomitant suspected non Alzheimer's pathologic change, cognitively unimpaired	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with MCI	Alzheimer's and concomitant suspected non Alzheimer's pathologic change with dementia
	$A^+ T^+ (N)^-$	Preclinical Alzheimer's disease	Alzheimer's disease with MCI (Prodromal AD)	Alzheimer's disease with dementia
	$A^+ T^+ (N)^+$			

Non-Alzheimer's continuum profiles are not included in table because the risk associated with different combinations of T+(N)-, T+(N)+, T-(N)+ among A- individuals has not been established

□ rate of short term clinical progression expected to be low

■ rate of short term clinical progression expected to be high



USE OF NIA-A FRAMEWORK FOR CLINICIANS

- The NIA-AA research framework defines AD biologically, by neuropathologic change or biomarkers, and treats cognitive impairment as a symptom/sign of the disease rather than the definition of the disease. This approach should enhance efforts to understand both the biology of AD and the multifactorial etiology of dementia, which has been obscured to some extent in the past by equating amnestic multidomain dementia with the presence of AD neuropathologic changes, and by equating the absence of the prototypical dementia syndrome with the absence of AD neuropathologic changes

DAL 2010 AL 2016: 1081 PRELIEVI PER BIOMARKER PZ CON MCI AMNESTICO O MULTIDOMINIO 775 ERANO COMPATIBILI CON UNO SPETTRO AD

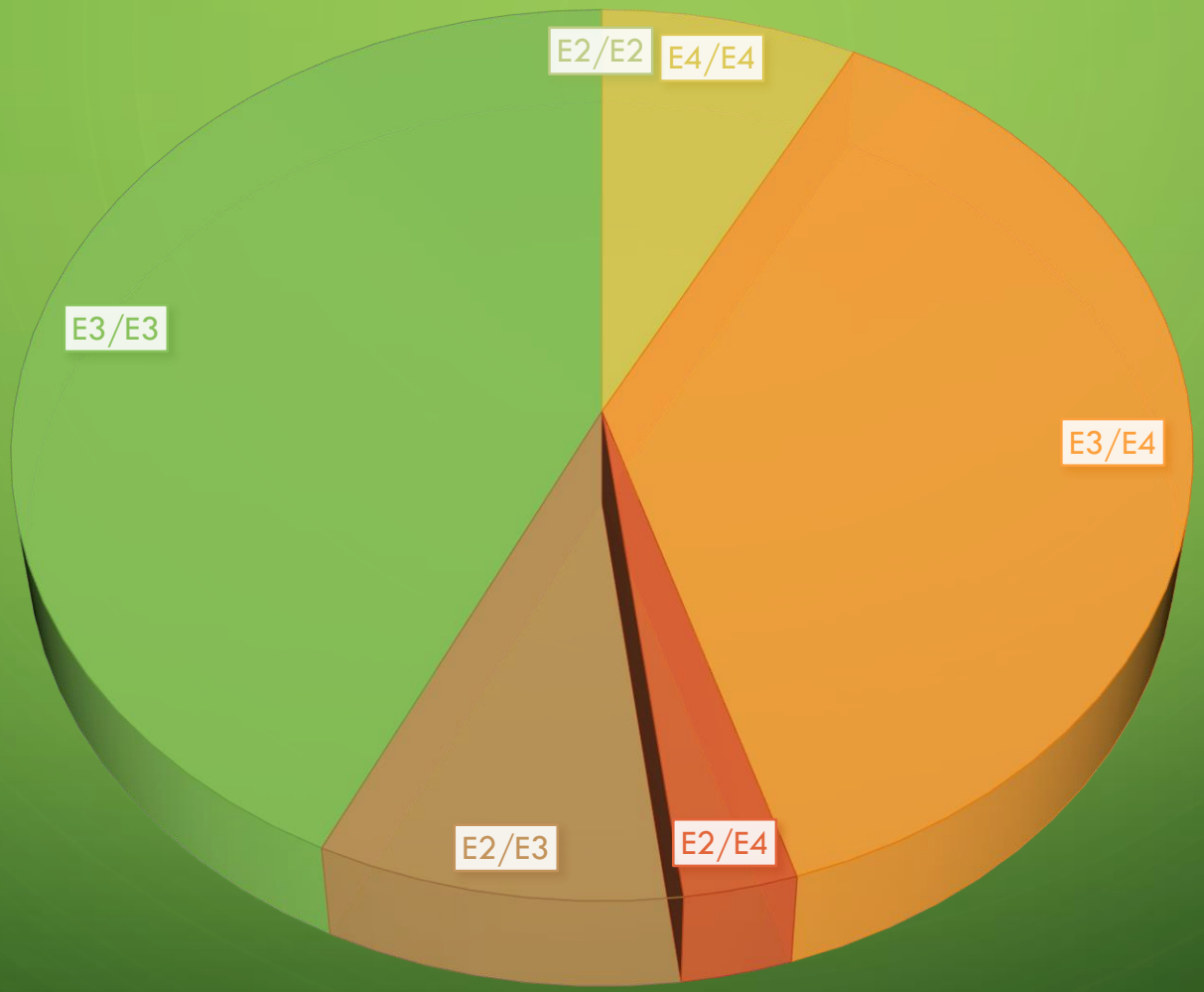
CSF COMPATIBILE CON A+T- (54,8%)

E4/E4	11	2,24%
E3/E4	107	26,10%
E2/E4	10	1,96%
E2/E3	39	9,80%
E3/E3	256	59,20%
E2/E2	2	0,56%

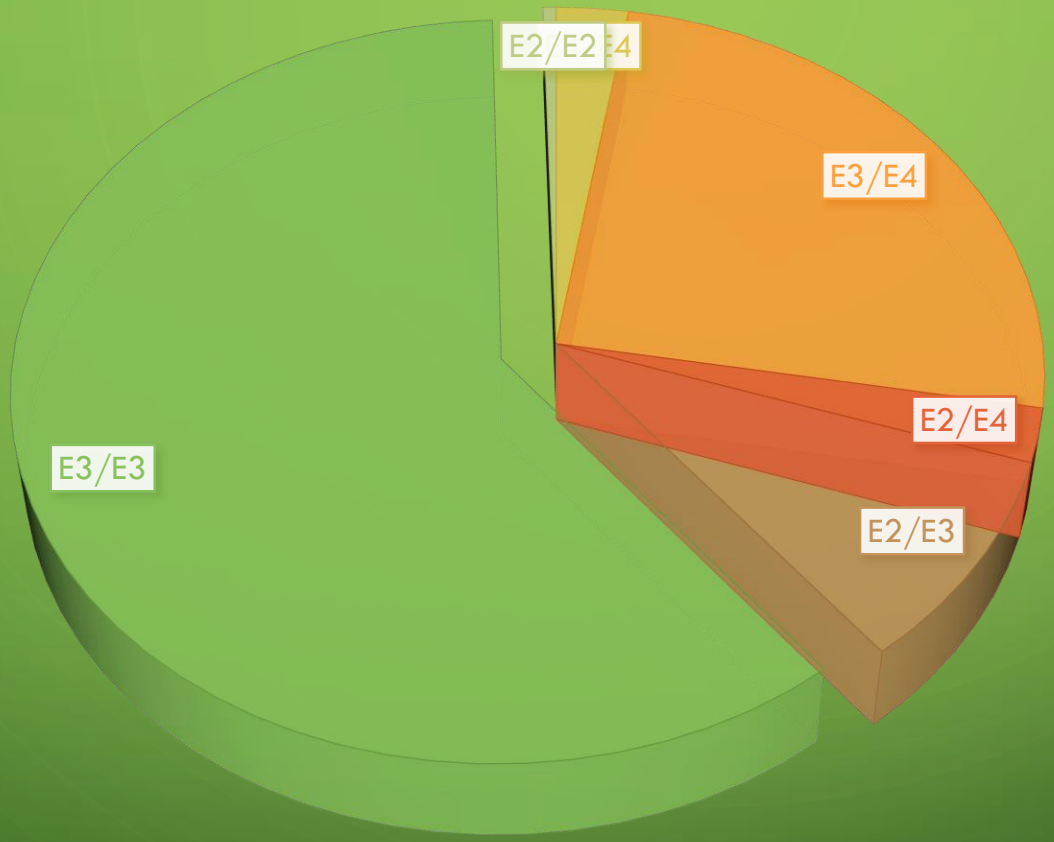
CSF COMPATIBILE CON A+T+ (45,2%)

E4/E4	27	7,70%
E3/E4	131	37,40%
E2/E4	10	3%
E2/E3	32	9,14%
E3/E3	150	42,80%
E2/E2	0	0,00%

CSF AD



CSF IAD



SAME PRESENTATION BUT DIFFERENT EVOLUTION

- Patients A+T- presents with clinical and neuropsychological signs similar to A+T- in early stages (encompassing both typical and atypical presentation)
- Their clinical progression is different
- Their pharmacological response to traditional drugs in use for dementia is excellent

- Patients A+T+ have more rapid progression and worst prognosis
- Do not respond to pharmacological treatment
- Develop more frequently behavioral simptoms
- Need use of neuroleptics

NOTEWORTHY

- CSF biomarkers negative for AD, either A-T+(N+) or A-T-(N+) represent an important result for our understanding of dementia.
- CSF non-AD individuals represents however about 30-35 % of other dementing disorders and deserve reliable tools for early diagnosis and possibly targeted treatments.
- Interpretation of data needs an expert on the field (dementia) able to conclude for a diagnosis in vivo.


THANK YOU