DEMENTIA UPDATE

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DISCLOSURES

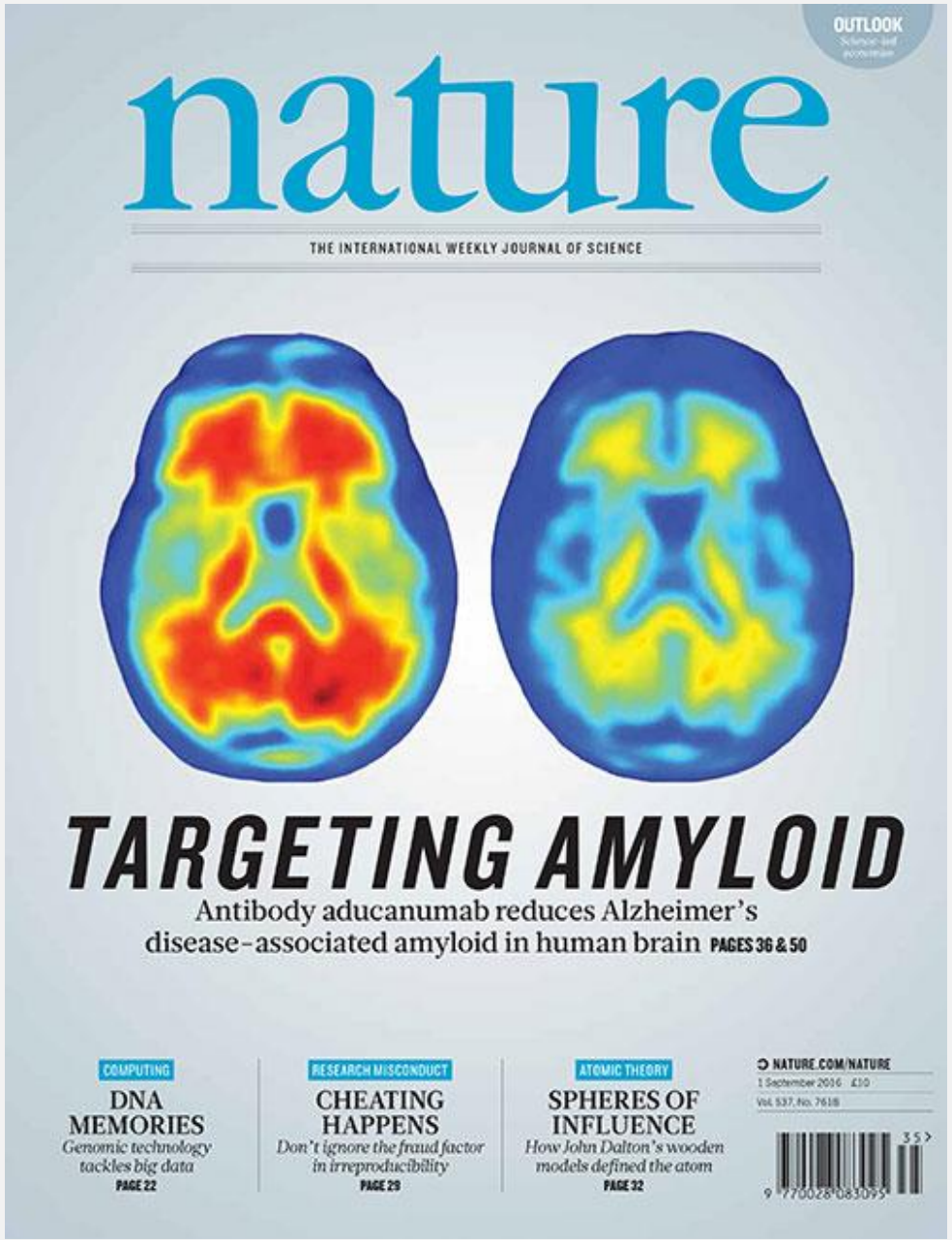
- Prior consulting for Eisai, Inc, 2022
- Co-investigator in multi-center clinical trials sponsored by Eisai, Biogen

OUTLINE

- Why do we care?
- ~~MCI & Dementia – Clinical Diagnosis of AD~~
- ~~MCI & Dementia – Pathological Diagnosis of AD~~
- MCI & Dementia – Clinicopathologic Diagnosis of AD
- How does this impact me?
- A day in the life
- Beyond amyloid & tau

WHY DO WE CARE?

WHY DO WE CARE?



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WHY DO WE CARE?

September 28, 2022

LECANEMAB CONFIRMATORY PHASE 3 CLARITY AD STUDY MET PRIMARY ENDPOINT, SHOWING HIGHLY STATISTICALLY SIGNIFICANT REDUCTION OF CLINICAL DECLINE IN LARGE GLOBAL CLINICAL STUDY OF 1,795 PARTICIPANTS WITH EARLY ALZHEIMER'S DISEASE

- *ALL KEY SECONDARY ENDPOINTS ALSO MET, DEMONSTRATING HIGHLY STATISTICALLY SIGNIFICANT RESULTS*
- *PROFILE OF AMYLOID-RELATED IMAGING ABNORMALITIES (ARIA) INCIDENCE WAS WITHIN EXPECTATIONS*
- *EISAI AIMS TO FILE FOR TRADITIONAL APPROVAL IN THE U.S., AND TO SUBMIT MARKETING AUTHORIZATION APPLICATIONS IN JAPAN AND EUROPE BY THE END OF EISAI FY2022, WHICH ENDS ON MARCH 31, 2023*

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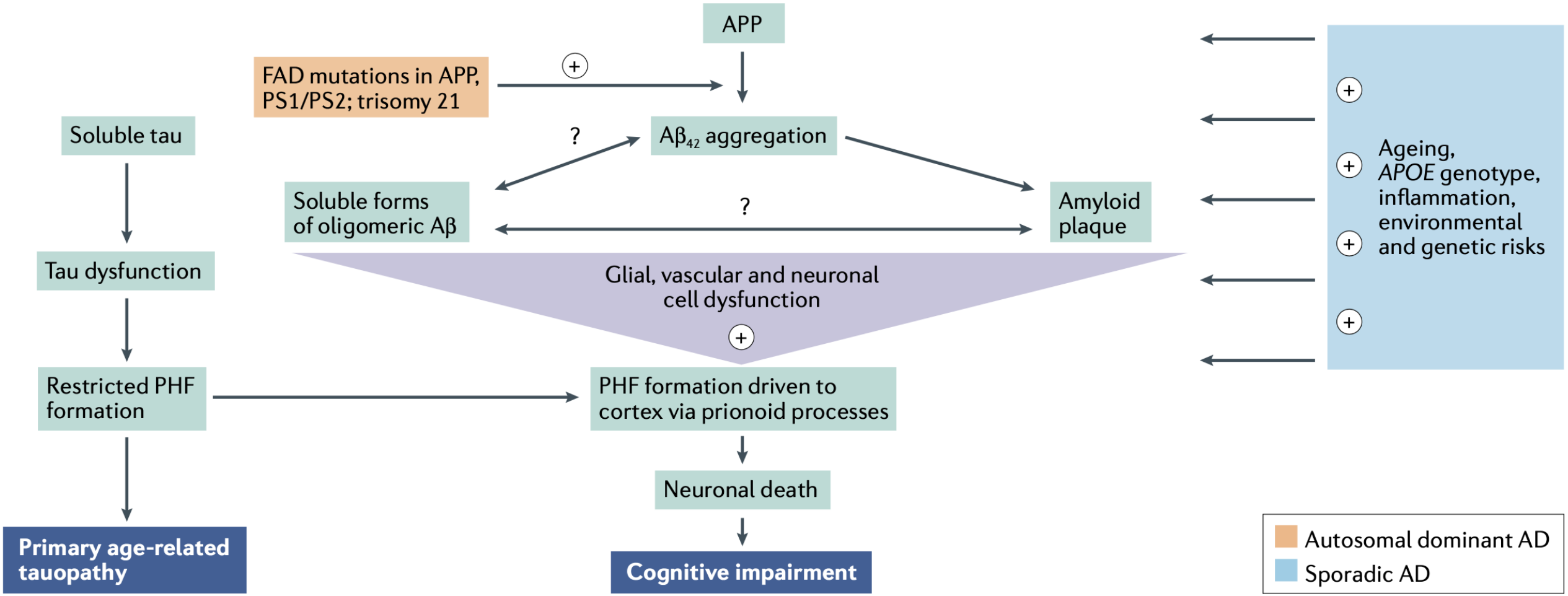
Year	Drug	Company	Mechanism of action	Target	Patient population	Outcome	Observations
2007	Tramiprosate	Neurochem	Unclear; may interact with Aβ oligomers	Soluble Aβ/Aβ oligomers	Mild to moderate AD	Lack of efficacy	–
2009	Tarenflurbil	Myriad Genetics/ Lundbeck	γ-Secretase modulator	Soluble Aβ	Mild AD	Lack of efficacy	Unlikely to have achieved adequate target engagement in the brain
2011	Semagacestat	Eli Lilly	γ-Secretase inhibitor	Soluble Aβ	Mild to moderate AD	Toxicity and lack of efficacy	Increases cognitive decline/no lowering of brain amyloid
2012	Bapineuzumab	Elan/Pfizer/ Johnson & Johnson	Anti-Aβ mAb	Soluble Aβ and plaque	Mild to moderate AD	Lack of efficacy	No significant removal of amyloid
2013	Gammagard	Baxter	Unclear; IVIG may bind soluble Aβ	Soluble Aβ	Mild to moderate AD	Lack of efficacy	–
2013	Solanezumab	Eli Lilly	Anti-Aβ mAb	Soluble Aβ	Mild to moderate AD	Lack of efficacy	No removal of amyloid
2016	Gantenerumab	Hoffman La Roche	Anti-Aβ mAb	Plaque	Mild AD	Lack of efficacy	Converted into an open-label study
2016	Solanezumab	Eli Lilly	Anti-Aβ mAb	Soluble Aβ	Mild AD	Lack of efficacy	No removal of amyloid
2016	Solanezumab	Eli Lilly	Anti-Aβ mAb	Soluble Aβ	Prodromal AD	Trial halted	–
2016	Verubecestat	Merck	BACE inhibitor	Soluble Aβ	Mild to moderate AD	Lack of efficacy	Increases cognitive decline/modest lowering of brain amyloid (~20 CL)

Year	Drug	Company	Mechanism of action	Target	Patient population	Outcome	Observations
2016	Verubecestat	Merck	BACE inhibitor	Soluble Aβ	Mild to moderate AD	Lack of efficacy	Increases cognitive decline/modest lowering of brain amyloid (~20 CL)
2018	Verubecestat	Merck	BACE inhibitor	Soluble Aβ	Prodromal AD	Lack of efficacy	Increases cognitive decline
2018	Atabecestat	Janssen	BACE inhibitor	Soluble Aβ	Asymptomatic at risk of AD	Toxicity	Increases cognitive decline
2018	Lanabecestat	AstraZeneca/Eli Lilly	BACE inhibitor	Soluble Aβ	Early AD	Lack of efficacy	Increases cognitive decline
2018	Lanabecestat	AstraZeneca/Eli Lilly	BACE inhibitor	Soluble Aβ	Mild AD	Lack of efficacy	Increases cognitive decline
2019	Crenezumab	AC Immune/ Hoffman La Roche	Anti-Aβ mAb	Soluble Aβ	Prodromal to mild AD	Lack of efficacy	–
2019	Elenbecestat	Biogen/Eisai	BACE inhibitor	Soluble Aβ	Prodromal to MCI due to AD	Lack of efficacy	Increases cognitive decline
2019	Umibecestat	Amgen/Novartis	BACE inhibitor	Soluble Aβ	Asymptomatic at risk of AD	Lack of efficacy	Increases cognitive decline
2019	Amilomotide	Novartis	Vaccine	Aβ	Asymptomatic at risk of AD	Trial halted	–
2020	Aducanumab	Biogen/Eisai	Anti-Aβ mAb	Plaque	MCI to early dementia	Evidence of efficacy	BLA given accelerated approval by the FDA but rejected by the CHMP of the EMA

+ Gantenerumab 2022, Lecanemab 2022

THE AMYLOID HYPOTHESIS



Karran & De Strooper, *Nature*, April 2022

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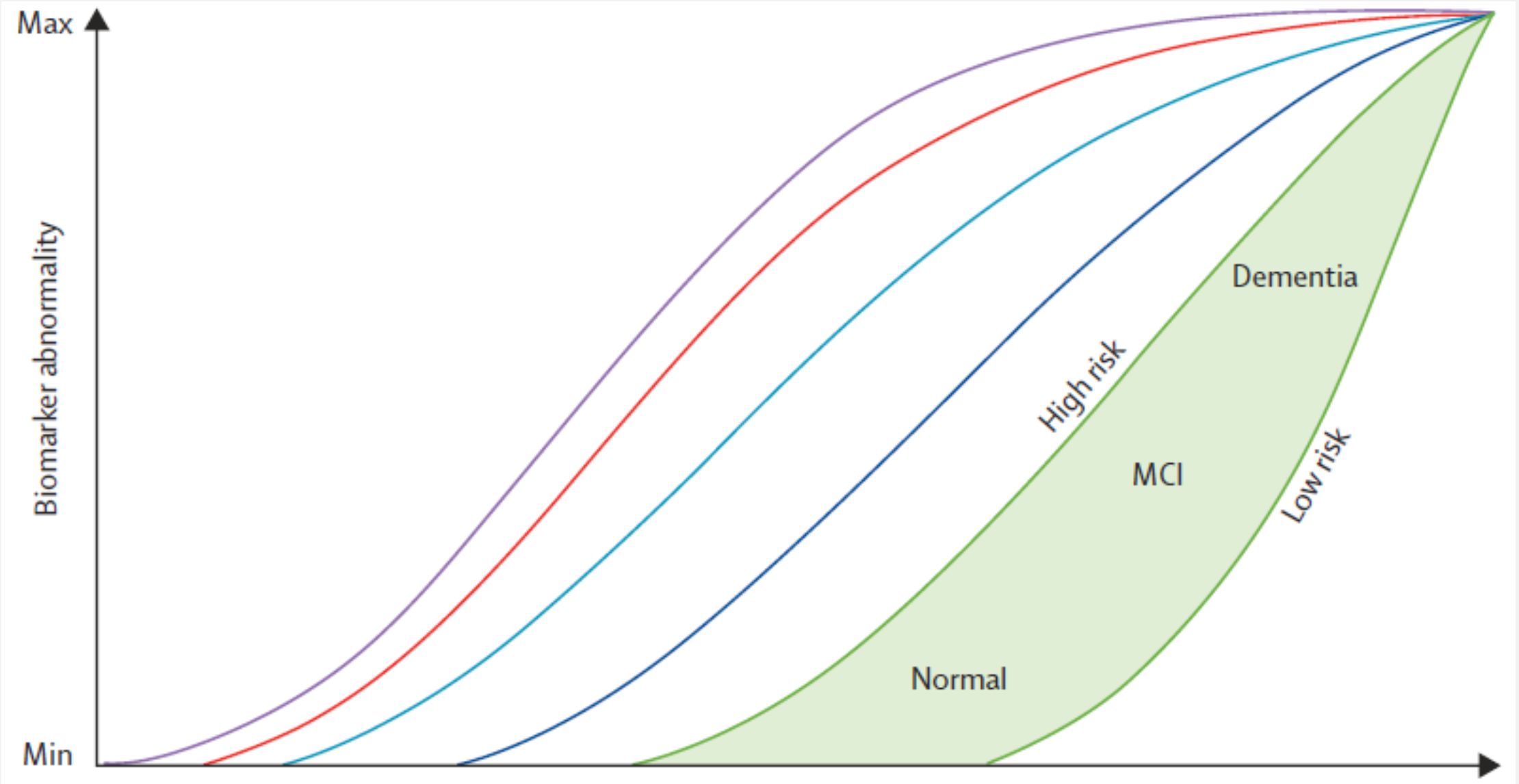

Lancet Neurol 2013; 12: 207–16

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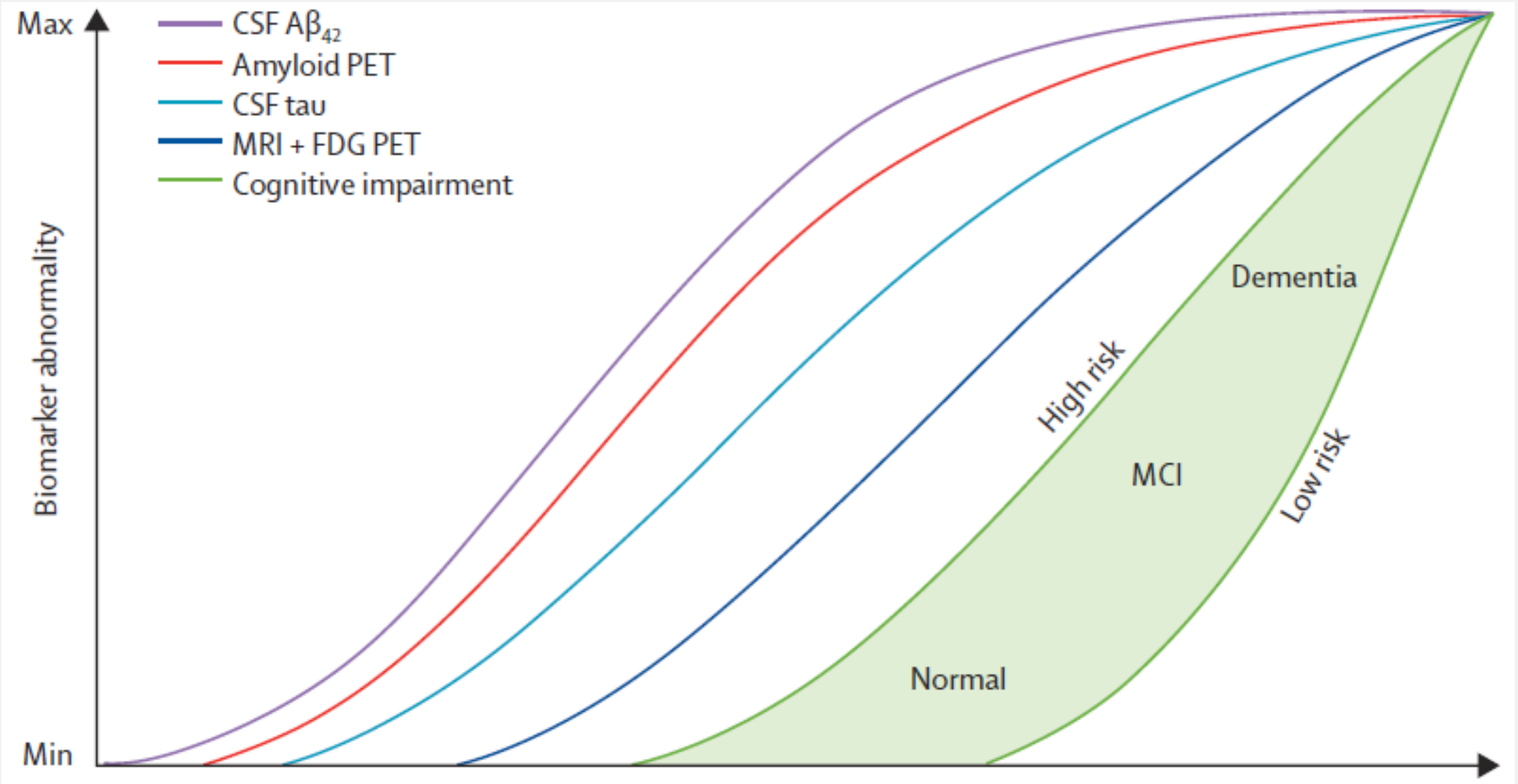

Lancet Neurol 2013; 12: 207–16

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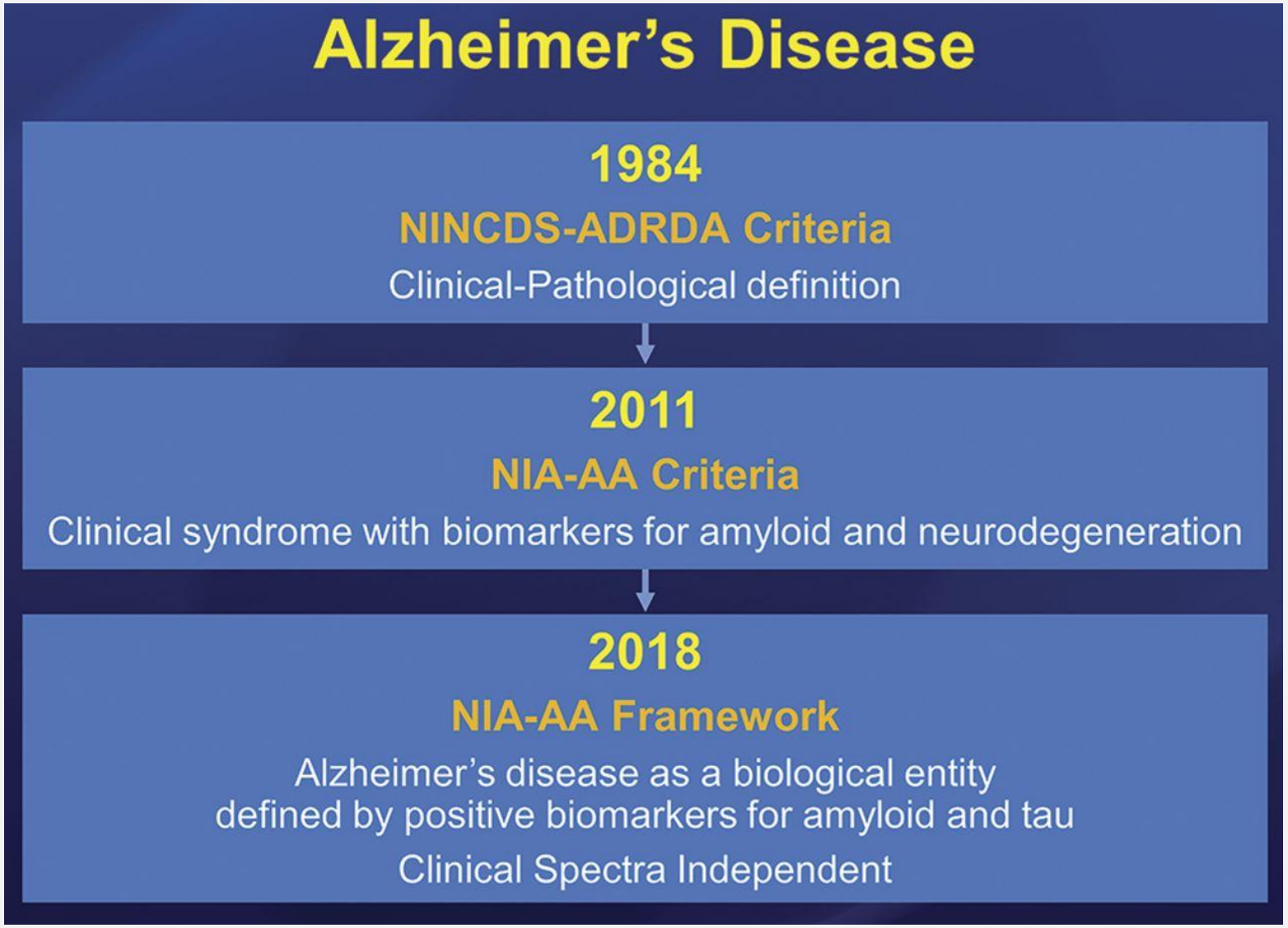
MCI & DEMENTIA – CLINICOPATHOLOGIC DIAGNOSIS

- SMC, MCI, Dementia
  - Functional labels
  - Agnostic as to pathology

- Alzheimer's disease, FTD, DLB, etc
  - Pathologic diagnoses
  - Can vary from normal to severe dementia

Temporal evolution of criteria and research frameworks for Alzheimer disease



Ronald C. Petersen Neurology 2018;91:395-402

2011 CONSENSUS CRITERIA FOR DIAGNOSING PROBABLE ALZHEIMER'S DISEASE ("AD")

Must meet all 3 criteria:

1. **Insidious onset** (gradually evolve over months to years)
2. **Progressive worsening** of cognition (report/observation)
3. **Initial/most prominent** cognitive deficit(s) fit one of the following **phenotypes**:

a. Amnestic (75%)

Impairment in learning and recall of recently learned information
Evidence of cognitive dysfunction in at least one other domain

b. Non-amnestic

Language presentation (logopenic variant primary progressive aphasia):

Deficits in word-finding and at least 1 other cognitive domain

Visuospatial presentation (posterior cortical atrophy):

Deficits in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, optic ataxia, oculomotor apraxia, and alexia and at least 1 other cognitive domain

Executive presentation

Deficits in impaired reasoning, judgment, and problem solving and at least 1 other cognitive domain

Corticobasal syndrome

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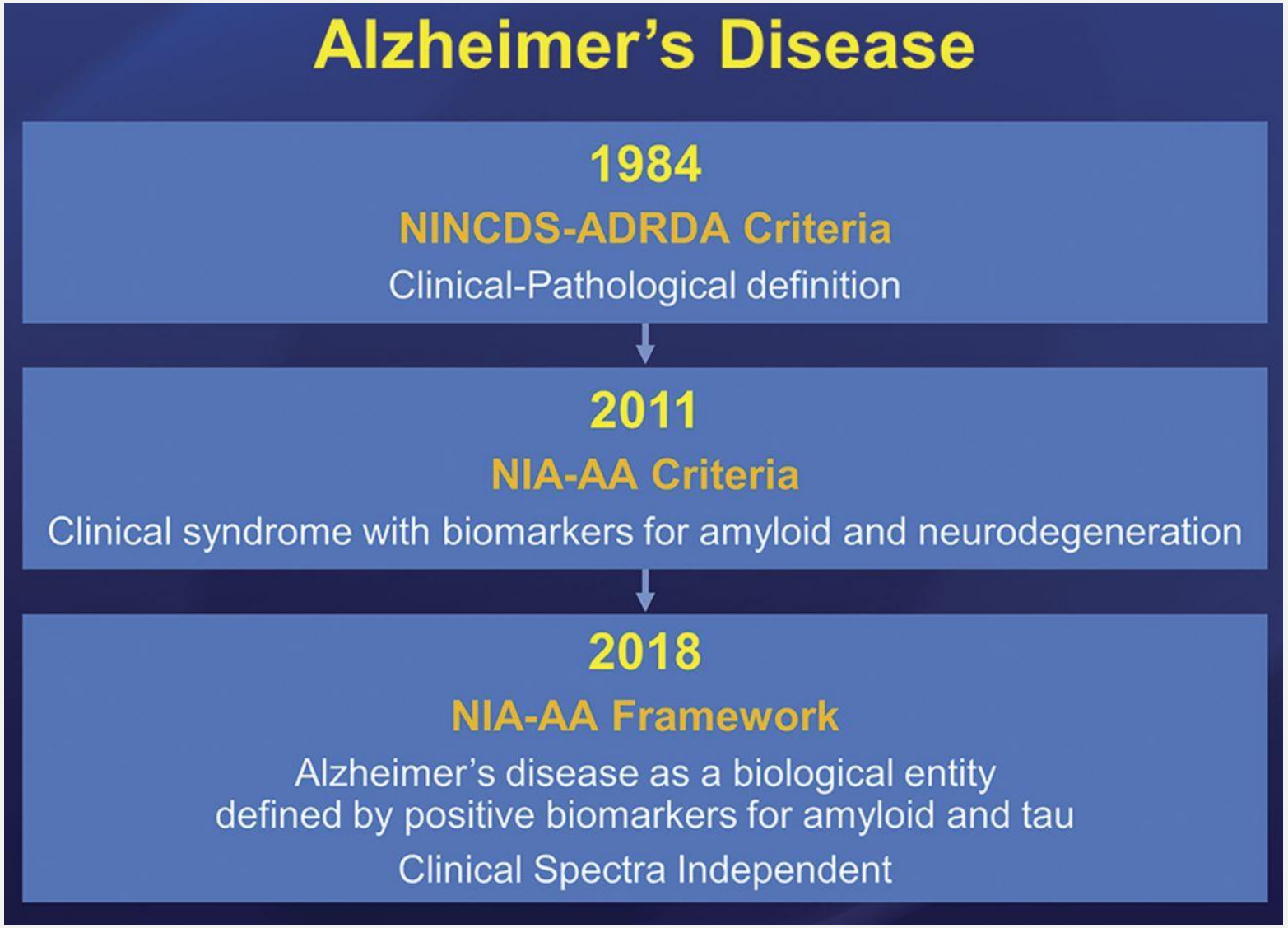
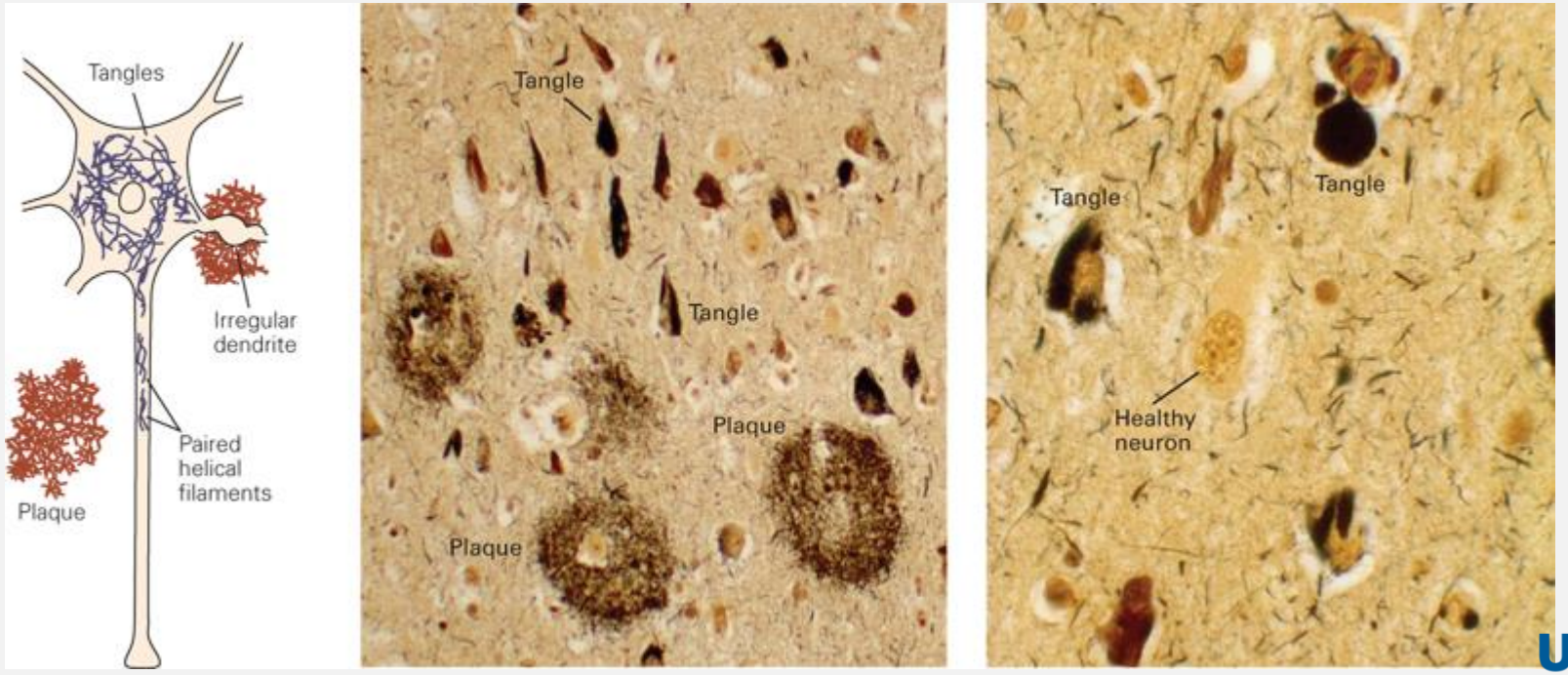
Temporal evolution of criteria and research frameworks for Alzheimer disease



Ronald C. Petersen Neurology 2018;91:395-402

ALZHEIMER'S DISEASE PATHOLOGY
ATN FRAMEWORK

- A: Biomarkers of fibrillary ***Amyloid β deposition***
- T: Biomarkers of ***tau pathology (neurofibrillary tangles)***
- N: Biomarkers of ***neurodegeneration or neuronal injury***



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AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

Definition

A: Aβ biomarkers determine whether or not an individual is in the Alzheimer's continuum.
T: Pathologic tau biomarkers determine if someone who is in the Alzheimer's continuum has Alzheimer's disease.

Staging severity
(N): Neurodegenerative/neuronal injury biomarkers **(C):** Cognitive symptoms

A and T indicate specific neuropathologic changes that define Alzheimer's disease, whereas (N) and (C) are not specific to Alzheimer's disease and are therefore placed in parentheses.

ATN: PRACTICAL APPLICATION OF A RESEARCH PARADIGM

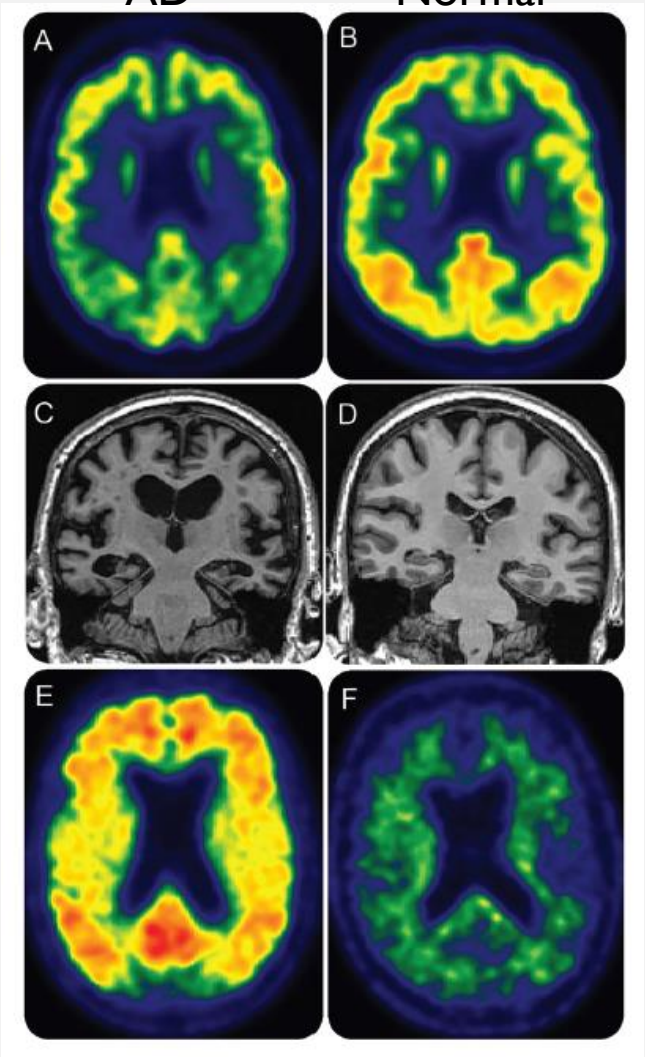
Currently available imaging for clinical purposes:

FDG-PET **(N)**

MRI **(N)**

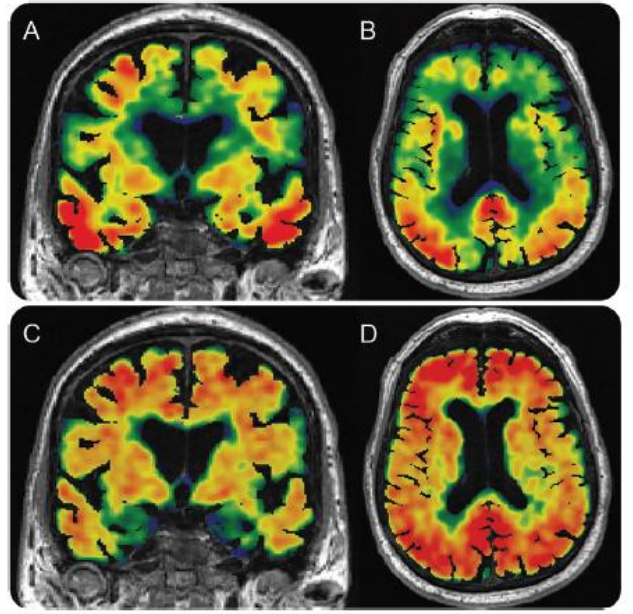
Amyloid-PET **(A)**

AD Normal



Research only
Tau-PET **(T)**

Coronal Axial



Amyloid PET **(A)**

Coronal Axial

Neurology. 2016 Aug 2;87(5):539-47.

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Temporal evolution of criteria and research frameworks for Alzheimer disease

	NINCDS–ADRDA (1984)[2]	IWG (2007)[3]	IWG (2010)[4]	NIA–AA (2011)[5,6]	IWG (2014)[7]	IWG–AA (2016)[8]	NIA–AA (2018)[1]	IWG (2021)
Applicable settings	Research and clinical	Research	Research	Research and clinical	Research	Research	Research	Research and clinical
Clinical requirements	Dementia (memory changes and another cognitive impairment)	Amnestic syndrome of a hippocampal type	Amnestic syndrome of a hippocampal type, posterior cortical variant, logopenic variant, or behavioural–frontal variant	Mild cognitive impairment (amnestic or non-amnestic) or dementia	Amnestic syndrome of a hippocampal type, posterior cortical variant, logopenic variant, or behavioural–frontal variant	None	None	Amnestic variant, posterior cortical atrophy, logopenic variant primary progressive aphasia, behavioural or dysexecutive frontal variant, corticobasal syndrome, semantic and nonfluent variants of primary progressive aphasias*
Biological requirements	None	CSF biomarkers, MRI atrophy, ^{18}F-fluorodeoxyglucose PET hypometabolism, amyloid PET positive, or Alzheimer's disease autosomal dominant mutation	Pathophysiological markers: CSF changes (low CSF Aβ42, high phosphorylated tau, or high total tau) or amyloid PET positive	Amyloid β marker (CSF or PET) or marker of degeneration (CSF tau, phosphorylated tau, ^{18}F-fluorodeoxyglucose-PET, and T1-weighted MRI)	CSF amyloid β and tau or amyloid PET positive	Amyloid β marker (CSF or PET) and tau marker (CSF or PET)	Amyloid β marker (CSF or PET) and tau marker (CSF or PET)	Amyloid β marker (CSF or PET) and tau marker (CSF or PET)

ADRDA=Alzheimer's Disease and Related Disorders Association (now the Alzheimer's Association) Work Group. IWG=International Working Group criteria. IWG–AA=International Working Group and Alzheimer's Association joint criteria. NIA–AA=US National Institute on Aging and Alzheimer's Association joint criteria. NINCDS=US National Institute of Neurological and Communicative Disorders and Stroke criteria.
*Cognitively unimpaired individuals are considered at-risk for Alzheimer's Disease.

Table 1: **Details of successive proposed criteria for Alzheimer's disease diagnosis**

Dubois & Villain et al, Lancet Neurology 2021

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	Likelihood of Alzheimer's disease as a primary diagnosis	Further investigation
Common Alzheimer's disease phenotypes (amnestic variant, logopenic variant of primary progressive aphasia, and posterior cortical atrophy)		
Amyloid positive, tau positive	Highly probable–established	None required
Amyloid positive, tau unknown	Probable	Consider a tau measure (PET, CSF)
Amyloid positive, tau negative	Probable	Consider an additional tau measure (PET, CSF)
Tau positive, amyloid unknown	Possible	Consider an amyloid measure (PET, CSF)
Tau positive, amyloid negative	Possible	Consider an additional amyloid measure (PET, CSF)
Amyloid negative, tau unknown	Unlikely	Full investigation of cause and consider a tau measure (PET, CSF)*
Amyloid unknown, tau negative	Unlikely	Full investigation of cause and consider an amyloid measure (PET, CSF)*
Amyloid negative, tau negative	Highly unlikely–excluded	Full investigation of cause*†
Amyloid unknown, tau unknown	Non-assessable	Consider tau and amyloid measures (PET, CSF)

Dubois & Villain et al, Lancet Neurology 2021

N Engl J Med. 2022 Nov 29. doi: 10.1056/NEJMoa2212948. Online ahead of print.

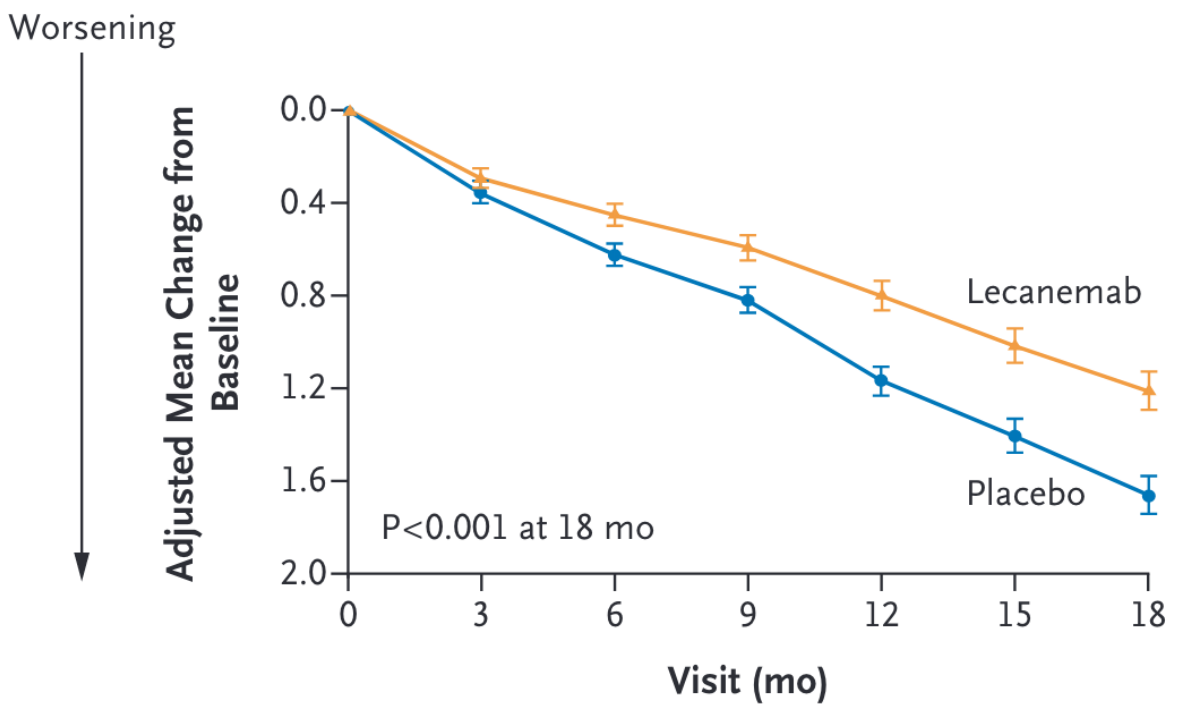
Lecanemab in Early Alzheimer's Disease

Christopher H van Dyck [1], Chad J Swanson [1], Paul Aisen [1], Randall J Bateman [1], Christopher Chen [1], Michelle Gee [1], Michio Kanekiyo [1], David Li [1], Larisa Reyderman [1], Sharon Cohen [1], Lutz Froelich [1], Sadao Katayama [1], Marwan Sabbagh [1], Bruno Vellas [1], David Watson [1], Shobha Dhadda [1], Michael Irizarry [1], Lynn D Kramer [1], Takeshi Iwatsubo [1]

Affiliations + expand

PMID: 36449413 DOI: 10.1056/NEJMoa2212948

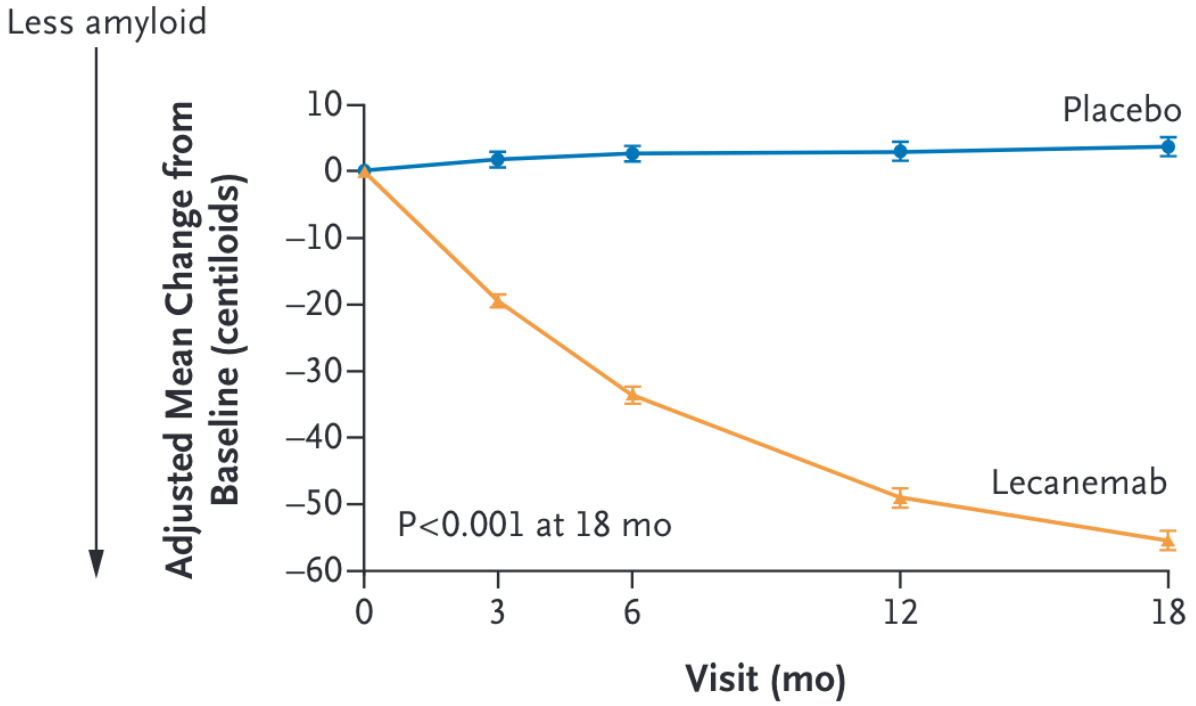
CDR-SB Score



No. of Participants

Lecanemab	859	824	798	779	765	738	714
Placebo	875	849	828	813	779	767	757

Amyloid Burden on PET



No. of Participants

Lecanemab	354	296	275	276	210
Placebo	344	303	286	259	205

van Dyke et al., NEJM 2022

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ARIA‡		
ARIA-E — no. (%)	113 (12.6)	15 (1.7)
Symptomatic ARIA-E — no. (%)§	25 (2.8)	0
ApoE ε4 noncarrier — no./total no. (%)	4/278 (1.4)	0/286
ApoE ε4 carrier — no./total no. (%)	21/620 (3.4)	0/611
ApoE ε4 heterozygote	8/479 (1.7)	0/478
ApoE ε4 homozygote	13/141 (9.2)	0/133
ARIA-E according to ApoE ε4 genotype — no./total no. (%)		
ApoE ε4 noncarrier	15/278 (5.4)	1/286 (0.3)
ApoE ε4 carrier	98/620 (15.8)	14/611 (2.3)
ApoE ε4 heterozygote	52/479 (10.9)	9/478 (1.9)
ApoE ε4 homozygote	46/141 (32.6)	5/133 (3.8)
ARIA-H — no. (%)	155 (17.3)	81 (9.0)
Microhemorrhage	126 (14.0)	68 (7.6)
Superficial siderosis	50 (5.6)	21 (2.3)
Macrohemorrhage	5 (0.6)	1 (0.1)
Symptomatic ARIA-H§	6 (0.7)	2 (0.2)
Isolated ARIA-H: no concurrent ARIA-E	80 (8.9)	70 (7.8)

van Dyke et al., NEJM 2022

HOW DOES THIS IMPACT ME?

- Clinical syndrome is still important
- Disease modifying therapy is coming (???)
- Biomarker-based diagnosis will likely become standard of care

A DAY IN THE LIFE

- Four questions
  - Is it neurodegenerative?
  - If yes, what is the underlying pathology?
  - Are there behavioral symptoms in need of treatment?
  - Are there appropriate research studies?

A DAY IN THE LIFE

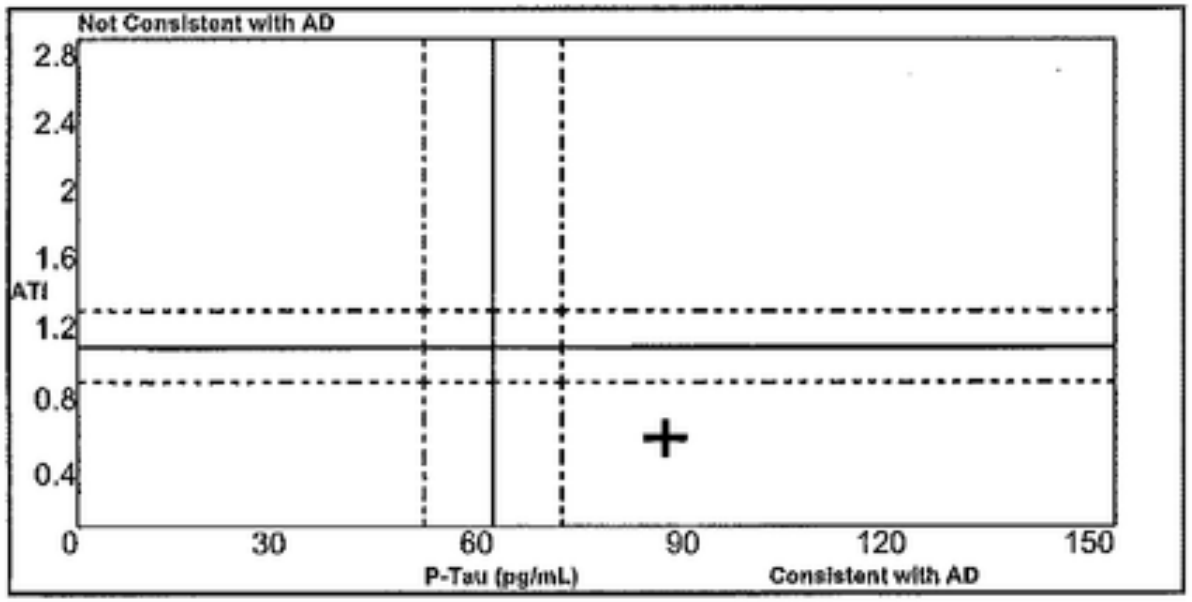
- Is it neurodegenerative?
  - History, history, history
  - Brain MRI, helpful or no?
  - FDG-PET?

A DAY IN THE LIFE

- What is the underlying pathology?
  - CSF AD biomarkers – just do it!
  - Amyloid PET
  - Tau PET

A DAY IN THE LIFE

Sample CSF AD result



Athena

Component Ref Range & Units	
P-Tau/Abeta42 <=0.023 ratio	0.076 ^
Abeta42 >1026 pg/mL	366 v
Total-Tau <=238 pg/mL	254 ^
Phospho-Tau(181P) <=21.7 pg/mL	27.7 ^

Mayo

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A DAY IN THE LIFE

ALZHEIMER AD IN- SEE COMMENTS
TERPRETATION

Comment: The elevated p-Tau/Abeta42 ratio is consistent with the
presence of pathological changes associated with Alzheimer's disease.

The p-Tau/Abeta42 ratio provides better concordance with
amyloid Positron Emission Tomography (PET) imaging when
compared to Abeta42, phospho-Tau and total-Tau individually. A cut-off of 0.023 provides optimal balance
between NPA (negative % agreement) and PPA (positive %
agreement) when compared to amyloid PET results. A
p-Tau/Abeta42 ratio of <=0.023 has a 92% NPA with normal
amyloid PET. A ratio of >0.023 has a 92% PPA with
abnormal amyloid PET.

Component Ref Range & Units	4/15/22 11:02 AM
P-Tau/Abeta42 <=0.023 ratio	0.076 ^
Abeta42 >1026 pg/mL	366 v
Total-Tau <=238 pg/mL	254 ^
Phospho-Tau(181P) <=21.7 pg/mL	27.7 ^

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A DAY IN THE LIFE

- Are there behavioral symptoms in need of treatment?
  - Treatable now!

A DAY IN THE LIFE

- Are there appropriate research studies?

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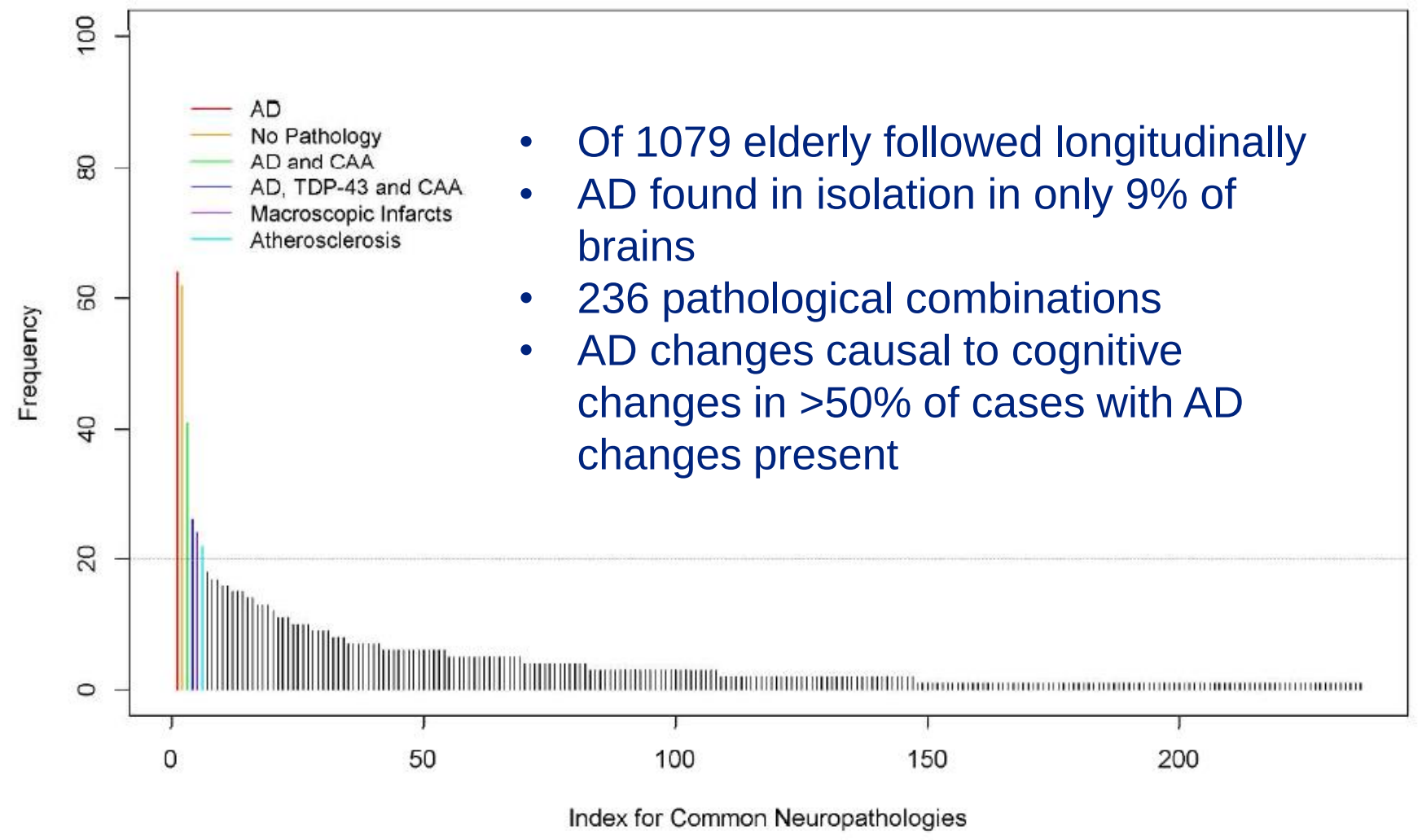
BEYOND AMYLOID



- Of 1079 elderly followed longitudinally
- AD found in isolation in only 9% of brains
- 236 pathological combinations
- AD changes causal to cognitive changes in >50% of cases with AD changes present

Ann Neurol. 2018 Jan;83(1):74-83.

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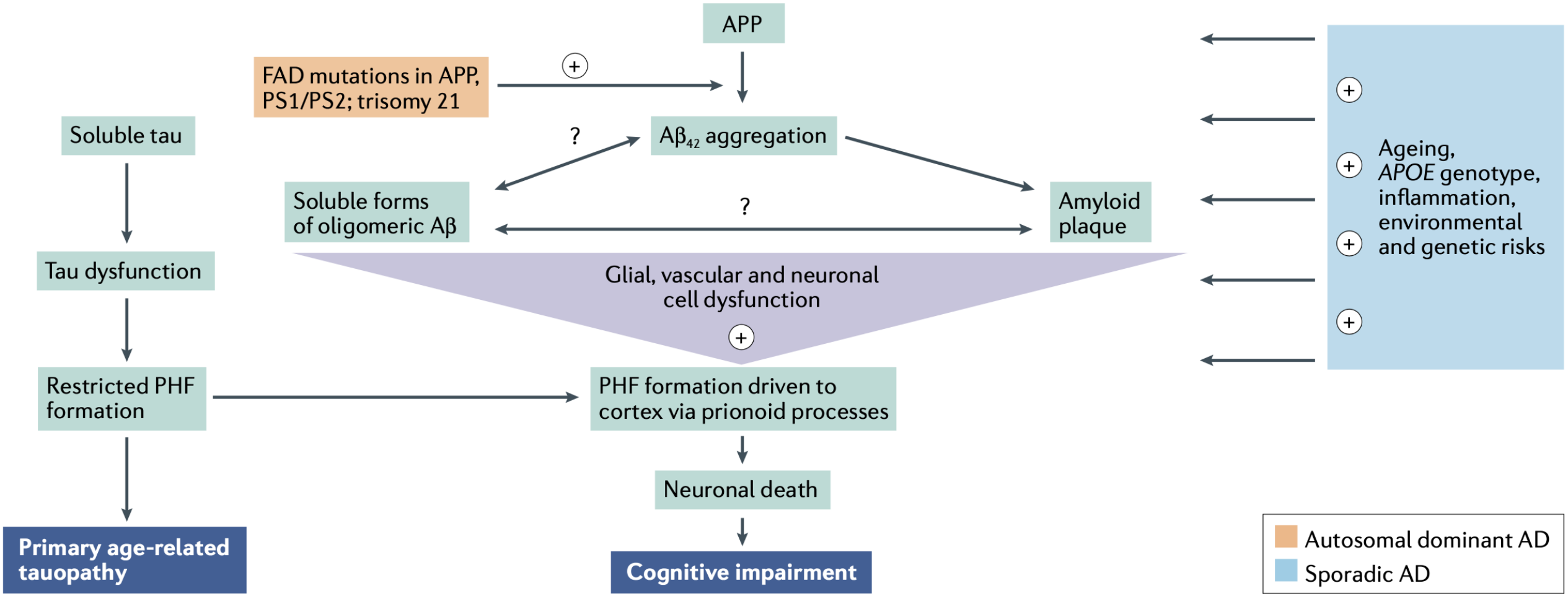
BEYOND AMYLOID & TAU



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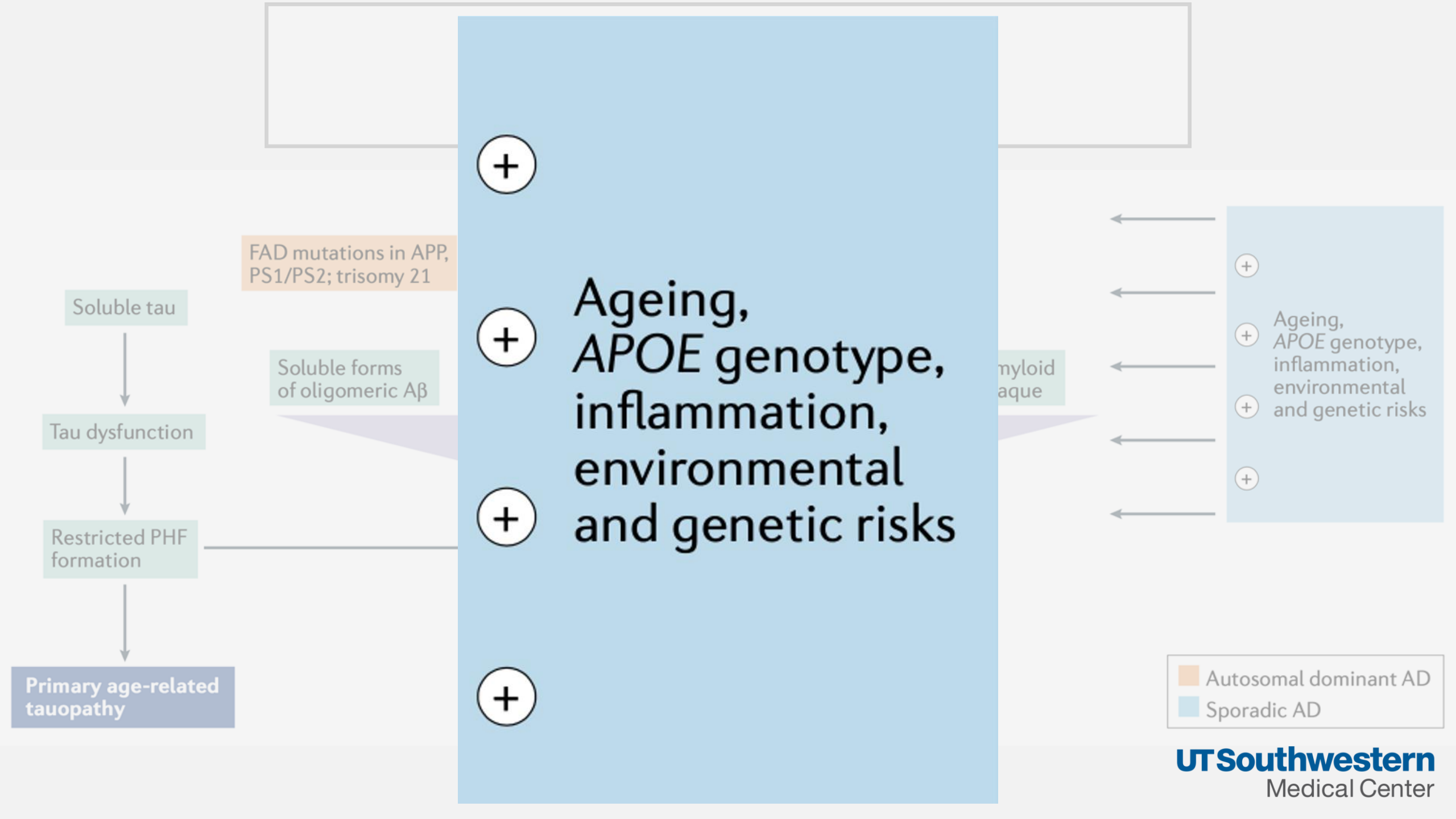
FAD mutations in APP, PS1/PS2; trisomy 21
Soluble tau
Tau dysfunction
Restricted PHF formation
Primary age-related tauopathy
Soluble forms of oligomeric Aβ
myloid aque
Ageing, APOE genotype, inflammation, environmental and genetic risks
Ageing, APOE genotype, inflammation, environmental and genetic risks
Autosomal dominant AD
Sporadic AD
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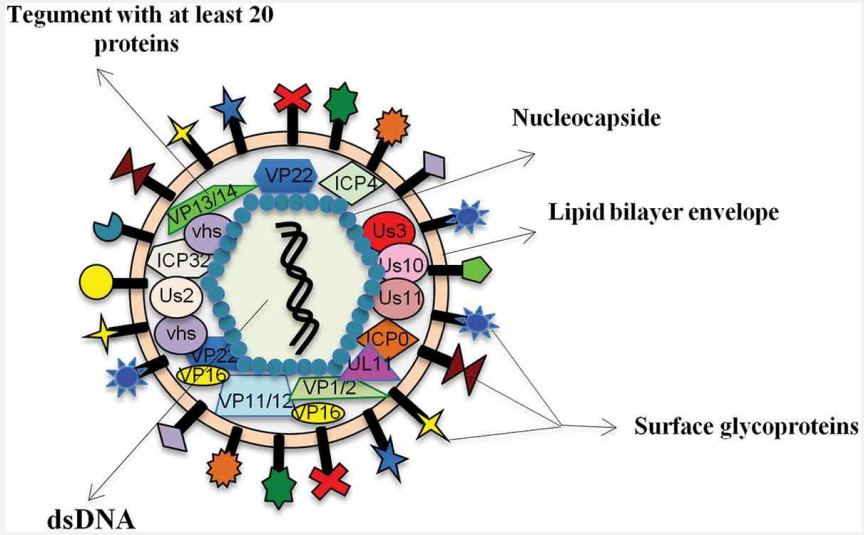
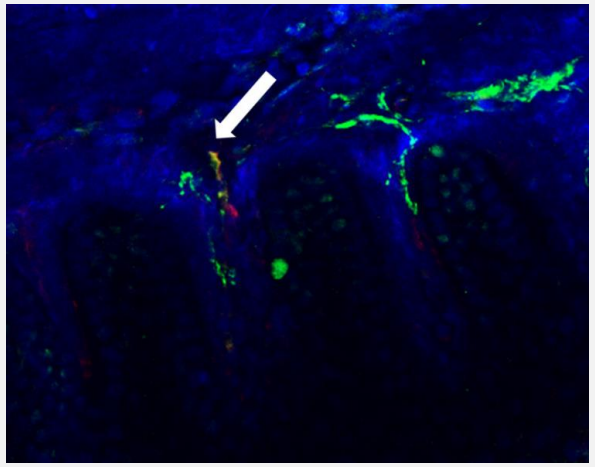
BEYOND AMYLOID & TAU

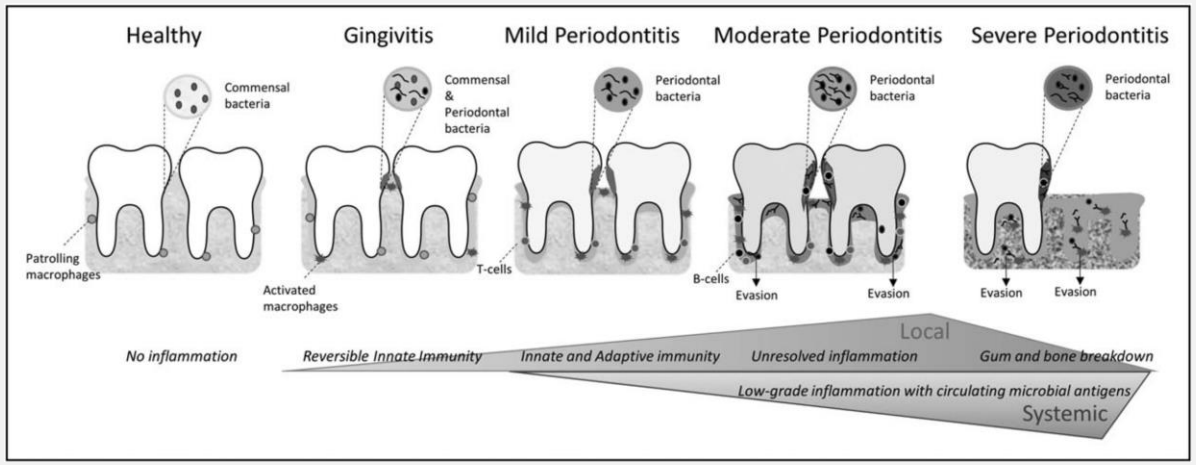
- Inflammation
- Infection
  - Viruses
  - Dental flora
- Skin biopsy – alpha-synuclein
- Neurofilament light



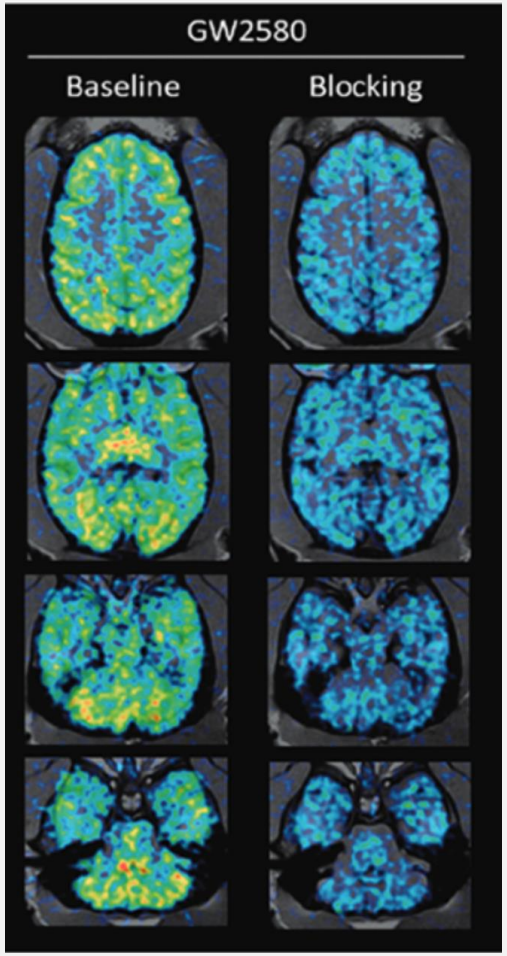
Mancuso et al., 2021



Han et al., 2021



Sadrameli et al., 2021



Zhou et al., 2021

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THANK YOU!

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