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ALZHEIMER'S DISEASE Knowledge Hub

Blood-Based Biomarkers: From Bench to Bedside in the APAC

Visit alzheimer.knowledgehub.wiley.com

for additional resources

Disclaimer

Paid honoraria for advisory board or speaker presentations for Eli Lilly, Eisai and Novo Nordisk

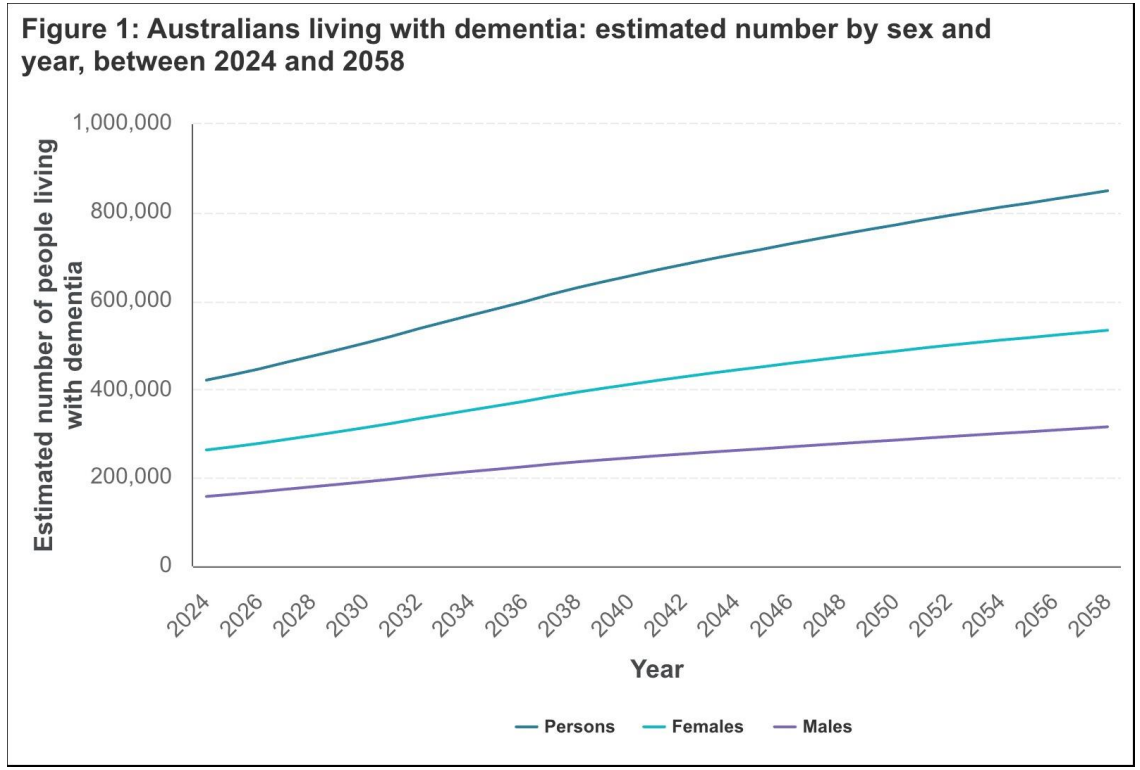
Department conducts clinical trials for multiple sponsors including Eisai, Eli Lilly, Roche, Novo Nordisk, MSD, BMS, Janssen

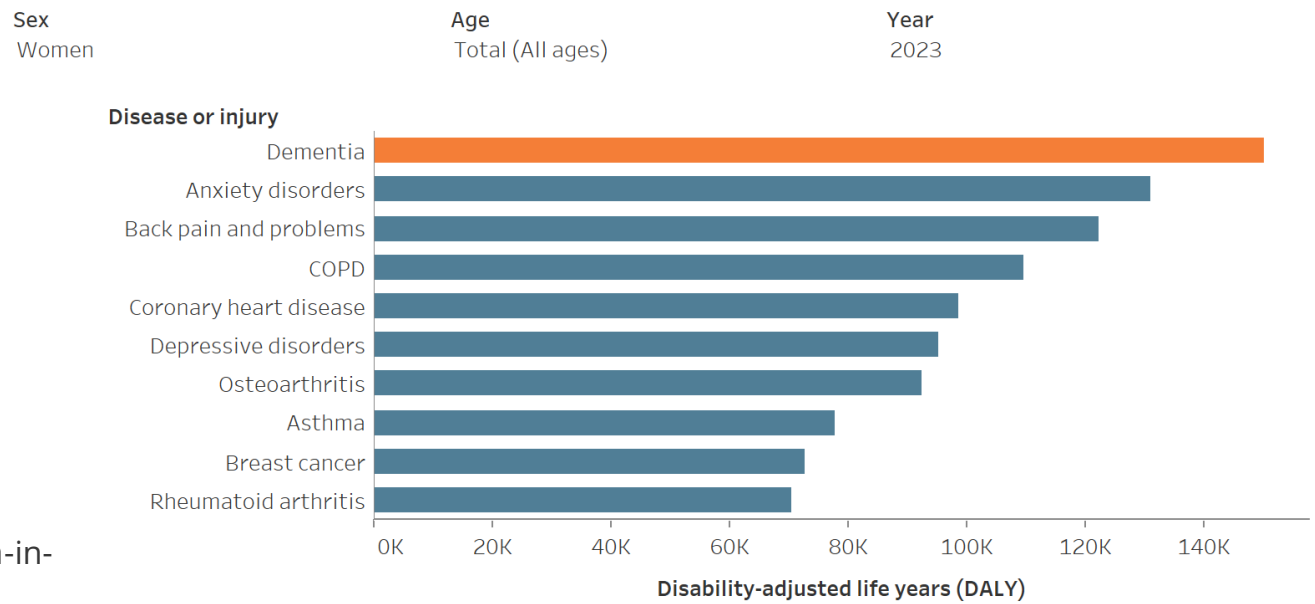
Research funding: Commonwealth Department of Health, Austin Medical Research Foundation and RACP Foundation

Setting the scene

Australia/New Zealand

- Estimated 446,500 people living with Dementia in Australia, and over 70,000 in New Zealand
- Leading cause of death for Australians
- Second leading cause of burden of disease in Australia (leading cause for women and those aged >80y)
- Total burden over 262,000 DALY
  - 59% from dying prematurely
  - 41% from impacts of living with dementia
- >50% never receive a formal diagnosis





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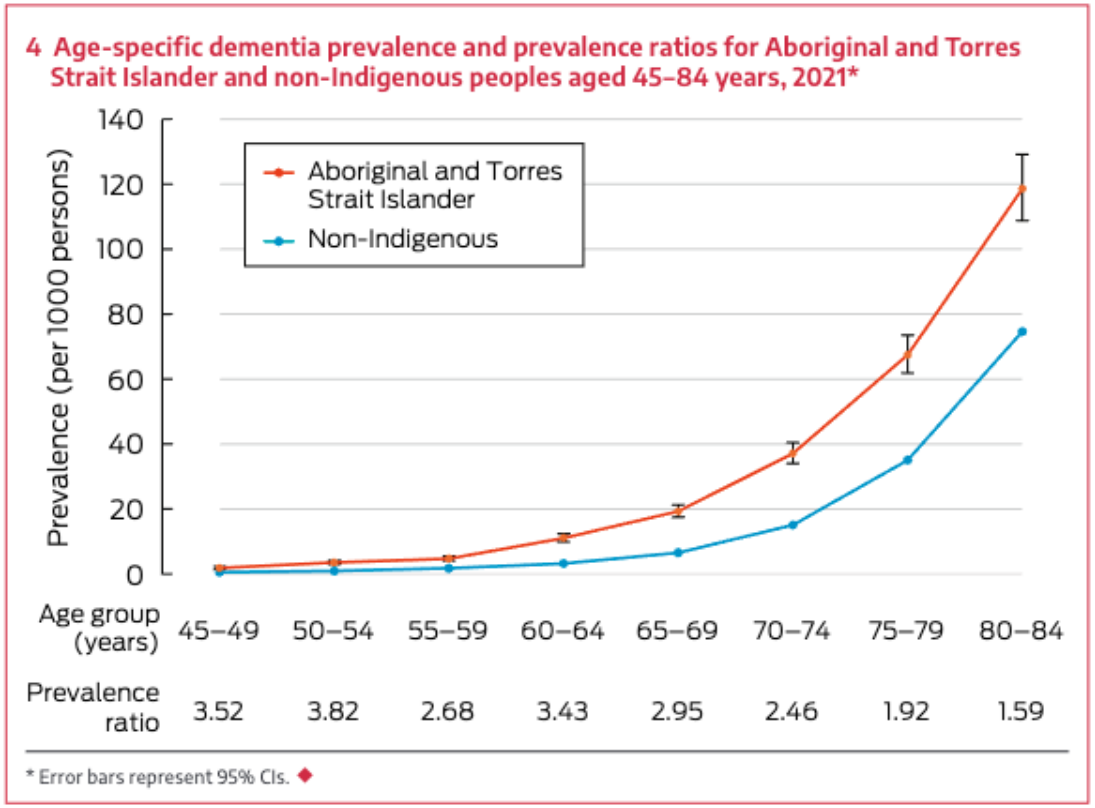
https://www.aihw.gov.au/reports/dementia/dementia-in-aus/contents/summary

Setting the scene

Indigenous Australians

- Dementia prevalence 3–5× higher than non-Indigenous Australians
- Earlier onset, often from age 45 years
- Community studies report prevalence up to 14% (ages 45+)
- Higher burden in remote communities (up to 3.5× higher)
- Leading cause of disease burden in those aged ≥75
- Driven by APOE4, social determinants, cardiovascular risk, and access inequities

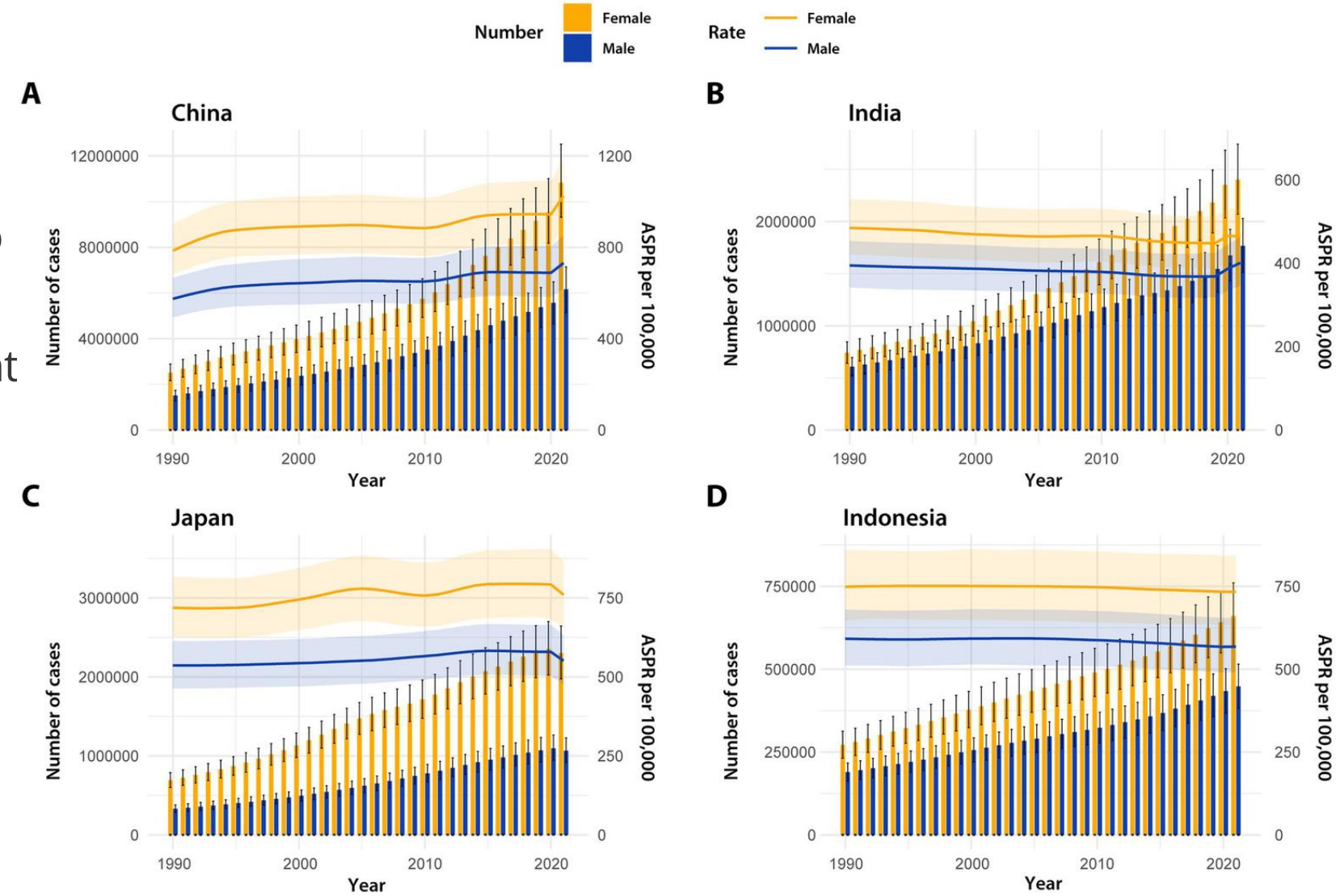


References: AIHW Dementia in Australia; Radford et al. 2019; Thompson et al., Lancet Reg Health West Pac 2022

Setting the scene

Asia Pacific Region

- Dementia cases projected to triple from ~23 million (2015) to ~71 million by 2050
- Asia–Pacific expected to account for >50% of global dementia cases by 2050
- Driven by population ageing, increased life expectancy, and growth in ≥65 population
- ~250% increase in dementia burden in Asia since 1990



References: Alzheimer's Disease International (2019); He et al., Frontiers in Public Health (2025); WHO (2021)

Defining Alzheimer's Disease

- Alois Alzheimer and Auguste D, 1906
- First described amyloid plaques, neurofibrillary tangles and atrophy in AD

Mufson et al 2015

Evolution of Diagnostic Criteria for AD

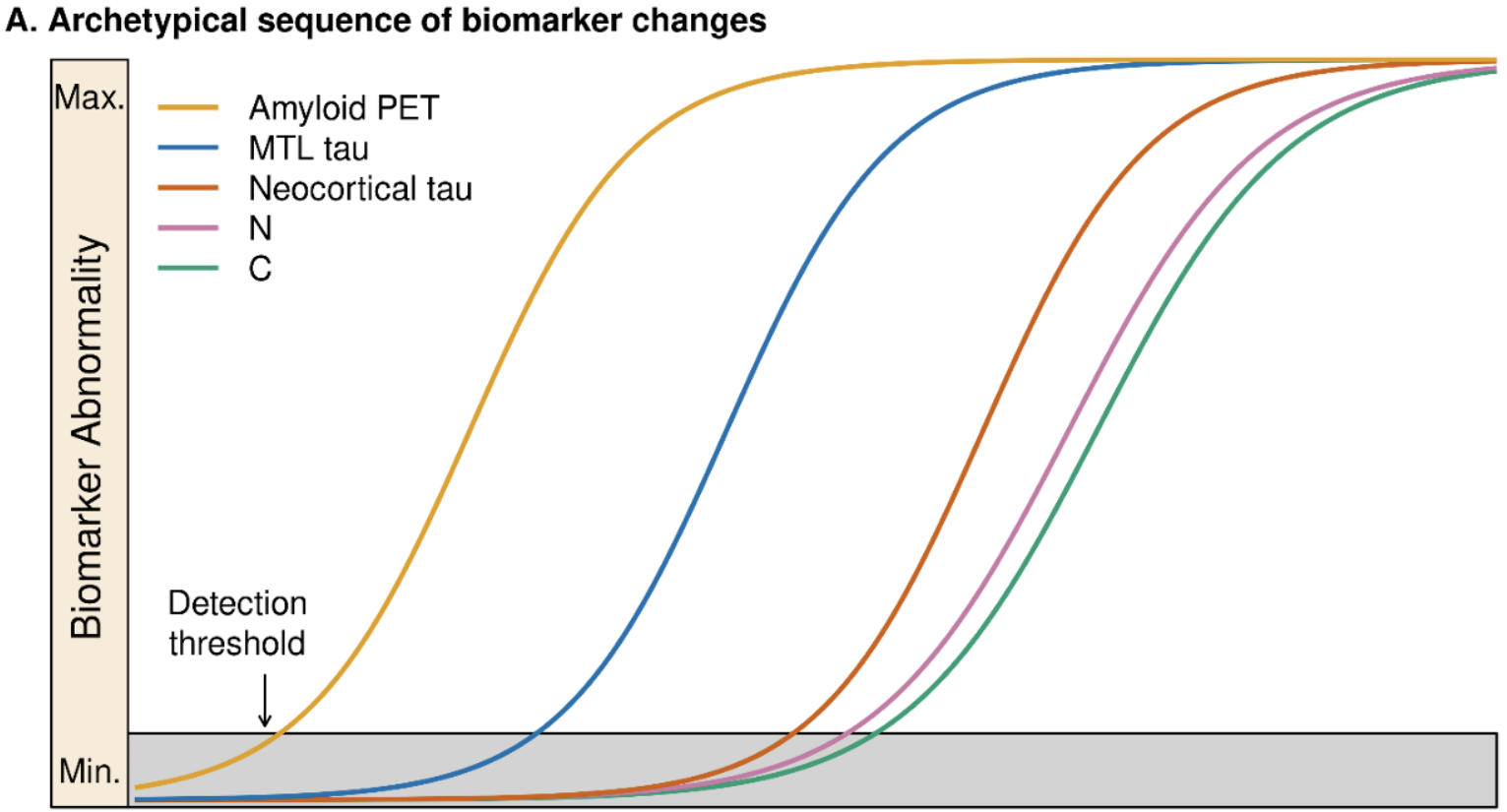
	NINCDS–ADRDA (1984)	IWG (2007)	IWG (2010)	NIA–AA (2011)	IWG (2014)	IWG–AA (2016)	NIA–AA (2018) "A/T/N-C"	IWG (2021, 2024)	AA (2024)
Setting	Research and clinical	Research	Research	Research and clinical	Research	Research	Research	Research and clinical	"Bridge between Research and clinical"
Clinical	Dementia (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	Cognitively unimpaired = "at risk for AD" Amnestic, posterior cortical atrophy, logopenic variant PPA, behavioural or dysexecutive frontal, corticobasal syndrome, semantic	None (asymptomatic/ genetic) to severe impairment; clinical staging on severity of cog/functional impairment; five phenotypes: am language, visu
		positive, or AD autosomal dominant mutation	p-tau, or high total tau) or Aβ PET positive	tau, p-tau, ^{18}F-FDG PET, and T1-weighted MRI)			(CSF or PET)	PET)	T2 [CS ma, PET] **Non-specific**: (NfL, GFAP, FDG PET, MRI) **Copathology**: (Vascular, alpha synuclein)

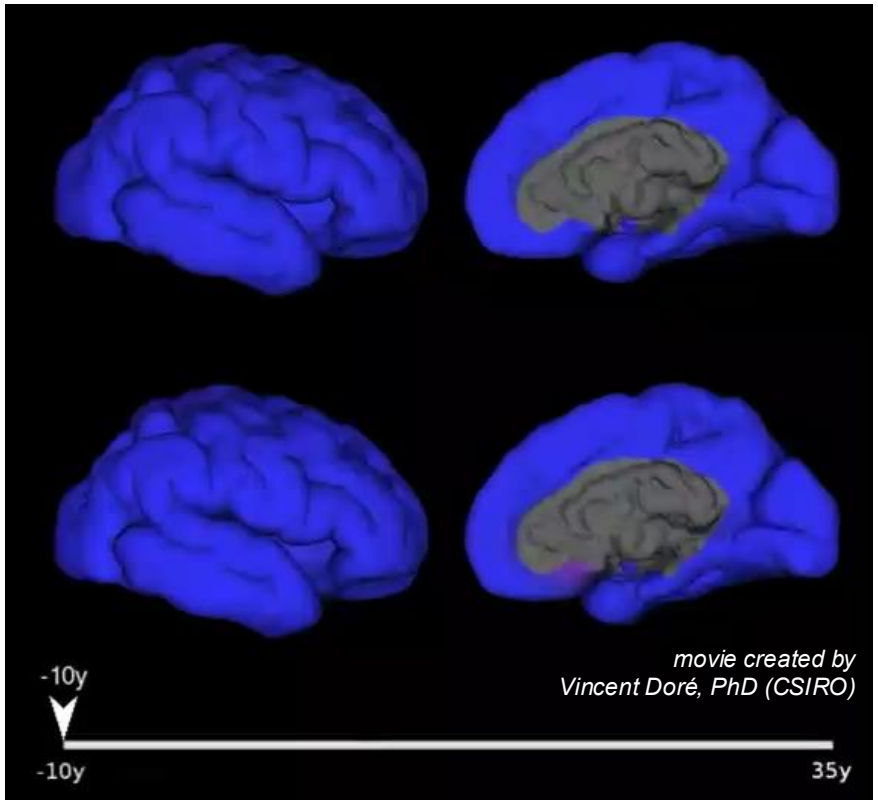
Clinical Only

Biological/Clinical

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.

AD Biomarker Changes





Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimer's Dement*. 2024; 20: 5143–5169.

Alzheimer's Association Criteria 2024

- 3 biomarkers categories:
  - Core AD (1=amyloid, 2=tau)
  - nonspecific (could be AD or other)
  - non-AD co-pathology
- AD Diagnosis
  - requires presence of Core AD biomarkers (*even in absence of Sx)*

TABLE 1 Categorization of fluid analyte and imaging biomarkers.

Biomarker category	CSF or plasma analytes	Imaging
Core Biomarkers		
Core 1		
A (Aβ proteinopathy)	Aβ 42	Amyloid PET
T_1: (phosphorylated and secreted AD tau)	p-tau217, p-tau181, p-tau231	
Core 2		
T_2 (AD tau proteinopathy)	MTBR-tau243, other phosphorylated tau forms (e.g., p-tau205), non-phosphorylated mid-region tau fragments[a]	Tau PET
Biomarkers of non-specific processes involved in AD pathophysiology		
N (injury, dysfunction, or degeneration of neuropil)	NfL	Anatomic MRI, FDG PET
I (inflammation) Astrocytic activation	GFAP	
Biomarkers of non-AD copathology		
V vascular brain injury		Infarction on MRI or CT, WMH
S α-synuclein	αSyn-SAA[a]	

Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimer's Dement*. 2024; 20: 5143–5169.

Biological Alzheimer's Disease Staging

TABLE 3 Biological staging.

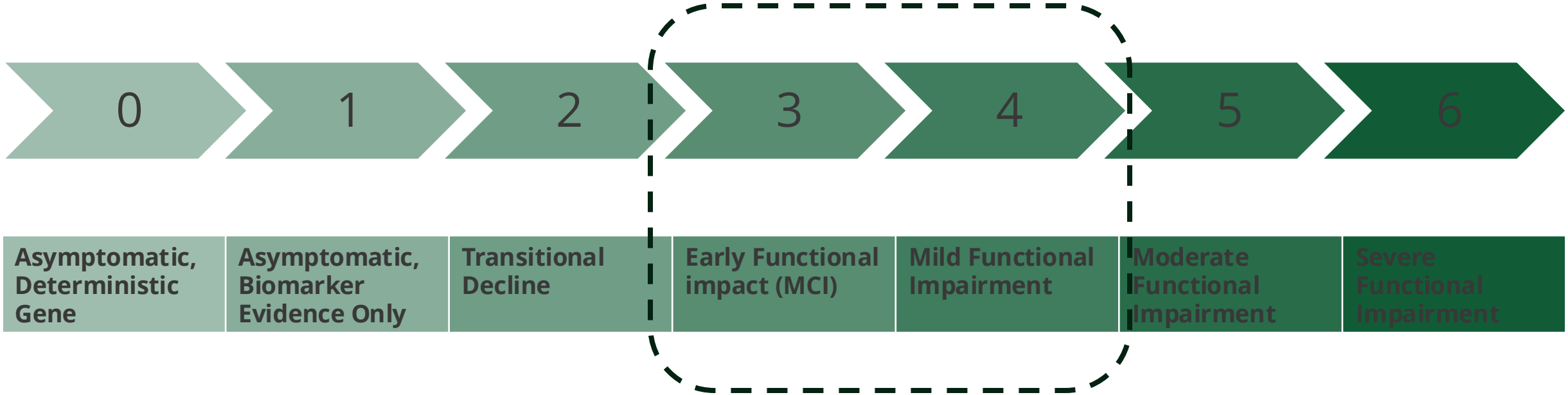
	Initial-stage biomarkers (A)	Early-stage biomarkers (B)	Intermediate-stage biomarkers (C)	Advanced-stage biomarkers (D)
PET	Amyloid PET $A+T_2-$	Tau PET medial temporal region $A+T_{2MTL}+$	Tau PET moderate neocortical uptake $A+T_{2MOD}+$	Tau PET high neocortical uptake $A+T_{2HIGH}+$
Core 1 fluid	CSF Aβ42/40, p-tau181/Aβ42, t-tau/Aβ42, and accurate[a] Core 1 plasma assays can establish that an individual is in biological stage A or higher, but cannot discriminate between PET stages A–D at present.			

TABLE 5 Conceptual biological staging with fluid biomarkers.

	Initial-stage biomarkers (A)	Early-stage biomarkers (B)	Intermediate-stage biomarkers (C)	Advanced-stage biomarkers (D)
Fluid staging	CSF Aβ42/40, p-tau181/Aβ42, t-tau/Aβ42, and accurate[b] plasma assays	Other p-tau forms (e.g., p-tau205[a])	MTBR-tau243[a]	Non-phosphorylated tau fragments[a]

Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimer's Dement*. 2024; 20: 5143–5169.

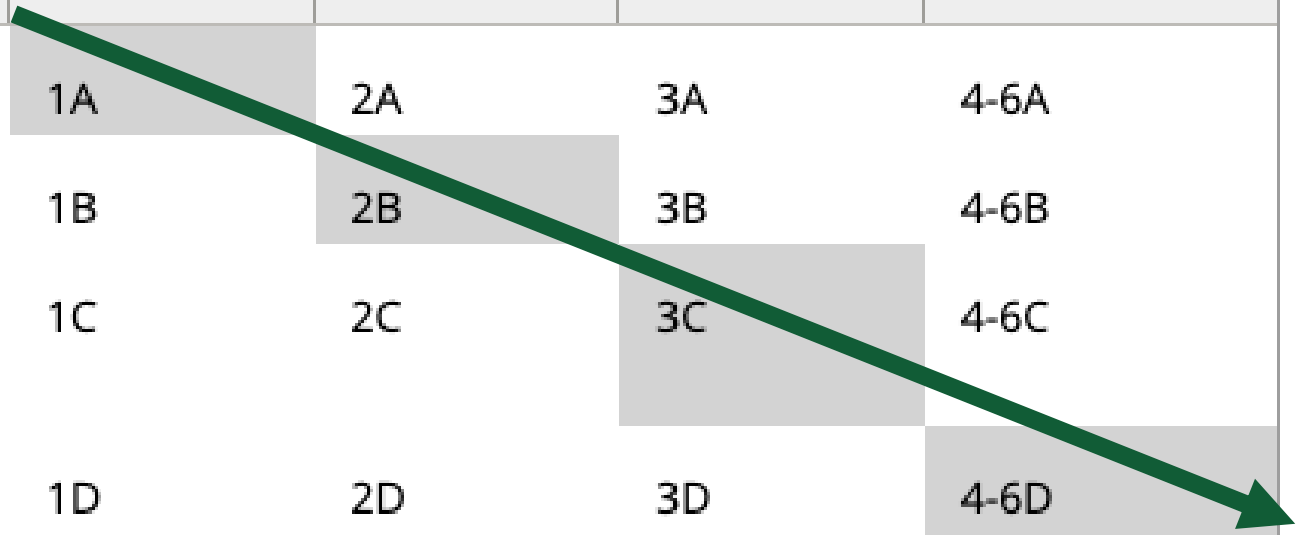
Clinical AD Staging



Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimer's Dement*. 2024; 20: 5143–5169.

Biological and Clinical AD Staging

	Stage 0	Clinical Stage 1	Clinical Stage 2	Clinical Stage 3	Clinical Stages 4–6
Initial biological stage (A)	X	1A	2A	3A	4-6A
Early biological stage (B)	X	1B	2B	3B	4-6B
Intermediate biological stage (C)	X	1C	2C	3C	4-6C
Advanced biological stage (D)	X	1D	2D	3D	4-6D



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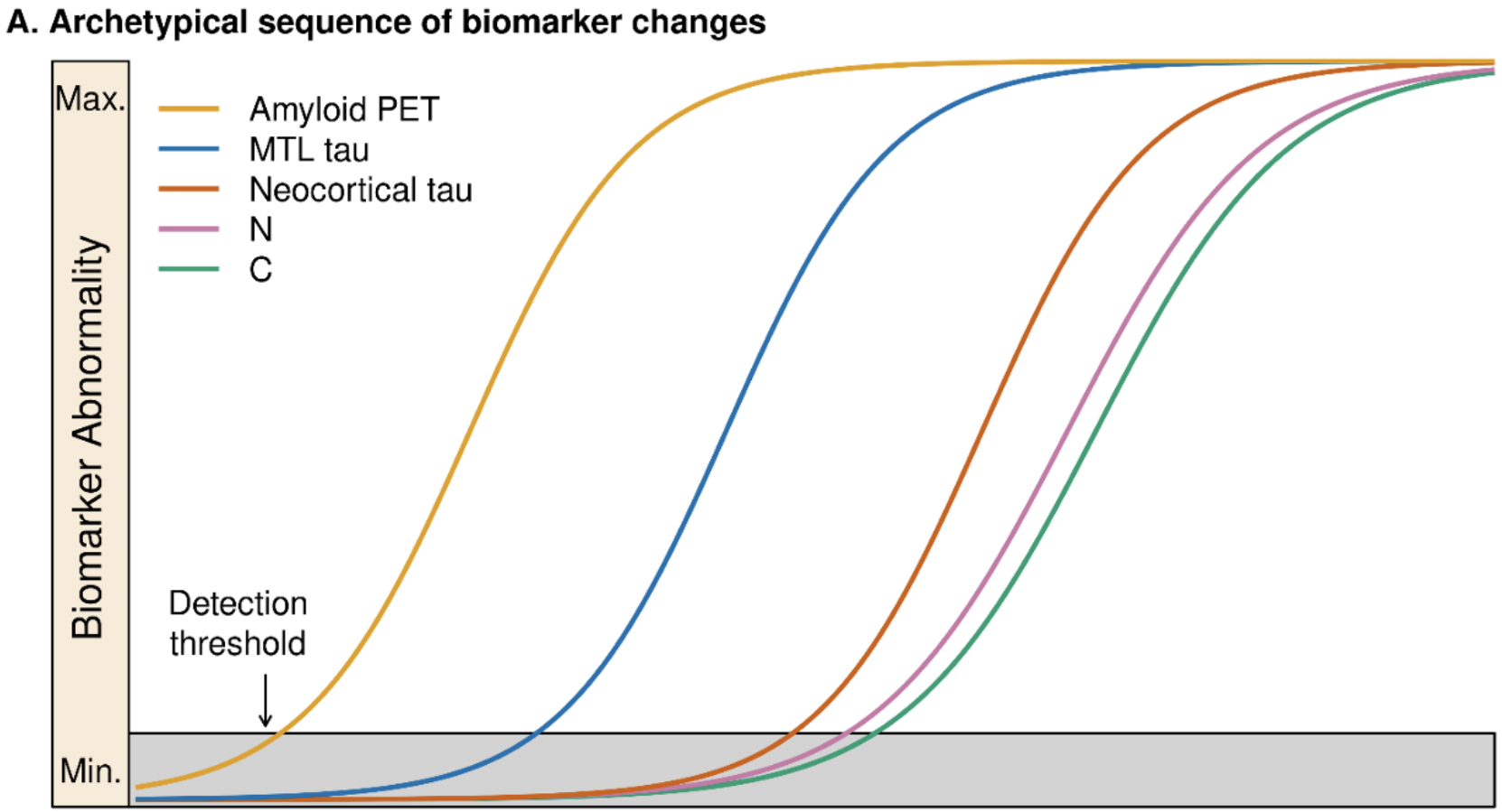
AD Staging and Co-pathology



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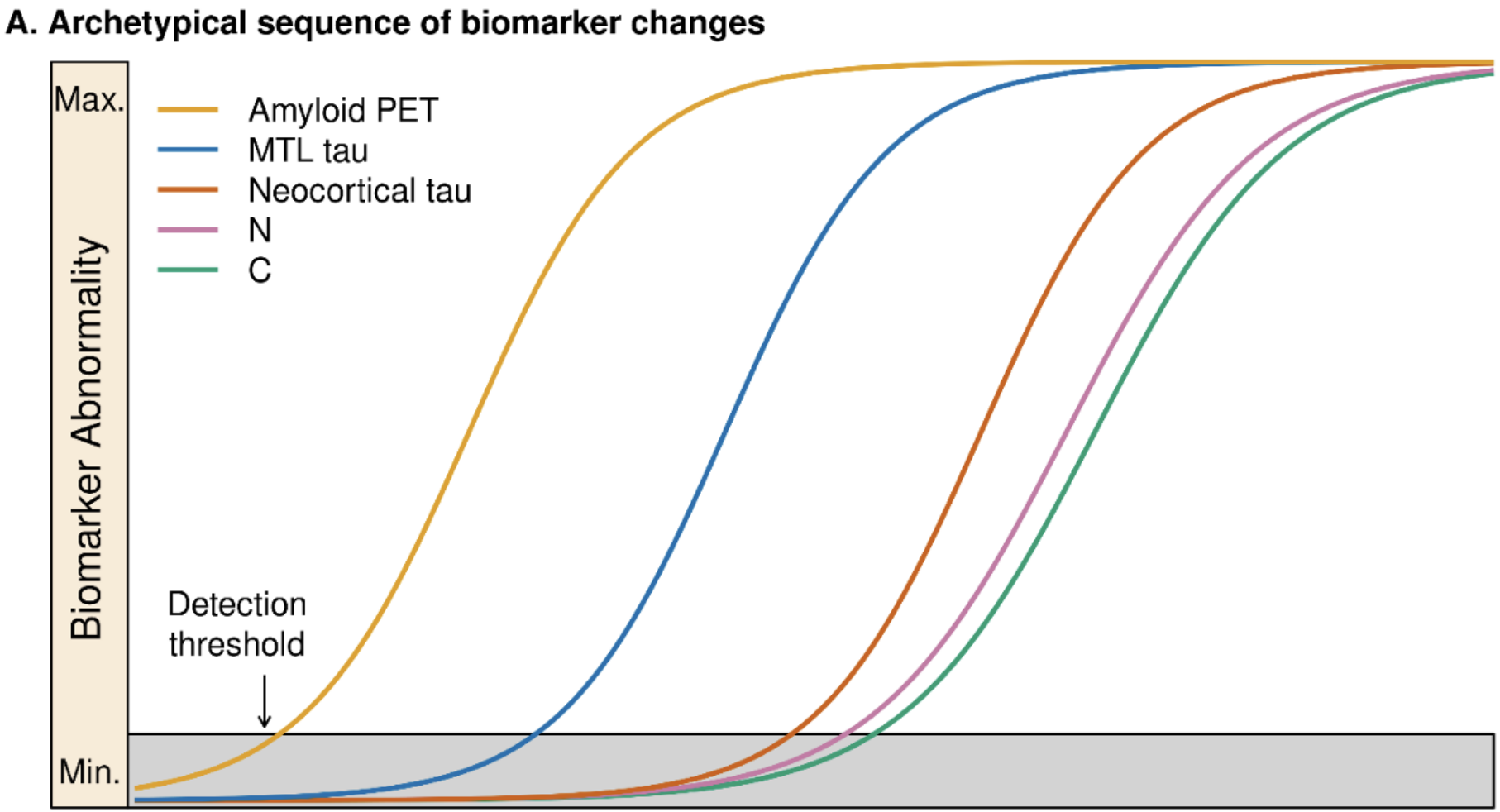
AD Staging and Co-pathology



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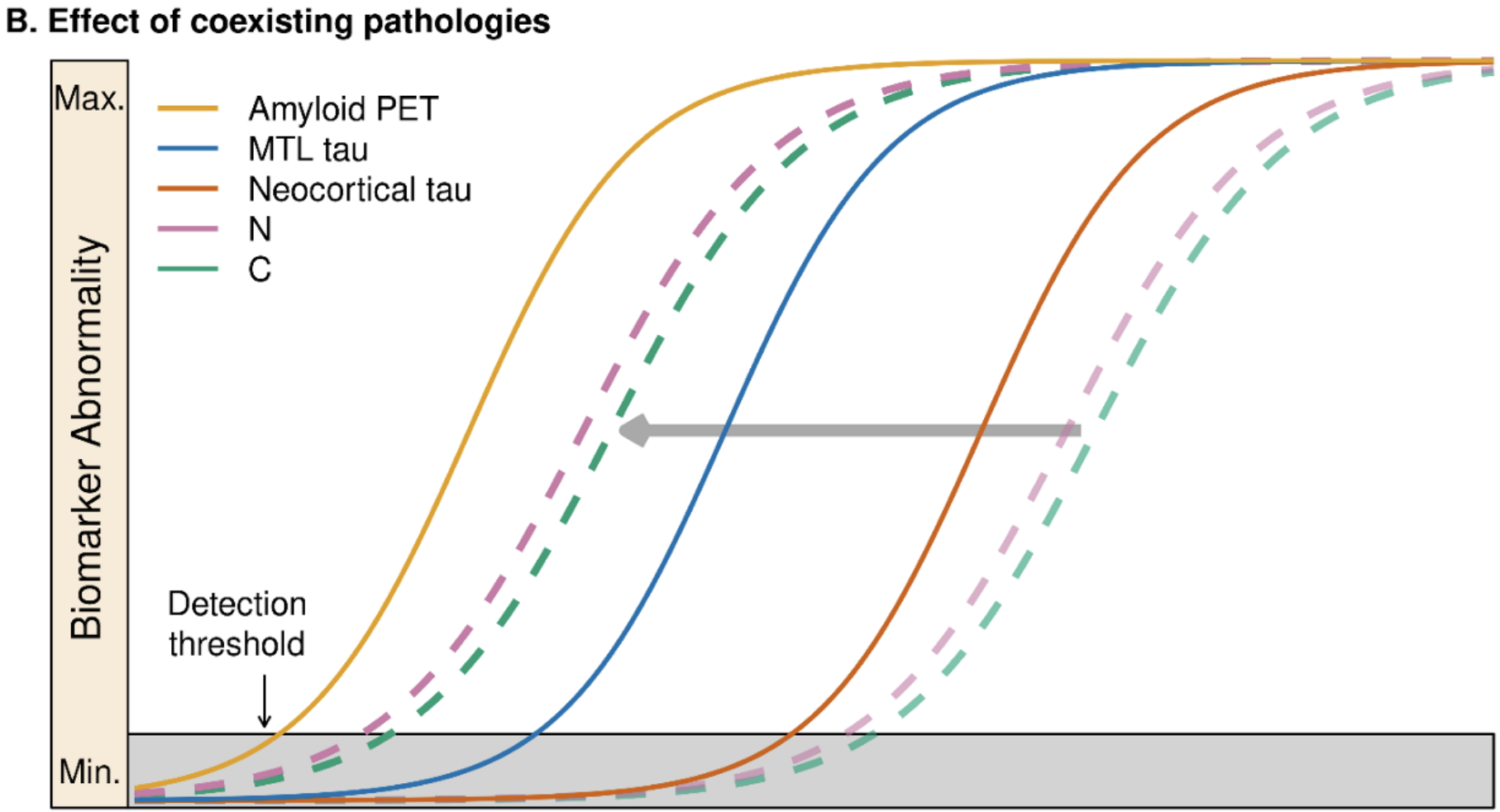
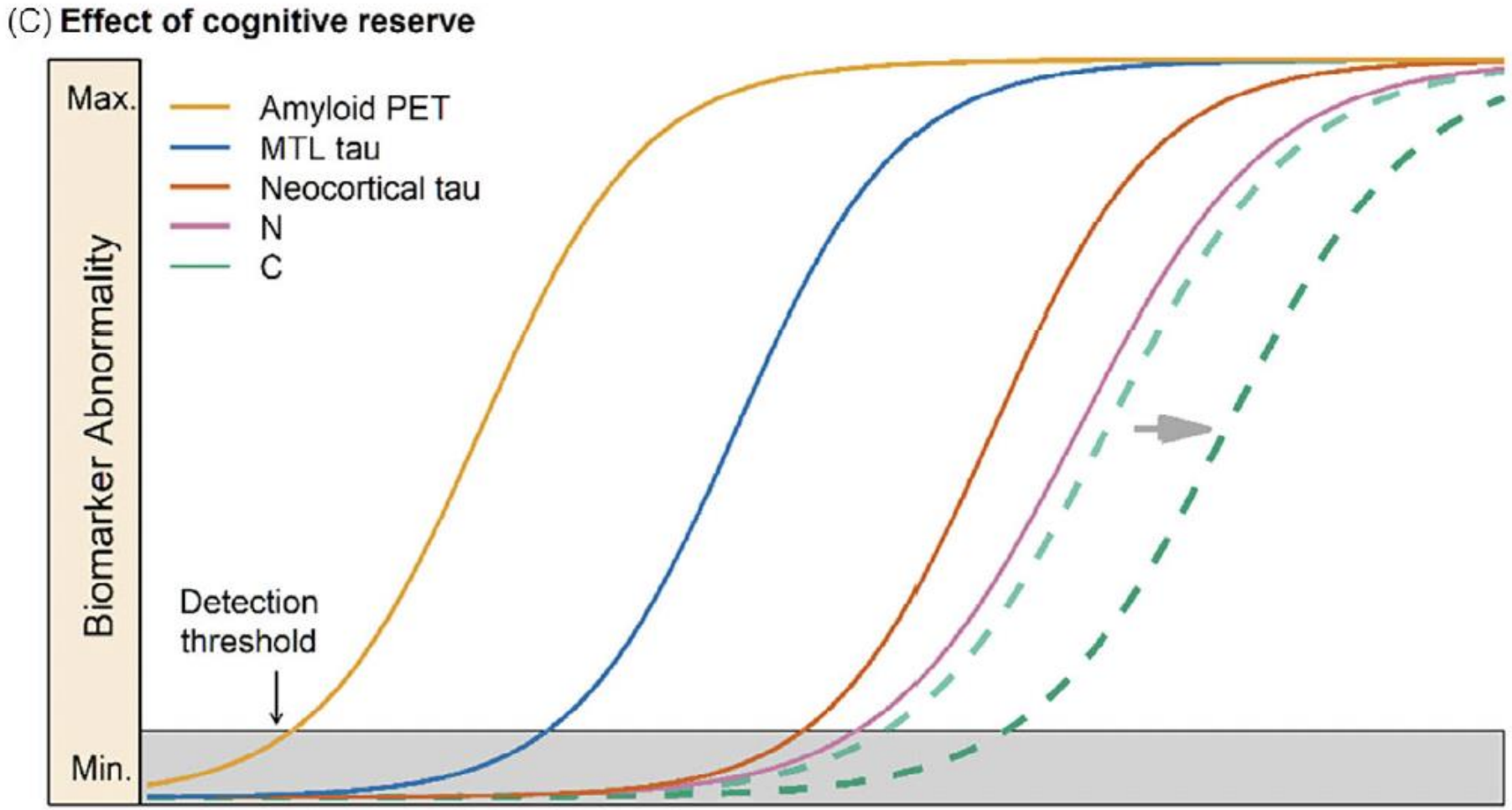
AD Staging and Co-pathology



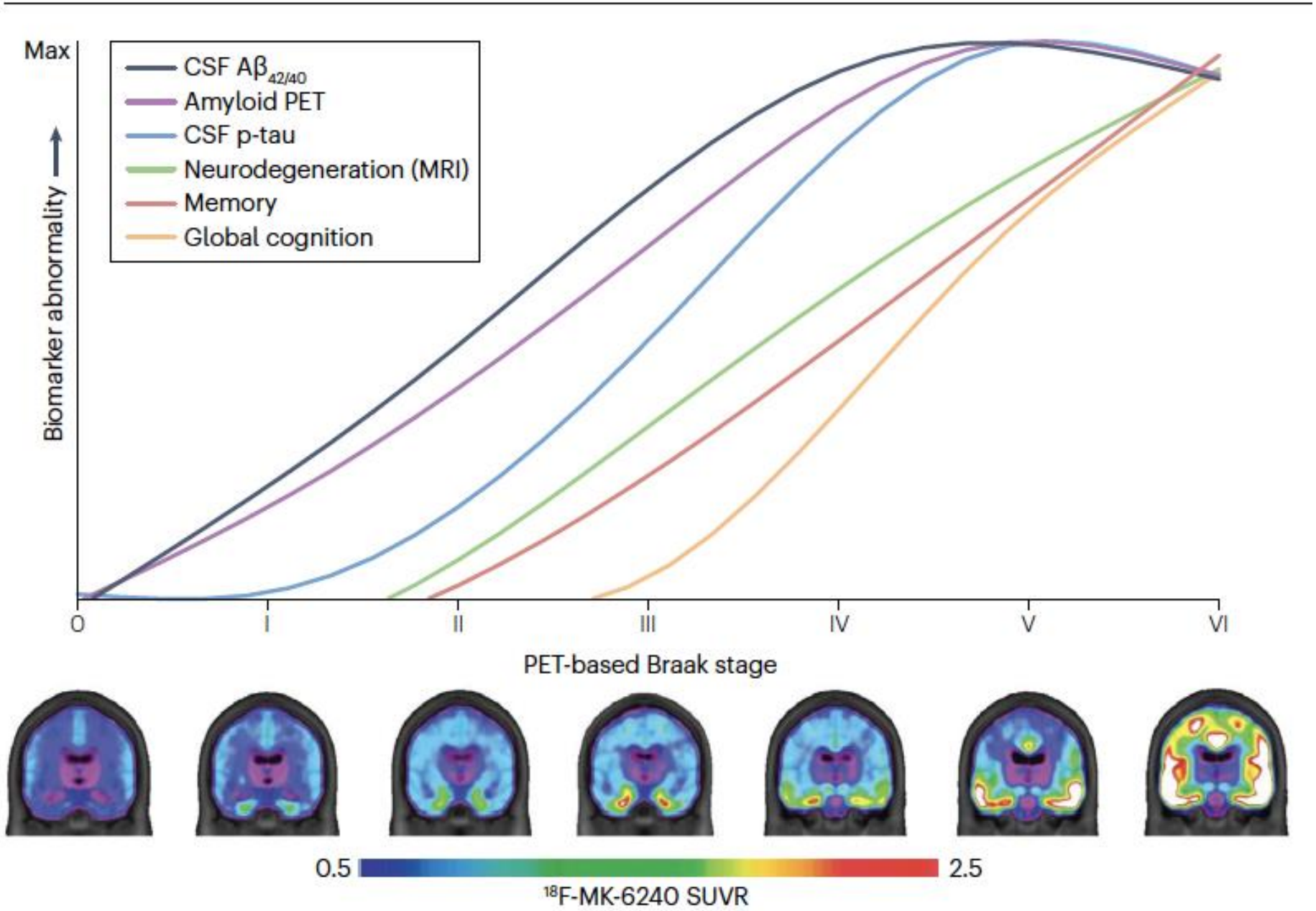
Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimer's Dement*. 2024; 20: 5143–5169.

AD Staging and Cognitive Reserve



Jack CR, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimer's Dement*. 2024; 20: 5143–5169.

Tau PET Staging

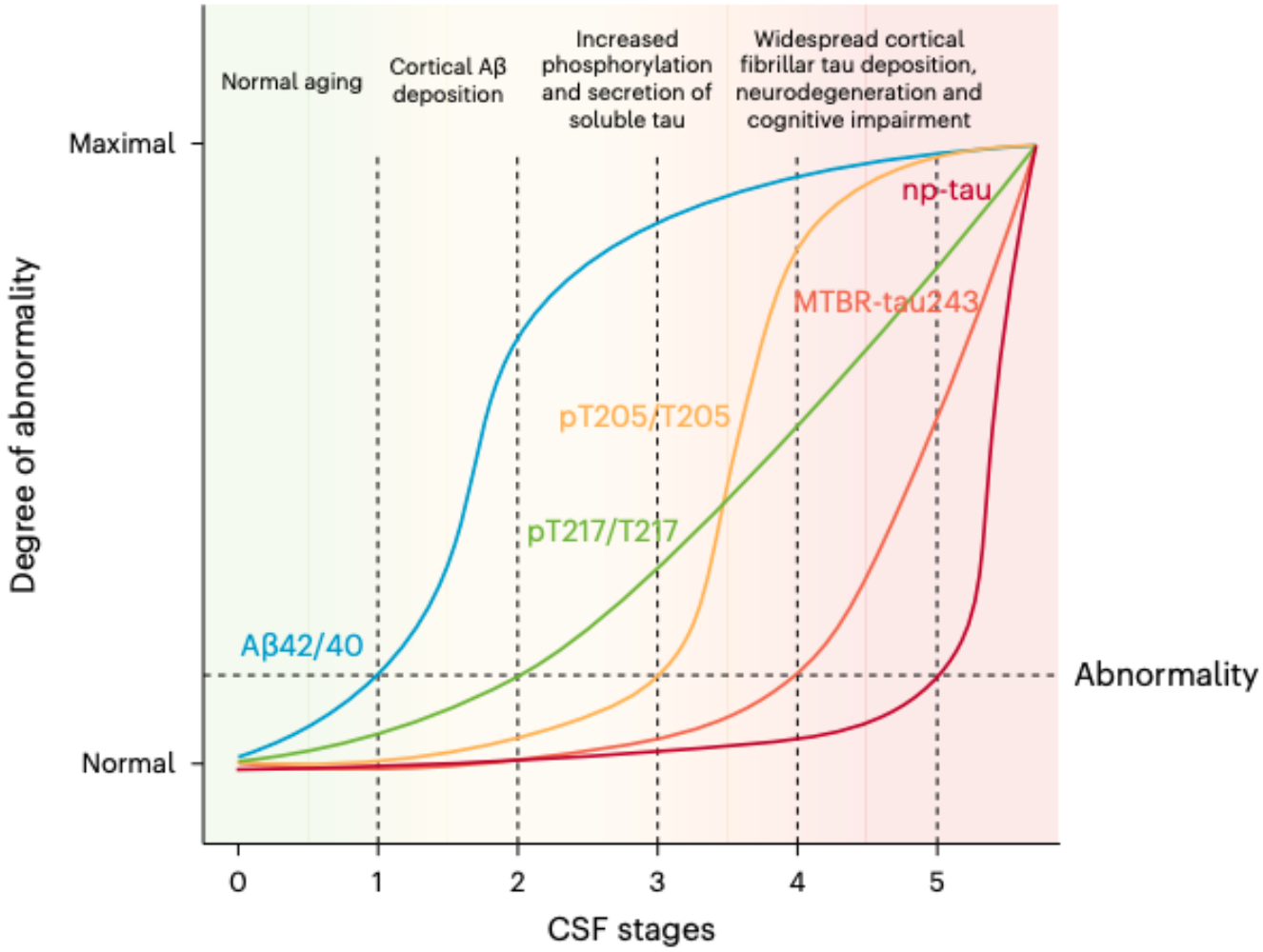


Nature Reviews Neurology | Volume 20 | April 2024 | 232–244

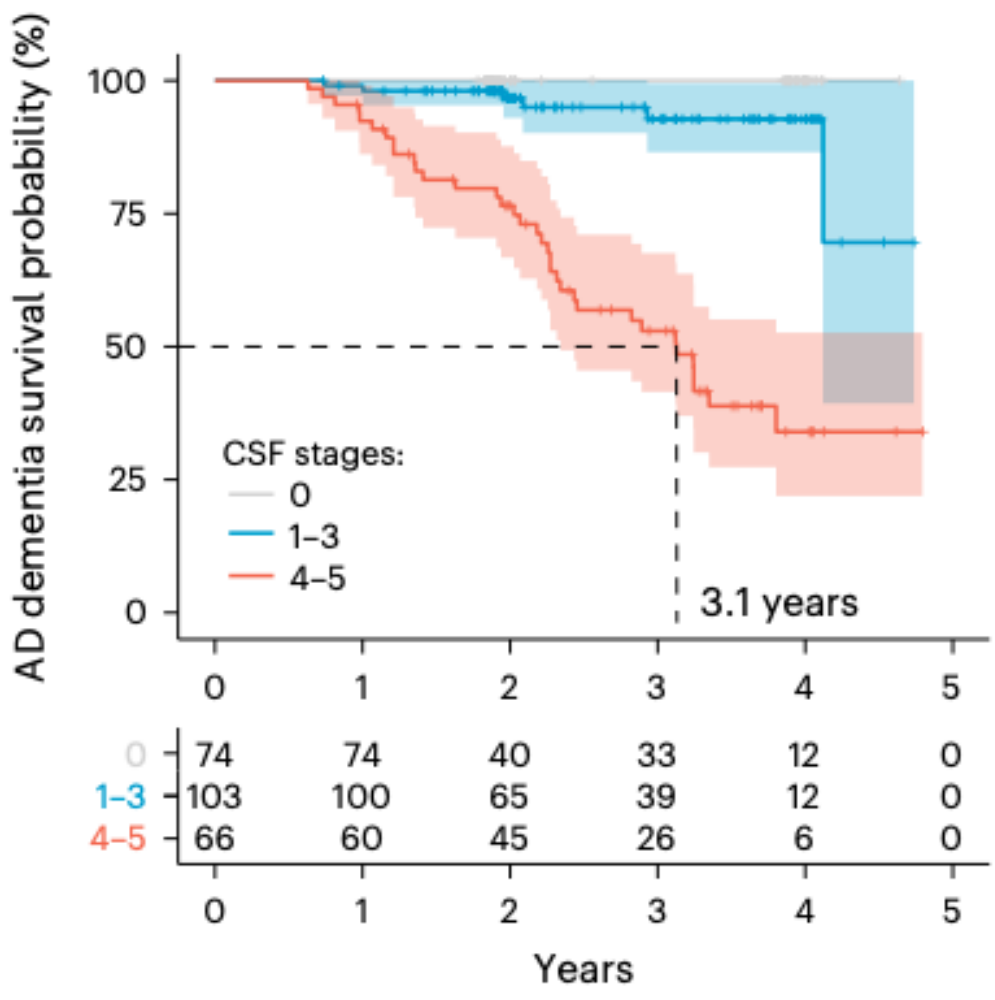
Therriault et al 2024

CSF-Based Alzheimer's Disease Staging

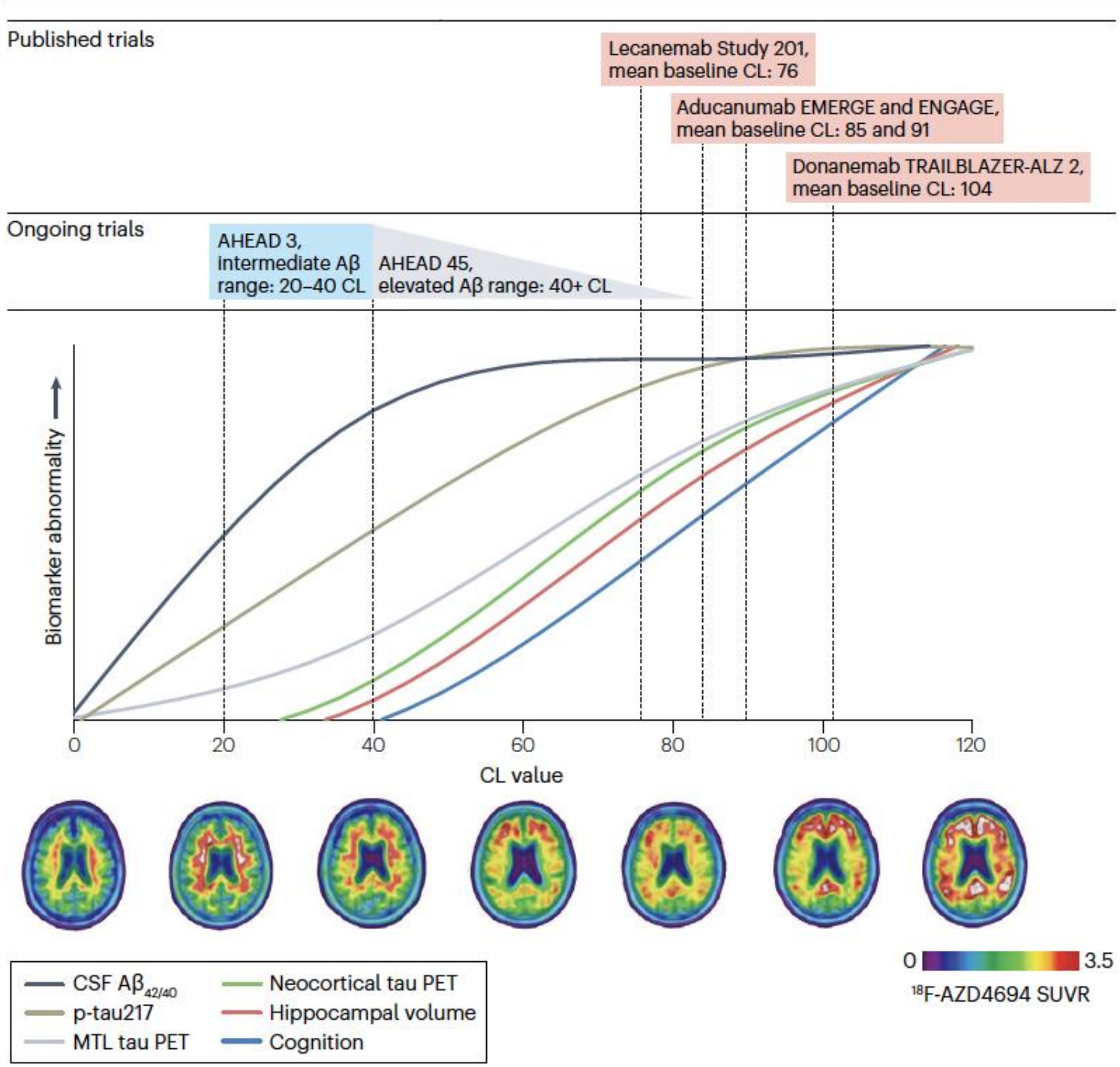
CSF Stages and Disease Progression



Progression from CU/MCI to AD dementia



Using biological disease staging to compare clinical trial cohorts



Therriault, J., Schindler, S.E., Salvadó, G. *et al.* Biomarker-based staging of Alzheimer disease: rationale and clinical applications. *Nat Rev Neurol* **20**, 232–244 (2024).

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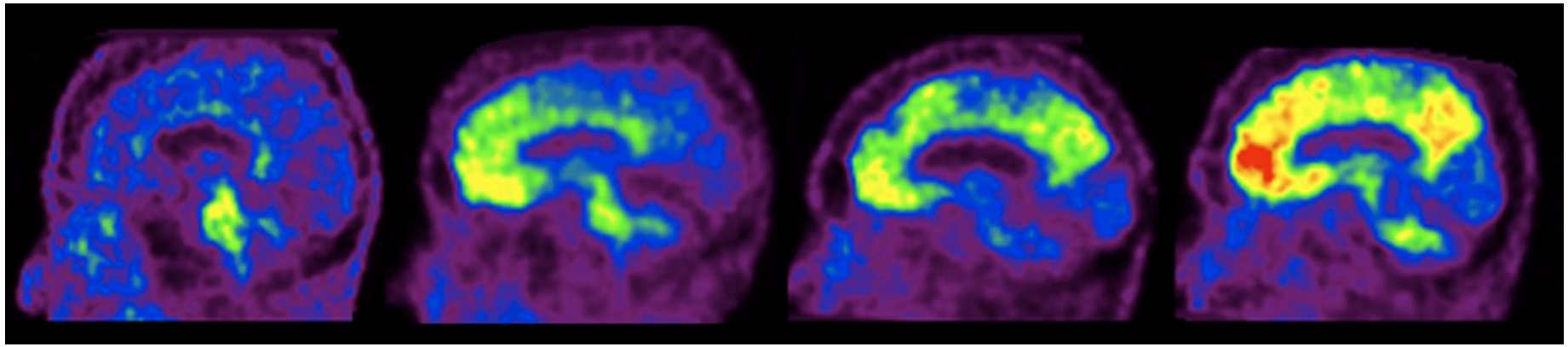
Amyloid PET Availability in Australia

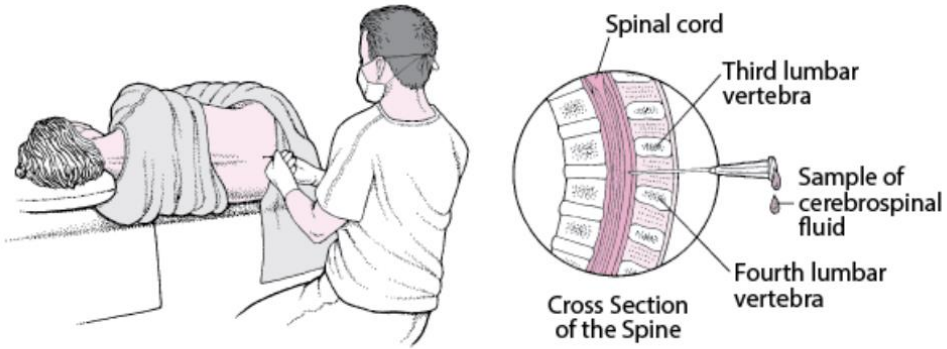
- No MBS rebate
- Increasing number of centres, but limited to metropolitan regions
- Self-funded or research agreements
- >$1000-$2000 (more?)
- High sensitivity and specificity c/w post mortem



CSF testing for clinical diagnosis of AD in Australia

- CSF testing for clinical use available via NDDL at Florey, Sydney (private cost)
- Detects alterations in, Abeta1-42, phospho-tau (P-tau), and total Tau (T-tau) in
- ~90% sensitivity and specificity for early diagnosis of Alzheimer's disease
- Provides greater diagnostic certainty than standard clinical and radiological assessments
  - More accessible, cost-effective and radiation-free compared with amyloid-PET
- Use remains limited in Australian clinical practice
  - Regional access
  - Concerns of perceived invasiveness
  - Lack of clinician confidence in interpreting results

NDDL
National Dementia Diagnostics Laboratory

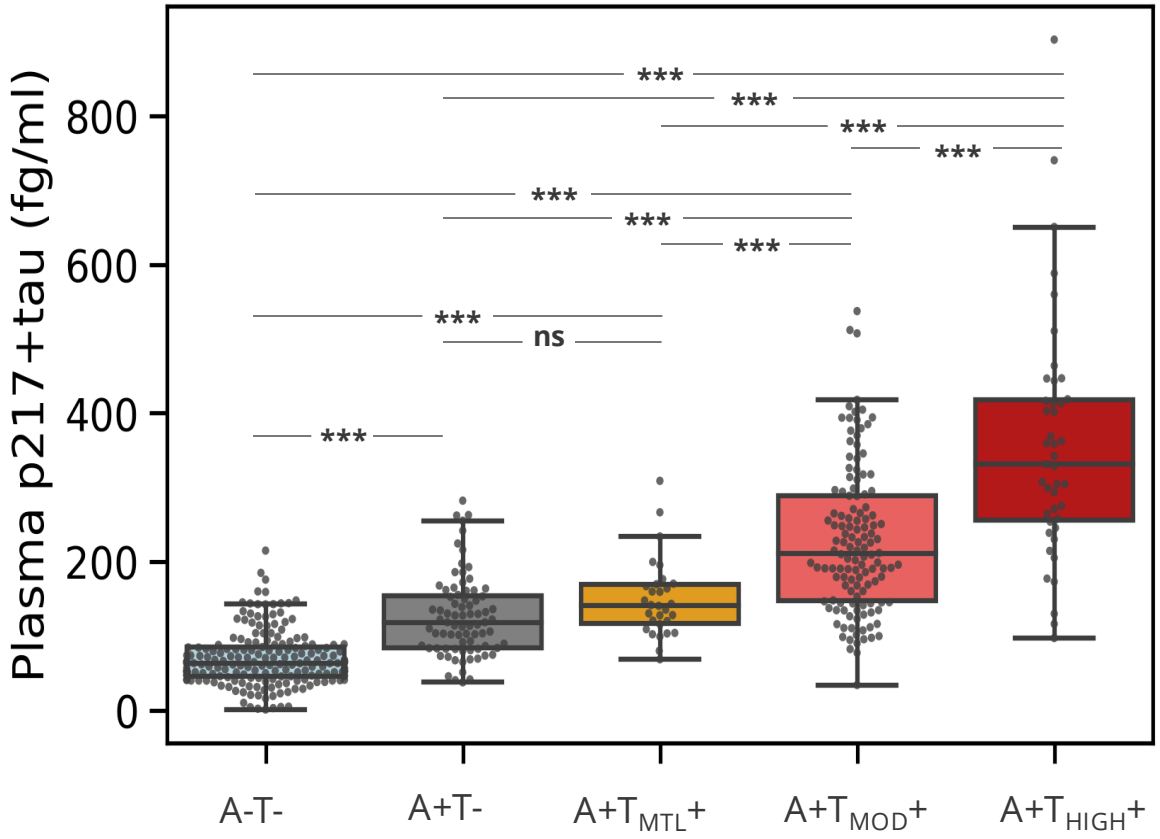


Eratne, Dhamidhu and Collins, Steven and Nestor, Peter and Pond, Dimity and Velakoulis, Dennis and Yates, Mark and Masters, Colin, Using Cerebrospinal Fluid Biomarkers to Diagnose Alzheimer's Disease in Australian Clinical Practice: Narrative Review (March 11, 2024)

Plasma p-tau-217 and Tau PET Staging

AA Staging

1. Initial stage: Aβ with no tau (A+T-)
2. Early stage: Aβ with tau limited to medial temporal region (A+T_{MTL}+)
3. Intermediate stage: Aβ with moderate tau in neocortex (A+T_{MOD}+)
4. Advanced stage: Aβ with high tau in neocortex (A+T_{HIGH}+)



Feizpour, Rowe et al., 2023

Blood-Based Biomarker Panels

Healius Pathology network

dorevitch pathology | healius

Healius Pathology Pty Ltd (ABN 84 007 190 043)
1761_DOR_C2N_PrecivityAD2_DrBrochure_V2_Mar01

AD Protein Biomarkers included in the PrecivityAD2™ blood test

Amyloid beta (Aß)
- Aß40
- Aß42

Tau
- phosphorylated-tau217 (p-tau217)
- non-phosphorylated-tau217 (np-tau217)

Introducing the

PrecivityAD2™ Blood Test

The PrecivityAD2™ blood test aids assessments of Alzheimer's disease in patients presenting with mild cognitive impairment or dementia

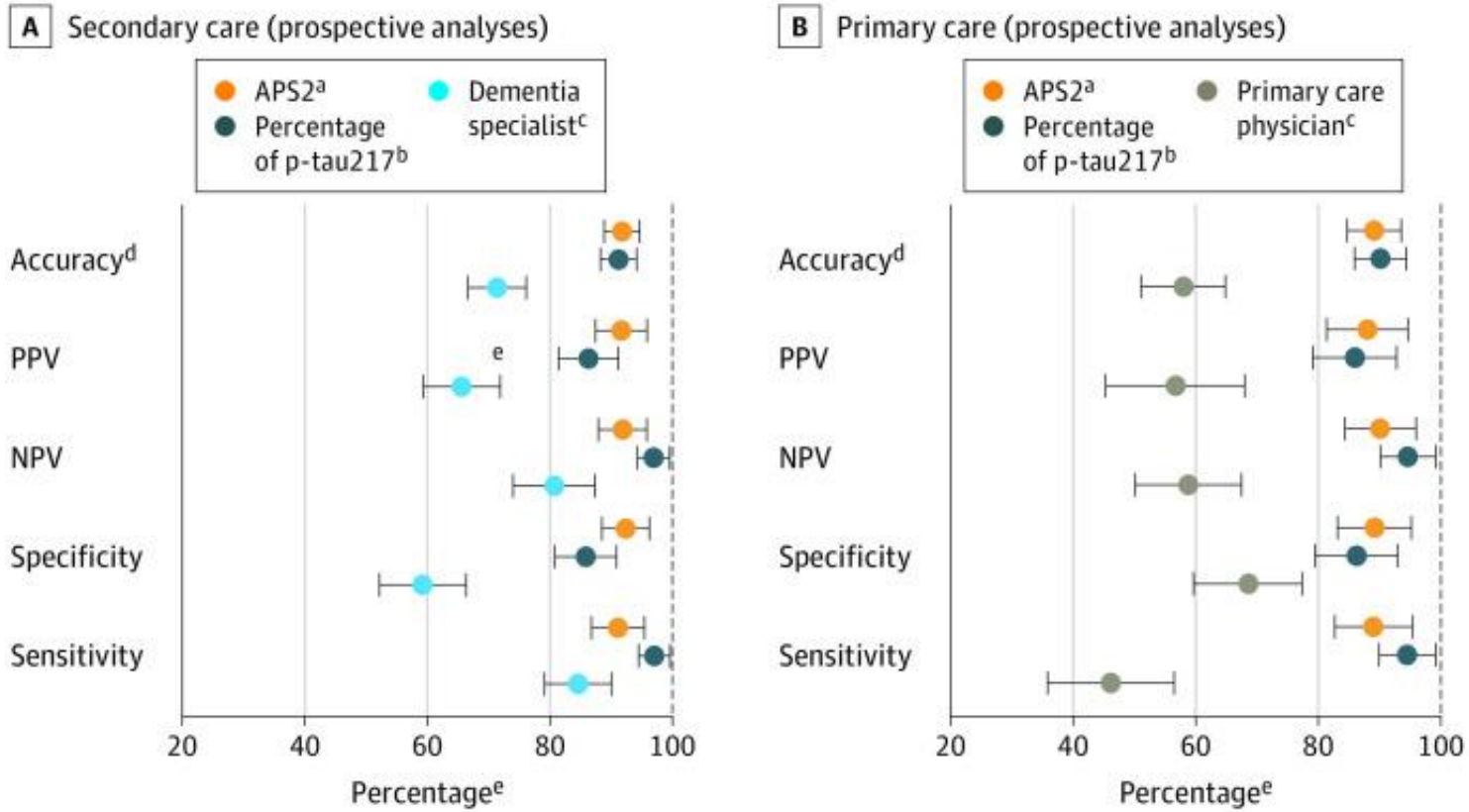
PrecivityAD2™ Blood Test Performance Metrics

Test Performance Characteristics[a]	
Positive Percent Agreement (Sensitivity)[b]	88%
Negative Percent Agreement (Specificity)[b]	89%
Positive Predictive Value - PPV[c]	90%
Negative Predictive Value - NPV[c]	87%
AUC-ROC[c]	0.94
Overall Accuracy[c]	88%

BBMs improve accuracy of clinical diagnosis* in primary and specialty care settings

Specialists:
Accuracy 71%→92%

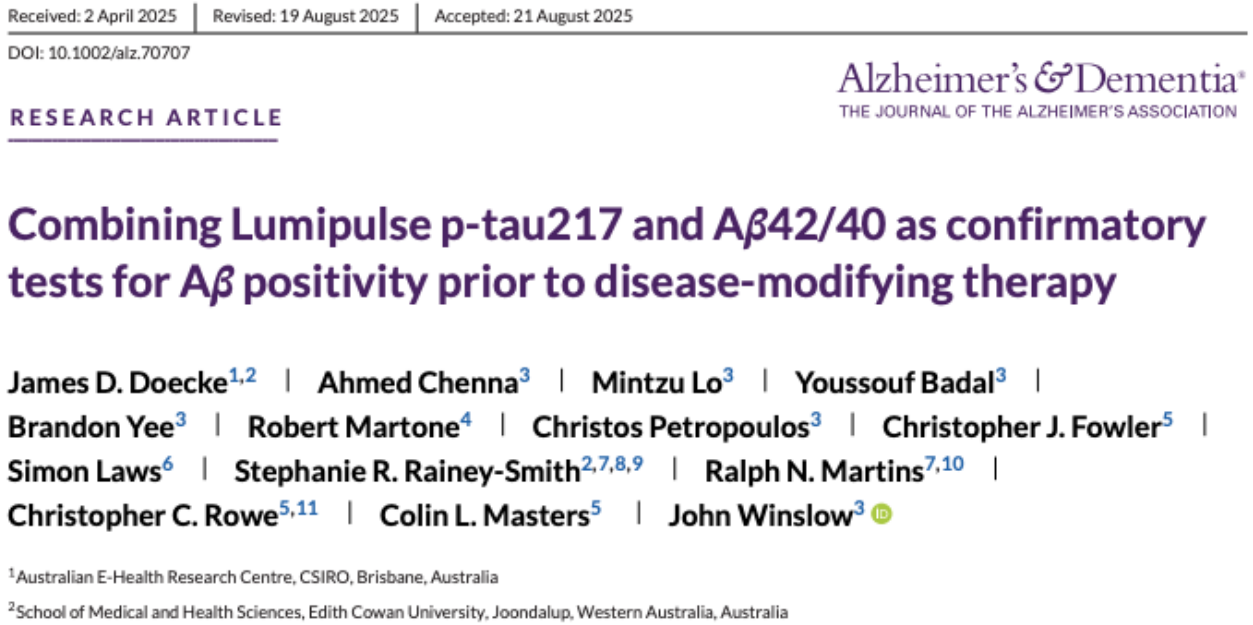
GPs:
Accuracy 58% → 89%



Palmqvist et al JAMA 2024, *clinical evaluation compared with CSF biomarkers

Fujirebio Lumipulse G pTau217/beta-amyloid 1-42 Ratio

- What?
  - First FDA-approved blood test (May 2025) as a confirmatory test for AD
  - Validated against amyloid PET
- Who?
  - Adults 55+ years with cognitive decline
- How?
  - "rule in test" to confirm AD pathology
    - Positive predictive value 92%
    - Negative predictive value = 97%
- How much?
  - Not available in Australia yet



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RESEARCH ARTICLE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Combining Lumipulse p-tau217 and Aβ42/40 as confirmatory tests for Aβ positivity prior to disease-modifying therapy

James D. Doecke[1,2] | Ahmed Chenna[3] | Mintzu Lo[3] | Youssouf Badal[3] | Brandon Yee[3] | Robert Martone[4] | Christos Petropoulos[3] | Christopher J. Fowler[5] | Simon Laws[6] | Stephanie R. Rainey-Smith[2,7,8,9] | Ralph N. Martins[7,10] | Christopher C. Rowe[5,11] | Colin L. Masters[5] | John Winslow[3]

[1]Australian E-Health Research Centre, CSIRO, Brisbane, Australia

[2]School of Medical and Health Sciences, Edith Cowan University, Joondalup, Western Australia, Australia

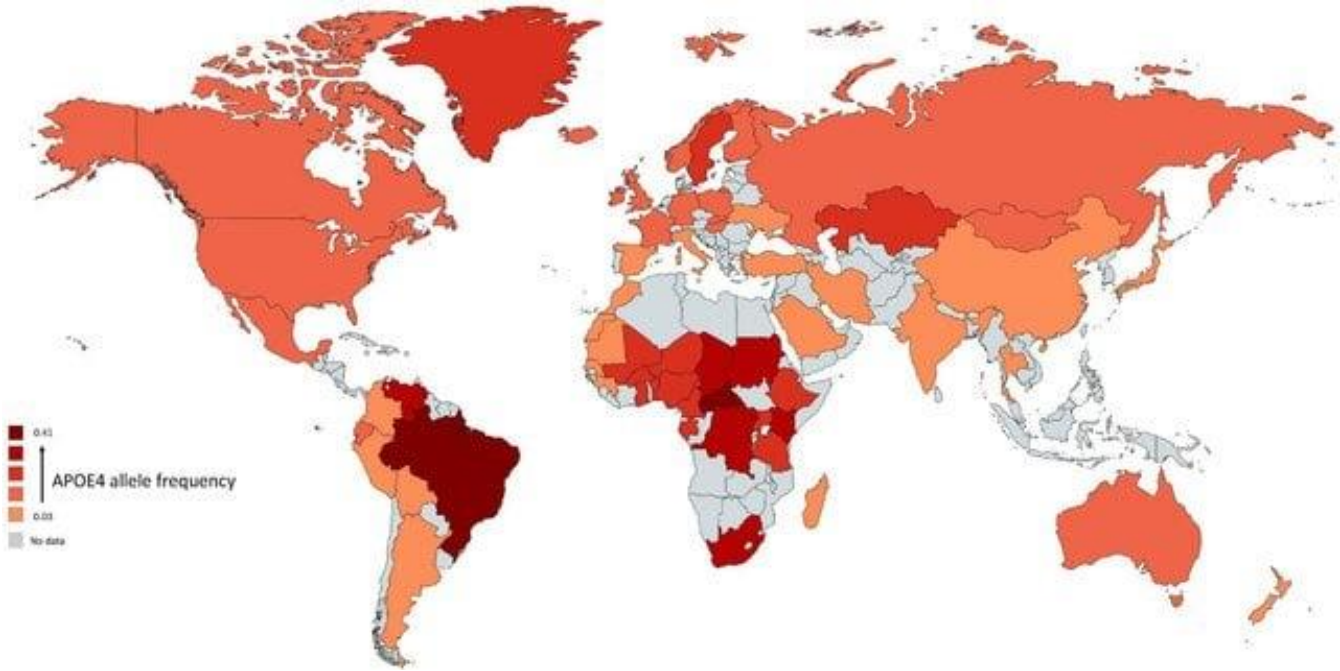
Roche Elecsys pTau 181

- What?
  - First blood test to support early diagnosis of Alzheimer's disease to have TGA approval in Australia
  - Validated against amyloid PET
- Who?
  - Adults 55-80 years with subjective cognitive impairment or suspected mild cognitive impairment
- How?
  - "rule out test" to exclude AD pathology
    - Negative predictive value = 93.4%
    - Positive predictive value 46.6%
- How much?
  - Cost ~$200
- NOT a confirmatory test, positive results need to be confirmed using a confirmatory test

Blood based biomarkers in the Asia-Pacific Context

Genetic Factors

- Lower APOE ε4 frequency in many Asia-Pacific populations vs Western cohorts
- Clinical implications:
  - Different baseline risk profiles for Alzheimer's disease
  - Potential variation in biomarker performance (including p-tau assays)
  - May influence predictive values (PPV/NPV) blood-based biomarkers
  - Need for region-specific validation and interpretation of biomarkers?
  - Importance of evaluating co-pathologies



References: Alzheimer's Disease International (2019); He et al., Frontiers in Public Health (2025); WHO (2021)

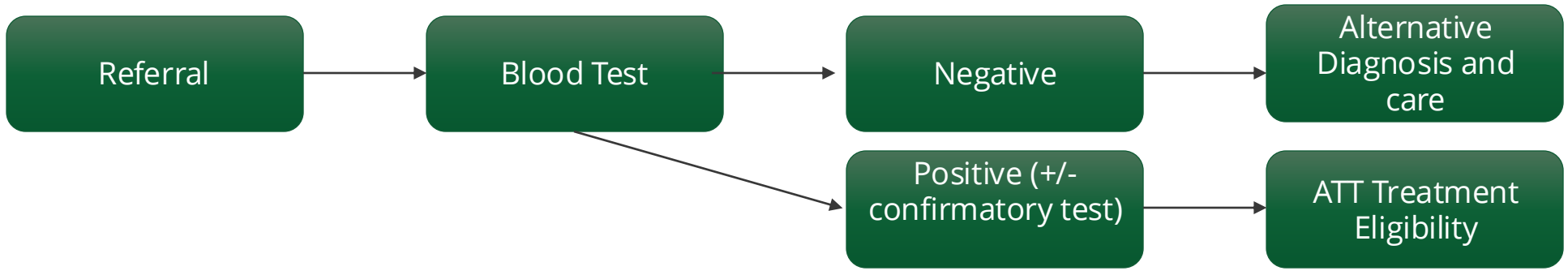
Paradigm Changes with Blood Base Biomarkers

Traditional Diagnostic Pathway

- Clinical assessment ± neuropsychology
- Amyloid PET: limited access, high cost
- CSF biomarkers: invasive
- Delayed or uncertain diagnosis
- Memory clinics overwhelmed

Blood-Based Biomarkers

- Earlier diagnosis (pre-dementia detection)
- Scalable triage before PET/CSF
- Enables therapy access
- Monitoring disease and treatment
- Improves equity of access
- Greater availability in primary care, rural/remote



Shift from syndromic to biological diagnosis: earlier, scalable, precise, treatment-ready care

Wiley Green 2024.potx