THE STORY BEHIND THE PLASMA P-TAU ISOFORMS

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CONFLICTS OF INTEREST

- Member of scientific advisory boards of Alzheon, Amyriad Therapeutics, Eisai, Enigma USA, Karuna, Lilly, Medesis, Novo Nordisk, Okutsa, Sharon Francis Foundation, TauRx
- Editorial board member of JPAD and The Neurotorium

LEARNING OBJECTIVES

- Give an update on the biologic definition of AD
- Describe the validation process for a new blood test for AD
- Explore the use of such a diagnostic test in clinical practice

PRESENTATION

- Updating the biologic definition of AD, from AT(N) to AT/NI/VS
- Importance of cohort studies in Canada
- P-tau isoforms in the blood reflect what is going on in the brain
- Validation process for a new diagnostic test
- Possible clinical use

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BIOLOGICAL DEFINITION OF AD - 2018

- Amyloid (A) — Amyloid PET or CSF
- Tau (T) — Tau PET or CSF
- Neurodegeneration (N) — MRI or FDG PET or CSF

MCI or dementia due to AD: A(+), T(+), N(+)

Adapted from Jack et al. NIA-AA Research framework: towards a biological definition of AD. Alzheimer's & Dementia 2018; 14(4), 535-62

BIOLOGICAL DEFINITION OF AD - 2023

Core biomarkers	Amyloid (A)	Aβ42/40	Amyloid PET
	Tau (T)	P-tau 181,217	Tau PET
Non-specific	Neurodegeneration (N)	Nfl	MRI, FDG-PET
	Neuroinflammation (I)	GFAP	
Co-pathologies	Vascular (V)		MRI
	α-Synuclein (S)	αSyn-sAA	

Adapted from Jack et al. October 9th 2023 draft alz.org/NIA-AA

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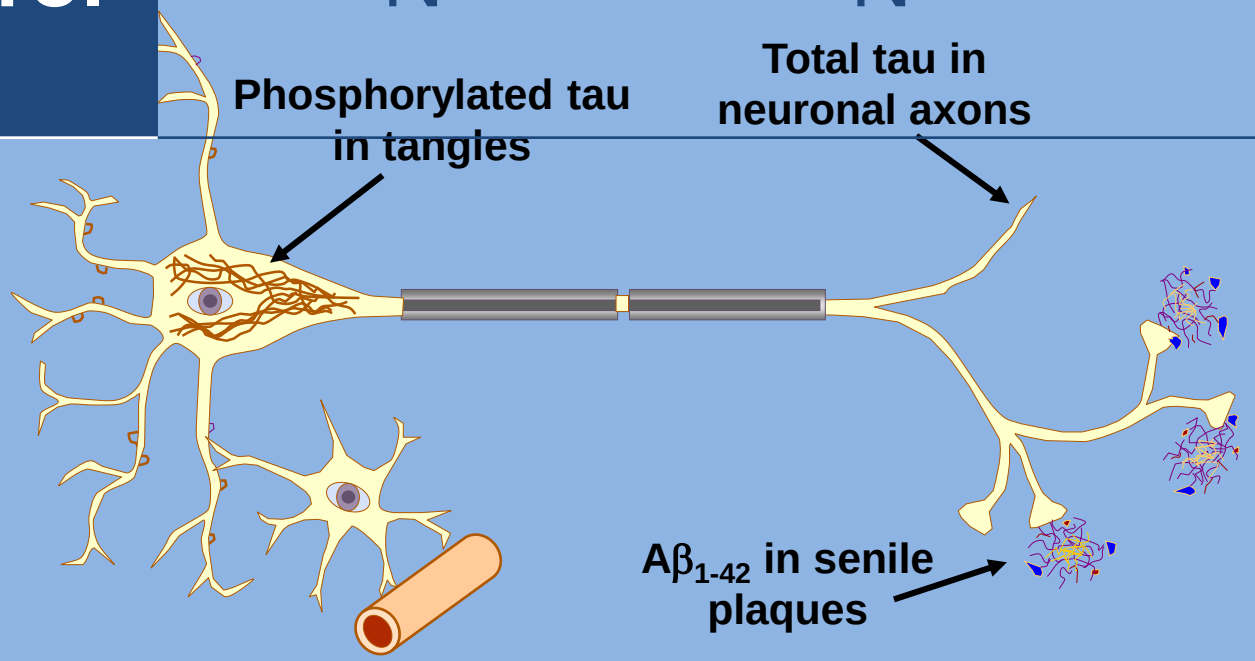
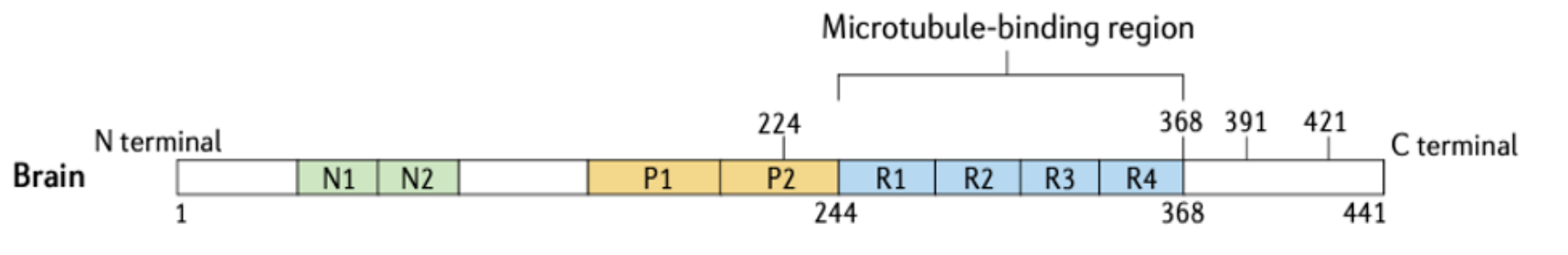
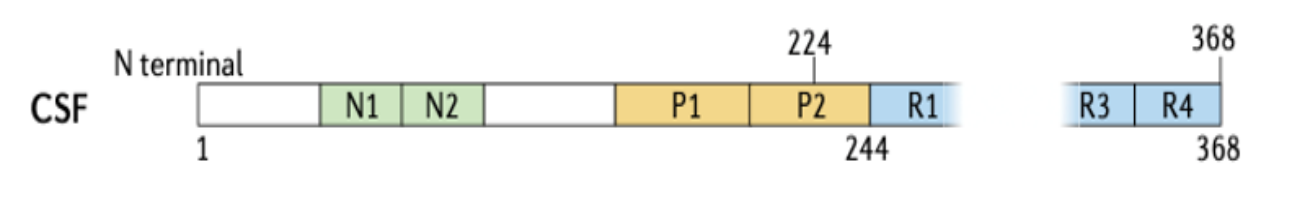
SPINAL FLUID (CSF) IN AD

	Aβ42	Tau	Ptau
AD	↓↓	↑↑	↑↑
MCI	↓ or N	↑ or N	↑ or N
Control	N	N	N



Tau fragments get shorter from the brain to the blood



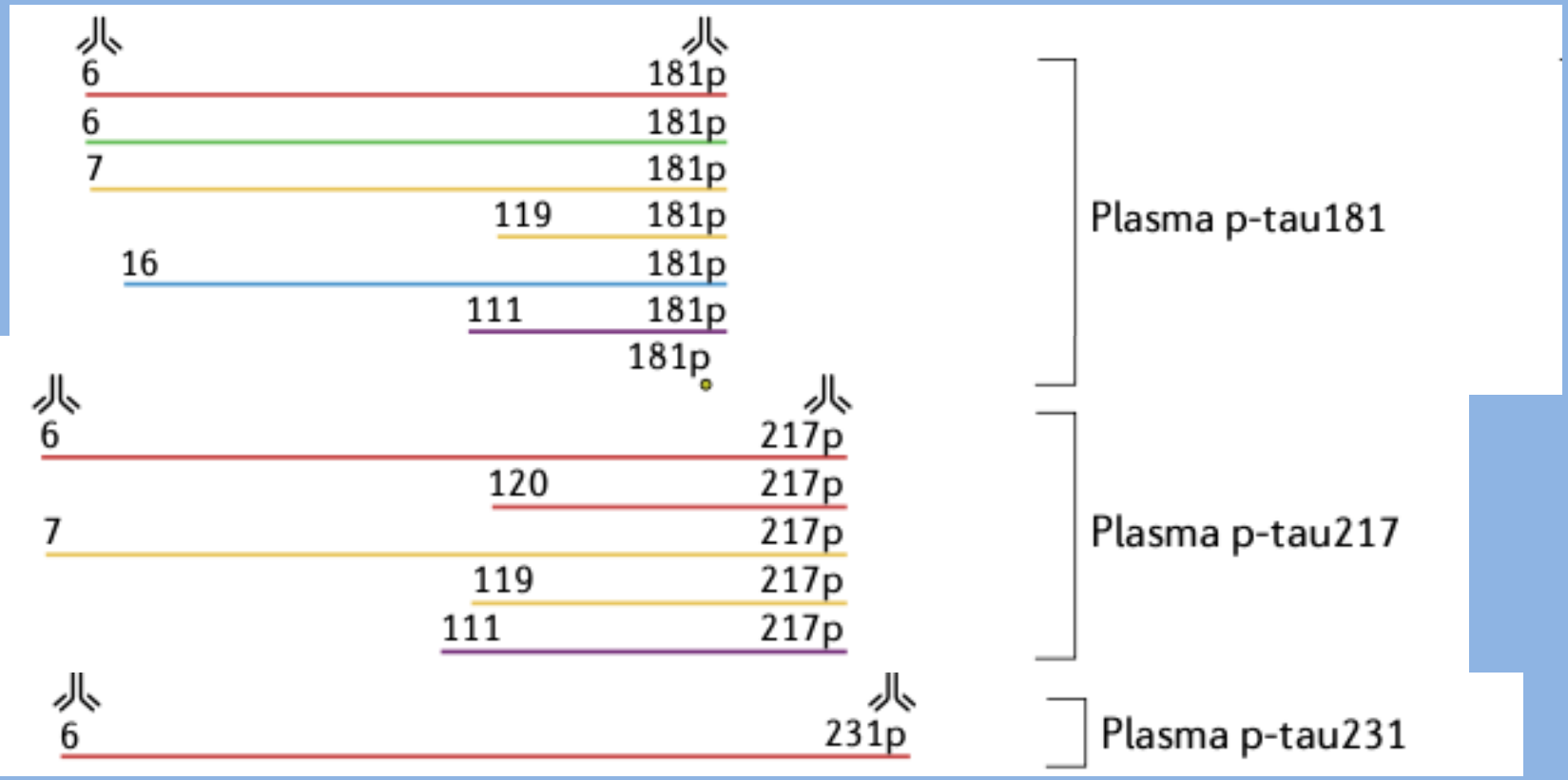


Brain tau: Mass spectrometric data show that tau is post-translationally modified at several positions, including truncations at amino acids 368,391 and 421

CSF tau extends from the N-terminal and mid-region forms make up the majority of the soluble pool, fractions of which are released into cerebrospinal fluid (CSF) and blood.

Blood tau extends from the N-terminal to the start of the microtubule binding region (around amino acid 254).

Epitopes of the established CSF p-tau and total tau assays



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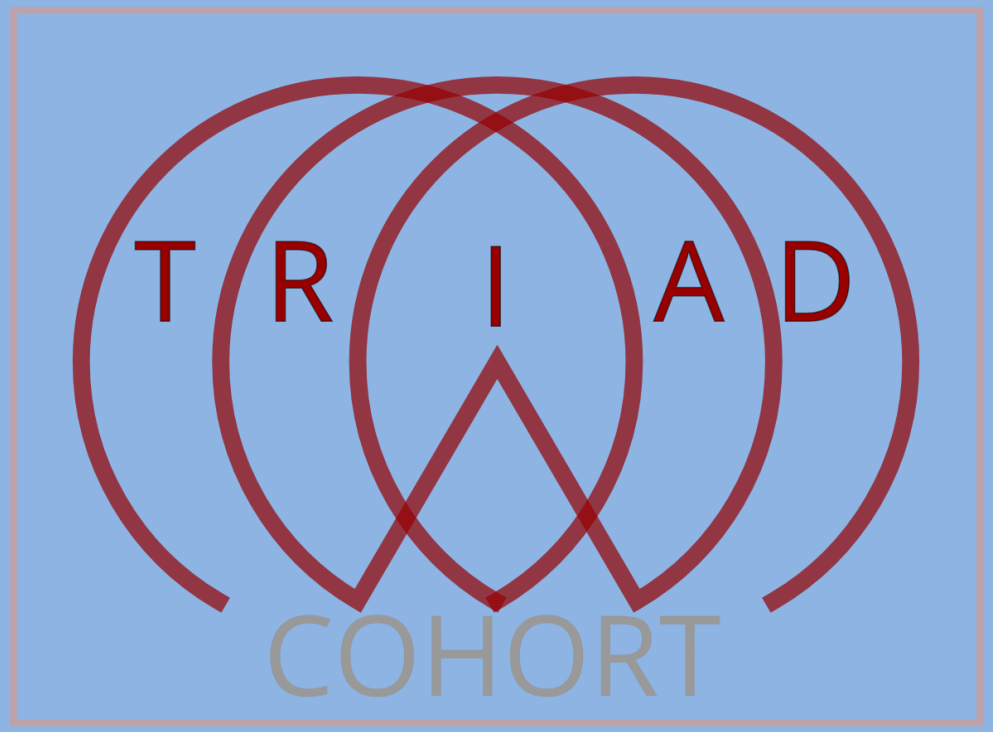
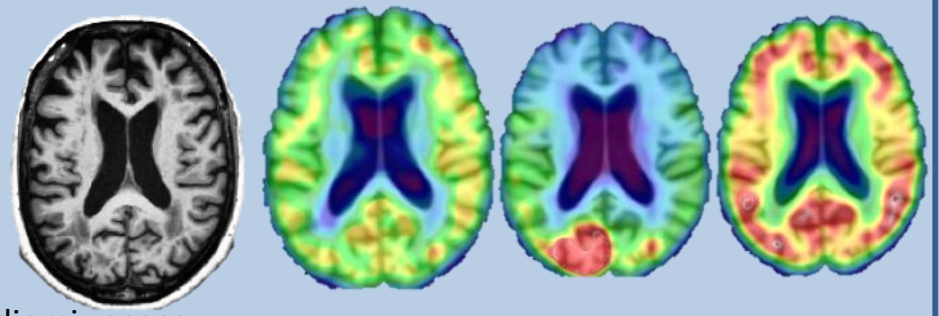


The Translational Biomarkers in Aging and Dementia (TRIAD) is a longitudinal, observational, biomarker based, cohort specially designed to study interactions between pathophysiological processes driving to dementia.

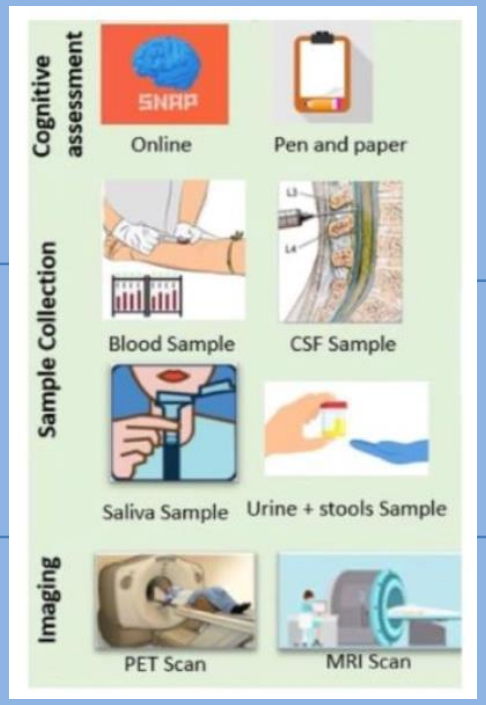
TRIAD Innovation

BIOVIE COHORT
Biomarqueurs de Vieillissement et de Démence

PET :Gold standard measures



Radiomic space



Biobank

genetics

CSF

saliva

blood

feces

urine

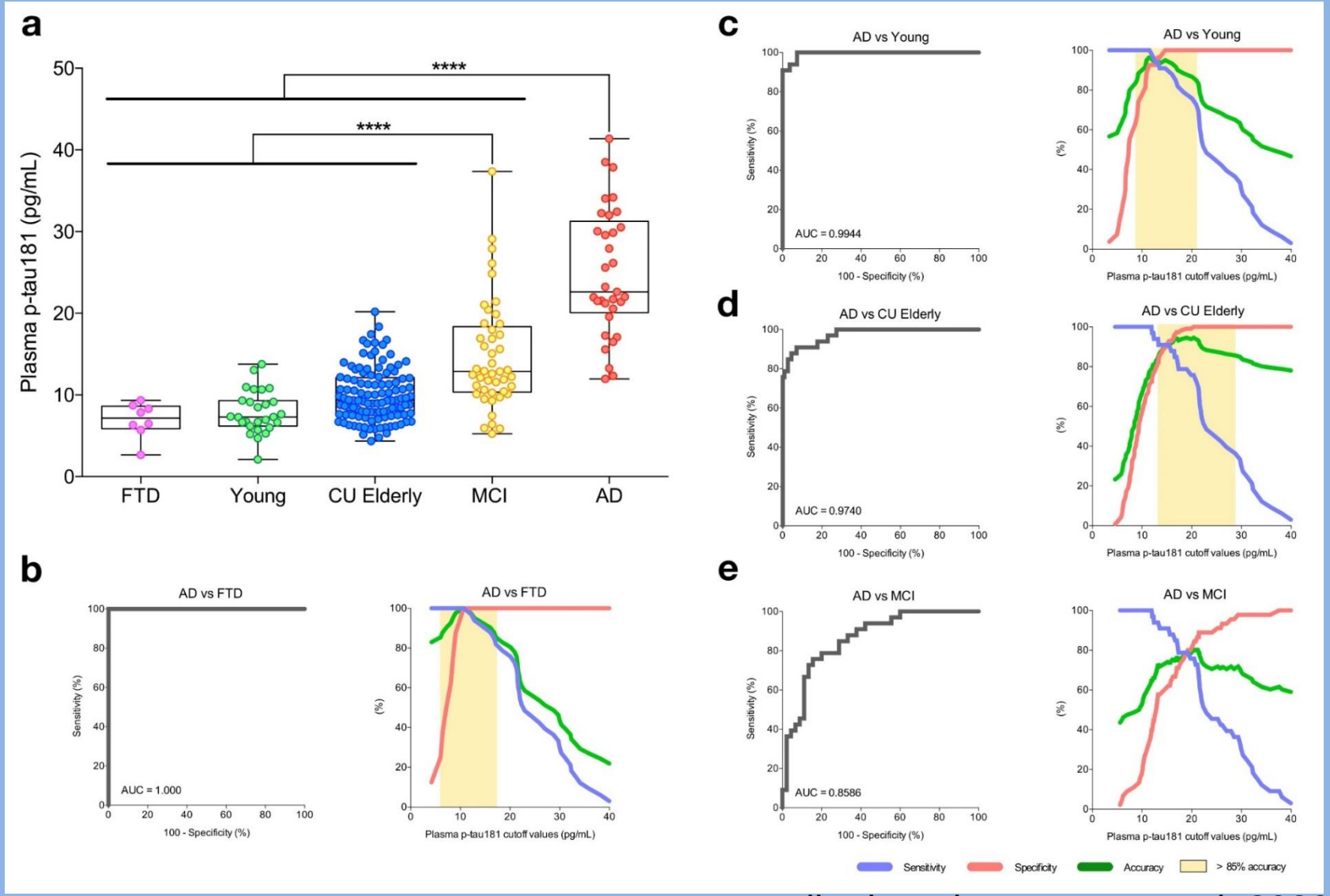
Cross-validation

Simoa

Microbiota
UCSD, USA

TRIAD validation cohort

P-tau181 in in relation to clinical diagnoses



Karikari *et al*., Lancet Neurol, 2020

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Plasma p-tau is a novel, promising blood-based biomarker for Alzheimer's disease

Plasma p-tau levels are increased in AD

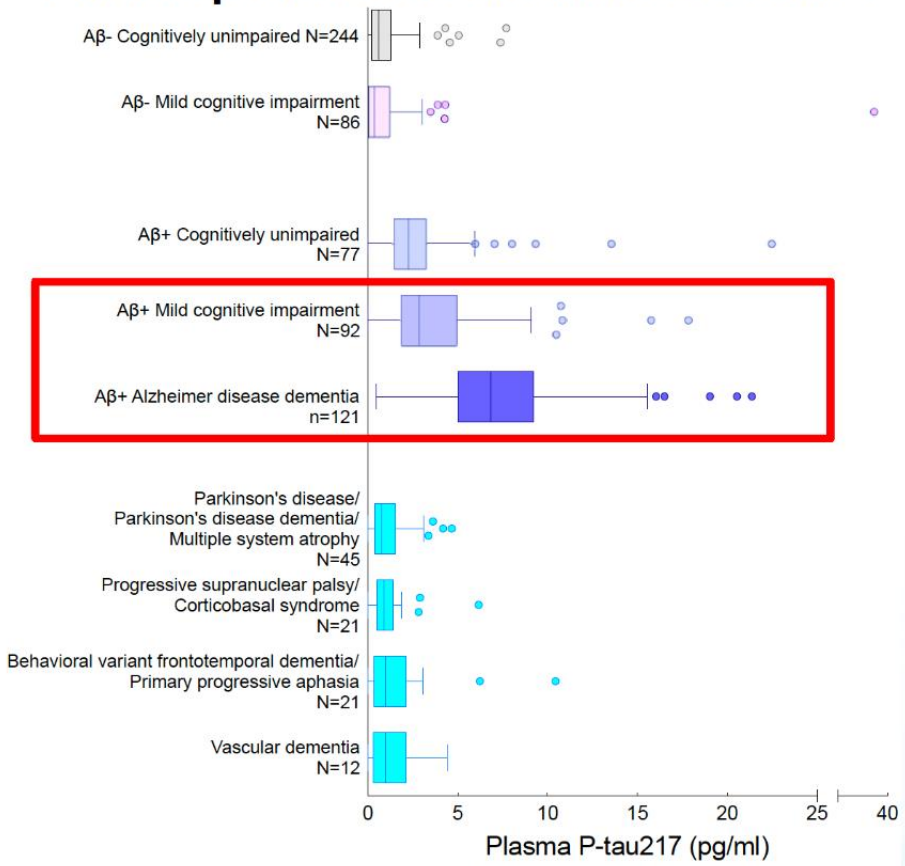


Figure adapted from Palmqvist S, et al. *JAMA*. 2020;324:772–781.[1]

Approximative ordering of Alzheimer's disease biomarker changes during the disease course

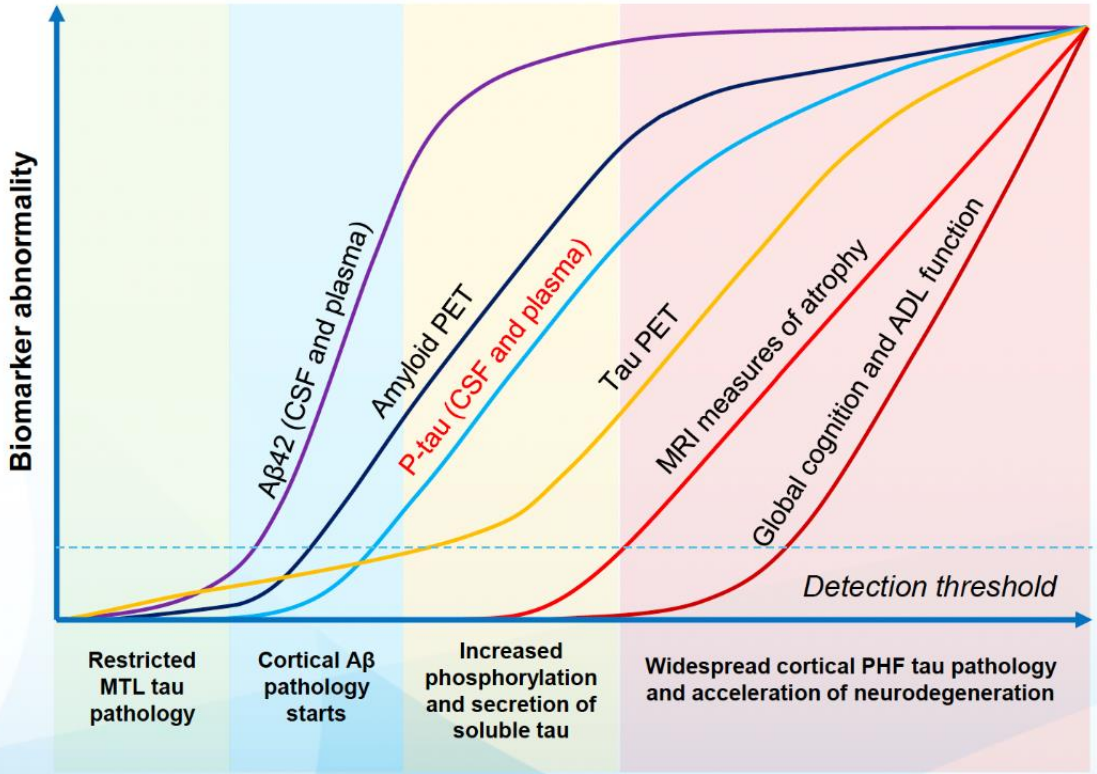
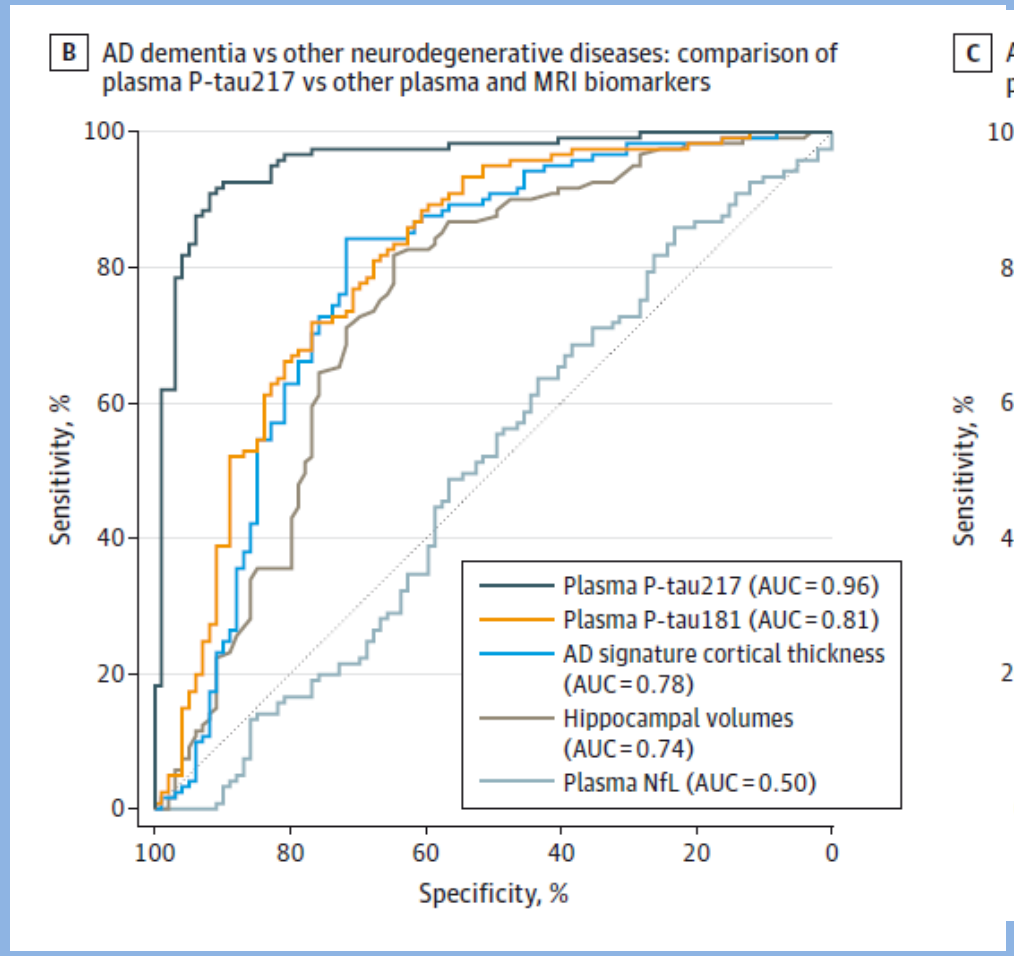
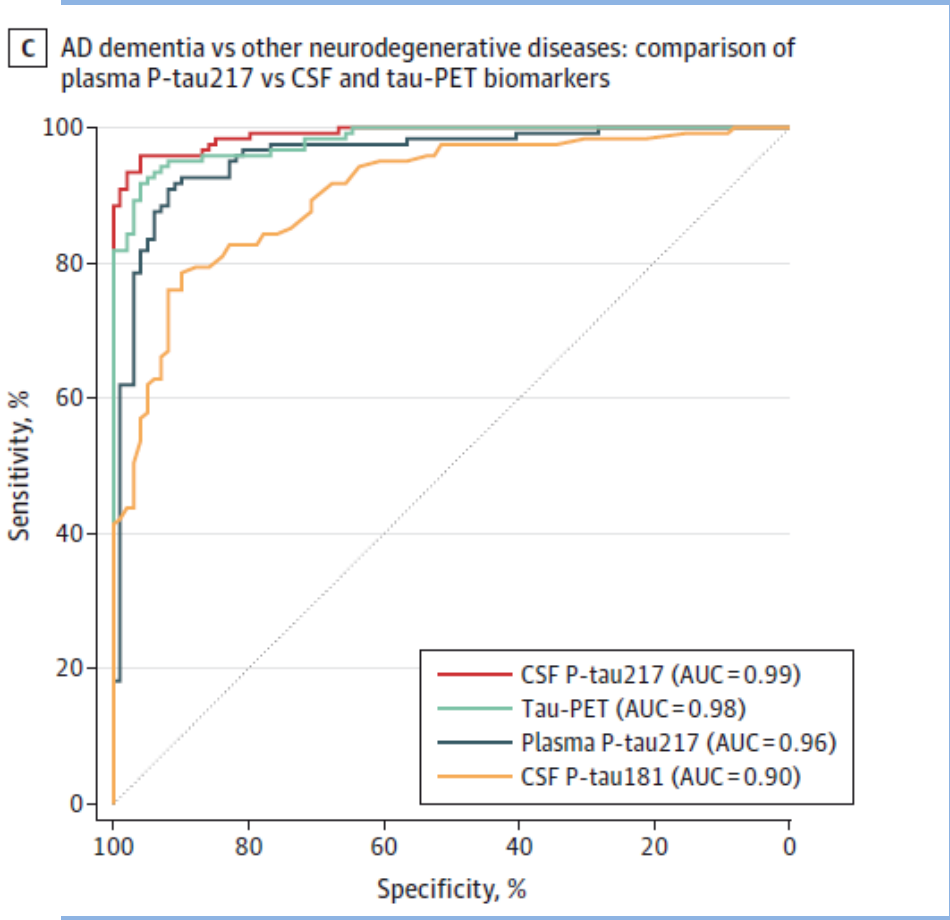


Figure adapted from Hansson O. *Nat Med*. 2021;27:954–963.[2]

Aβ, amyloid beta; ADL, activities of daily living; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; MTL, medial temporal lobe; p-tau, phosphorylated tau; PET, positron emission tomography; PHF, paired helical filaments; t-tau, total tau. 1. Palmqvist S, et al. *JAMA*. 2020;324:772–781; 2. Hansson O. *Nat Med*. 2021;27:954–963.

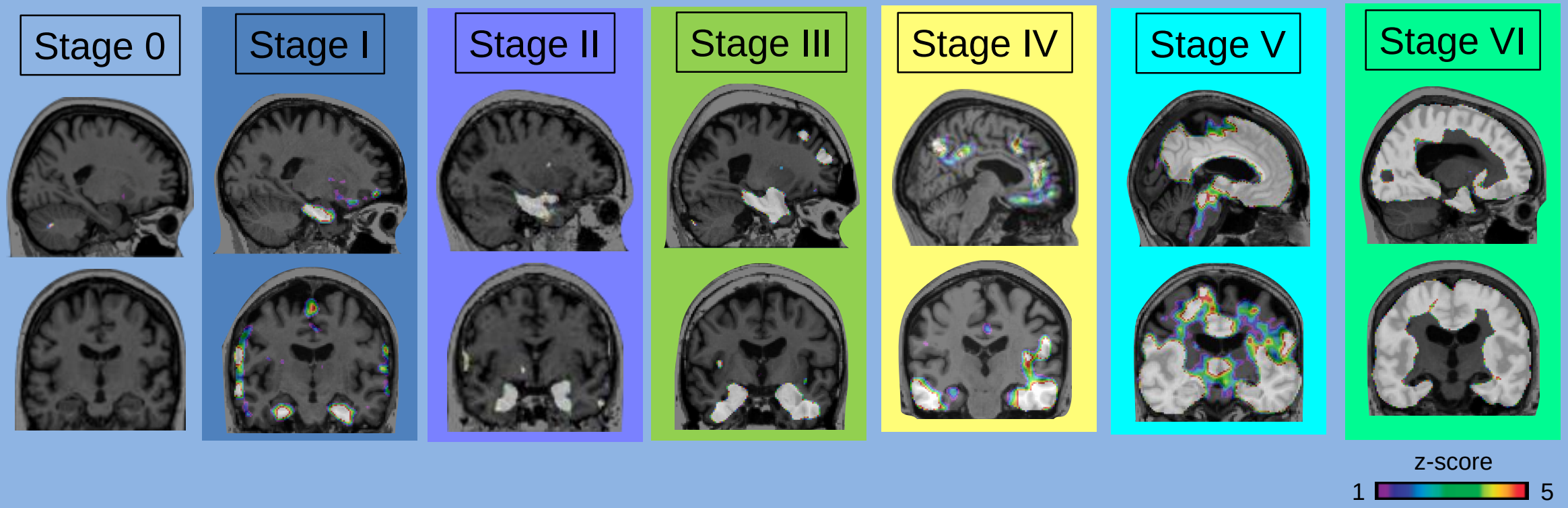
Lilly MSD plasma P-tau217 in Alzheimer's disease – compared with other markers, including P-tau181

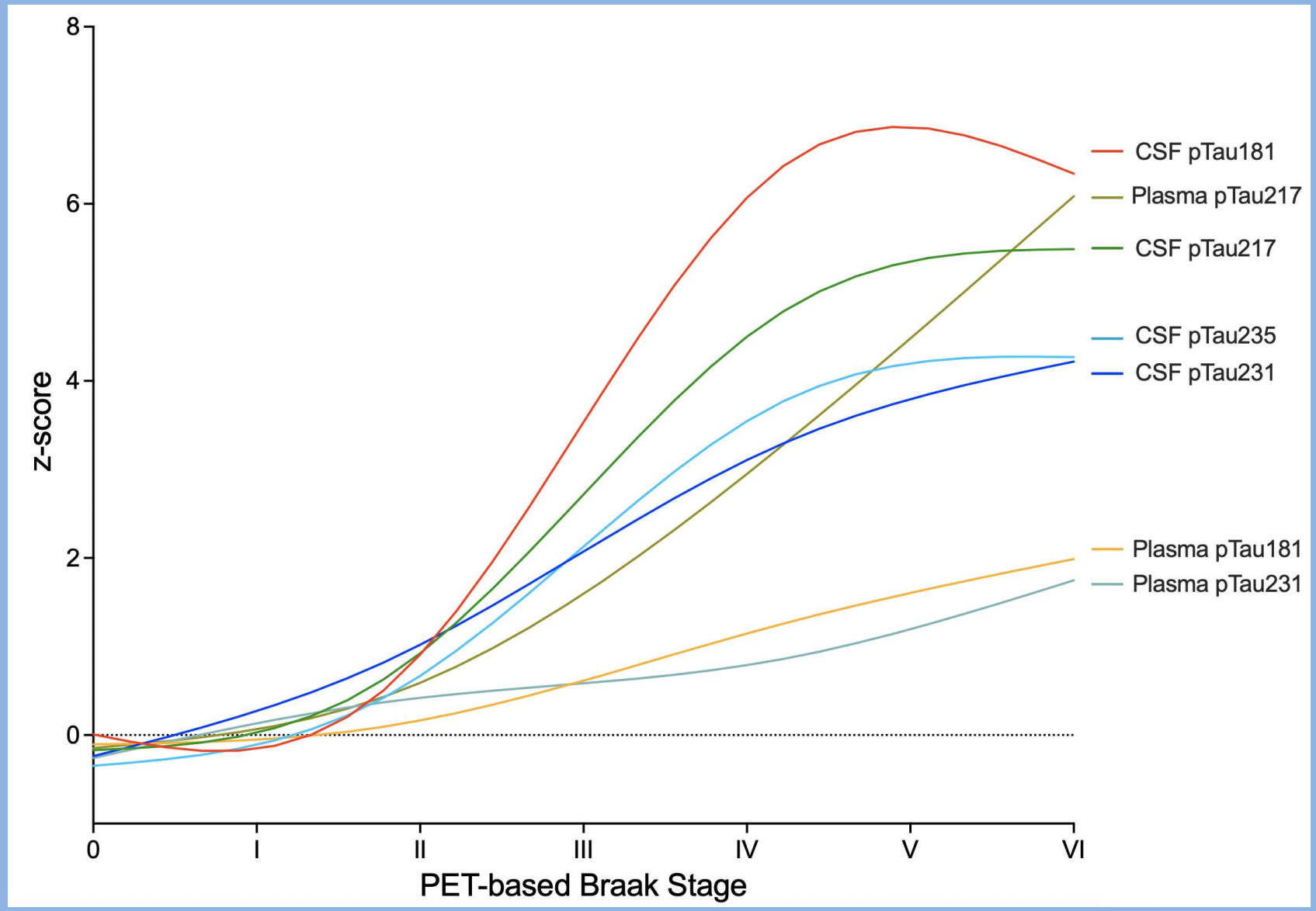




Palmqvist *et al.*, 2020, JAMA

Alzheimer’s disease stages PET




8
6
4
2
0
Z-score
0
I
II
III
IV
V
VI
PET-based Braak Stage
CSF pTau181
Plasma pTau217
CSF pTau217
CSF pTau235
CSF pTau231
Plasma pTau181
Plasma pTau231

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Regulatory requirements for a class 3 IVD medical device

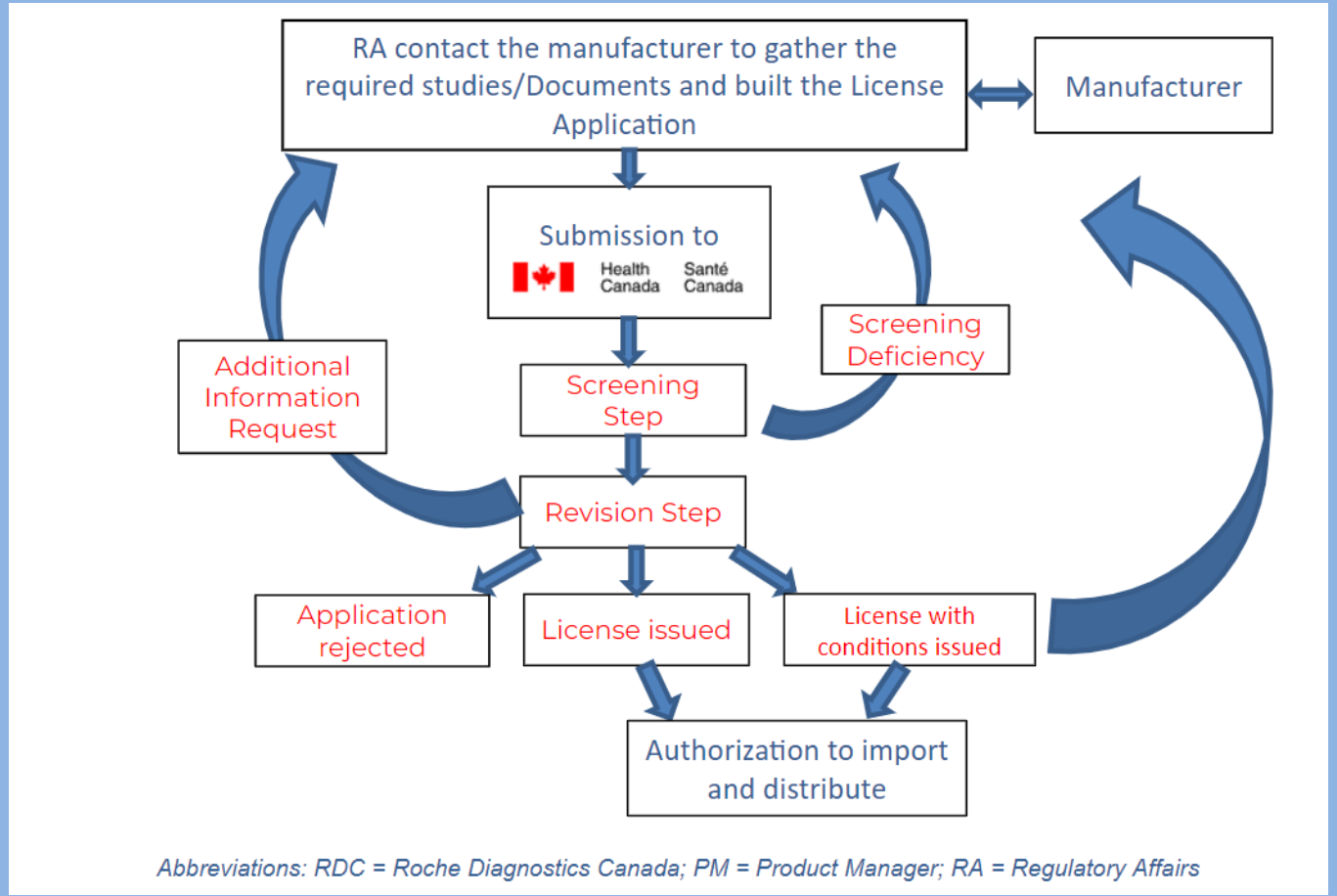
(like the Alzheimer's Assays)

Health Canada Regulatory Approval Process for IVDs

To obtain access to the Canadian market, *in vitro* diagnostic device manufacturers will need to secure a license, in order to obtain that the following is needed (simplified overview of the process):

- Application form
- Quality Management Certificate
- Labeling
- Device description
- Design Philosophy
- Marketing history
- Manufacturing sites
- Canadian Declaration of Conformity
- Performance studies (technical and clinical)

Current process of registration in Canada



Abbreviations: RDC = Roche Diagnostics Canada; PM = Product Manager; RA = Regulatory Affairs

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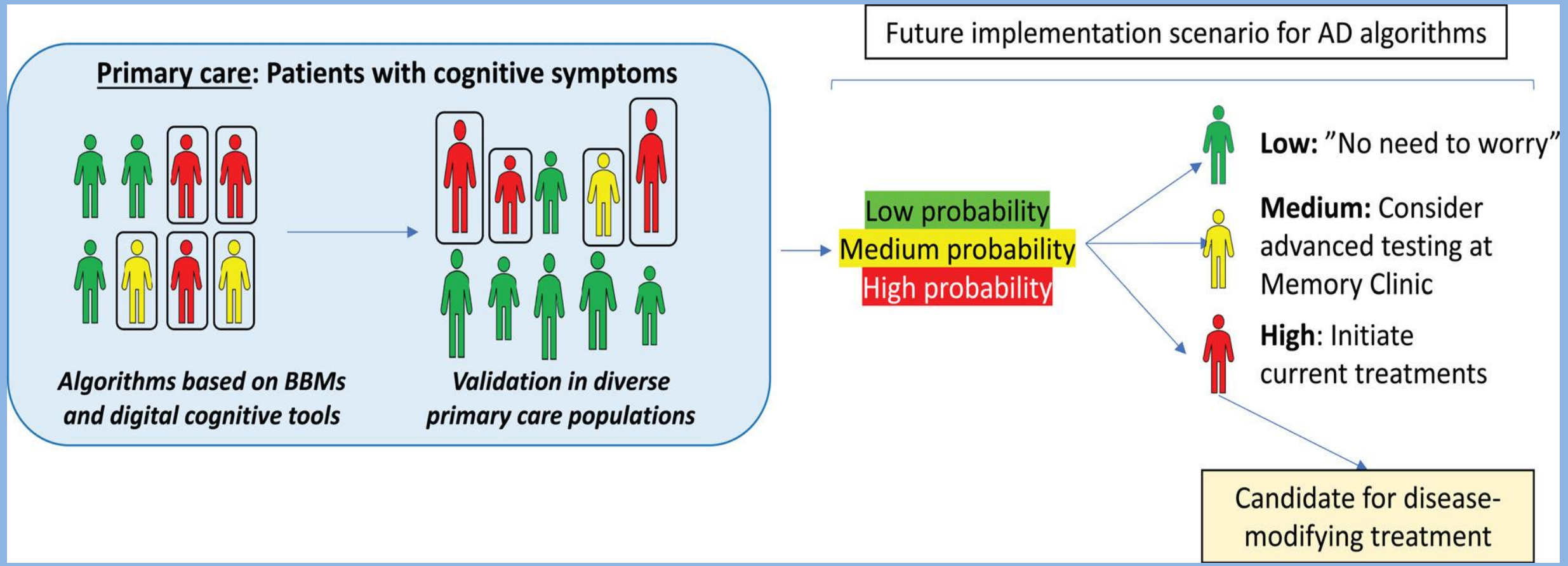

Primary care: Patients with cognitive symptoms
Algorithms based on BBMs and digital cognitive tools
Validation in diverse primary care populations
Future implementation scenario for AD algorithms
Low probability
Medium probability
High probability
Low: "No need to worry"
Medium: Consider advanced testing at Memory Clinic
High: Initiate current treatments
Candidate for disease-modifying treatment

SOME ISSUES NEED OF RESOLUTION

- Standardization of assays
- Clinical cutoffs
- Impact of chronic kidney disease, obesity
- Value of combining P-tau with ApoE genotype

CONCLUSIONS

- The etiologic diagnosis of MCI and dementia requires biomarkers
- Changes in biological fluids such as CSF/blood precede changes in PET and are more accessible/less costly
- There is currently more sensitivity for changes in CSF compared to blood
- The availability of plasma biomarkers such as P-tau isoforms may help find persons who require CSF or PET imaging and those who do not – ready for specialty clinics, not yet for primary care clinics

MOVING FORWARD IN CANADA

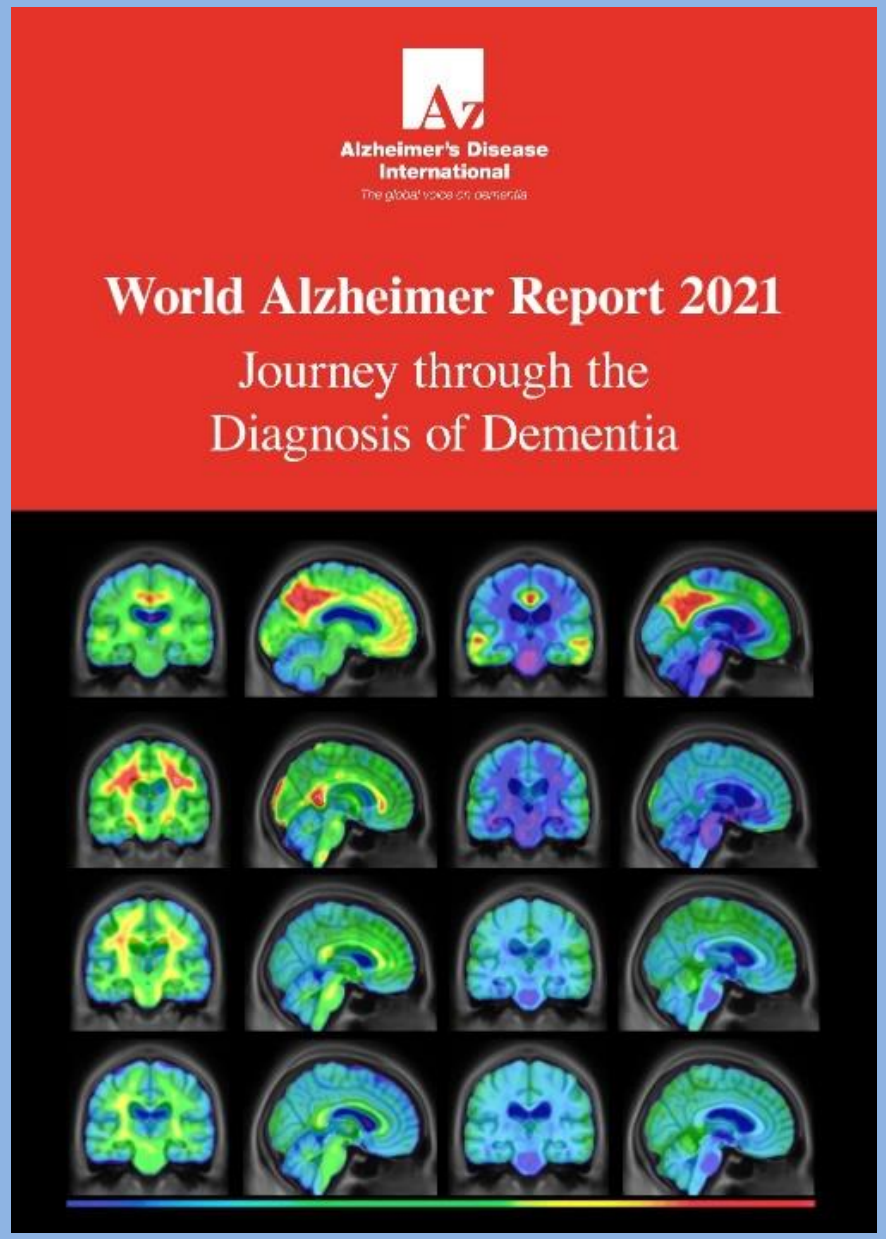
- Write our evidence-based appropriate use recommendations
- Develop industry partnership to get approval from Health Canada for specific assays of key P-tau isoforms
- Calculate costs savings in the diagnostic workup
- Open dialogue with provincial reimbursement bodies

SPECIAL THANKS

- Participants of the TRIAD/BIOVIE and other observational cohorts
- Drs Alonso Montoya, Pedro Rosa-Neto, Henrik Zetterberg for sharing slides

KEY REFERENCES

- Hansson et al. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. Alzheimer's Dement 2022;18:2669-2686. doi:10.1002/alz.12756
- Angioni et al. Blood biomarkers from research to clinical practice. J Prev Alz Dis 2022;4(9):569-579. doi:10.14283/jpad.2022.85
- Hansson et al. Blood biomarkers for Alzheimer's disease in clinical practice and trials. Nature Aging 2023;3(5):506-519. doi:10.1038/s43587-023-00403-3



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