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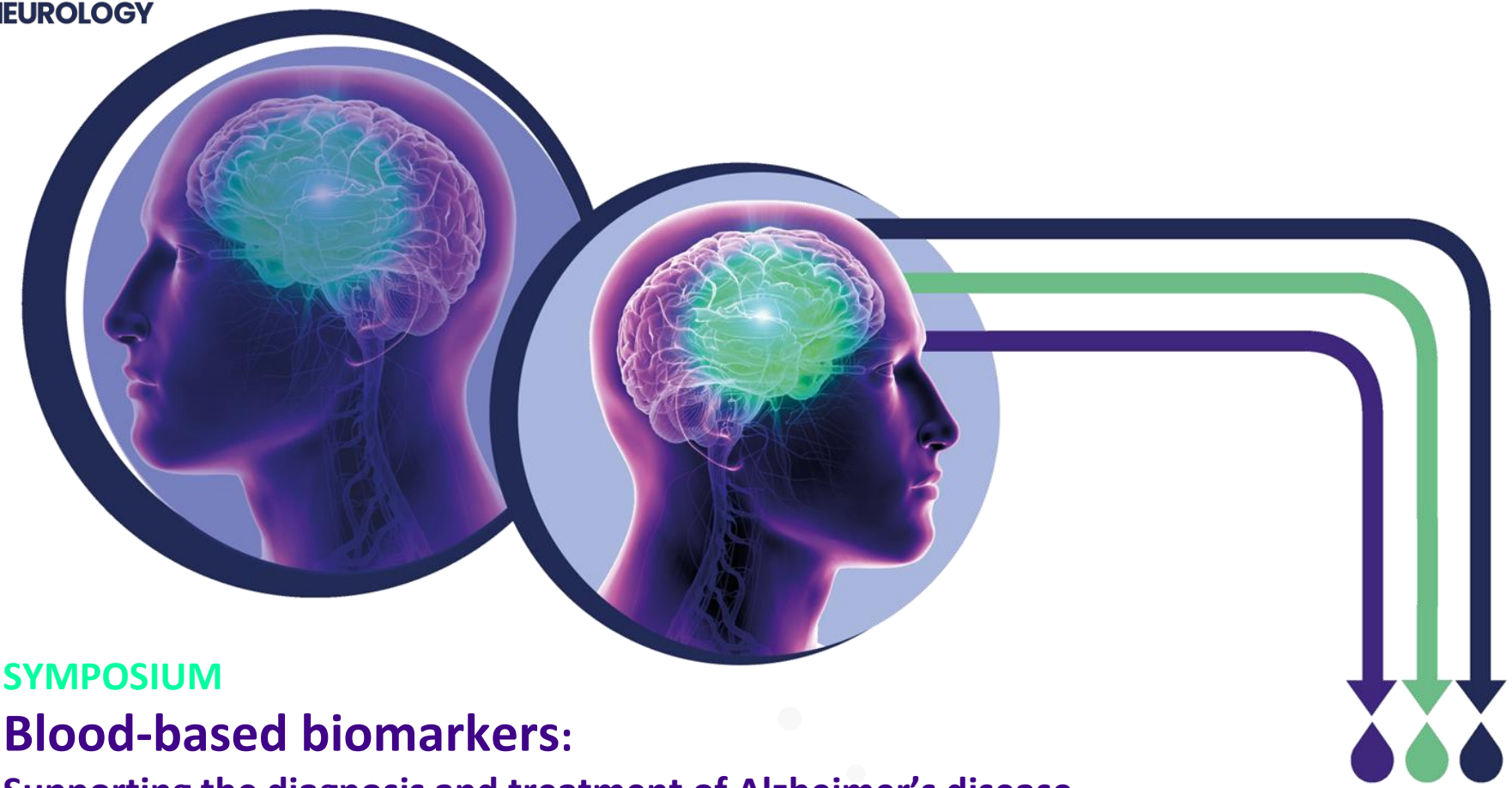

SYMPOSIUM

Blood-based biomarkers:

Supporting the diagnosis and treatment of Alzheimer's disease

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Expert panel

Prof. Jeffrey Cummings (Chair)
University of Nevada, Las Vegas, NV, USA

Prof. Liana Apostolova
Indiana University School of Medicine, Indianapolis, IN, USA

Prof. Oskar Hansson
Lund University, Lund, Sweden

Prof. Charlotte Teunissen
Amsterdam UMC, Amsterdam, Netherlands

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Agenda

Time	Presentation	Speaker(s)
09:10	Introduction and welcome	Prof. Jeffrey Cummings
09:20	Moving towards a biological diagnosis of Alzheimer's disease: The time is now	Led by Prof. Liana Apostolova
09:50	Blood-based biomarkers in Alzheimer's disease: Advantages and limitations	Led by Prof. Oskar Hansson
10:20	Integrating blood-based biomarkers in Alzheimer's disease: How and when?	Led by Prof. Charlotte Teunissen
10:50	Panel Discussion	All faculty
11:05	Meeting summary and close	Prof. Jeffrey Cummings

Learning objectives

- Recognize the importance of a timely and accurate biological diagnosis of Alzheimer's disease to inform treatment decisions
- Assess clinical data for diagnostic Alzheimer's disease blood-based biomarkers and identify their advantages and limitations
- Evaluate how blood-based biomarkers can be integrated into the diagnostic workup of patients and facilitate disease management

Moving towards a biological diagnosis of Alzheimer's disease: The time is now

Prof. Liana Apostolova
Indiana University School of Medicine,
Indianapolis, IN, USA

AD facts and figures

The timely diagnosis of AD is an unmet need in clinical practice

>55 million people worldwide are living with dementia
This number is expected to rise to 139 million by 2050[1]

1 in 3 people over the age of 65 die with AD or another dementia[2]

Diagnosis is often **delayed** by **~2–3 years** after symptom onset[3]

AD accounts for **60–80%** of all dementia cases[1]

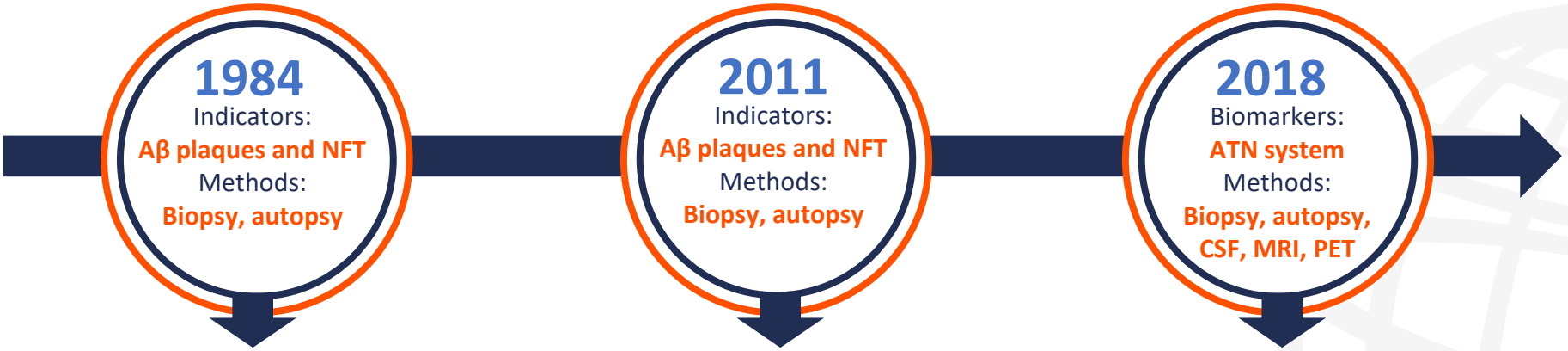
Diagnostic inaccuracy for AD is **~25%**[3]

Globally, an estimated **75%** of people with dementia are not diagnosed[1]

AD, Alzheimer's disease.

1. Gauthier S, et al. World Alzheimer Report 2022. Available at: https://www.alzint.org/u/World-Alzheimer-Report-2022.pdf (accessed 22 March 2023);
2. *Alzheimers Dement*. 2021;17:327–406; 3.Sabbagh MN, et al. *Neurol Ther*. 2017;6(Suppl. 1):83–95.

The evolution of AD diagnosis



NINCDS-ADRDA Criteria

- One stage of disease: Dementia
- Diagnostic criteria: Unlikely, probable, possible, definite
- Neuropsychological testing diagnoses probable and possible dementia
- Hard to discriminate AD from other dementias

NIA-AA Criteria

- Three stages of disease: Preclinical, MCI, AD
- New AD major symptoms
- Two diagnostic biomarkers (non-clinical): Aβ levels, ND or injury
- Differentiate between AD and non-AD dementia

NIA-AA Framework

- Three stages of disease: Preclinical, MCI, AD
- Goal: Observational and interventional research; AD biomarker diagnosis in living patients
- **ATN system**

Aβ, amyloid-beta; AD, Alzheimer's disease; ATN, amyloid/tau/neurodegeneration; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; ND, neurodegeneration; NFT, neurofibrillary tangles; NIA-AA, National Institute of Aging–Alzheimer's Association; NINCDS-ADRDA, National Institute of Neurological and Communicative Diseases and Stroke–Alzheimer's Disease and Related Disorders Association; PET, positron emission tomography.

Lee, JC, et al. *Exp Mol Med*. 2019;51:1–10.

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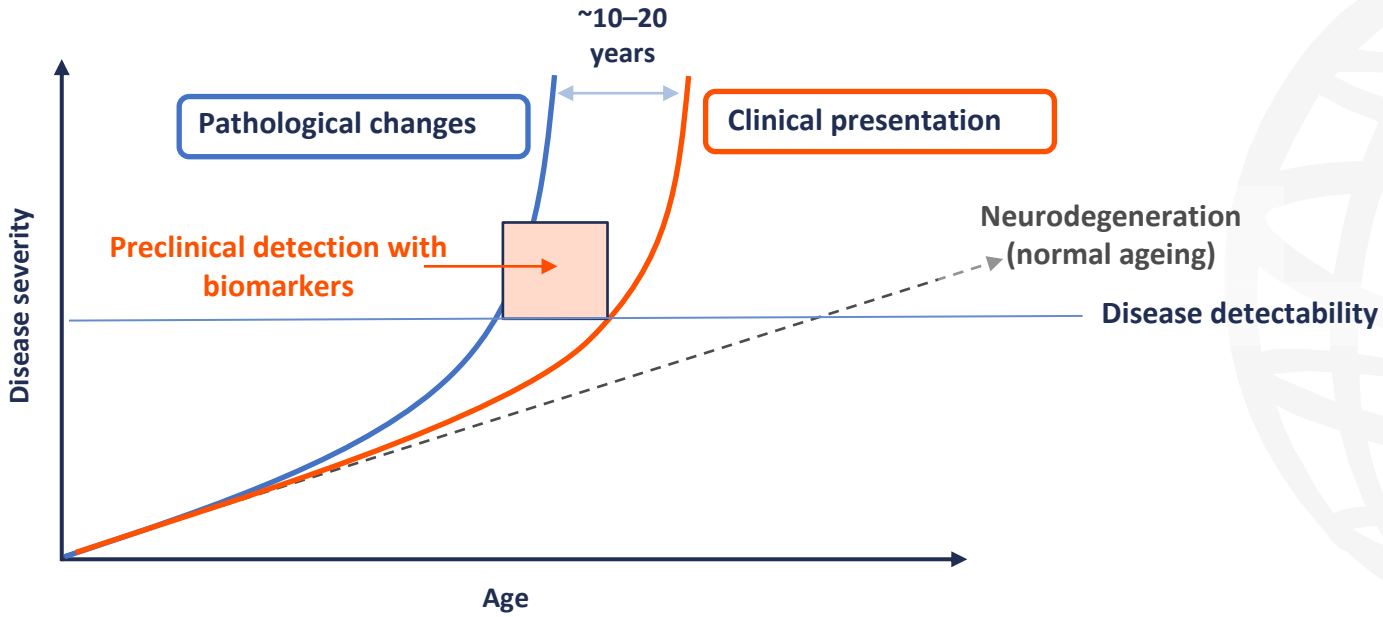
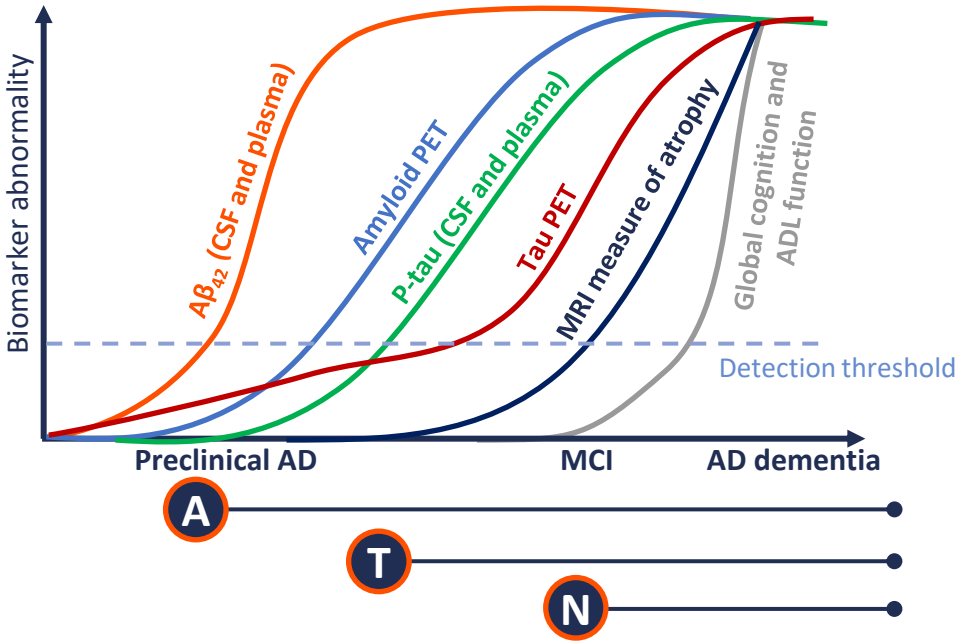
Detecting preclinical AD



AD, Alzheimer's disease.
Khan TK, et al. *Front Neurosci.* 2018;12:275.

Biomarkers and the ATN classification

Biomarker trajectories in AD[1–3]



Aβ, amyloid-beta; AD, Alzheimer's disease; ADL, activities of daily living; ATN, amyloid/tau/neurodegeneration; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; p-tau, phosphorylated tau; PET, positron emission tomography.

1. Hansson O. *Nat Med*. 2021;27:954–63; 2. McDade E, et al. *Alzheimers Dement (N Y)*. 2020;6:e12069; 3. Counts SE, et al. *Neurotherapeutics*. 2017;14:35–53.

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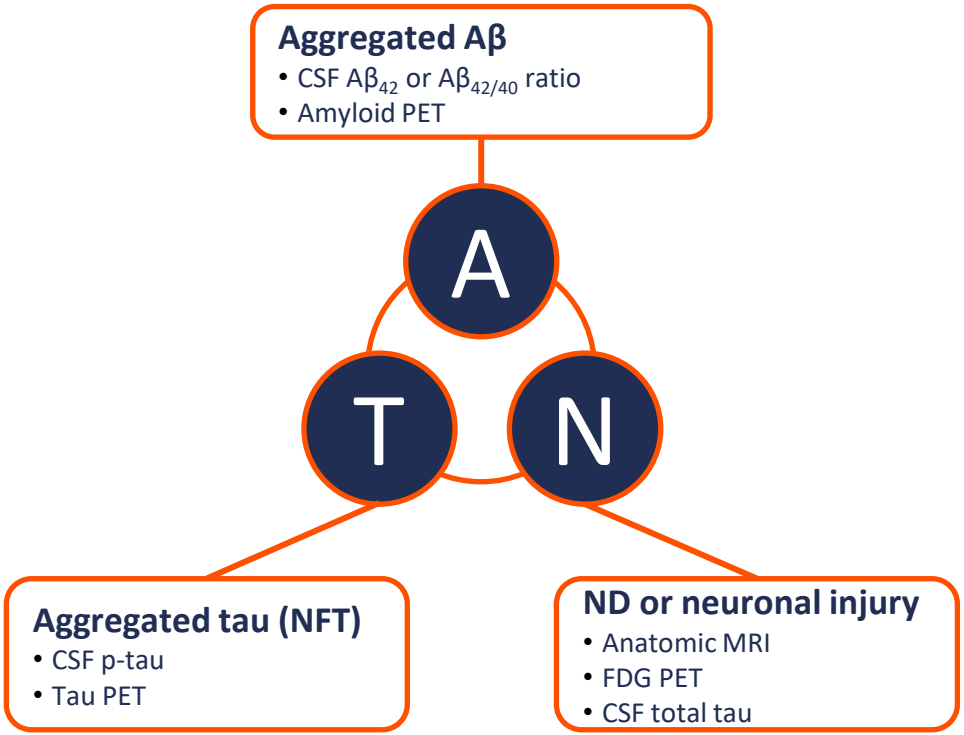
Biomarker-based definition of AD



ATN profile	Biomarker category	
A - T - N -	Normal AD biomarkers	
A + T - N -	AD pathologic change	AD continuum
A + T + N -	AD	AD continuum
A + T + N +	AD	AD continuum
A + T - N +	AD and concomitant suspected non-AD pathologic change	AD continuum
A - T + N -	Non-AD pathologic change	
A - T - N +	Non-AD pathologic change	
A - T + N +	Non-AD pathologic change	

Aβ, amyloid-beta; AD, Alzheimer's disease; ATN, amyloid/tau/neurodegeneration; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; ND, neurodegeneration; NFT, neurofibrillary tangle; PET, positron emission tomography; p-tau, phosphorylated tau.

Jack CR, et al. *Alzheimers Dement*. 2018;14:535–62.

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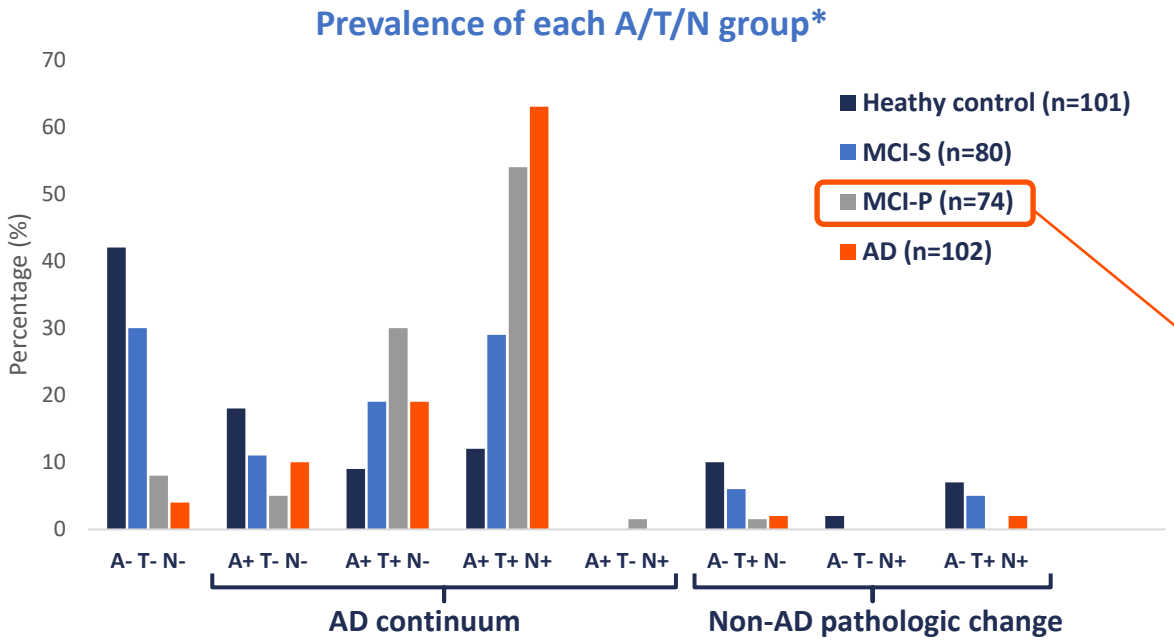
ATN biomarker scheme in practice

Participants from the Alzheimer's Disease Neuroimaging Initiative (ADNI)



48% of MCI individuals progressed to AD within 36 months

*ATN classification was assessed with CSF biomarkers: Aβ biomarker "A" with CSF $A\beta_{42}$, the tau pathology biomarker "T" with CSF p-tau, the biomarker of neurodegeneration "N" with CSF t-tau. Aβ, amyloid-beta; AD, Alzheimer's disease; ATN, amyloid/tau/neurodegeneration; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; MCI-P, MCI progressed to AD; MCI-S, MCI stable; p-tau, phosphorylated tau; t-tau, total tau.

Ekman U, et al. *Sci Rep*. 2018;8:8431.

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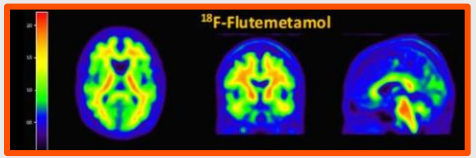
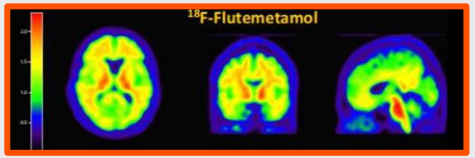
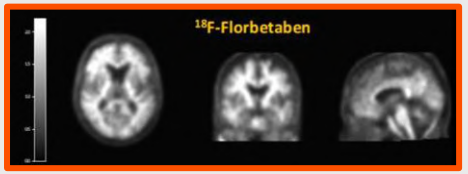
Advantages and limitations of current AD biomarkers

Modality	Advantages	Limitations
Amyloid/tau PET	• Highly discriminative for AD[1] • Suitable for patients with contraindications to lumbar puncture[1]	• Expensive[1–3] • Limited availability[1,3] • Uses radiation[1,2]
CSF	• Highly discriminative for AD[1] • Relatively cheap[1] • Enables analyses of inflammation, tau pathology and neurodegeneration[1]	• Invasive[1,3] • Reluctance around lumbar puncture[2]
Structural MRI	• Measures cerebral atrophy[3]	• Relatively late event (compared to CSF and PET measures)[3] • Cannot directly detect core pathophysiological features (Aβ, tau)[3]

Aβ, amyloid-beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; PET, positron emission tomography.

1. Hardy-Sosa A, et al. *Front Aging Neurosci*. 2022;14:683689; 2. Porteinsson AP, et al. *J Prev Alzheimers Dis*. 2021;3:371–86; 3. Baird AL, et al. *Front Neurol*. 2015;16:236.

Distribution of Aβ by amyloid PET

FDA and EMA approved radiotracers	Aβ negative example	Aβ positive example	Sensitivity/specificity
[^{18}F]Florbetapir[1,2]			92–96%*/100%
[^{18}F]Flutemetamol[1,3]			86%/100%†
[^{18}F]Florbetaben[1,4]			98%/89%‡

Images are cropped from original Figure 1 "Illustrative PET images derived from the five most commonly used amyloid tracers on different patients" in Pemberton HG, et al. *Eur J Nucl Med Mol Imaging*. 2022;49:3508–28, used under CC BY 4.0. *Sensitivity was 92% in people who had an autopsy within 2 years of PET imaging, and 96% for those who had an autopsy within 1 year of PET imaging; †With the 2012 NIA-AA criteria; ‡In detecting/excluding neuritic plaques.

Aβ, amyloid-beta; EMA, European Medicines Agency; FDA, United States Food and Drug Administration; NIA-AA, National Institute of Aging–Alzheimer's Association; PET, positron emission tomography. 1. Pemberton HG, et al. *Eur J Nucl Med Mol Imaging*. 2022;49:3508–28; 2. Clark CM, et al. *Lancet Neurol*. 2012;11:669–78; 3. Salloway S. et al. *Alzheimers Dement (Amst)*. 2017;9:25–34; 4. Sabri O, et al. *Alzheimers Dement*. 2015;11:964–74.

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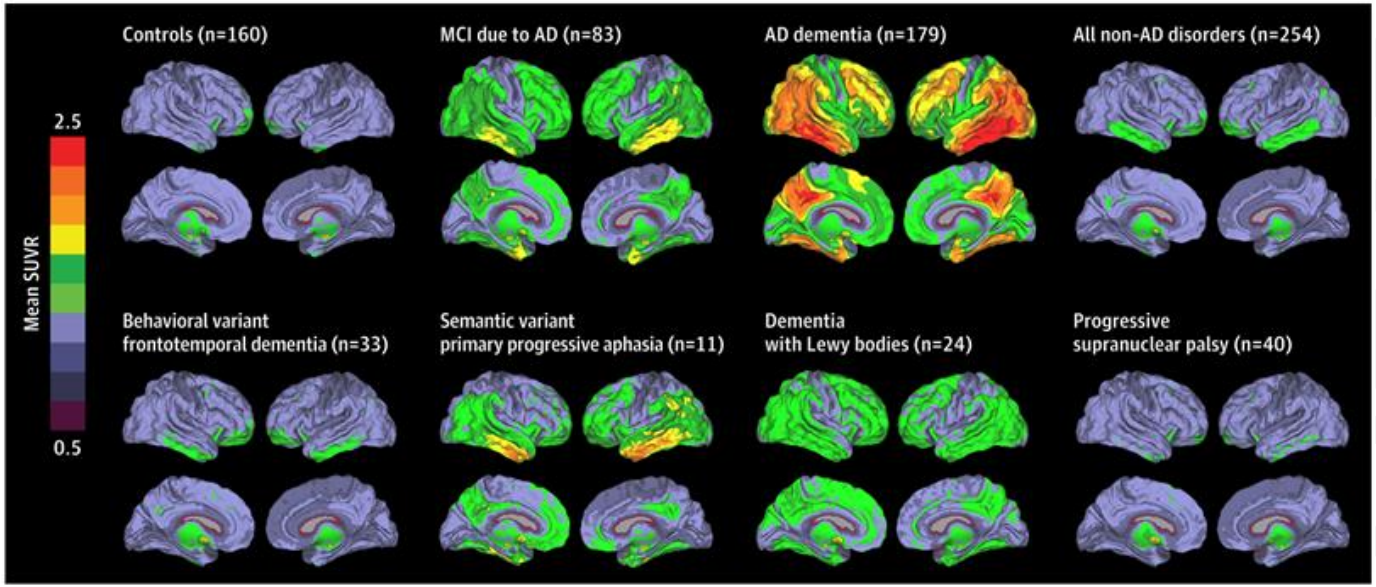
Distribution of tau aggregates by tau-PET

Mean whole-brain [^{18}F]flortaucipir uptake across groups



[^{18}F]Flortaucipir PET has an estimated **sensitivity of 89.9% and specificity of 90.6% for AD** vs other neurodegenerative diseases*

*A multicentre cross-sectional study including 719 participants.
AD, Alzheimer's disease; MCI, mild cognitive impairment; PET, positron emission tomography; SUVR, standardized uptake value ratio.
Ossenkoppele R, et al. *JAMA*. 2018;320:1151–62.

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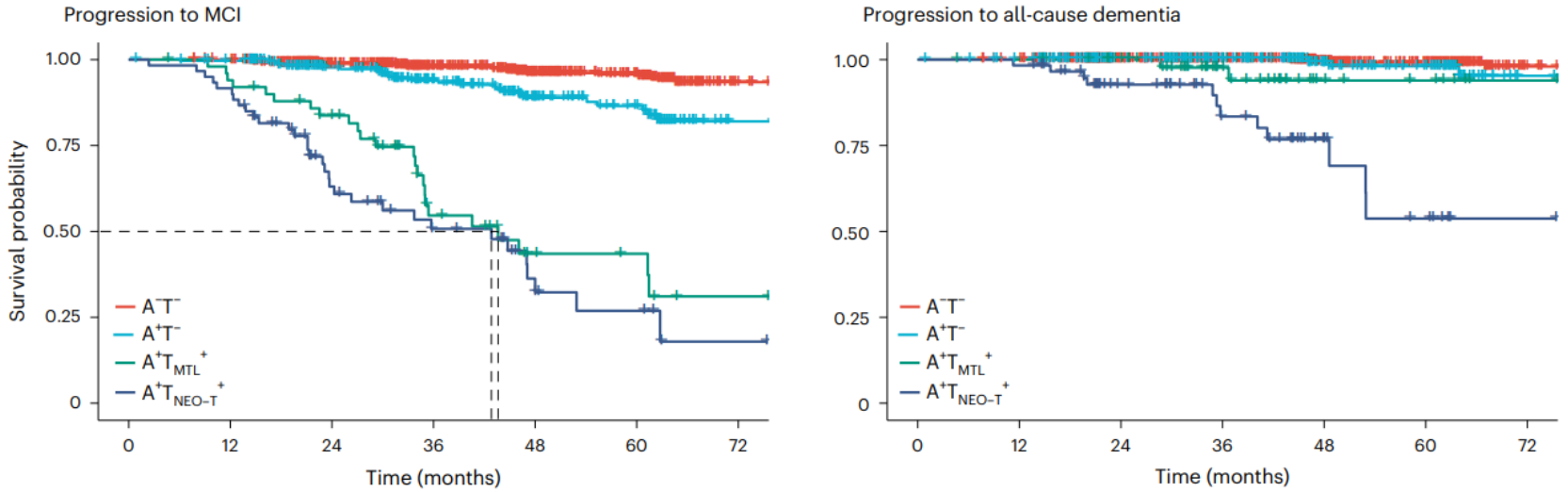
Amyloid and tau-PET positive CUI are at high risk for future cognitive decline*



A+ T+ CUI have an increased risk for future development of MCI and all-cause dementia. This supports the NIA-AA criteria-based classification of A+ T+ cognitively unimpaired individuals as 'preclinical AD' **especially when 'T' is defined by PET.**

Images are cropped from original Figure 2 "Progression to MCI or all-cause dementia in the different AT biomarker profiles." in Ossenkoppele R, et al. *Nat Med.* 2022;28:2381–87, used under CC BY 4.0.
*A multicentre study in 1325 participants with an average 3.5 years clinical follow-up data.
AD, Alzheimer's disease; A, amyloid; CUI, cognitively unimpaired individuals; MCI, mild cognitively impaired; MTL, medial temporal lobe; Neo-T, temporal neocortical; NIA-AA, National Institute of Aging–Alzheimer's Association; PET, positron emission tomography; T, tau.
Ossenkoppele R, et al. *Nat Med.* 2022;28:2381–87.

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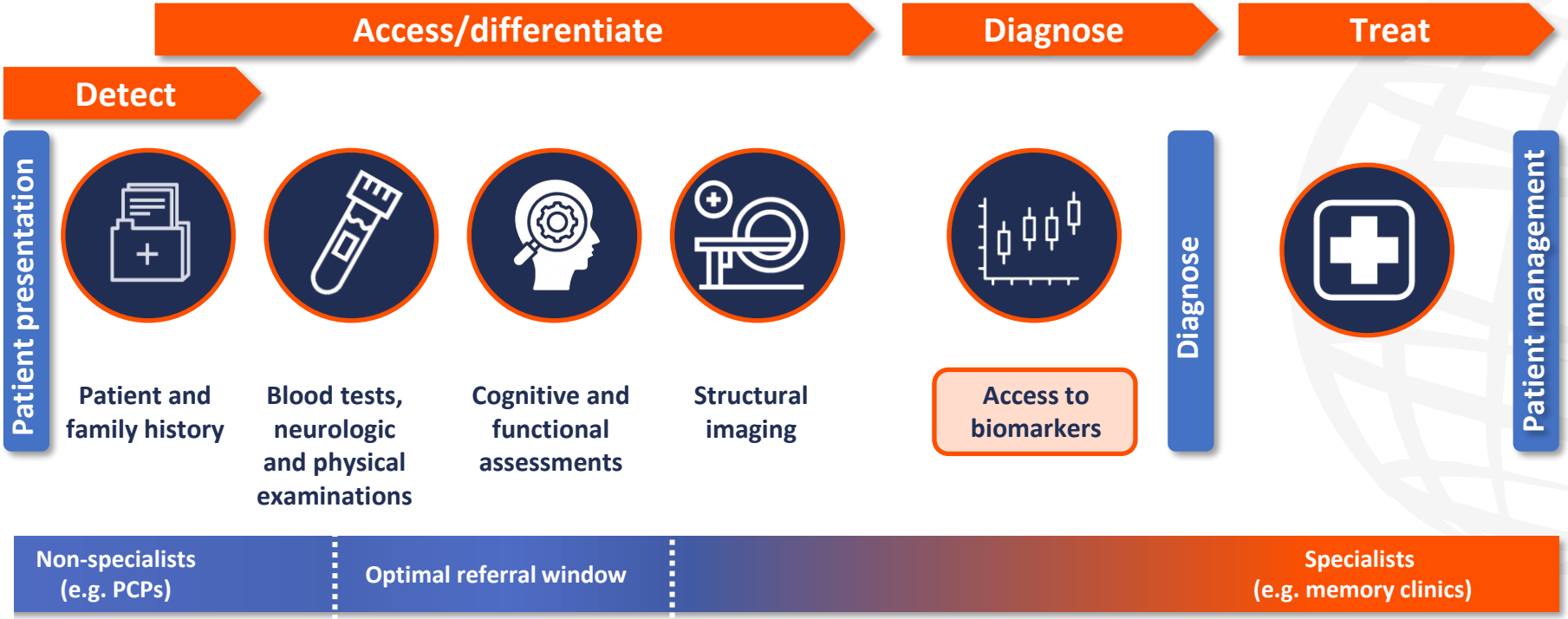
Key stages to a timely AD diagnosis



AD, Alzheimer's disease; PCP, primary care professional.

Porteinsson AP, et al. *J Prev Alzheimers Dis*. 2021;3:371–86.

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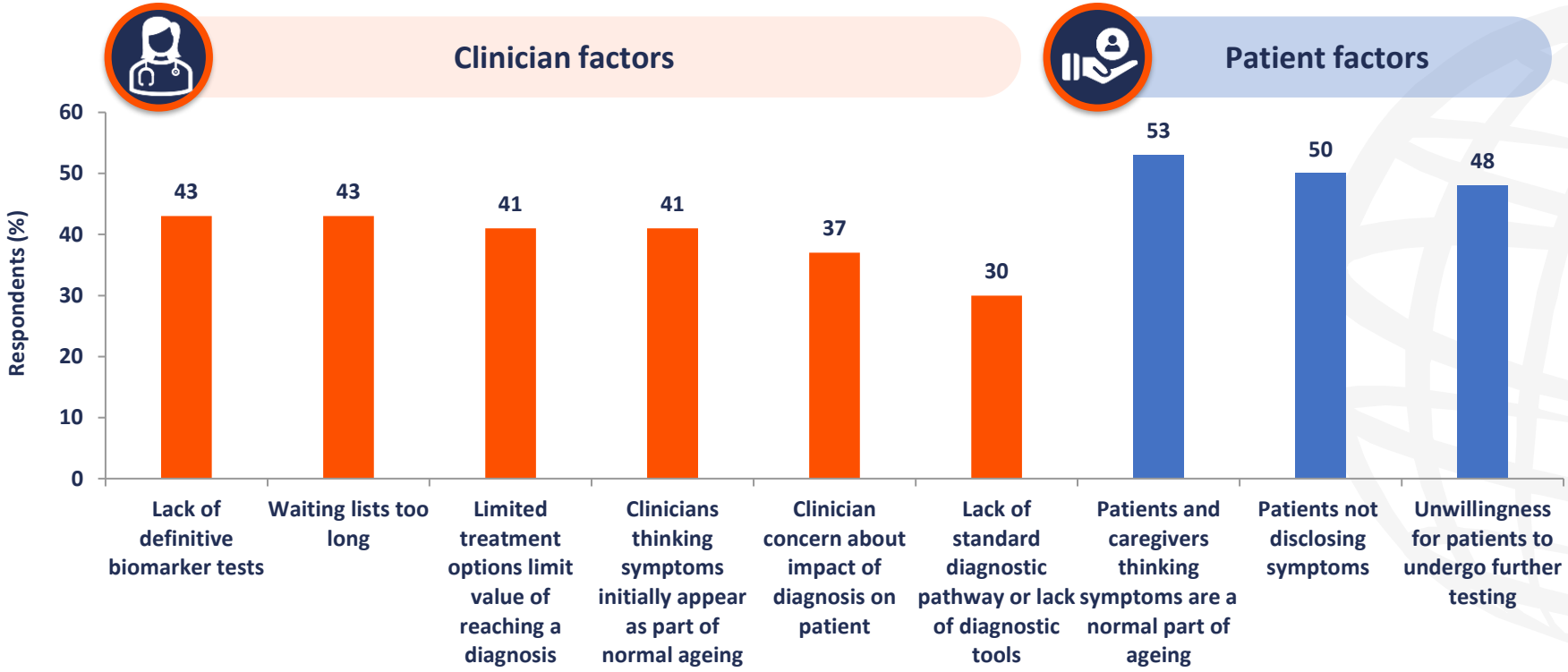
Barriers to diagnosis of MCI or AD as perceived by HCPs*



*Data from a cross-sectional survey of 1,365 PCPs and specialists (geriatricians, neurologists, psychiatrists and psychogeriatricians) from Europe (France, Germany, Italy, Spain and the UK), USA and Canada, who routinely manage patients with complaints of age-related cognitive impairment.
AD, Alzheimer's disease; HCP, healthcare provider; MCI, mild cognitive impairment; PCP, primary care physician.
Judge D, et al. *Int J Alzheimers Dis*. 2019;2019:3637954.

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Summary

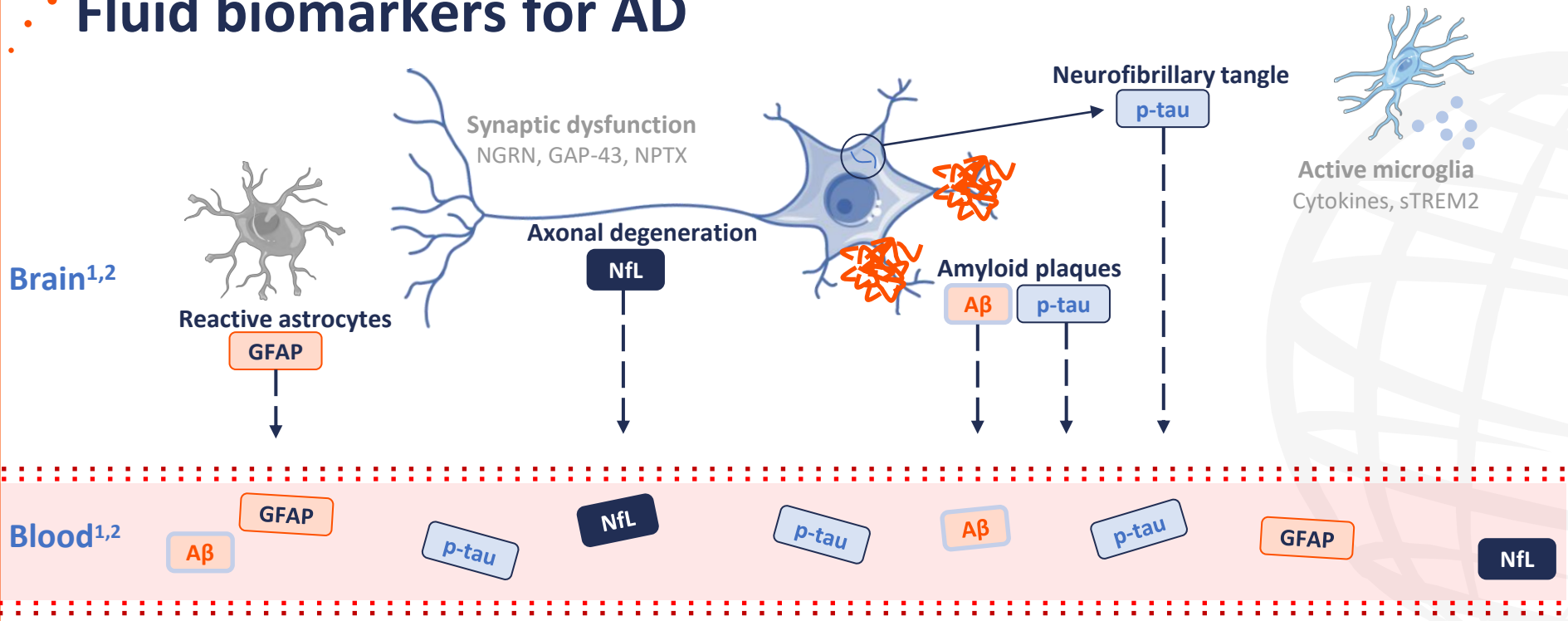
- To allow for early disease management, a timely and accurate diagnosis of AD, based on underlying biology is imperative
- Based on the nature of the pathologic process, biomarkers for AD can be classified into three main groups according to the ATN system
- Although AD biomarkers measured by PET or CSF are highly indicative of AD pathophysiology, challenges such as high cost, invasiveness of procedures and low accessibility limit their use

AD, Alzheimer's disease; ATN, amyloid/tau/neurodegeneration; CSF, cerebrospinal fluid; PET, positron emission tomography.

Blood-based biomarkers in Alzheimer's disease: Advantages and limitations

Prof. Oskar Hansson
Lund University,
Lund, Sweden

Fluid biomarkers for AD



Aβ, amyloid-beta; AD, Alzheimer's disease; GAP-43, growth associated protein 43; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; NGRN, neugrin; NPTX, neuronal pentraxin; p-tau, phosphorylated tau; sTREM2, soluble triggering receptor expressed in myeloid cells 2.

1. Hansson O. *Nat Med*. 2021;27:954–63; 2. Teunissen CE, et al. *Lancet Neurol*. 2022;21:66–77.

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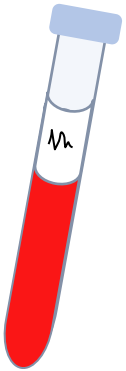
Technologies for BBM measurements



ELISA	Protein concentration is measured by antibody pairs (capture and detection) able to specifically capture the analyte of interest, with fluorescence proportional to the amount of analyte within the sample
Electrochemiluminescence immunoassays	The detection antibody is labelled with an electrochemically active molecule that generates an electrochemiluminescence signal which is proportional to the amount of analyte within the sample
Single molecule array	Sandwich immunocomplexes are coupled to magnetic beads. Each single bead is loaded into its own single well with the corresponding substrate, and a fluorescence signal is then generated
Immunoprecipitation mass spectrometry	Antibodies coupled to beads are used to isolate the analyte of interest from samples. The analyte is then eluted and quantified by mass spectrometry using an isotope-labelled form of the target as an internal standard

BBM, blood-based biomarker; ELISA, enzyme-linked immunosorbent assay.

Teunissen CE, et al. *Lancet Neurol.* 2022;21:66–77.

Plasma $A\beta_{42/40}$ assays in AD

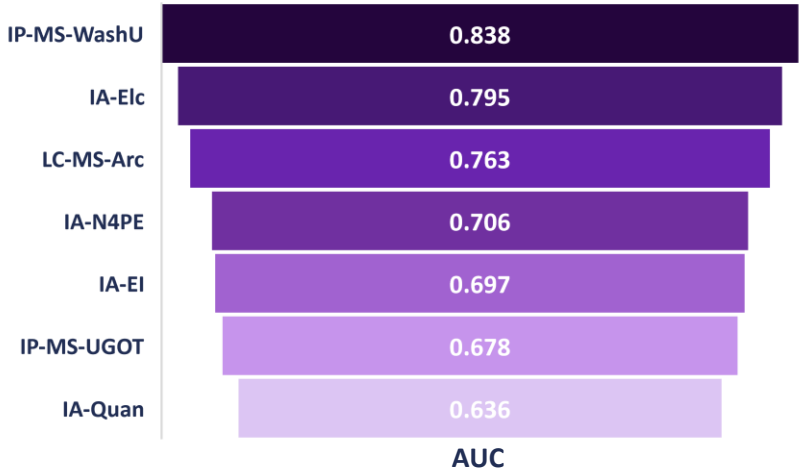
Head-to-head comparison of different plasma Aβ assays in patients with early AD

N=408
Mean age=71.6 years
Two independent cohorts

BioFINDER

AD Neuroimaging Initiative

ROC analysis for abnormal Aβ status*



Mass spectrometry-based methods performed best

Plasma $A\beta_{42/40}$ quantified using certain mass spectrometry-based methods showed better discriminative accuracy than immunoassays when identifying individuals with abnormal Aβ status according to CSF $A\beta_{42/40}$ levels and $A\beta_{42/40}$ PET

*Data are for the BioFINDER subcohort with IPS-MS-UGOT and IA-Quan $A\beta_{42/40}$ (Aβ+, n=91; Aβ-, n=136).
Aβ, amyloid-beta; AD, Alzheimer's disease; AUC, area under the curve; CSF, cerebrospinal fluid; IA-EI, immunoassay from Euroimmun; IA-Elc, Elecsys immunoassay from Roche Diagnostics; IA-N4PE, N4PE Simoa immunoassay from Quanterix; IA-Quan, Simoa immunoassay from Quanterix; IP-MS-WashU, immunoprecipitation-coupled mass spectrometry method developed at Washington University; IP-MS-UGOT, immunoprecipitation-coupled mass spectrometry method developed at the University of Gothenburg; LC-MS-Arc, antibody-free liquid chromatography-mass spectrometry method developed by Araclon; PET, positron emission tomography; ROC, receiver operating curve.

Janelidze S, et al. *JAMA Neurol*. 2021;78:1375–82.

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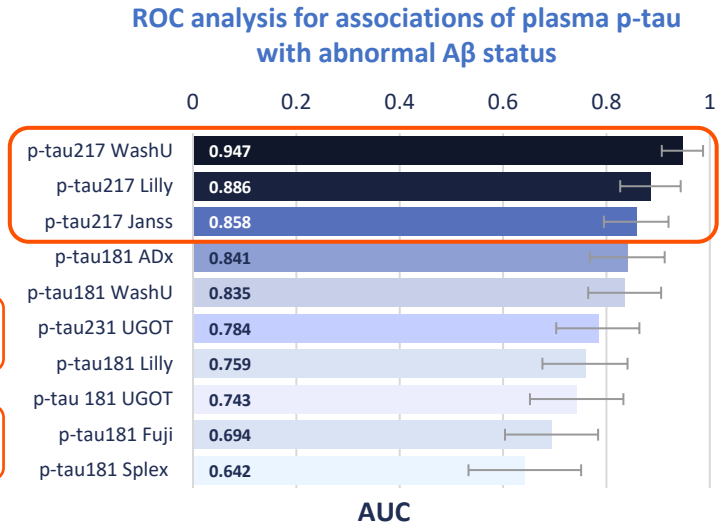
Plasma p-tau assays in AD

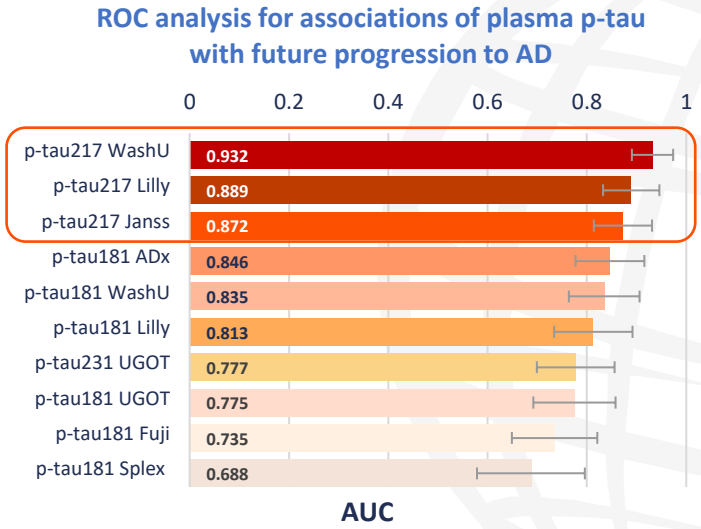
Head-to-head comparison of 10 different plasma p-tau assays in patients with MCI

N=135
Mean age=72.4 years
Baseline MCI

71 participants had abnormal Aβ status

45 participants progressed to AD during follow-up





The **mass spectrometry-based p-tau217** (p-tau217 WashU) exhibited **significantly better performance** than all other plasma p-tau biomarkers when **detecting abnormal Aβ status in patients with MCI (p_{diff}<0.015) and identifying those who subsequently develop AD**

Aβ, amyloid-beta; AUC, area under curve; AD, Alzheimer's disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; p-tau, phosphorylated tau; p-tau181 Adx, Simoa immunoassay developed by ADx Neurosciences; p-tau181 Fuji, lumipulse immunoassay developed by Fujirebio; p-tau181 Lilly, Meso Scale Discovery immunoassay developed by Lilly Research Laboratories; p-tau181 Splex, Splex immunoassay from Meso Scale Discovery; p-tau181 UGOT, 2 Simoa immunoassay developed at the University of Gothenburg; p-tau181 washU, mass spectrometry assay developed at Washington University; p-tau217 Janss, Single molecule arrays immunoassay developed by Janssen Research and Development; p-tau217 Lilly, Meso Scale Discovery immunoassay developed by Lilly Research Laboratories; p-tau217 washU, mass spectrometry assay developed at Washington University; p-tau231 UGOT, 2 Simoa immunoassay developed at the University of Gothenburg; ROC, receiver operating curve.

Janelidze S, et al. *Brain*. 2022;doi: 10.1093/brain/awac333.

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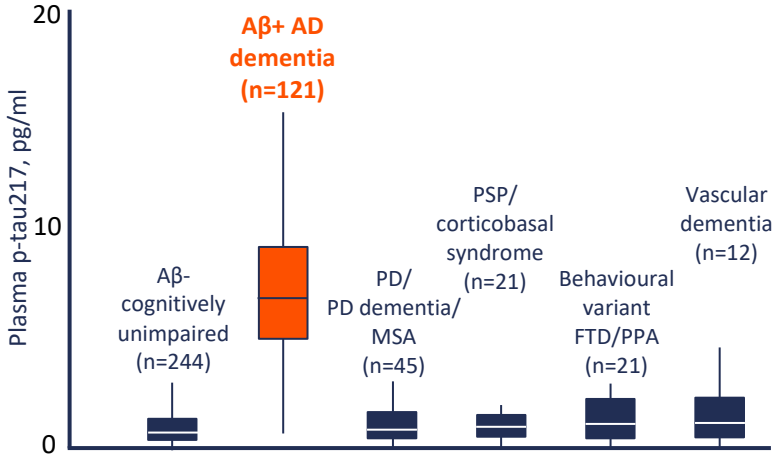
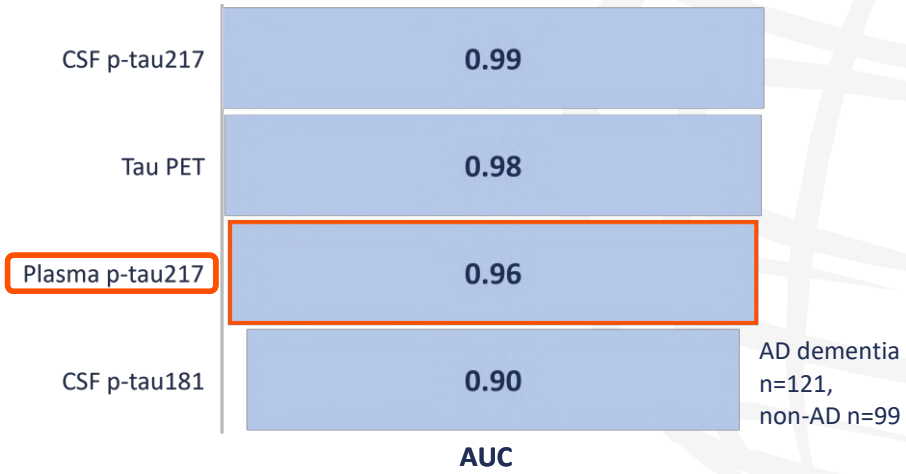
Differential diagnosis of AD versus other dementias

Discriminative accuracy of plasma p-tau217 for AD vs other neurodegenerative diseases in the BioFINDER-2 Study

Levels of p-tau217 in plasma across diagnostic groups[1]



AD dementia vs other neurodegenerative diseases: ROC analysis for comparison of plasma p-tau217 vs CSF and PET[1]



Plasma p-tau217 levels are increased by 300–700% in symptomatic AD[2]

Plasma p-tau can differentiate AD from non-AD diseases similar to CSF p-tau and tau-PET

Aβ, amyloid-beta; AD, Alzheimer's disease; AUC, area under curve; CSF, cerebrospinal fluid; FTD, frontotemporal dementia; MSA, multiple system atrophy; PD, Parkinson's disease; PET, positron emission tomography; PPA, primary progressive aphasia; PSP, progressive supranuclear palsy; p-tau, phosphorylated tau; ROC, receiver operating curve.

1. Palmqvist S, et al. *JAMA.* 2020;32:772–81; 2. Angioni D, et al. *J Prev Alzheimers Dis.* 2022;9:569–79.

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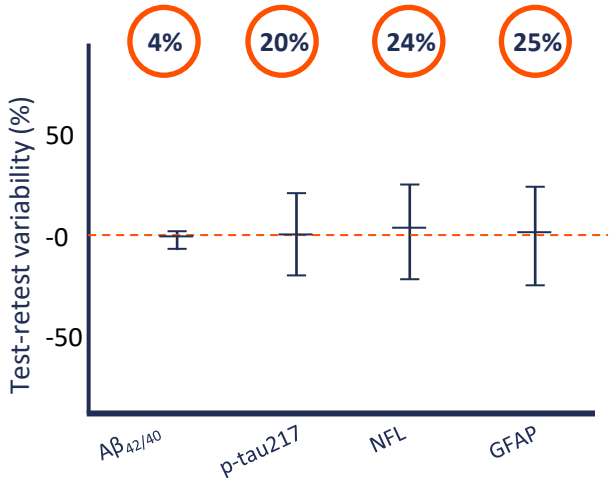
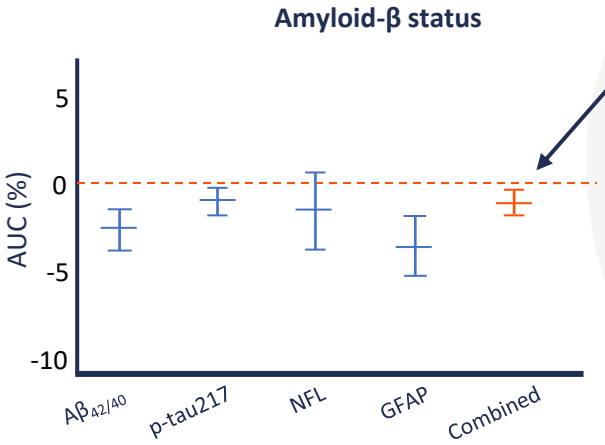
Clinical robustness of plasma BBMs

Test-retest variability of plasma biomarkers in AD and its effects on clinical prediction models

Test-retest for plasma biomarker variability



Simulating effects of variability on model performance



Combining plasma biomarkers into a multi-variable panel can mostly neutralize the effects of test-retest variability

Plasma p-tau217 is least influenced by simulating the addition of test-retest variability to real clinical data

Aβ, amyloid-beta; AD, Alzheimer's disease; BBM, blood-based biomarker; GFAP, glial fibrillary acidic protein; NFL, neurofilament light chain; p-tau, phosphorylated tau.

Cullen NC, et al. *Alzheimers Dement*. 2022;doi: 10.1002/alz.12706.

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Effect of comorbidities on performance of BBMs

Minor effects in symptomatic populations

Chronic kidney disease[1]

Increased BMI[2]

Further studies needed to determine effects

Cardiovascular disease[1,2]

Sex[3]

Race and ethnicity[4]

Assessing how **comorbidities might potentially impact plasma biomarker levels** will be important for their future interpretation in the context of clinical screening, diagnosis and/or prognosis at the population level

BBM, blood-based biomarker; BMI, body mass index.

1. Mielke M, et al. *Nat Med*. 2022;28:1398–405; 2. Binette AP, et al. *Alzheimers Dement*. 2022;doi: 10.1002/alz.12787; 3. Tsiknia AA, et al. *Mol Psychiatry*. 2022;27:4314–22; 4. Schindler SE, et al. *Neurology*. 2022;99:e245–57.

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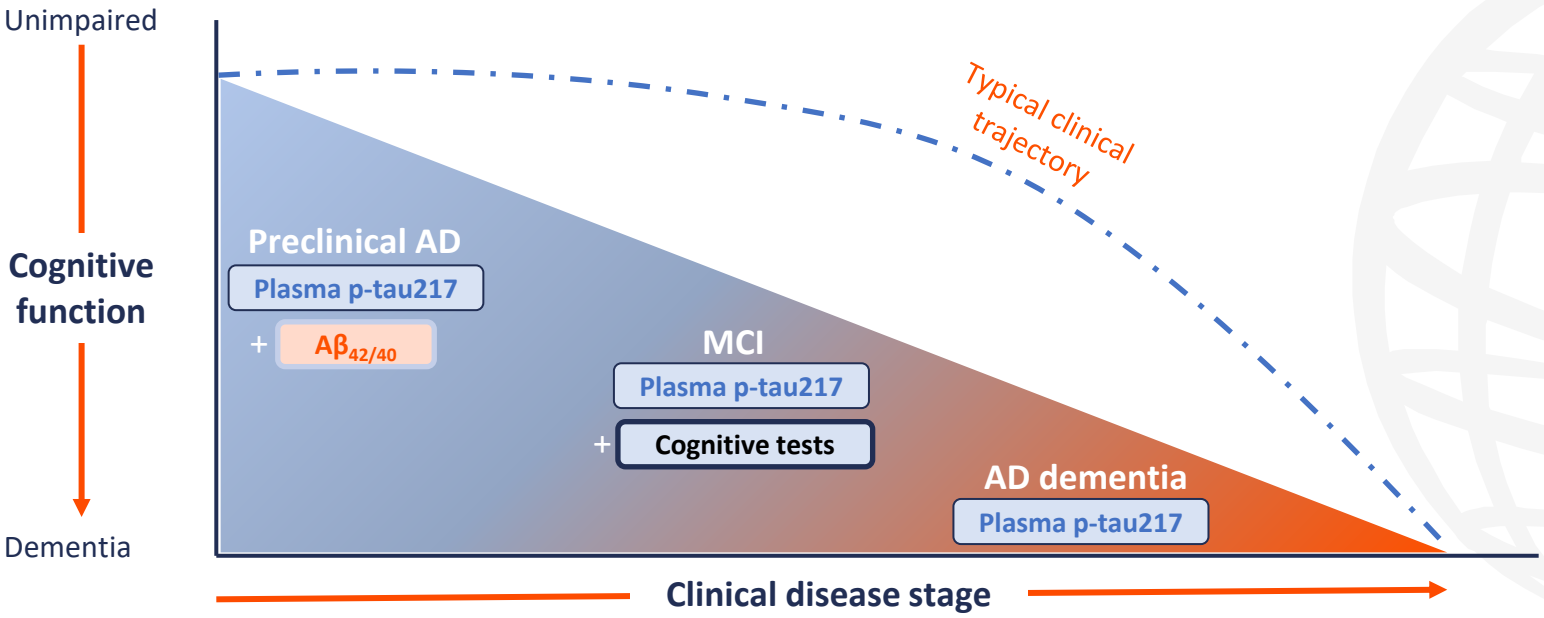
BBMs across the clinical continuum of AD



Aβ, amyloid-beta; AD, Alzheimer's disease; BBM, blood-based biomarker; MCI, mild cognitive impairment; p-tau, phosphorylated tau.

Leuzy A, et al. *EMBO Mol Med.*2022;14:e14408.

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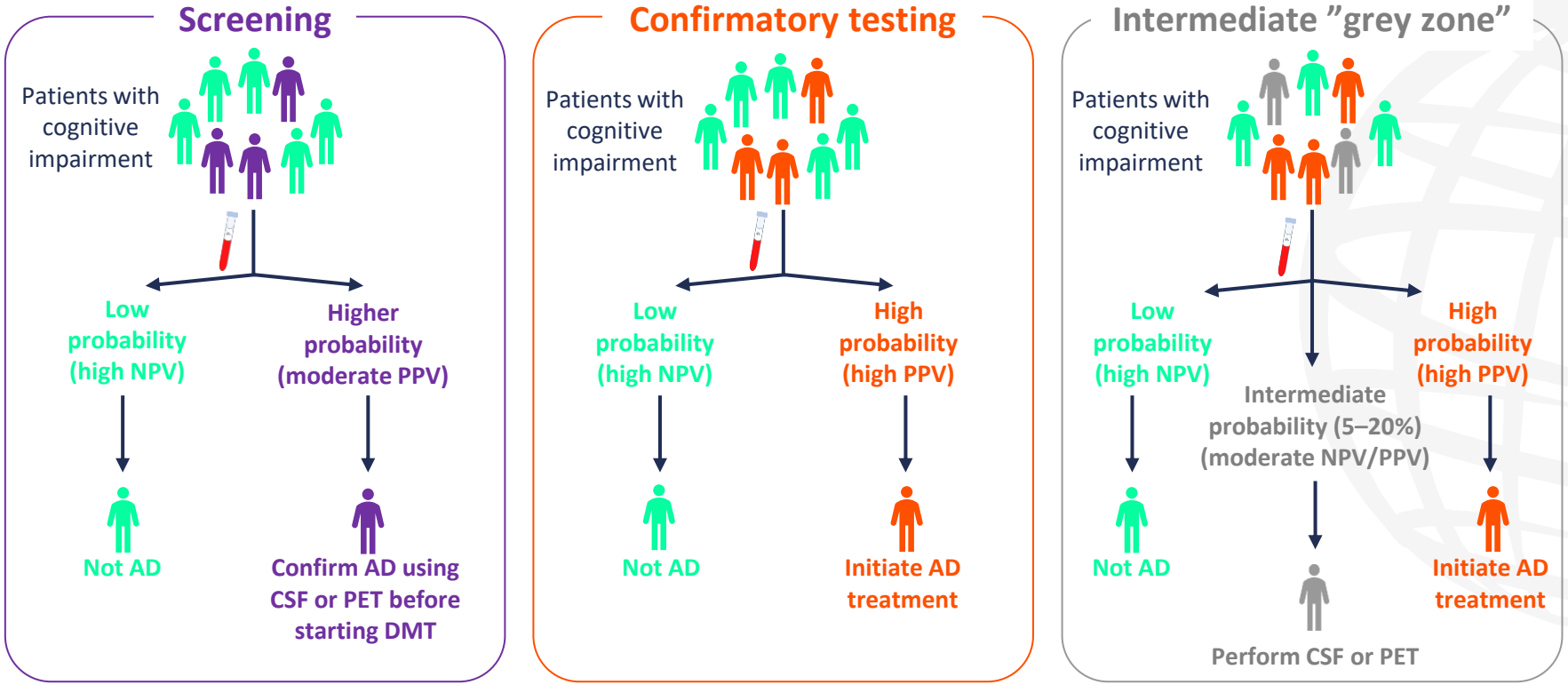
Integrating BBMs in clinical practice



AD, Alzheimer's disease; BBM, blood-based biomarker; CSF, cerebrospinal fluid; DMT, disease modifying therapy; NPV, negative predictive value; PET, positron emission tomography; PPV, positive predictive value.

1. Hansson O, et al. *Alzheimers Dement*. 2022;18:2669–86; 2. Hansson O. *Nat Med*. 2021;27:954–63.

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Summary

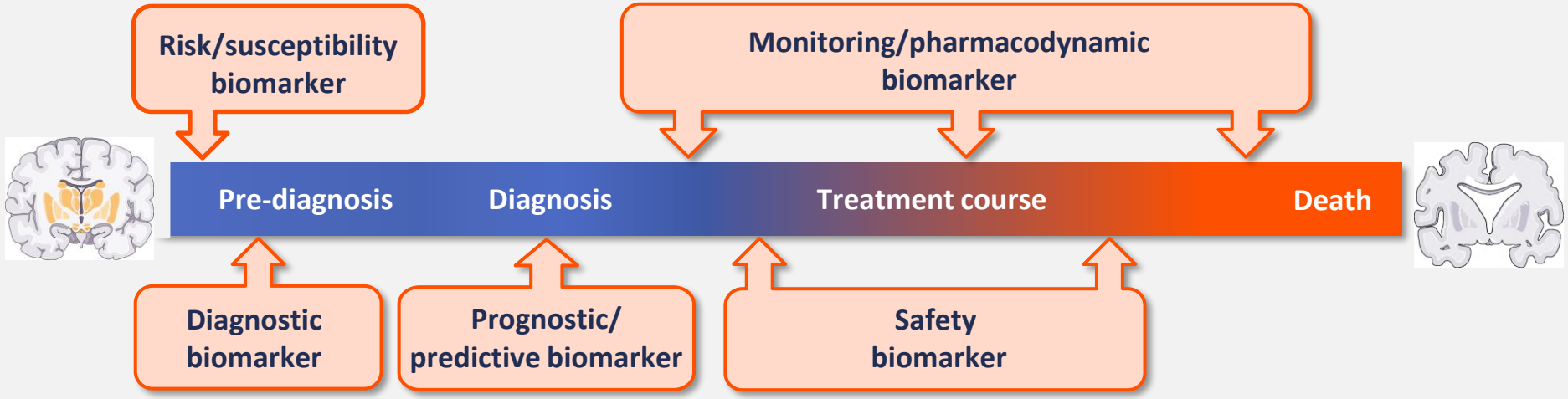
- There is insufficient evidence to support the use of BBMs as stand-alone diagnostic markers; results should be confirmed whenever possible with CSF or PET
- Plasma p-tau217 is a very specific and highly accurate marker for detection of AD pathology in patients with cognitive impairment
- Further studies are needed to evaluate their use in clinical practice and how comorbidities may influence BBM levels

AD, Alzheimer's disease; BBM, blood-based biomarker; CSF, cerebrospinal fluid; PET, positron emission tomography; p-tau, phosphorylated tau.

Integrating blood-based biomarkers in Alzheimer's disease: How and when?

Prof. Charlotte Teunissen
Amsterdam UMC
Amsterdam, Netherlands

Biomarkers across the clinical continuum



Cagney DN, et al. *Neuro Oncol*. 2018;20:1162–72.

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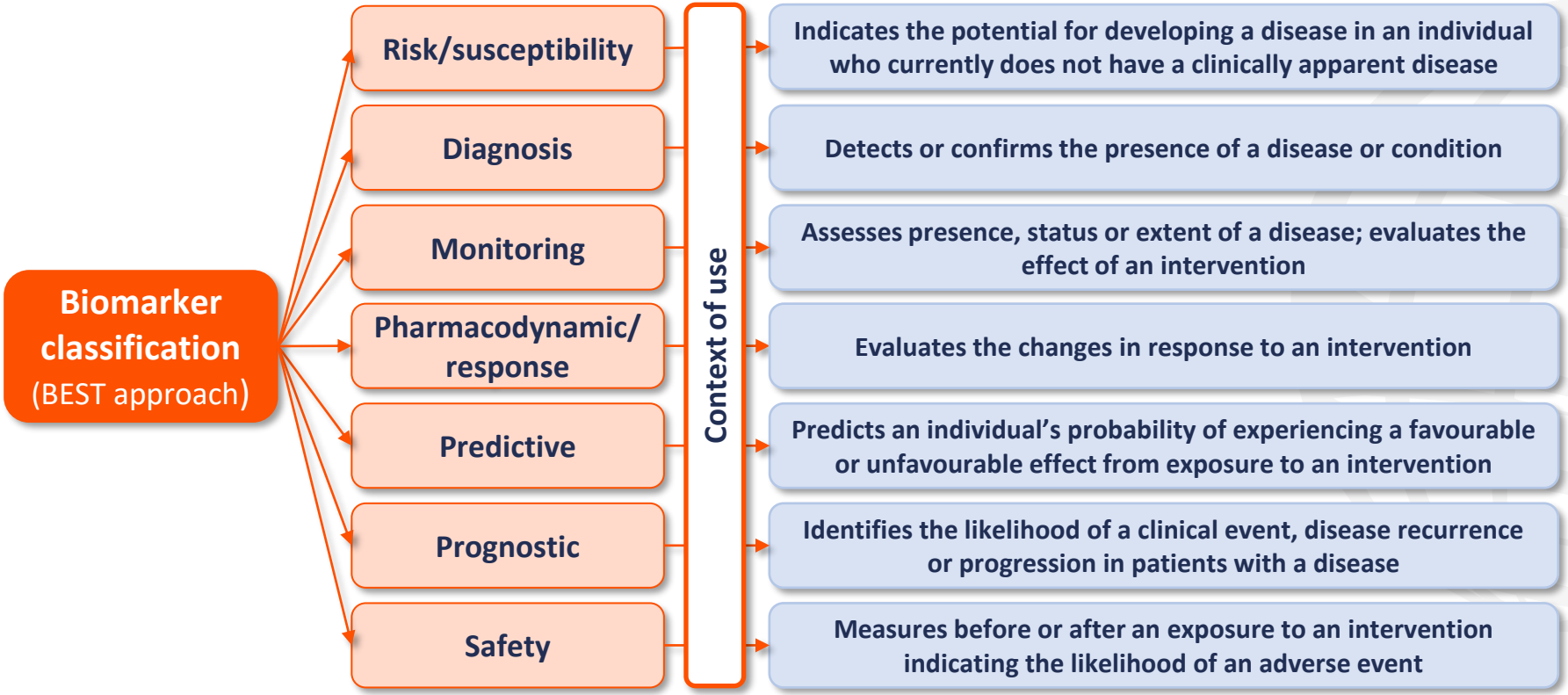
Potential uses of BBM



BBM, blood-based biomarker; BEST, Biomarkers, Endpoints and Other Tools.

Cummings J, Kinney J. *Medicina (Kaunas).* 2022;58:952.

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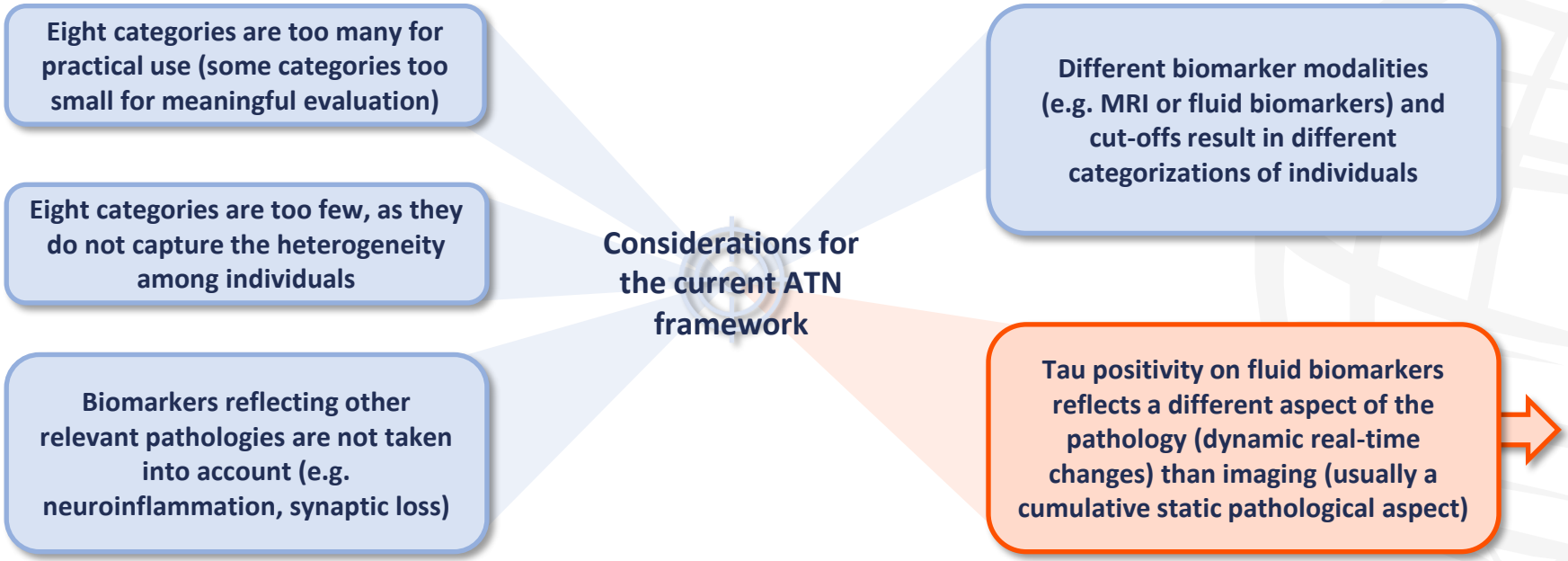
Revisiting the ATN framework (1 of 2)

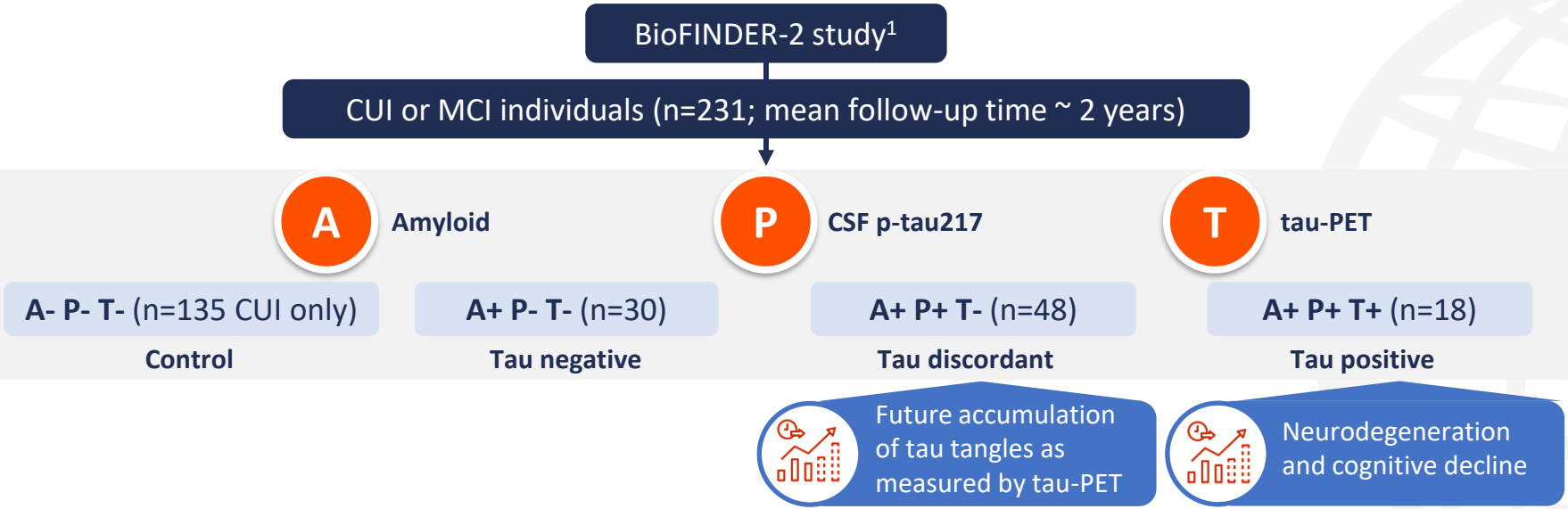


ATN, amyloid/tau/neurodegeneration; MRI, magnetic resonance imaging.

van der Flier WM, et al. *JAMA Neurol*. 2022;79:968–70.

Revisiting the ATN framework (2 of 2)

Should the ATN criteria be updated?



- **CSF p-tau generally becomes abnormal before tau-PET[2]**
- The tau-discordant A+ P+ T- group represents an interesting population for monitoring the effects of interventions with disease-modifying agents on tau accumulation in early AD, and could be helpful in examining the emergence of tau aggregates in AD[1]

AD, Alzheimer's disease; ATN, amyloid/tau/neurodegeneration; CUI, cognitively unimpaired individuals; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; PET, positron emission tomography; p-tau, phosphorylated tau.

1. Groot C, et al. *Brain*. 2022;doi:10.1093/brain/awac329; 2. Mattsson-Calgren N. et al. *Sci Adv*. 2020;6: eaaz2387.

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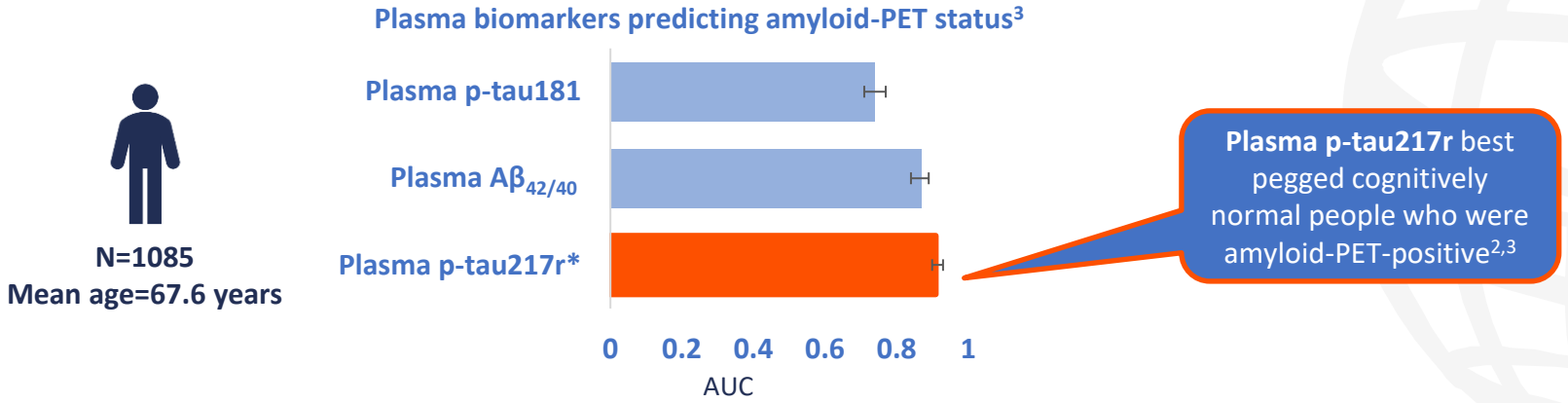
BBMs as screening tools

OBJECTIVE → **Avoid unnecessary examinations needed to confirm a diagnosis of AD prior to inclusion in clinical trials, potentially reducing the cost and burden associated with invasive and costly PET/CSF testing[1]**

EXAMPLE: AHEAD 3-45 study
Evaluating lecanemab in participants with preclinical Alzheimer's disease and elevated amyloid[2]



Preliminary analysis of the AHEAD 3-45 study demonstrated an improvement of positive predictive value from **28.9% PET eligible to 61.5% PET confirmed** with a plasma pre-screen[1]

*A ratio of p-tau to np-tau was calculated for each epitope (p-tau181r and p-tau217r) to normalize for interindividual differences in np-tau concentrations.
Aβ, amyloid-beta; AD, Alzheimer's disease; AUC, area under curve; BBM, blood-based biomarker; CSF, cerebrospinal fluid; np-tau, non-phosphorylated tau; PET, positron emission tomography; p-tau, phosphorylated tau.

1. Angioni D, et al. *J Prev Alzheimers Dis.* 2022;9:569–79; 2 Rafii MS, et al. *Alzheimers Dement.* 2022;doi:10.1002/alz.12748; 3. Rissman RA, et al. *J Prev Alzheimers Dis.* 2022;9(Suppl. 1):LB2.

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BBMs as an inclusion criterion

OBJECTIVE

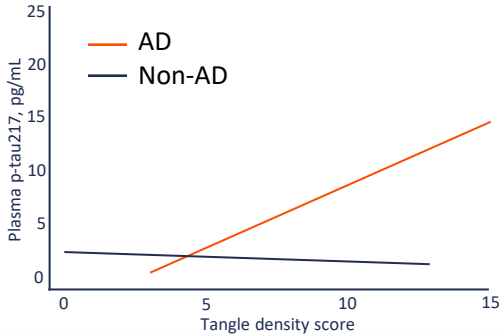
Determine if abnormal BBMs can result in valid predictions of the presence of AD pathological changes (>90%–95%), reducing the need for PET/CSF in AD trials[1]

EXAMPLE: TRAILBLAZER-ALZ3
Evaluating donanemab in people with preclinical AD who have elevated plasma p-tau217[2]

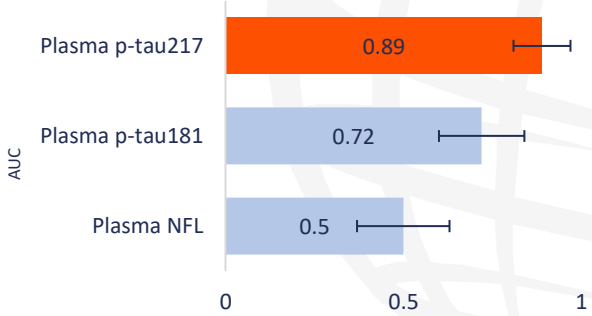
Inclusion criteria[2]

- ☑ 65–80 years old
- ☑ Normal cognition
- ☑ **Elevated plasma p-tau217**
- ☑ Adequate literacy, vision and hearing
- ☑ Reliable study partner

Correlation between plasma p-tau217 concentration and total tangle density score[3]



Intermediate-to-high likelihood of AD vs non-AD[3]



Plasma p-tau217 is able to distinguish participants with neuropathologically defined AD from participants without diagnostic levels of AD histopathology, and its performance is not significantly different from key CSF- or PET-based measures

AD, Alzheimer's disease; AUC, area under curve; BBM, blood-based biomarker; CSF, cerebrospinal fluid; NFL, neurofilament light chain; PET, positron emission tomography; p-tau, phosphorylated tau.

1. Hansson O, et al. *Alzheimers Dement.* 2022;18:2669–86; 2. ClinicalTrials.gov. NCT05026866. Available at: www.clinicaltrials.gov/ct2/show/NCT05026866 (accessed 9 January 2023); 3. Palmqvist S, et al. *JAMA*. 2020;324:772–81.

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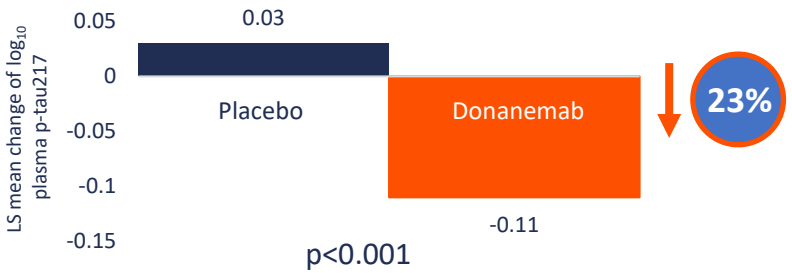
BBMs as a pharmacodynamic marker (1 of 2)

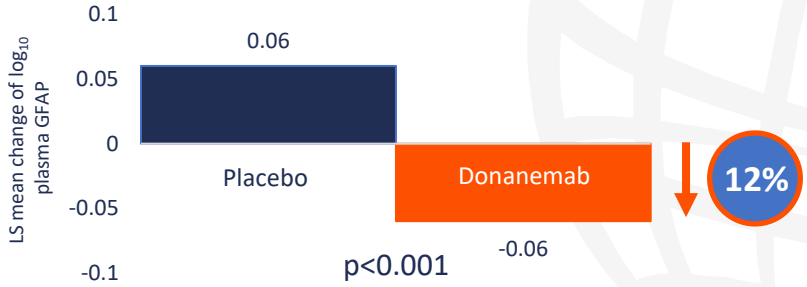
OBJECTIVE → **Potential to detect direct target engagement and disease-modifying effects[1]**

EXAMPLE: Secondary analysis of the TRAILBLAZER-ALZ randomized clinical trial[2]
Analyses of the association of donanemab treatment with plasma biomarkers associated with AD

Plasma p-tau217 biomarker change from baseline at 76 weeks[2]



Plasma GFAP biomarker change from baseline at 76 weeks[2]



Significant reductions in plasma biomarkers p-tau217 (23%) and GFAP (12%) from baseline, compared with placebo, were observed **following donanemab treatment** in patients with early symptomatic AD[2]

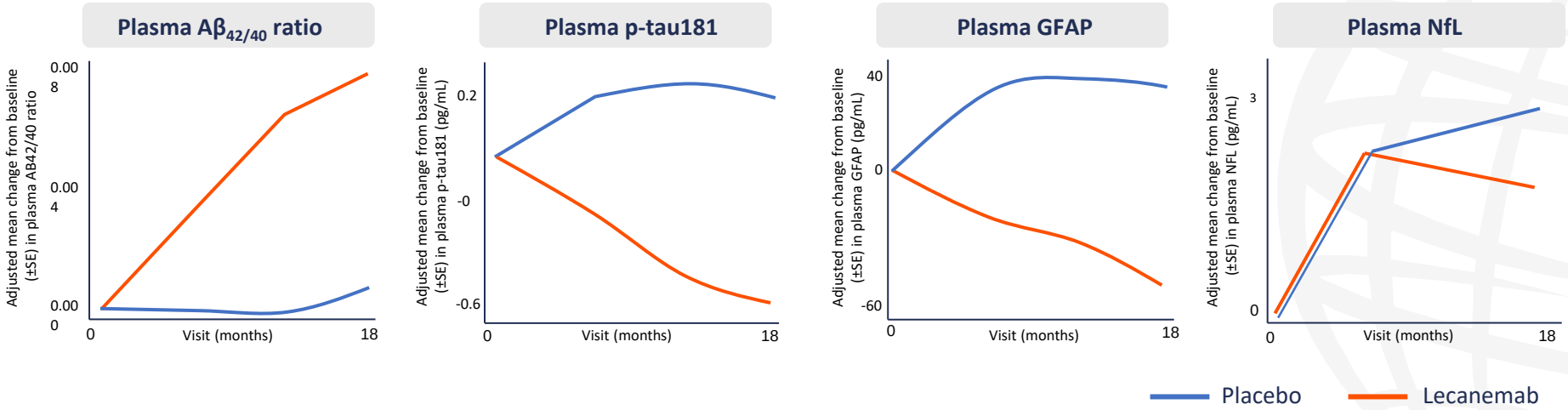
AD, Alzheimer's disease; BBM, blood-based biomarker; GFAP, glial fibrillary acidic protein; LS, least square; PET, positron emission tomography; p-tau, phosphorylated tau.

1. Angioni D, et al. *J Prev Alzheimers Dis.* 2022;9:569–79; 2. Pontecorvo MJ, et al. *JAMA Neurol*. 2022;79:1250–59.

BBMs as a pharmacodynamic marker (2 of 2)

EXAMPLE: CLARITY AD

Evaluate efficacy and safety of lecanemab in people with early Alzheimer's disease



Plasma markers of amyloid, tau, neurodegeneration, and neuroinflammation (plasma GFAP) **were reduced to a greater extent with lecanemab than with placebo**; NfL was less sensitive to neurodegeneration than the other biomarkers

Aβ, amyloid-beta; BBM, blood-based biomarker; GFAP, glial fibrillary acidic protein; NfL, neurofilament light chain; p-tau, phosphorylated tau.

van Dyck CH, et al. *N Engl J Med*. 2023;355:9–21.

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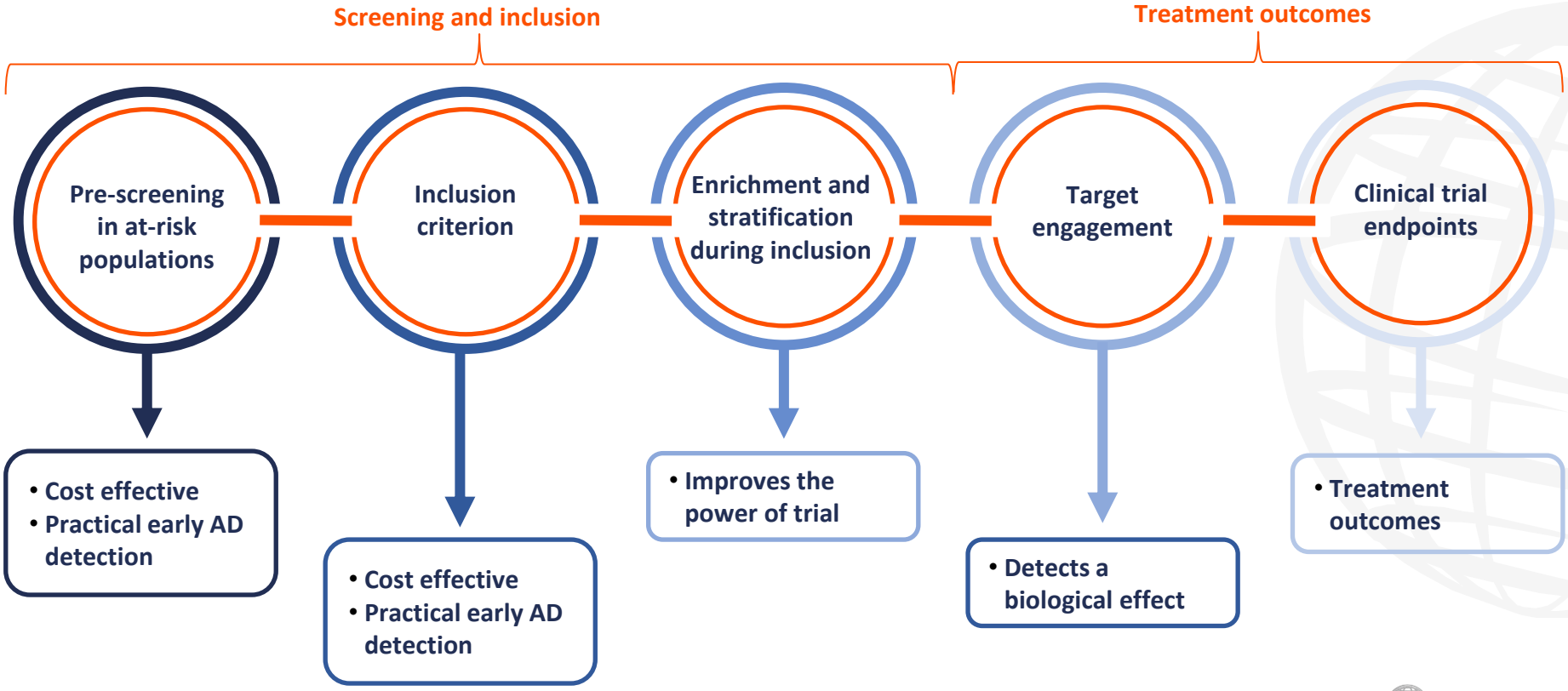
Looking ahead: Integrating BBMs into clinical trial design[1,2]



AD, Alzheimer's disease; BBM, blood-based biomarker.

1. Teunissen CE, et al. *Lancet Neurol*. 2022;21:66–77; 2. Hansson O, et al. *Alzheimers Dement*. 2022;18:2669–86.

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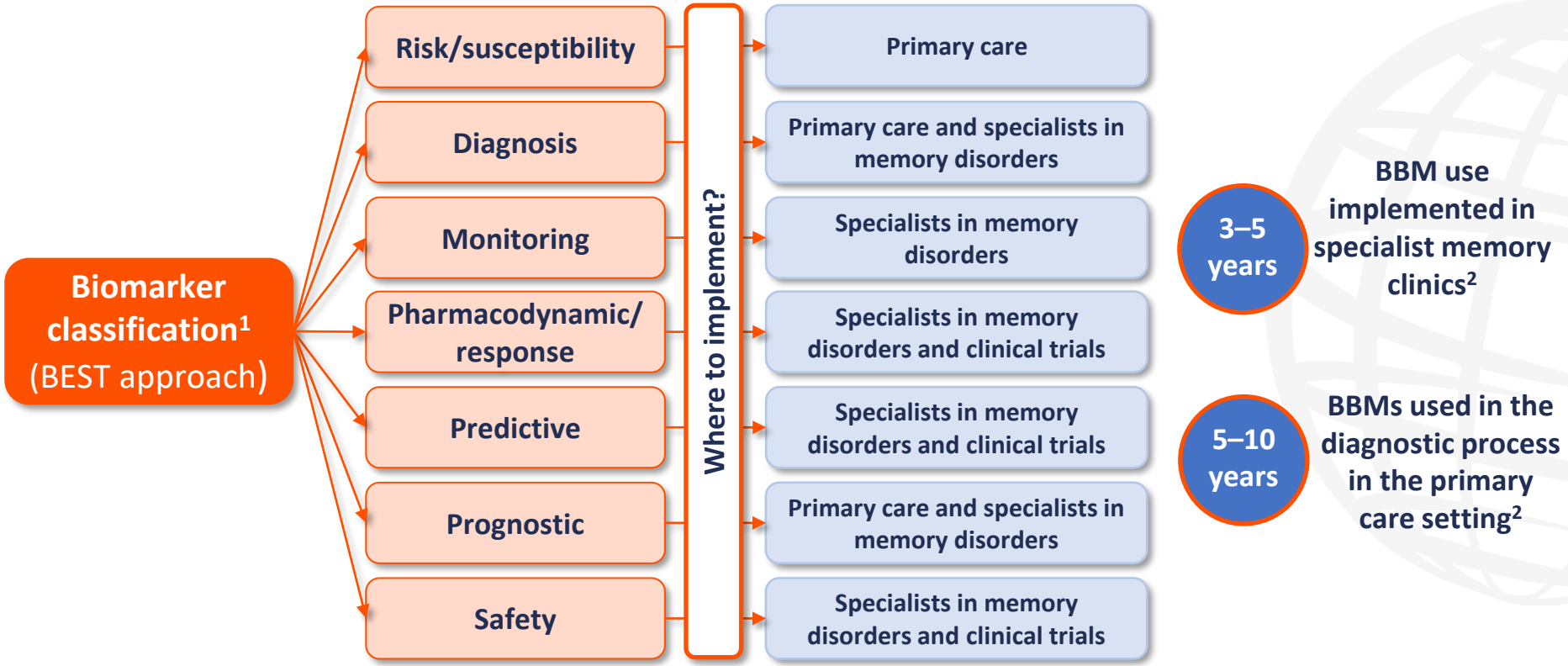
Potential role of BBMs in clinical practice



BBM, blood-based biomarker; BEST, Biomarkers, Endpoints and Other Tools.

1. Angioni D, et al. *J Prev Alzheimers Dis.* 2022;9:569–79; 2. Teunissen CE, et al. *Lancet Neurol*. 2022;21:66–77.

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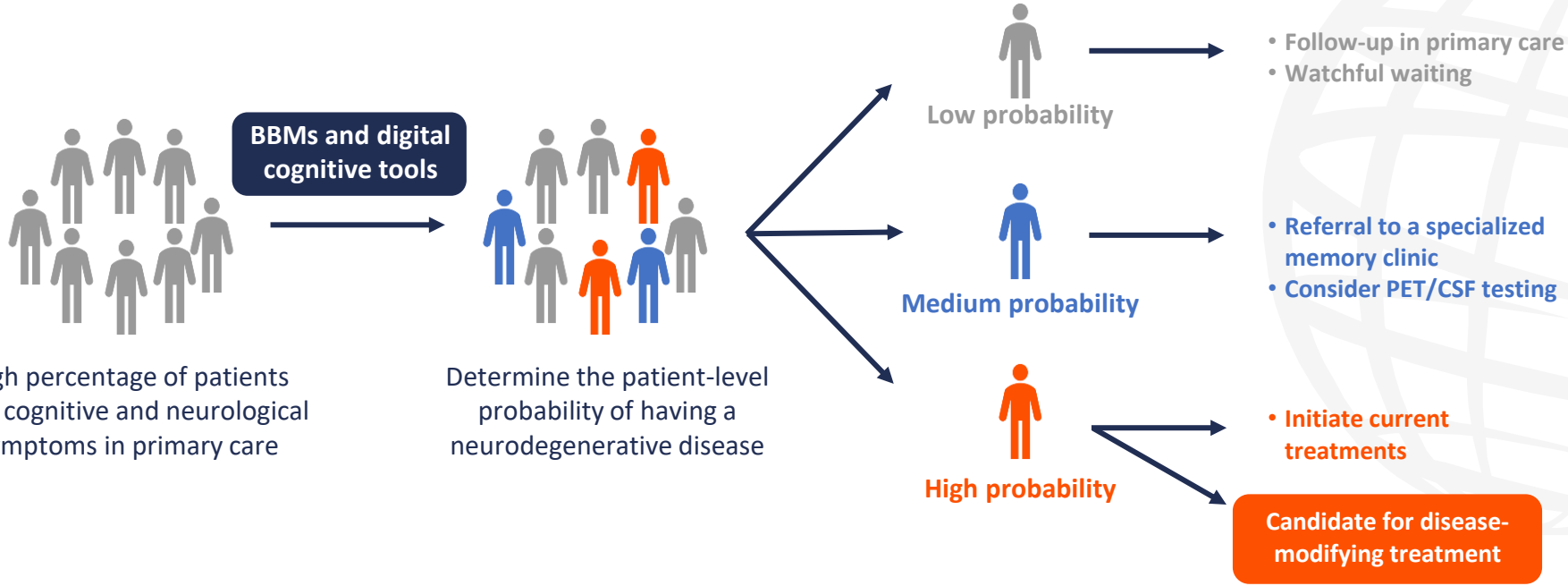
Looking ahead: Integrating BBMs into primary care[1,2]

BBMs together with clinical assessments could be used to determine the patient-level probability of having a neurodegenerative disease like AD. Prospective studies are needed to validate use.



AD, Alzheimer's disease; BBM, blood-based biomarker; CSF, cerebrospinal fluid; PET, positron emission tomography.

1. Hansson O, et al. *Alzheimers Dement*. 2022;18:2669–86; 2. Hansson O. *Nat Med*. 2021;27:954–63.

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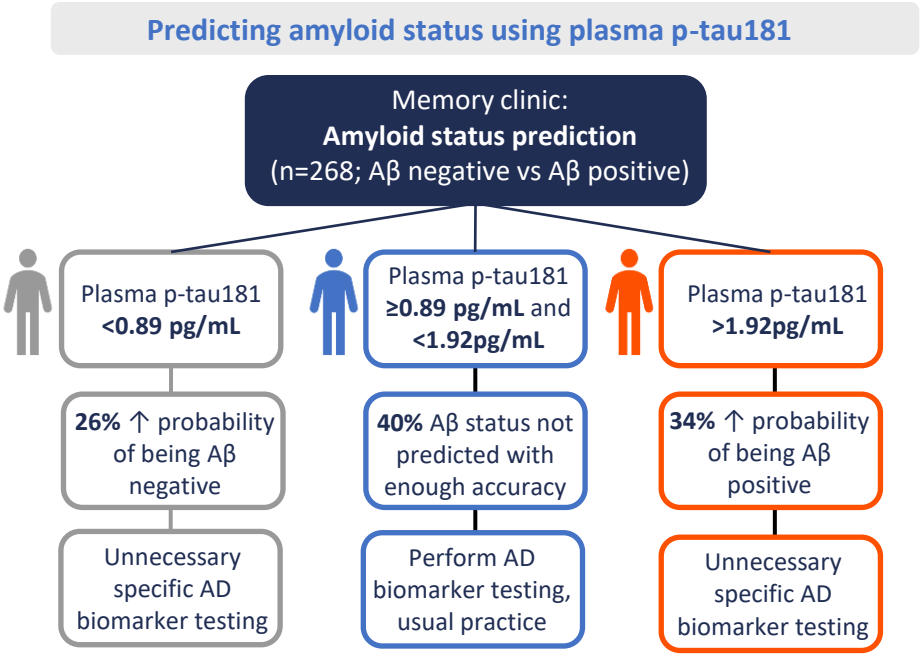
Clinical applicability of BBMs: Prospective memory clinic cohort*



Plasma p-tau181 predicts amyloid status with high accuracy (85% sensitivity and specificity) and could potentially be used to avoid CSF/amyloid PET testing in approximately 60% of subjects in a memory clinic setting

*385 subjects were included in the cohort, 349 with cognitive impairment and 36 cognitively unimpaired individuals.
Aβ, amyloid-beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; PET, positron emission tomography; p-tau181, phosphorylated tau.
Sarto, J et al. *Neurology*. 2023;100:e860–73.

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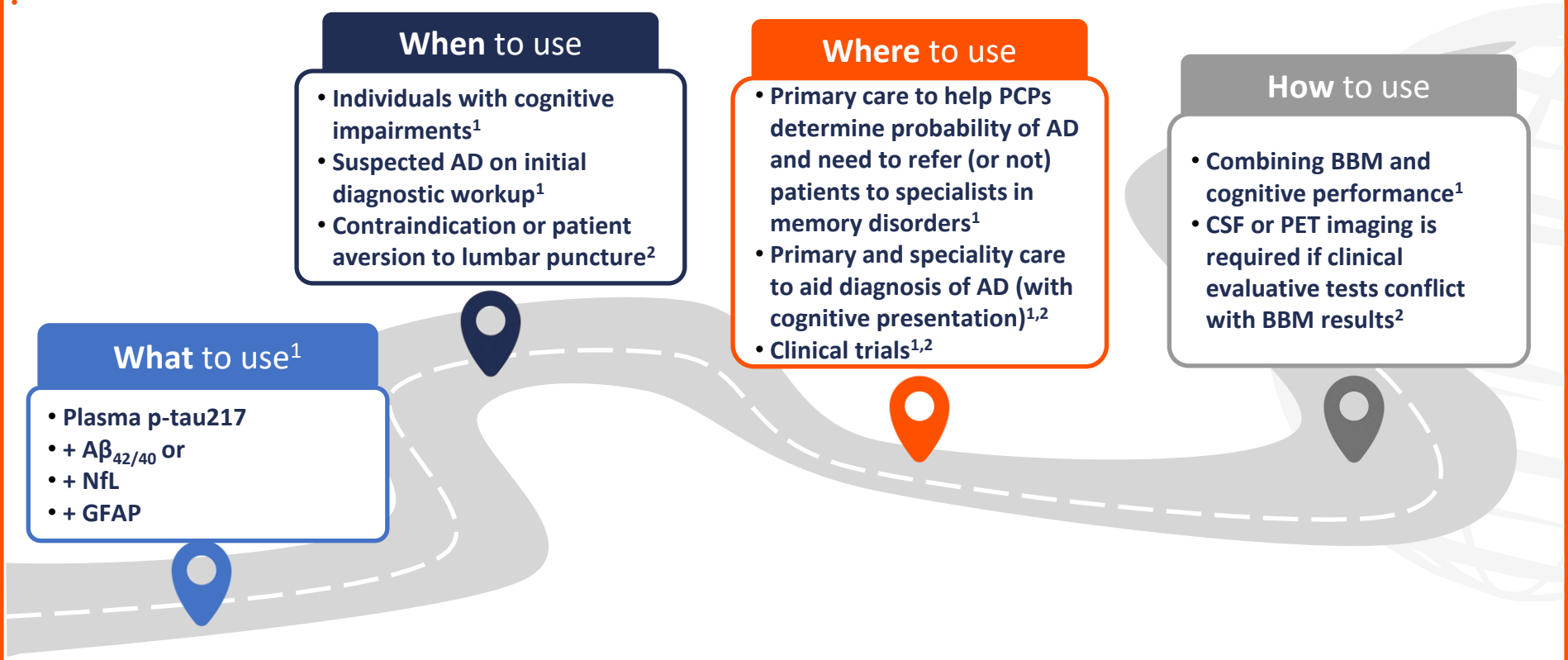
Road to implementing BBMs into clinical practice



What to use[1]

- Plasma p-tau217
- + $A\beta_{42/40}$ or
- + NfL
- + GFAP

When to use

- Individuals with cognitive impairments[1]
- Suspected AD on initial diagnostic workup[1]
- Contraindication or patient aversion to lumbar puncture[2]

Where to use

- Primary care to help PCPs determine probability of AD and need to refer (or not) patients to specialists in memory disorders[1]
- Primary and speciality care to aid diagnosis of AD (with cognitive presentation)[1,2]
- Clinical trials[1,2]

How to use

- Combining BBM and cognitive performance[1]
- CSF or PET imaging is required if clinical evaluative tests conflict with BBM results[2]

Aβ, amyloid beta; AD, Alzheimer's disease; BBM, blood-based biomarker; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; NfL, neurofilament light; PCP, primary care physicians; PET, positron emission tomography; p-tau, phosphorylated tau.

1. Leuzy A, et al. *EMBO Mol Med.*2022;14: e14408; 2. Hansson O, et al. *Alzheimers Dement*. 2022;18:2669–86.

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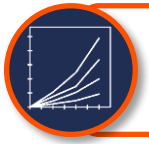
Summary and close

To allow for early disease management, a timely and accurate diagnosis of AD based on underlying biology, is imperative



High performing assays for plasma p-tau will revolutionise the diagnostic workup of patients in specialist clinics and in the longer-term, primary care

Emerging blood-based biomarkers together with clinical assessments have the potential to determine the patient-level probability of having a neurodegenerative disease

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