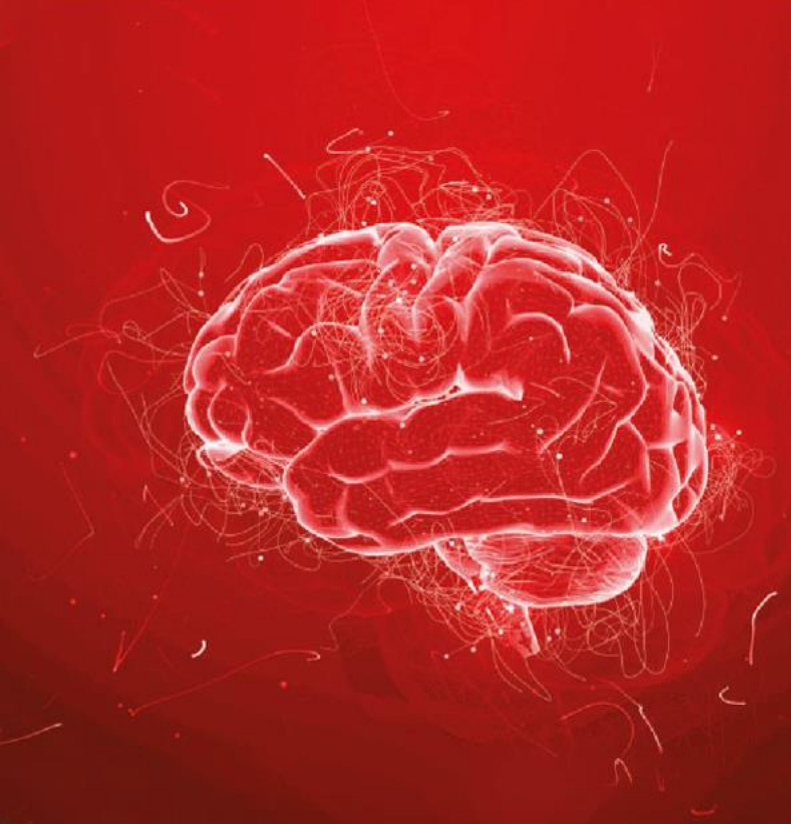

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THE POTENTIAL OF FLUID BIOMARKERS IN ALZHEIMER'S DISEASE DIAGNOSIS

Lilly

Personal Disclosures

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Diagnosing Alzheimer's Disease

Historically, the diagnosis of AD focused on clinical symptoms and involved:[1]

- Medical and family history, including psychiatric history and cognitive and behavioral changes[2]
- Cognitive testing, e.g., problem-solving, memory and language[2]
- Blood tests and brain imaging to rule out other potential causes of symptoms[2]
- Informant interview providing input on changes in the patient's thinking and behavior[2]
- Physical and neurological examinations[2]

The diagnostic workup of AD is complex and a multidisciplinary process[2]

Diagnosis by exclusion; no mention of pathophysiology with limited circumstances in which CSF or PET neuroimaging is used to assess the presence of amyloid[2]

AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; PET=Positron Emission Tomography.

1. Hampel H, et al. Designing the Next-Generation Clinical Care Pathway for Alzheimer's Disease. *Nat Aging*. 2022;2(8):692-703. 2. 2020 Alzheimer's Disease Facts and Figures. *Alzheimers Dement*. 2020;16(3):391-460.

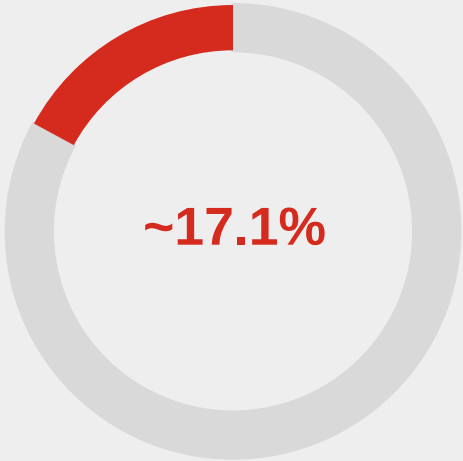
Diagnosing AD: The Need for Biomarkers

Clinical diagnosis has limited accuracy in predicting AD pathology when compared to neuropathology at autopsy, or to CSF or PET.[1,2]

Patients with clinically defined probable AD[1]

Non-AD at autopsy

Patients with clinically defined AD dementia by age 70[2]



CSF amyloid negative

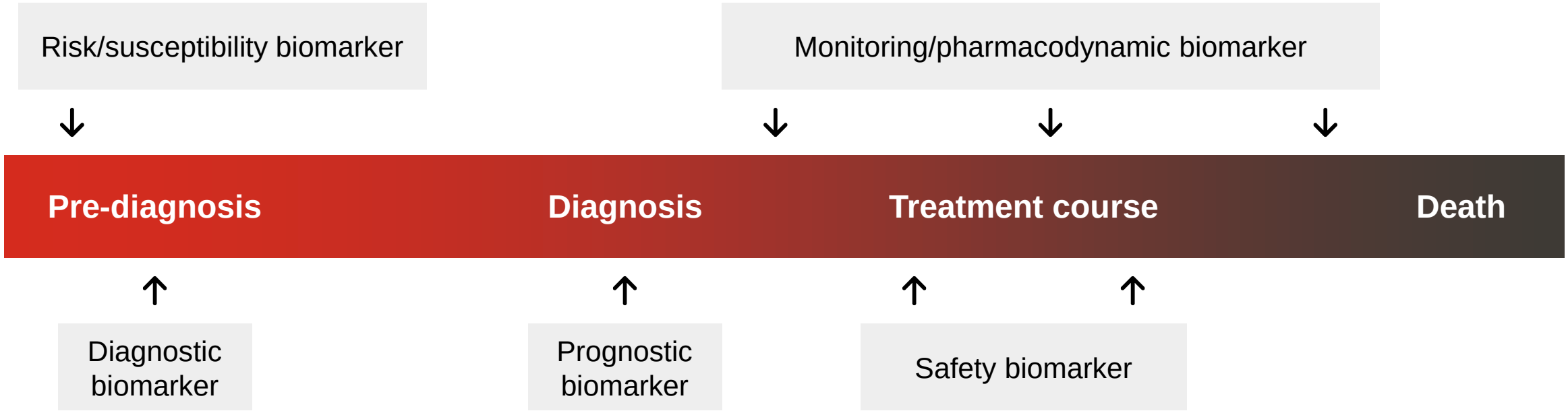
Patients with clinically defined AD dementia by age 70[2]

Amyloid-PET negative

*In a study by the National Institute of Aging Alzheimer's Disease Centers on the accuracy of the clinical diagnosis of AD, 88 of 526 subjects that were diagnosed as clinical probable AD did not meet neuropathologic criteria.[1]
AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; PET=Positron Emission Tomography.

1. Beach TG, et al. Accuracy of the Clinical Diagnosis of Alzheimer's Disease at National Institute on Aging Alzheimer Disease Centers, 2005-2010. *J Neuropathol Exp Neurol*. 2012;71(4):266-273. 2. Jansen WJ, et al. Prevalence Estimates of Amyloid Abnormality Across the Alzheimer Disease Clinical Spectrum. *JAMA Neurol*. 2022;79(3):228-243.

Need for Biomarkers Across the AD Clinical Continuum[1]



Modified from: Cagney DN, et al. *Neuro Oncol*. 2018[2]

AD=Alzheimer's Disease.

1. Cummings J, Kinney J. Biomarkers for Alzheimer's Disease: Context of Use, Qualification, and Roadmap for Clinical Implementation. *Medicina (Kaunas)*. 2022;58(7):952. 2. Cagney DN, et al. The FDA NIH Biomarkers, EndpointS, and Other Tools (BEST) Resource in Neuro-Oncology. *Neuro Oncol*. 2018;20(9):1162-1172.

Potential Uses of Biomarkers in AD

Biomarker classification *BEST* approach[1,2]

BIOMARKER TYPE	CONTEXT OF USE	WHERE TO IMPLEMENT
Risk/susceptibility	Indicates the potential for developing a disease in individual who currently does not have a clinically apparent disease	Primary care
Diagnosis	Detects or confirms the presence of a disease or condition	Primary and MDS care
Prognostic	Identifies the likelihood of a clinical event, disease recurrence or progression in patients with a disease	Primary and MDS care
Monitoring	Assesses presence, status or extent of a disease; evaluates the effect of an intervention	MDS care
Pharmacodynamic/ response	Evaluates the changes in response to an intervention	MDS care and clinical trials
Predictive	Predicts an individual´s probability of experiencing a favorable or unfavorable effect from exposure to an intervention	MDS care and clinical trials
Safety	Measures before or after an exposure to an intervention indicating the likelihood of an adverse event	MDS care and clinical trials

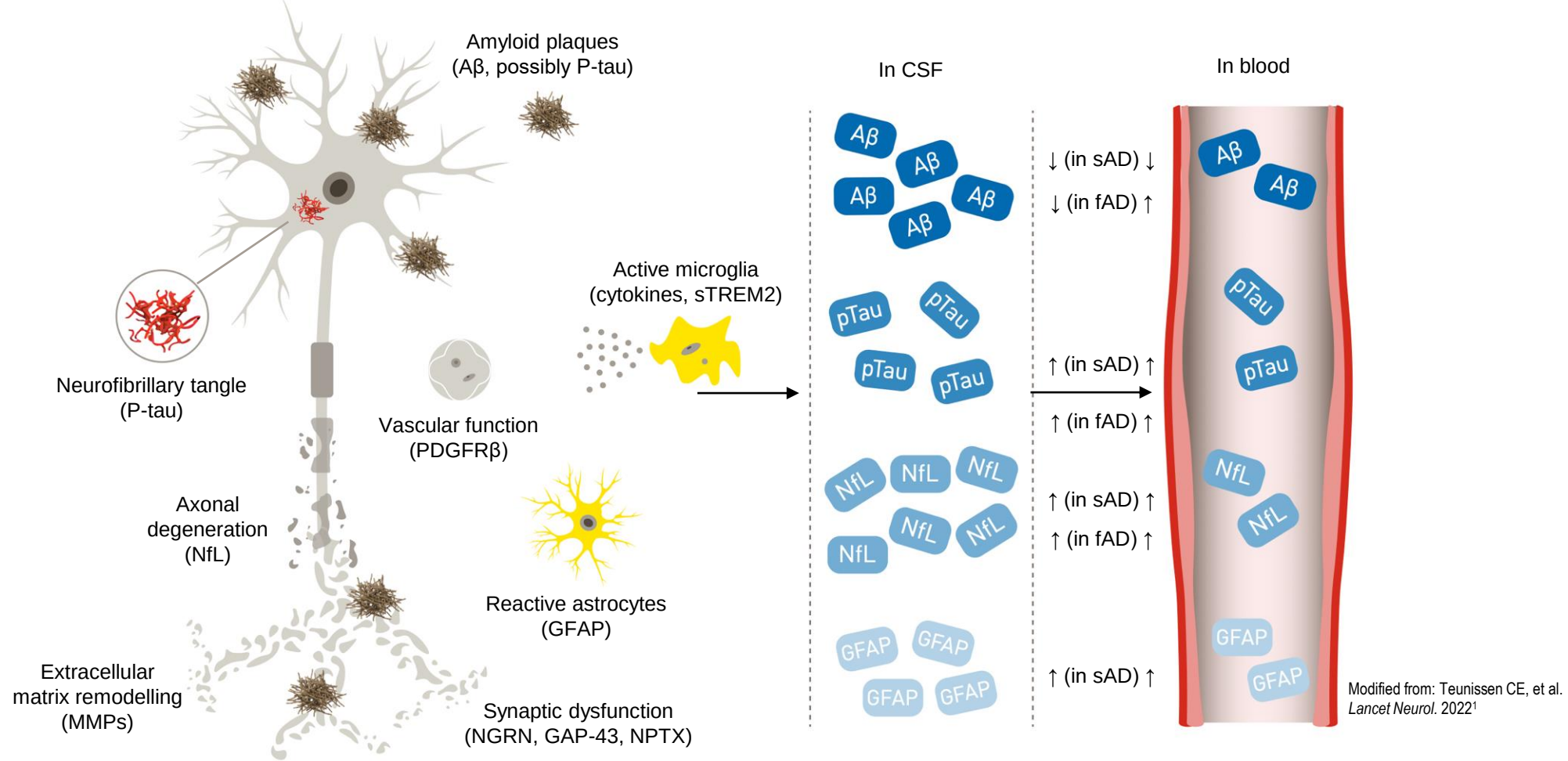
Modified from: Cummings J, Kinney J. *Medicina (Kaunas)*. 2022[1]; Angioni D, et al. *J Prev Alzheimers Dis*. 2022[2]

AD=Alzheimer's Disease; BEST=Biomarkers, EndpointS, and other Tools; MDS=Memory Disorder Specialist.

1. Cummings J, Kinney J. Biomarkers for Alzheimer's Disease: Context of Use, Qualification, and Roadmap for Clinical Implementation. *Medicina (Kaunas)*. 2022;58(7):952. 2. Angioni D, et al. Blood Biomarkers from Research Use to Clinical Practice: What Must Be Done? A Report from the EU/US CTAD Task Force. *J Prev Alzheimers Dis*. 2022;9(4):569-579.

Which Fluid Biomarkers Can We Measure?[1]

Pathological mechanisms involved in AD and their associated biofluid-based biomarkers[1]



Modified from: Teunissen CE, et al. *Lancet Neurol.* 2022[1]

Aβ=Amyloid-Beta; AD=Alzheimer's Disease; CSF=Cerebrospinal Fluid; fAD=Familial Alzheimer's Disease; GAP-43=Growth-Associated Protein 43; GFAP=Glial Fibrillary Acidic Protein; MMP=Matrix Metalloproteinase; NfL=Neurofilament Light Chain; NGRN=Neugrin, Neurite Outgrowth Associated; NPTX=Neuronal Pentraxin; PDGFRβ=Platelet-Derived Growth Factor Receptor Beta; P-tau=Phosphorylated tau; sAD=Sporadic Alzheimer's Disease; sTREM2=Soluble Triggering Receptor Expressed on Myeloid Cells 2.

1. Teunissen CE, et al. Blood-Based Biomarkers for Alzheimer's Disease: Towards Clinical Implementation. *Lancet Neurol.* 2022;21(1):66-77.