Amsterdam UMC
University Medical Centers

Fluid Biomarkers for Alzheimer's disease and other dementias

Prof.dr. Charlotte Teunissen

Disclosures

Research support	Collaboration contracts with commercial entities	Editorial boards
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* All contracts concord with European ethical standards and privacy regulations, and are approved by Amsterdam UMC

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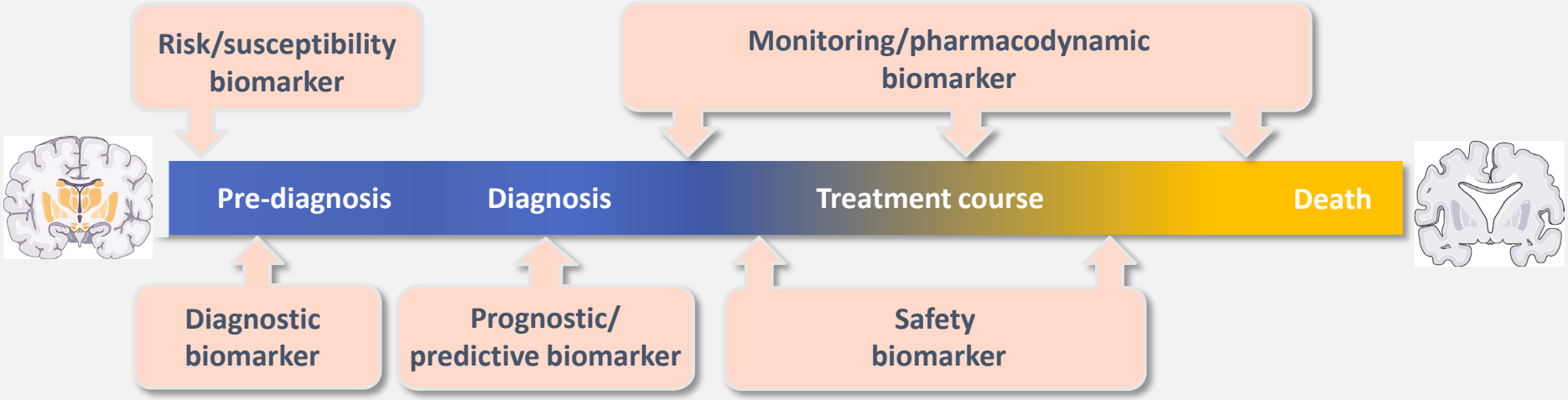
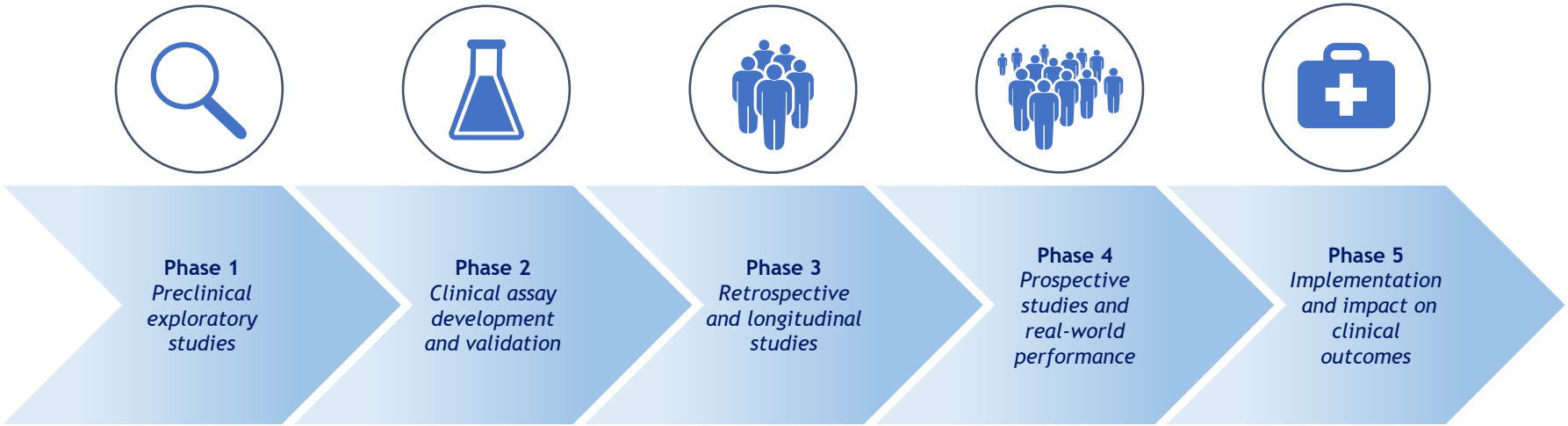
Long preclinical phase: need for biomarkers for timely detection

Biomarkers across the clinical continuum



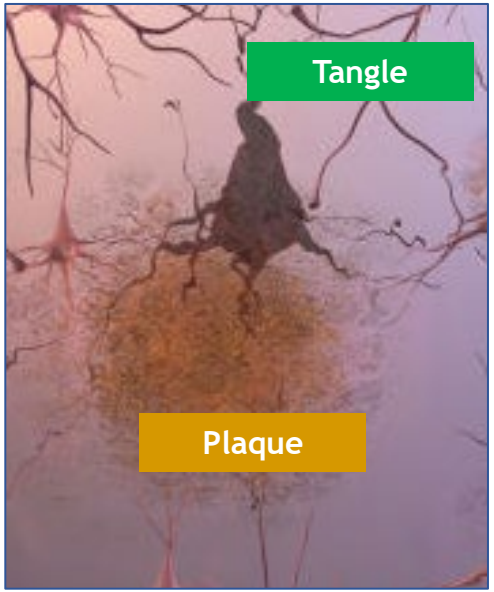
Cagney DN, et al. Neuro Oncol. 2018

Roadmap for development of biomarkers



Teunissen CE et al. Lancet Neurol 2022

The Alzheimer CSF biomarkers

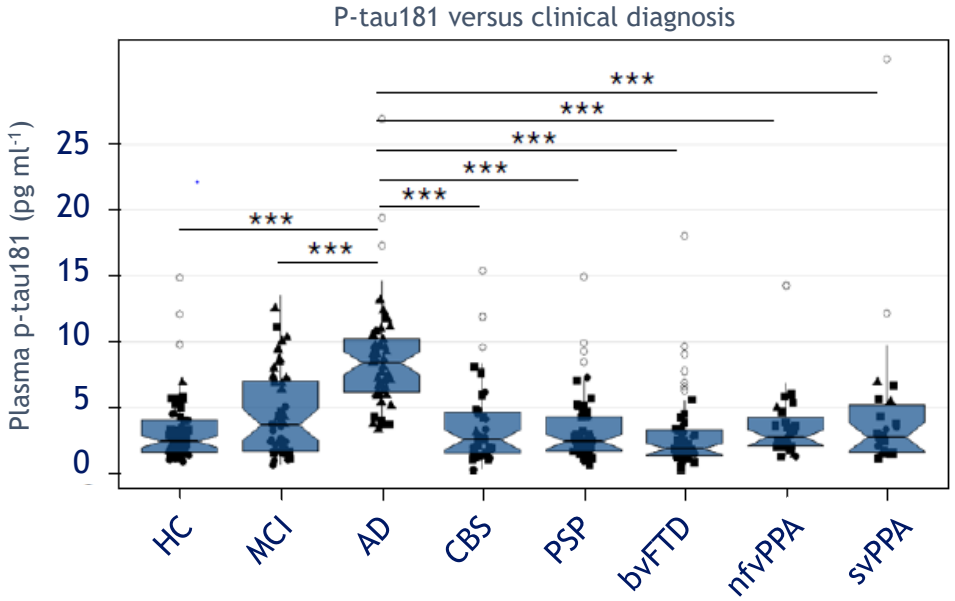


(p-)tau ↑

Amyloid beta ↓

PET

p-tau181: specifically increased in AD

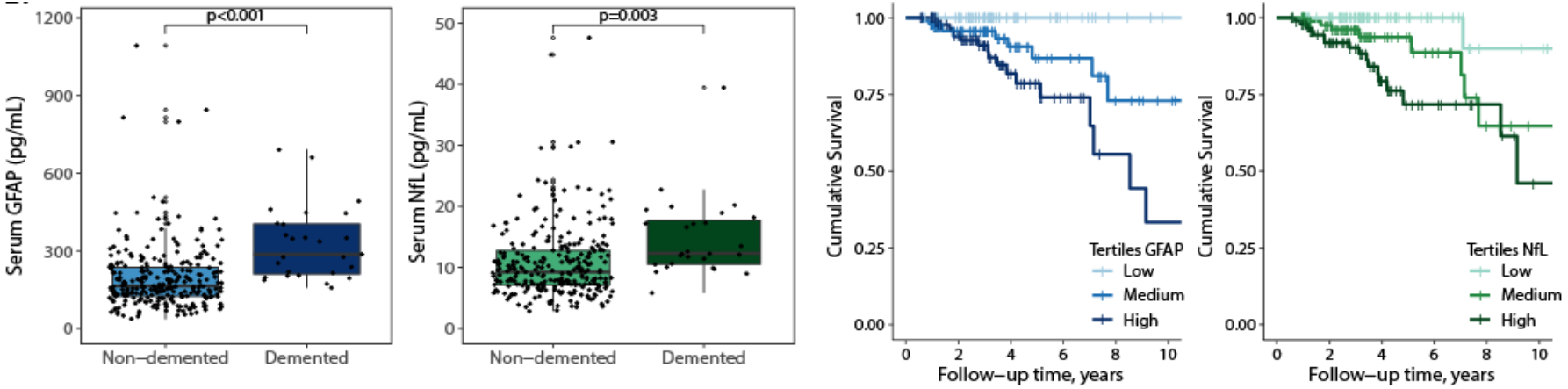


***p<0.0001.

1. Thijssen EH et al. Nat Med 2020;26:387–97. 2. Mielke MM et al. Alzheimers Dement 2018;14:989–97. 3. Janelidze S et al. Nat Med 2020;26:379–86. 4. Palmqvist S et al. JAMA 2020;324:772-81. 5. Bayoumy S et al. Alzheimers Res Ther 2021;13:198. 6. Smirnov DS et al. Acta Neuropathol 2022;143:487–503. 7. Leuzy A et al. JAMA Neurol 2022;79:149–58.

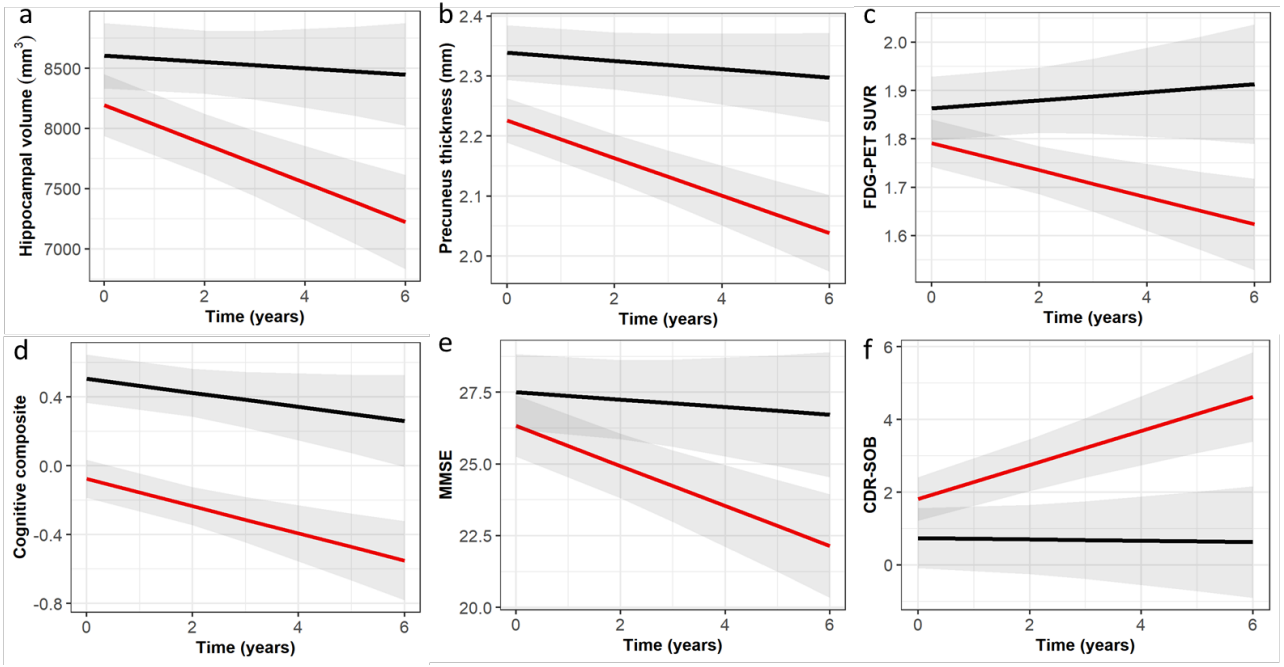
Glial fibrillary acidic protein (GFAP) and neurofilamnet light (NfL) are predictive for cognitive decline and conversion to dementia (SCD)

Longitudinal studies



Verberk et al, Lancet healthy longevity 2021

GFAP is prognostic for brain atrophy and cognitive decline in familial AD



Amyloid negative

Amyloid positive

Chatterjee, Vermunt et al. Alz and Dem, 2022

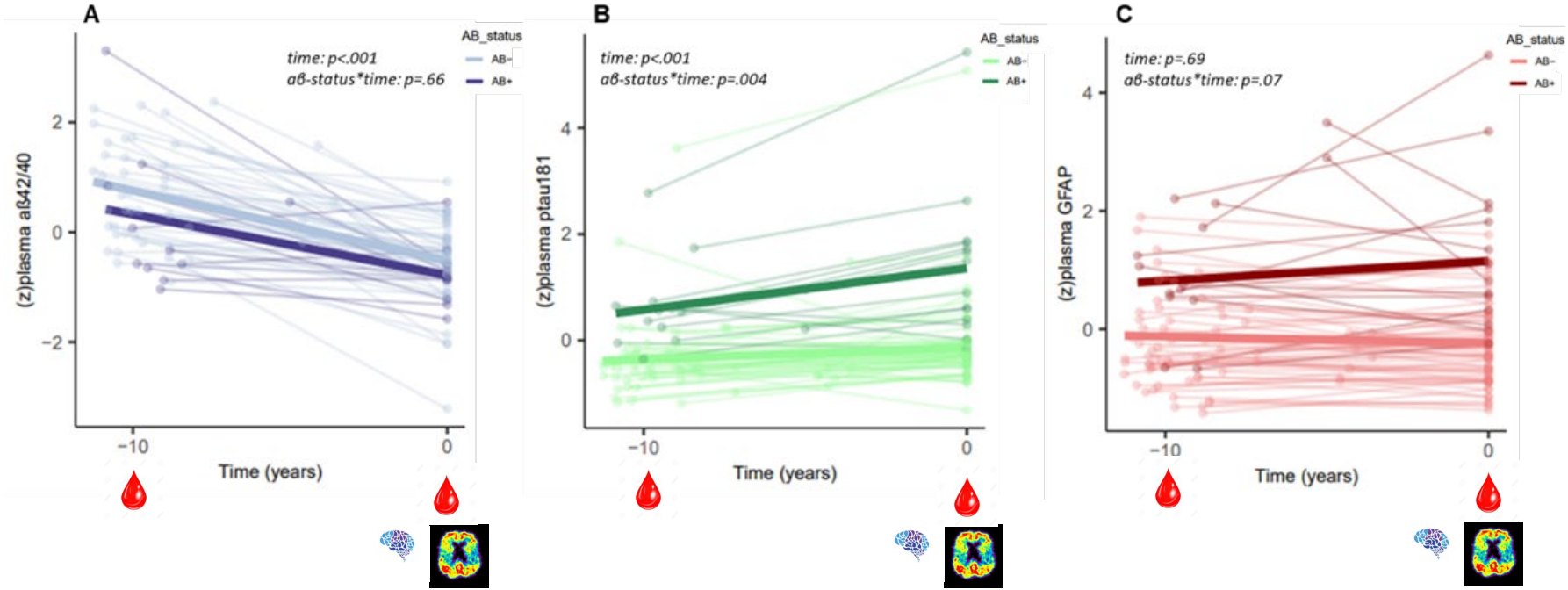
One step further: population cohorts

Predictive value of plasma biomarkers for Amyloid positivity in people median age 58 years?

Netherlands Twin Registry

Den Braber et al., Brain Communications 2023

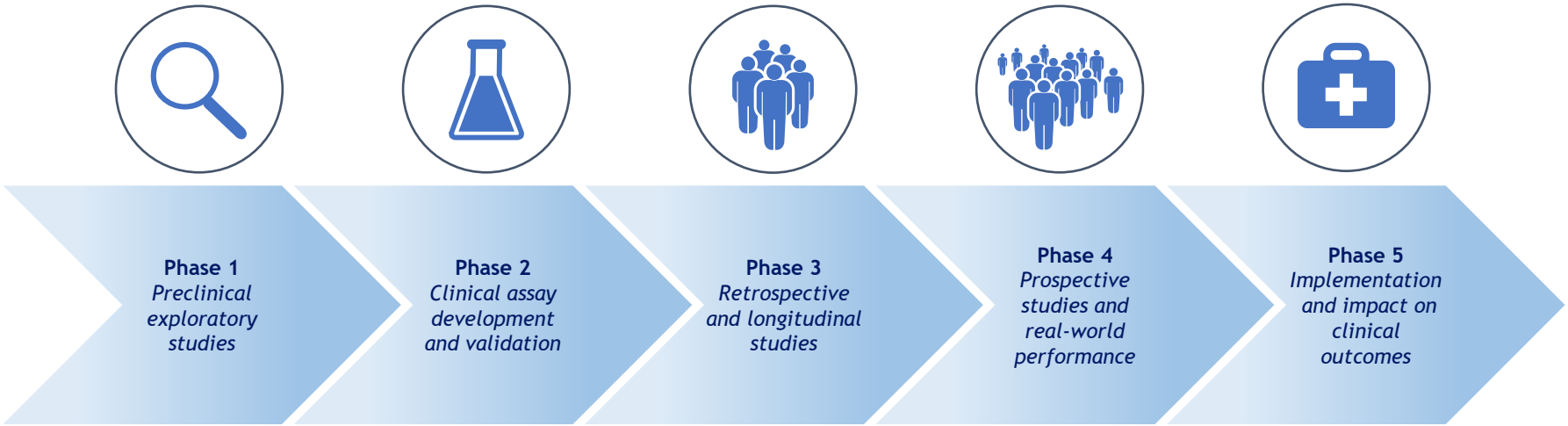
Early changes (age 58!) in all markers
Longitudinal increase for pTau (trend for GFAP) in A+



Den Braber et al., Brain Communications 2023

What is needed for clinical implementation?

Five-phase roadmap for development of blood-based biomarkers of AD



Start prospective studies in memory clinics
Start exploration primary care implementation

Teunissen CE et al. Lancet Neurol 2022





	Phase 1 *Preclinical exploratory studies*	Phase 2 *Clinical assay development and validation*	Phase 3 *Retrospective and longitudinal studies*	Phase 4 *Prospective studies and real-world performance*	Phase 5 *Implementation and impact on clinical outcomes*	
Primary aims	Biomarker identification and leads prioritisation: a) Hypothesis driven (Aβ, pTau, GFAP, NfL) b) Unbiased -omics data (proteomics, transcriptomics, etc)	*Technical:* a) LDTs and RUO assay development and validation (Aβ, pTau, GFAP, NfL)	*Technical:* a) Define criteria for a positive test—eg, cutoffs (Aβ, pTau, GFAP, NfL)	*Technical:* a) IVD assay development and validation (Aβ, pTau, GFAP, NfL)	*Regulatory:* a) Integration in clinical guidelines (Aβ, pTau, GFAP, NfL)	**Technical**
		Clinical: a) Analysis of diagnostic accuracy in case-control studies (Aβ, pTau, GFAP, NfL)	*Clinical:* a) Diagnostic accuracy for early disease detection—eg, preclinical, prodromal (Aβ, pTau, GFAP, NfL)	*Clinical:* a) Establish diagnostic performance prospectively (Aβ, pTau, GFAP, NfL)	*Clinical:* a) Impact of biomarker testing on clinical decision making (Aβ, pTau, GFAP, NfL)	**Clinical**
Secondary aims	*Not applicable*	*Technical:* a) Reproducibility of assays between laboratories (Aβ, pTau, GFAP, NfL) b) Preanalytical factor assessment (Aβ, pTau, GFAP, NfL) c) SOPs sample handling and storage (Aβ, pTau, GFAP, NfL)	*Technical:* a) Head-to-head comparisons of platforms and biomarker isoforms (Aβ, pTau, GFAP, NfL)	*Technical:* a) Reference methods and materials (Aβ, pTau, GFAP, NfL) b) Feasibility of biomarker implementation and adherence of patients to subsequent clinical work-up (Aβ, pTau, GFAP, NfL)	*Regulatory:* a) In-vitro diagnostic assay certification (Aβ, pTau, GFAP, NfL) b) Cost assessment and reimbursement (Aβ, pTau, GFAP, NfL)	**Technical**
		Clinical: a) Relation with gold standard measures—CSF, PET, autopsy (Aβ, pTau, GFAP NfL) b) Identification of covariates—age, sex, ethnicity, lifestyle—influencing biomarker concentrations in patients and healthy controls (Aβ, pTau, GFAP, NfL) c) Relation with disease characteristics —eg, cognitive performance (Aβ, pTau, GFAP, NfL) d) Disease specificity assessment for differential diagnosis (Aβ, pTau, GFAP, NfL)	*Clinical:* a) Impact of covariates on biomarker discriminatory performance (Aβ, pTau, GFAP, NfL) b) Develop algorithms for likelihood of positive results based on combinations of biomarkers (Aβ, pTau, GFAP, NfL) c) Analyse dynamics along Alzheimer's disease continuum and predictive capabilities in longitudinal studies (Aβ, pTau, GFAP, NfL) d) Establish context-of-use criteria for clinical settings and trials (Aβ, pTau, GFAP, NfL)	*Clinical:* a) Validate context-of-use in clinical settings and trials (Aβ, pTau, GFAP, NfL) b) Establish predictive values (Aβ, pTau, GFAP, NfL) c) Define the potential cost-effectiveness of biomarker implementation (Aβ, pTau, GFAP, NfL) d) Monitor false negatives (Aβ, pTau, GFAP, NfL)	*Clinical:* a) Monitor diagnostic and prognostic performance across different settings (Aβ, pTau, GFAP, NfL) b) Guidelines for biomarker interpretation in primary care settings (Aβ, pTau, GFAP, NfL) c) Compare the cost–outcome effectiveness of different biomarker protocols and approaches (Aβ, pTau, GFAP, NfL)	**Clinical**

Teunissen CE et al. Lancet Neurol 2022





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Teunissen CE et al. Lancet Neurol 2022

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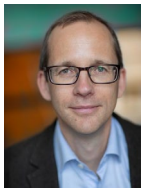
REVIEW ARTICLE

The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease

Oskar Hansson[1,2,*] | Rebecca M. Edelmayer[3] | Adam L. Boxer[4] | Maria C. Carrillo[3] | Michelle M. Mielke[5] | Gil D. Rabinovici[4] | Stephen Salloway[6] | Reisa Sperling[7] | Henrik Zetterberg[8,9,10,11,12] | Charlotte E. Teunissen[13]










Other international initiatives:

World Health Organization

Targetted Product Profile for AD bloodtest

alzheimer's association

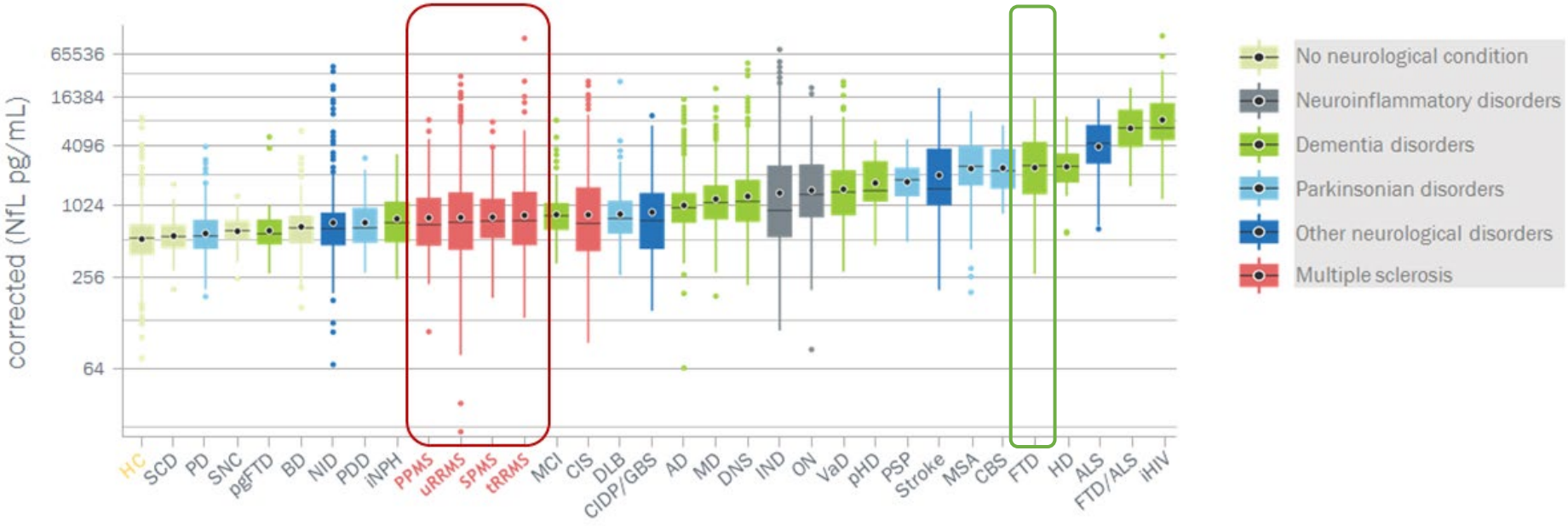
Revision of diagnostic criteria

GLOBAL CEOINITIATIVE ON ALZHEIMER'S DISEASE

Product profile

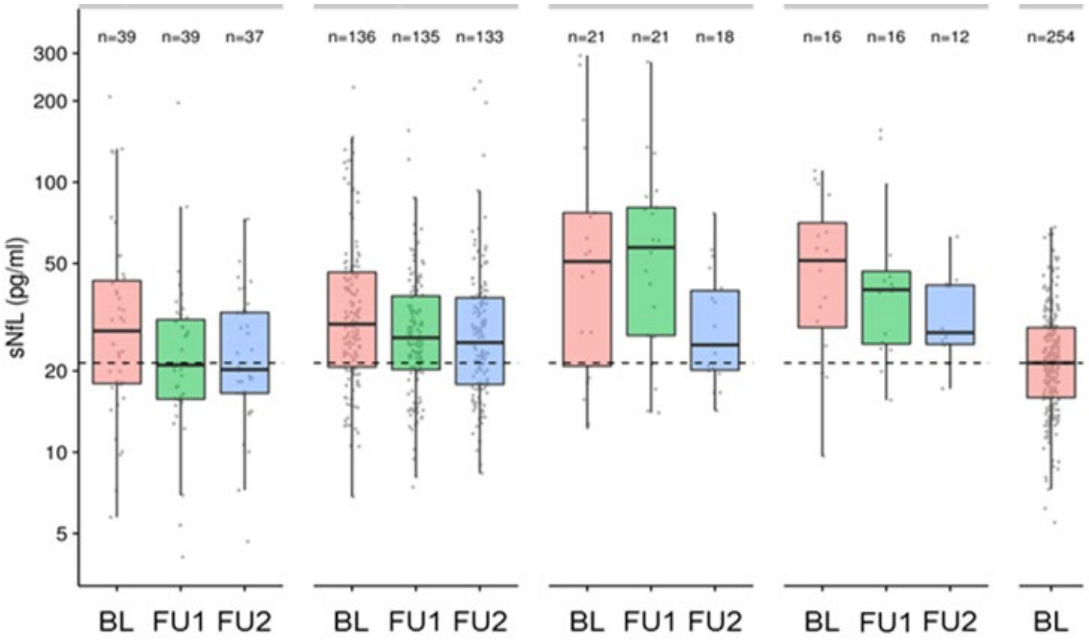
Implementation example of advanced blood biomarker: NfL, a cross disease biomarker for axonal damage

Meta-analysis, >10,000 data points



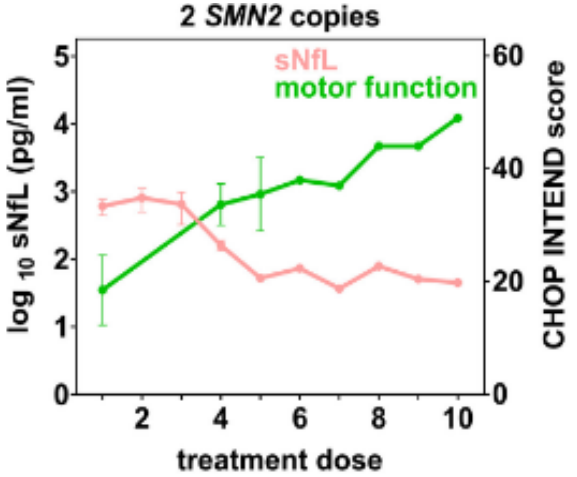
Bridel et al., JAMA Neurology 2019

NfL is a treatment response biomarker in Multiple Sclerosis

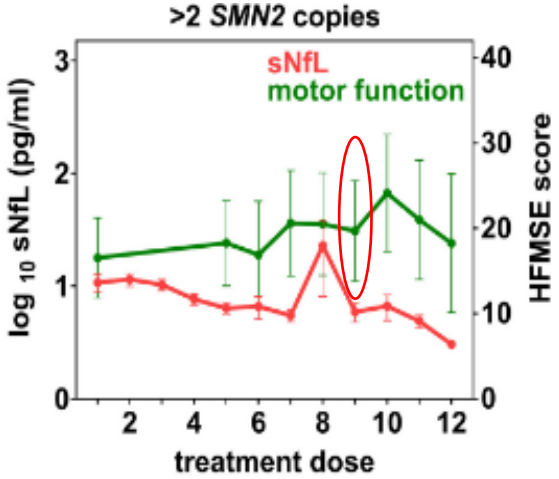


Disanto et al. Annals of Neurology 2017

NfL decreases upon nusinersen treatment and inversely correlates with motor function score in SMA



NfL inversely correlates with motor function score in patients with 2 *SMN2* copies



Motor function score varies widely in patients with >2 *SMN2* copies

What is needed for refunding in the Netherlands?

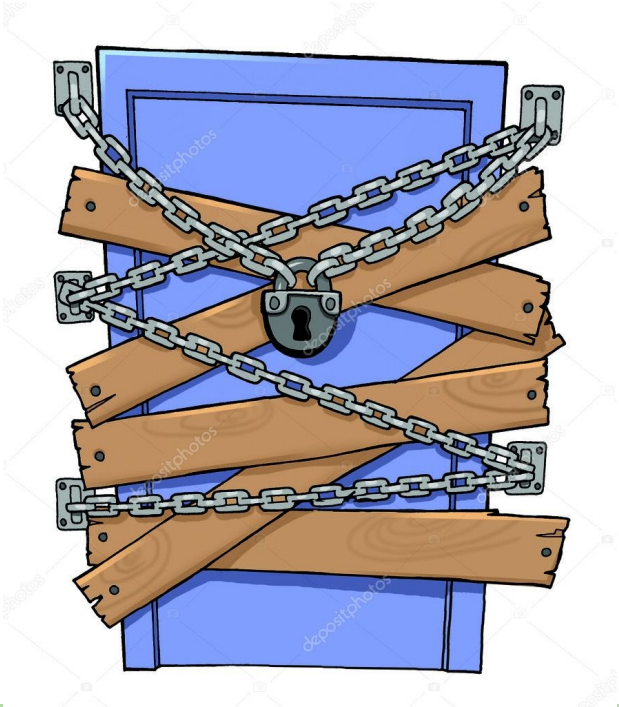
- EMA approval?

Our journey:

Application for Qualification Opinion for NfL in pediatric neurology.
-> advice to focus on e.g. SMA
-> discussion
-> support letter and scientific advice for pediatric neurology (October 2022)

What is needed for refunding in the Netherlands?

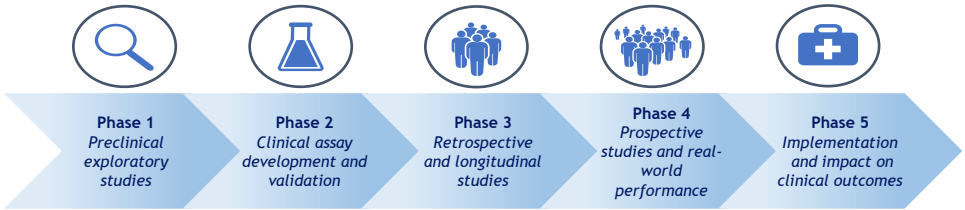
- EMA approval?
- Who decides? FMS?
- Guideline adoption required?



Puzzling....

Summary

- Revolutionary development in blood biomarkers for Alzheimer's, other dementias and neurology
- Clinical implementation activities have started!



Big THANK YOU from the Neurochemistry lab Amsterdam UMC