

Blood Biomarkers for Alzheimer's Disease and Neurodegeneration in Individuals with Genetic Intellectual Disabilities: A Systematic Review

L.E.A. Koster¹, F.H. Duits², E.G.B. Vijverberg², G.N. Perez¹, I.M.W. Verberk³, C.E. Teunissen⁴, A.M. van Eeghen^{1,5}

Background

- Genetic disorders with intellectual disabilities (GenID) have a markedly elevated dementia risk → up to 5× in non-DS ID, and a ~90% lifetime AD risk in Down syndrome due to APP triplication
- Cognitive testing is complicated by atypical symptoms, variable baseline functioning, higher comorbidity, and the lack of reliable diagnostic tools
- Other dementia diagnostics (e.g., lumbar puncture and neuroimaging) are poorly tolerated, invasive, and expensive
- Blood-based biomarkers (BBM) are minimally invasive and cost-effective, with growing evidence for their clinical relevance in the general population
- Their diagnostic and prognostic value specifically within GenID populations remained poorly understood

Methods

- PRISMA-guided systematic review, registered in PROSPERO (CRD42025064231)
- Search of MEDLINE, Embase & Cochrane Library up to 16 April 2026
- Inclusion criteria:
 - Human participants with GenID
 - Biomarkers: pTau, tTau, GFAP, NfL, Aβ (plasma or serum)
- Subanalyses for diagnostic value (AD vs. non-AD) and prognostic value (progression/decline)
- Quality appraisal with QUADAS-2 (diagnostic) and QUAPAS (prognostic) tools

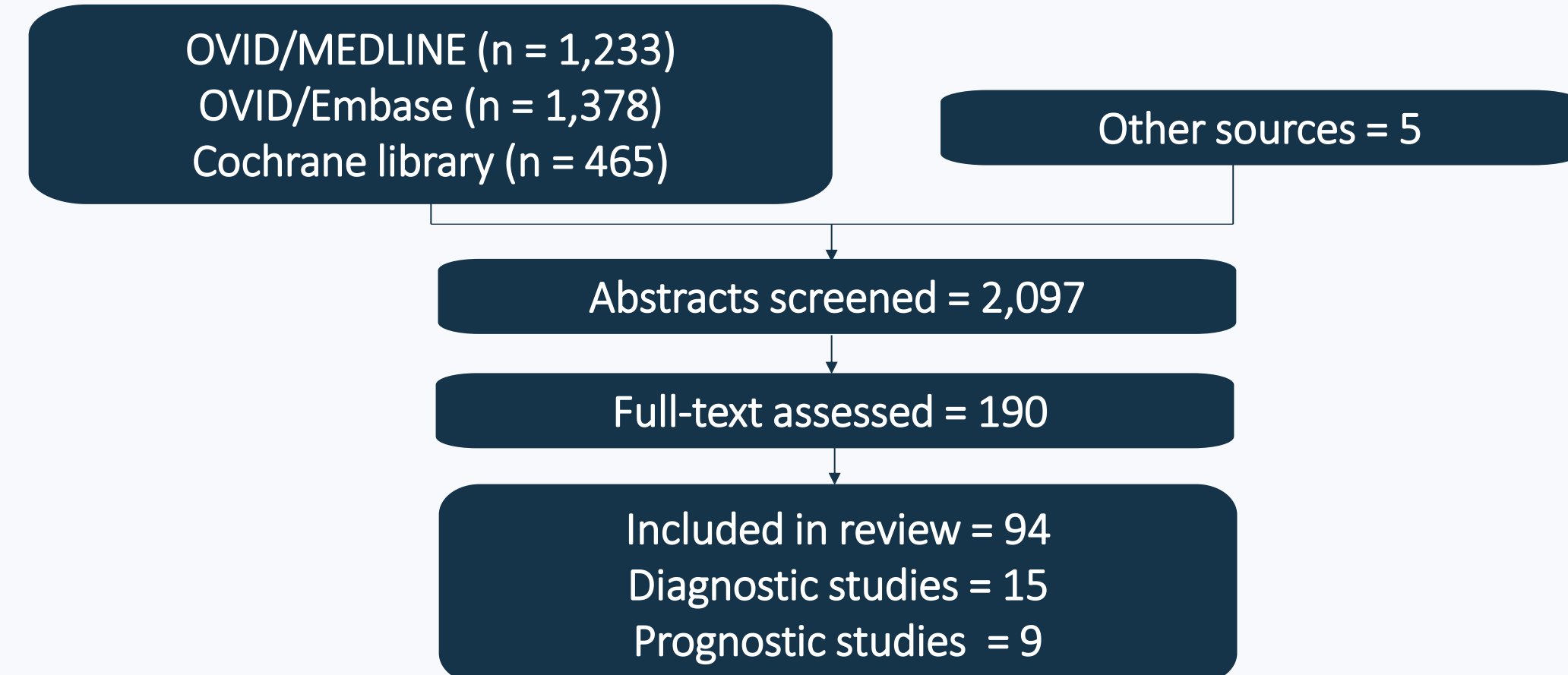


Fig 1. PRISMA flowchart



AIM

To provide an overview of the existing literature on BBM for AD and ND in GenID & evaluate their diagnostic and prognostic value for dementia

1997-2026 publication period of included studies

94% of studies analyzed plasma; 5% used serum; 1% did not specify

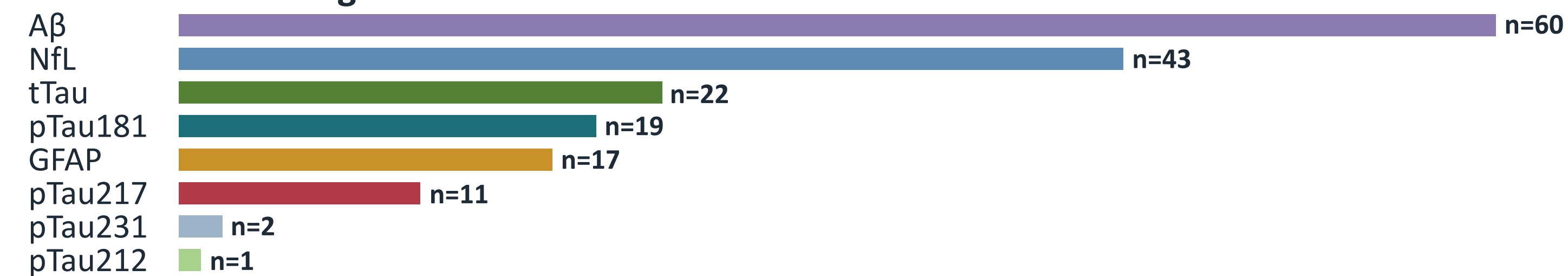
73% of studies were cross-sectional; 19% longitudinal, 3% trials, 3% case-control, and 1% case report

Study Landscape

Genetic disorders represented



Biomarkers investigated



Several STUDIES drew from overlapping cohorts (ABC-DS, DABNI).

Results: Biomarker Performance in DS-AD

pTau181

- Most extensively studied pTau isoform to date
- Excellent diagnostic accuracy: AD vs non-AD AUC 0.80-0.95
- Aβ-PET positivity AUC 0.81-0.82
- Elevated from mid-30s; HR 2.63 for incident AD

pTau217

- Strongest overall performer across all markers
- DS non-AD vs DS-AD AUC up to 0.96
- AUC for tau-PET positivity 0.94
- Best prognostic marker: HR 4.15 for progression
- Leading biomarker candidate for AD trials

GFAP

- Outstanding diagnostic accuracy: AUC 0.93-0.95
- Rises early (from mid-20s)
- Strongest prognostic marker: HR 2.99 (vs NfL 2.02)
- Outperforms NfL in most head-to-head comparisons

NfL

- High diagnostic accuracy: AD vs non-AD AUC 0.90-0.96
- Strongly correlated with pTau181 and PET markers
- Predicts progression (HR 2.02), less specific for AD
- 1pg/mL increase associated with 1.04× higher AD risk

Aβ (40/42)

- Inconsistent diagnostic value: AUC 0.56-0.94 across cohorts
- Limited as a reliable standalone marker
- Improves multimarker models (AUC up to 0.96)
- Lower Aβ42/40 ratio predicts higher AD risk (HR ≈11)

tTau

- Modest, inconsistent diagnostic accuracy: AUC 0.49-0.82
- Limited utility as a standalone marker
- Weak-to-moderate correlation with cognition & PET
- Improves multimarker models (AUC 0.93-0.96)

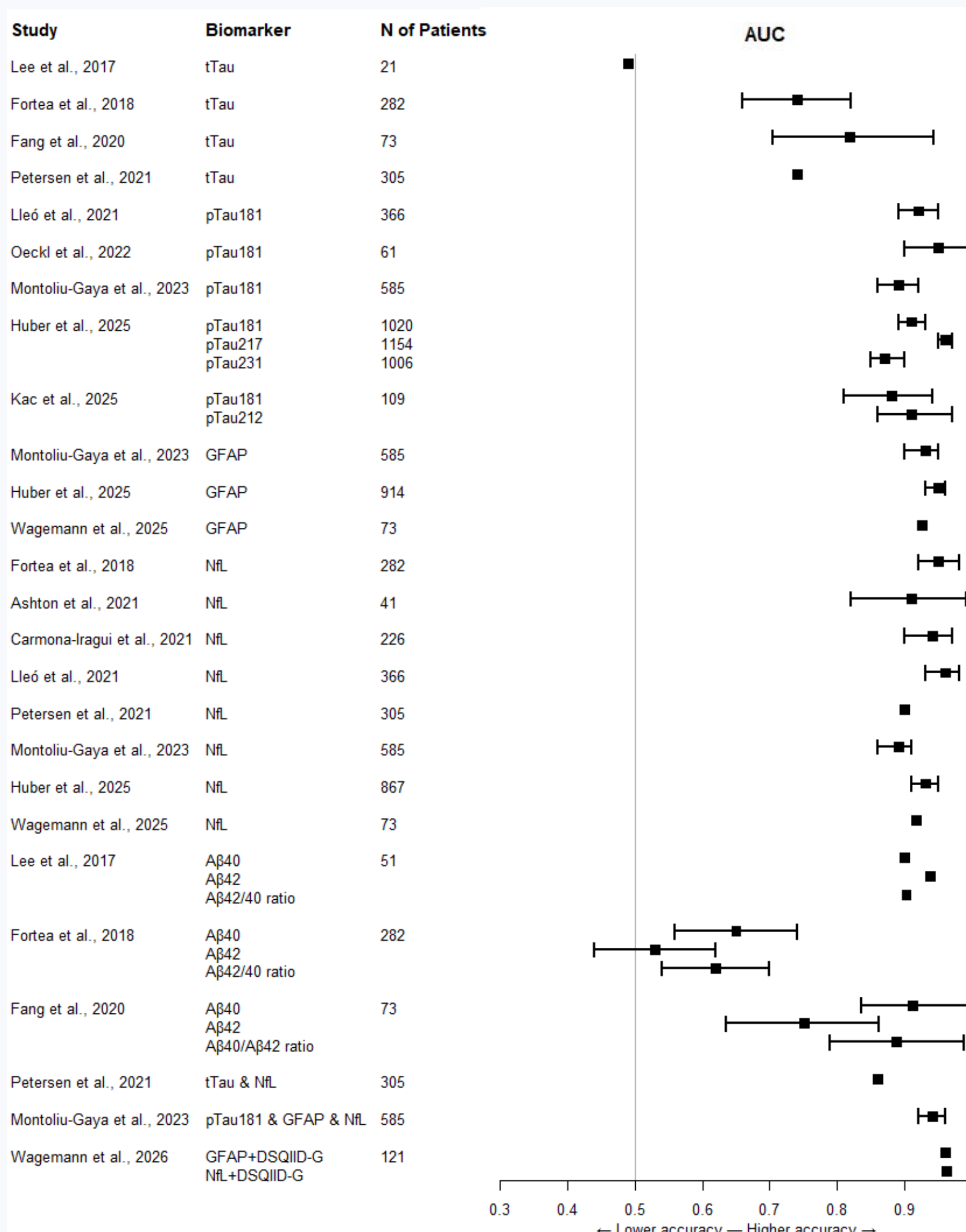


Fig 2. Diagnostic accuracy for AD in DS

Results: Non-DS GenID

- Adults with TSC: GFAP showed good discrimination of TSC from controls; tTau, pTau181, NfL, and Aβ showed limited or inconsistent performance
- Children and young adults with FXS: Aβ40 and Aβ42 were elevated versus healthy controls
- Children with RS: NfL was elevated versus controls and associated with greater disease severity
- ID + drug-resistant epilepsy: GFAP and NfL elevated vs controls, with high sensitivity but low specificity for suspected dementia; pTau217 largely normal

Conclusions

- pTau181, pTau217, GFAP, and NfL show strong diagnostic and prognostic value for DS-AD; Aβ and tTau are unreliable as standalone biomarkers
- Findings largely mirror patterns seen in the general population
- Evidence in non-DS GenID is sparse and fragmented; only one study linked BBM to dementia diagnosis
- Study quality is generally limited, and some cohorts overlap across included studies

BBM may offer a minimally invasive, cost-effective alternative to CSF and neuroimaging, improving dementia diagnosis in this high-risk population; baseline measurements may further enhance longitudinal assessment through within-person comparisons. However, further research is needed before confident clinical implementation.

Future Research Priorities

- Longitudinal studies of BBM trajectories across diverse GenID aetiologies
- Condition- and comorbidity-specific reference values (e.g., epilepsy, renal function, BMI)
- Definition of clinically meaningful within-person changes over time
- Comparative panel studies to identify the optimal biomarker combination and assay platform
- Evaluation of cost-effectiveness, feasibility, and optimal screening intervals across care settings

Affiliations

1: Emma Center for Personalized Medicine, Emma Children's Hospital, Amsterdam UMC location Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands. 2: Department of Neurology, Amsterdam UMC location Vrije Universiteit Amsterdam, Amsterdam, The Netherlands. 3: Department of Clinical Chemistry, Amsterdam UMC location Vrije Universiteit Amsterdam, Amsterdam, The Netherlands. 4: Department of Neurochemistry Laboratory, Amsterdam UMC location Vrije Universiteit Amsterdam, Amsterdam, The Netherlands. 5: 's Heeren Loo Zorggroep, Amersfoort, The Netherlands. This project has been supported by the J.Th.Guepin Stichting Onderzoek Down Syndroom and 's Heeren Loo. Pictures are retrieved from Flaticon/Freepik.



Contact

L.E.A. Koster
Emma Children's Hospital, Amsterdam UMC
Meibergdreef 9, 1105 AZ Amsterdam
l.e.a.koster@amsterdamumc.nl