Framework for the development and validation of new fluid biomarkers for Alzheimer's disease (AD) diagnosis

Colour codes indicate the levels of evidence for each blood-based biomarker:
Blue: mostly accomplished for this marker; **Purple:** somewhat accomplished for this marker; **Red:** no results that address this aspect for this marker.

Phase 1

Preclinical exploratory studies

Biomarker identification and leads prioritisation:

a) Hypothesis driven (Aβ, pTau, GFAP, NfL)
b) Unbiased -omics data (proteomics, transcriptomics)

Phase 2

Clinical assay development and validation

Technical:
LDTs and RUO assay development and validation (Aβ, pTau, GFAP, NfL)

Clinical:
Analysis of diagnostic accuracy in case-control studies (Aβ, pTau, GFAP, NfL)

Phase 3

Retrospective and longitudinal studies

Technical:
Define criteria for a positive test e.g., cut-offs (Aβ, pTau, GFAP, NfL)

Clinical:
Diagnostic accuracy for early disease detection e.g., preclinical, prodromal (Aβ, pTau, GFAP, NfL)

Phase 4

Prospective studies and real-world performance

Technical:
IVD assay development and validation (Aβ, pTau, GFAP, NfL)

Clinical:
Establish diagnostic performance prospectively (Aβ, pTau, GFAP, NfL)

Phase 5

Implementation and impact on clinical outcomes

Regulatory:
Integration in clinical guidelines (Aβ, pTau, GFAP, NfL)

Clinical:
Impact of biomarker testing on clinical decision making (Aβ, pTau, GFAP, NfL)

Phase 2 secondary aims and levels of achievement of blood-based biomarker development and validation for AD

Technical secondary aims

a) Reproducibility of assays between laboratories (Aβ, pTau, GFAP, NfL)
b) Pre-analytical factor assessment (Aβ, pTau, GFAP, NfL)
c) SOPs for sample handling and storage (Aβ, pTau, GFAP, NfL)

Clinical secondary aims

a) Relation with gold standard measures; e.g., CSF, 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; e.g., cognitive performance (Aβ, pTau, GFAP, NfL)
d) Disease specificity assessment for differential diagnosis (Aβ, pTau, GFAP, NfL)

Progress achieved in the biomarker implementation roadmap

- Phases 1 and 2 of the roadmap have largely been achieved for Aβ, pTau, and NfL
- Research continues on phases 1 and 2 for GFAP, and phase 3 for all biomarkers
- Phases 4 and 5 need to be undertaken for all biomarkers

Abbreviations: Aβ, amyloid β; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; IVD, in vitro diagnostic; LDT, laboratory-developed test; NfL, neurofilament light chain; pTau, phosphorylated tau; RUO, research use only; SOP, standard operating procedure

Reference: Teunissen CE, et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. Lancet Neurol. 2022;21(1):66–77.

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