



Keynote 5: Integration of Biomarkers and Quantitative Modeling – Analytical Validation and Standardization of Fluid Biomarkers

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CONFIDENTIAL



Integration of Biomarkers and Quantitative Modeling Analytical Validation and Standardization of Fluid Biomarkers

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Long preclinical phase in dementias



No symptoms

Clinical disease



20 years



Biomarkers needed in dementia trials

- ✓ Inclusion of the right patients in preclinical phase
- ✓ Target engagement
- ✓ Side effect monitoring
- ✓ Outcome measures in preclinical phase
 - ✓ Phase 2: Biomarker endpoints
 - ✓ Phase 3: Surrogacy. To replace clinical outcomes



Biomarker portfolio for trials

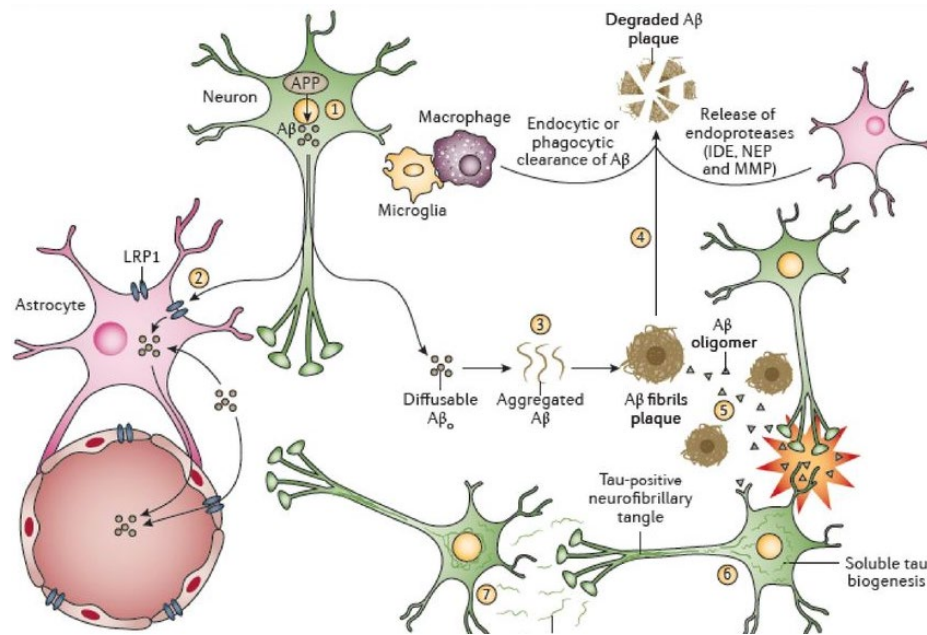
Inclusion/outcomes:

Core pathologies:

CSF abeta, (p)Tau

Plasma abeta, (p)Tau

GFAP



(Side) effects:

Axonal damage

Neurofilament light

Outcome measures (CSF):

Synaptic dysfunction:

Neurogranin, SNAP-25, NPTX2, VAMP-2

Microglia damage:

Trem-2, YKL-40



Inclusion: prescreening in preclinical phase

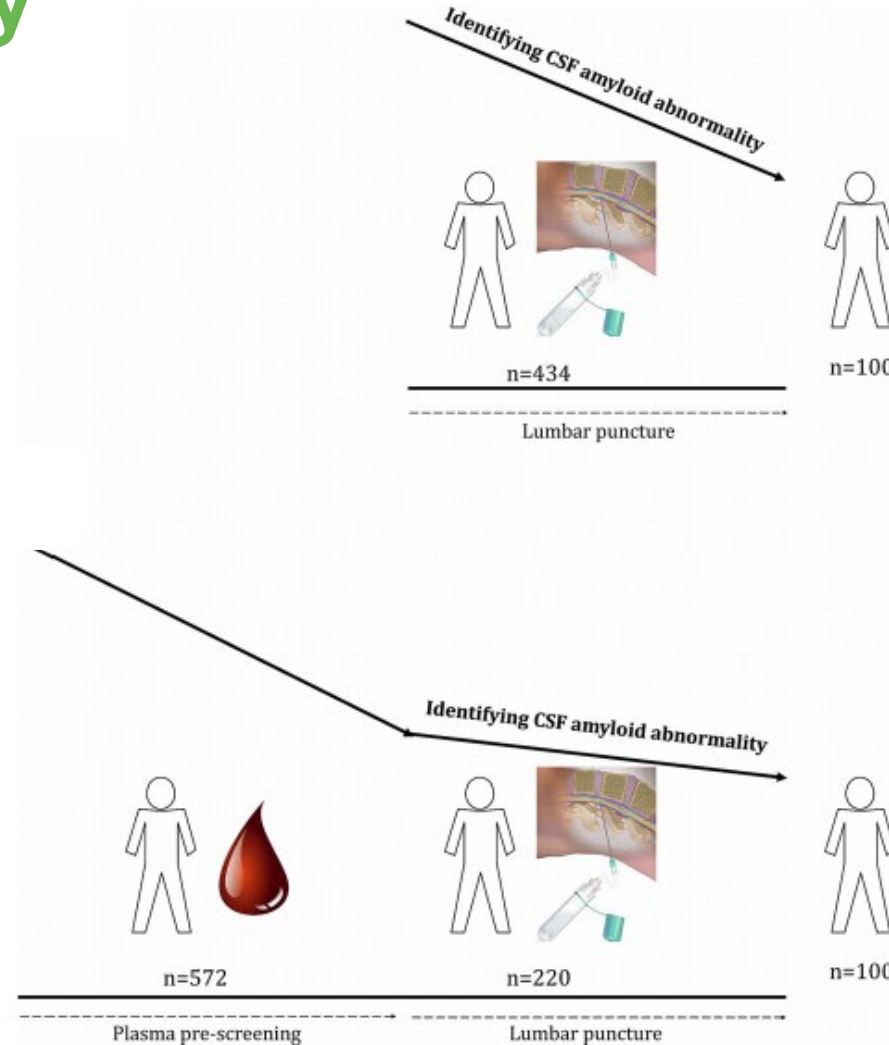
Plasma amyloid beta ratio to predict progression in early stages of AD





Prescreening in early stage AD for trial inclusion:

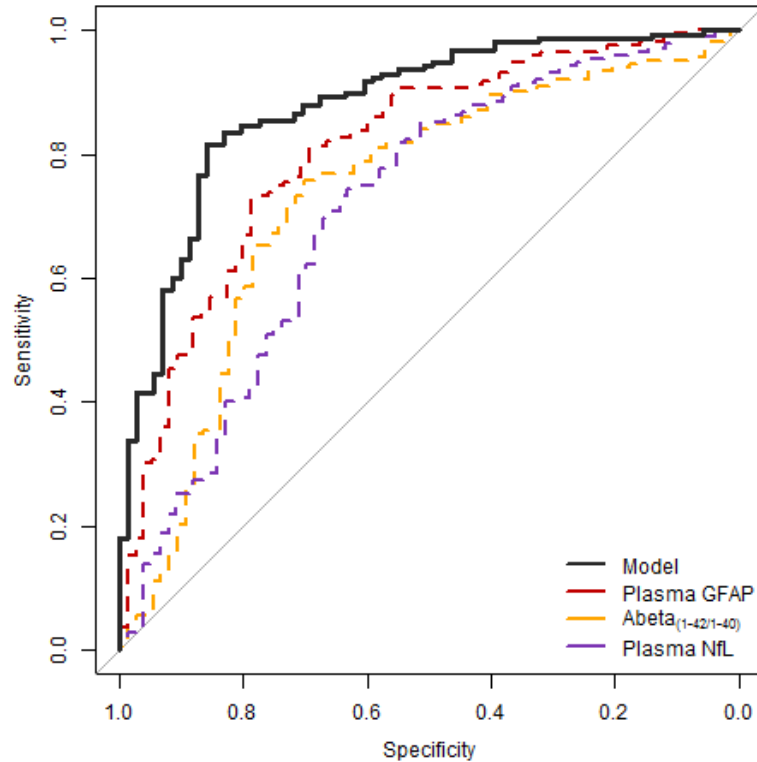
From 434 to 220 lumbar punctures





Inclusion

Multiplexing markers better predicts PET positivity



Multiplex analysis:

➤ AUC = 88%

➤ Sensitivity = 82%, specificity = 86%

Abeta_(1-42/1-40): AUC=73%

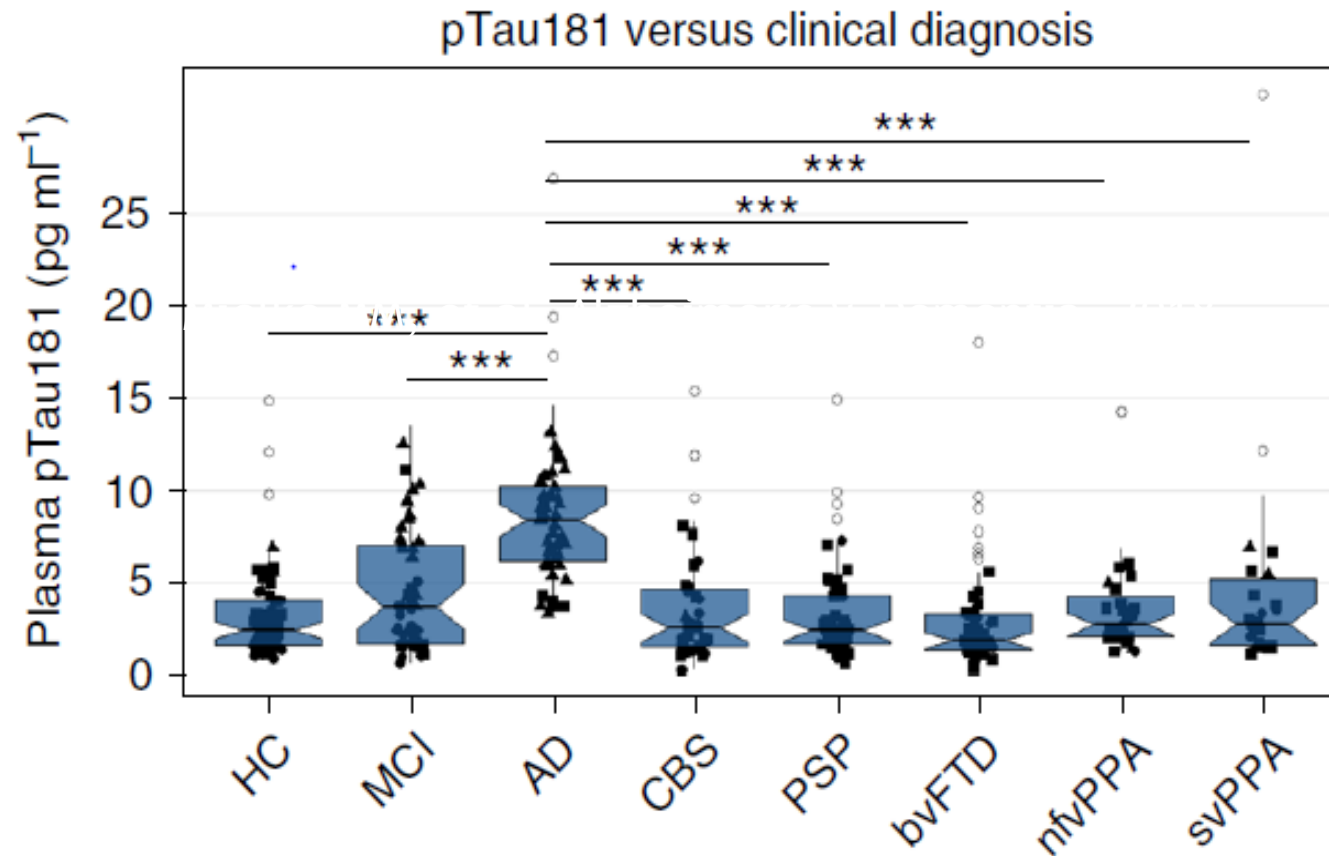
GFAP: AUC=81%

NfL: AUC=71%

Inclusion



Plasma pTau181: Specifically increased in AD



Outcome measures:

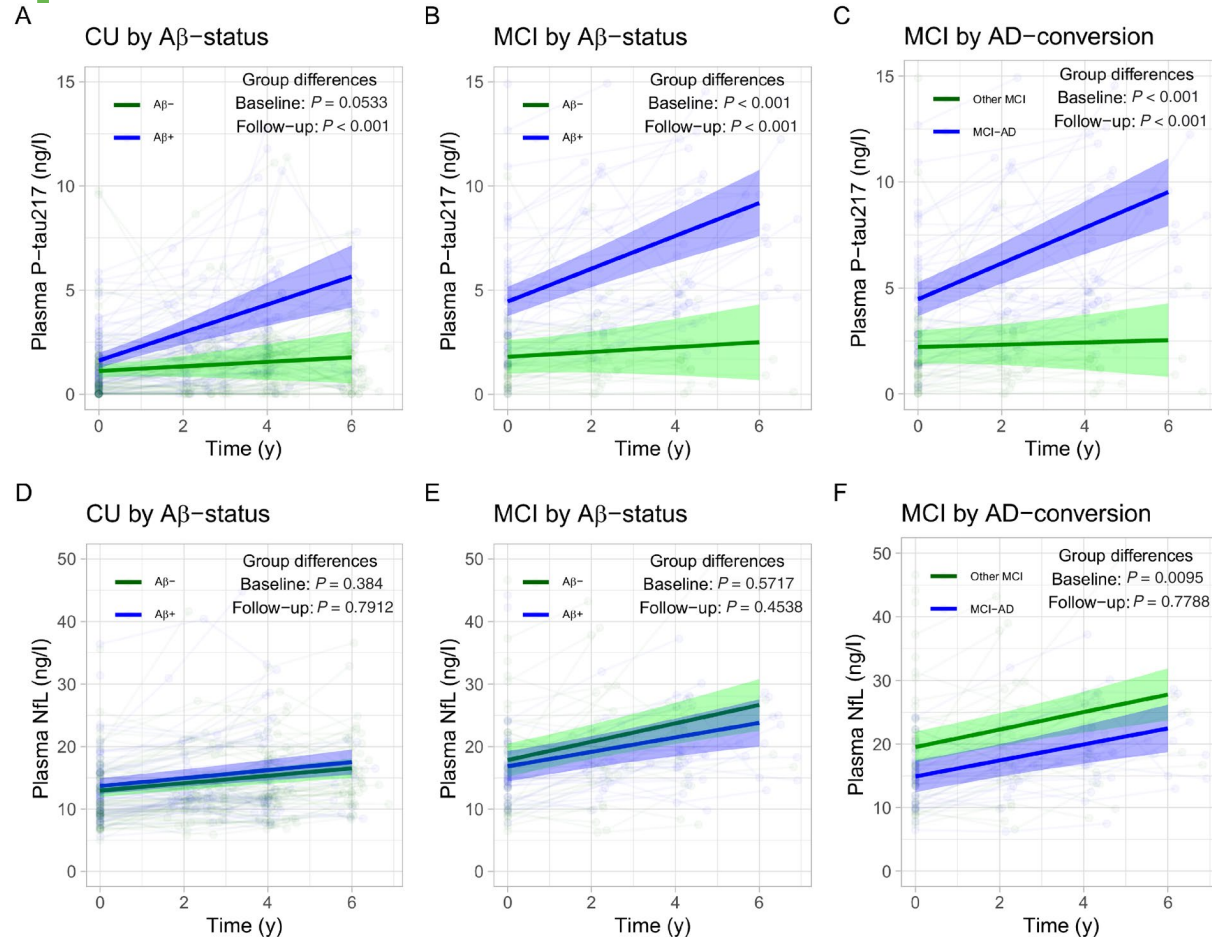


Longitudinal plasma p-tau217 and NfL across the AD stages

Detect reduction in pTau slope

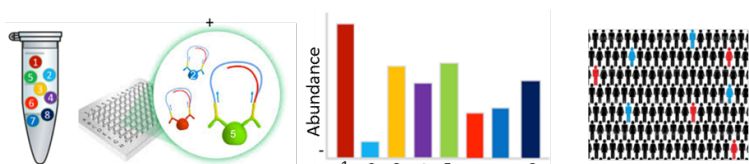
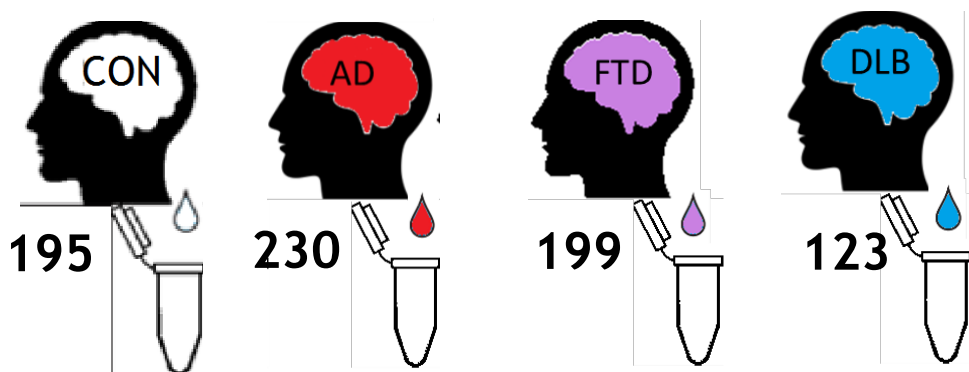
N=109 per arm to for CU

N=71 per arm for MCI





Proteomics analyses to identify novel inclusion and outcome measures



>1500 proteins

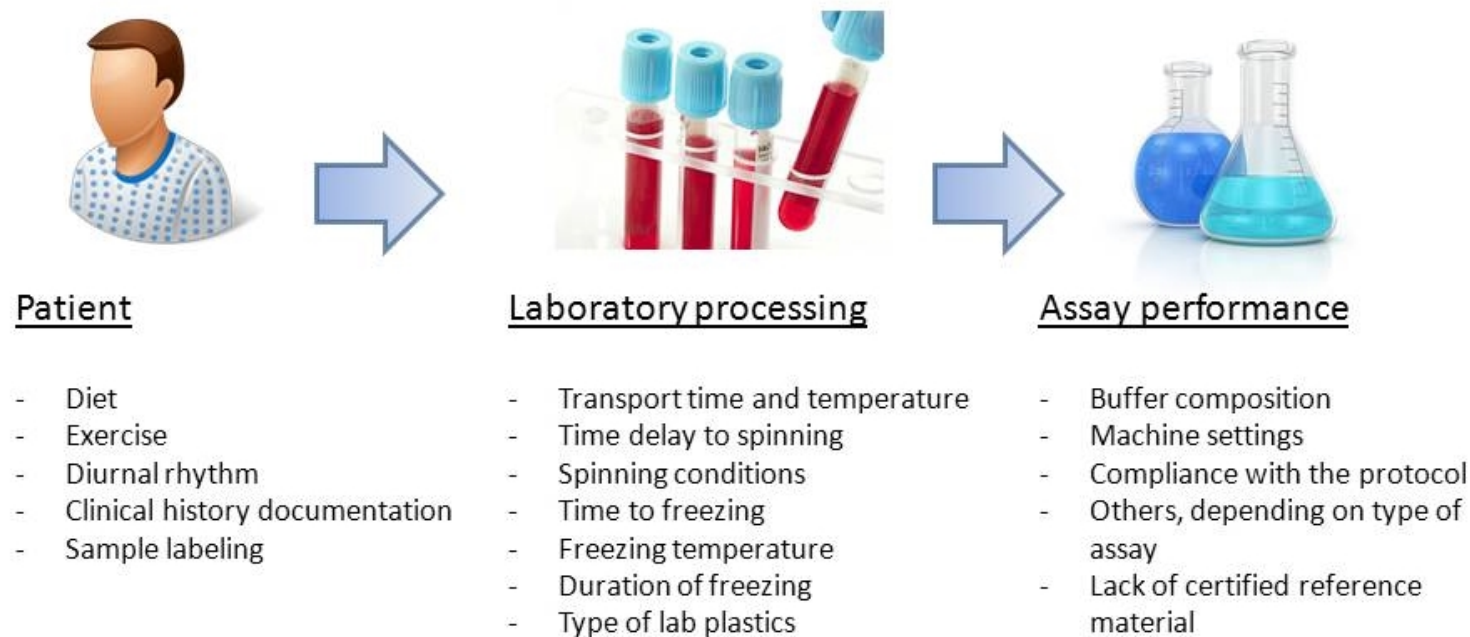
(b)PRIDE project



Standardisation



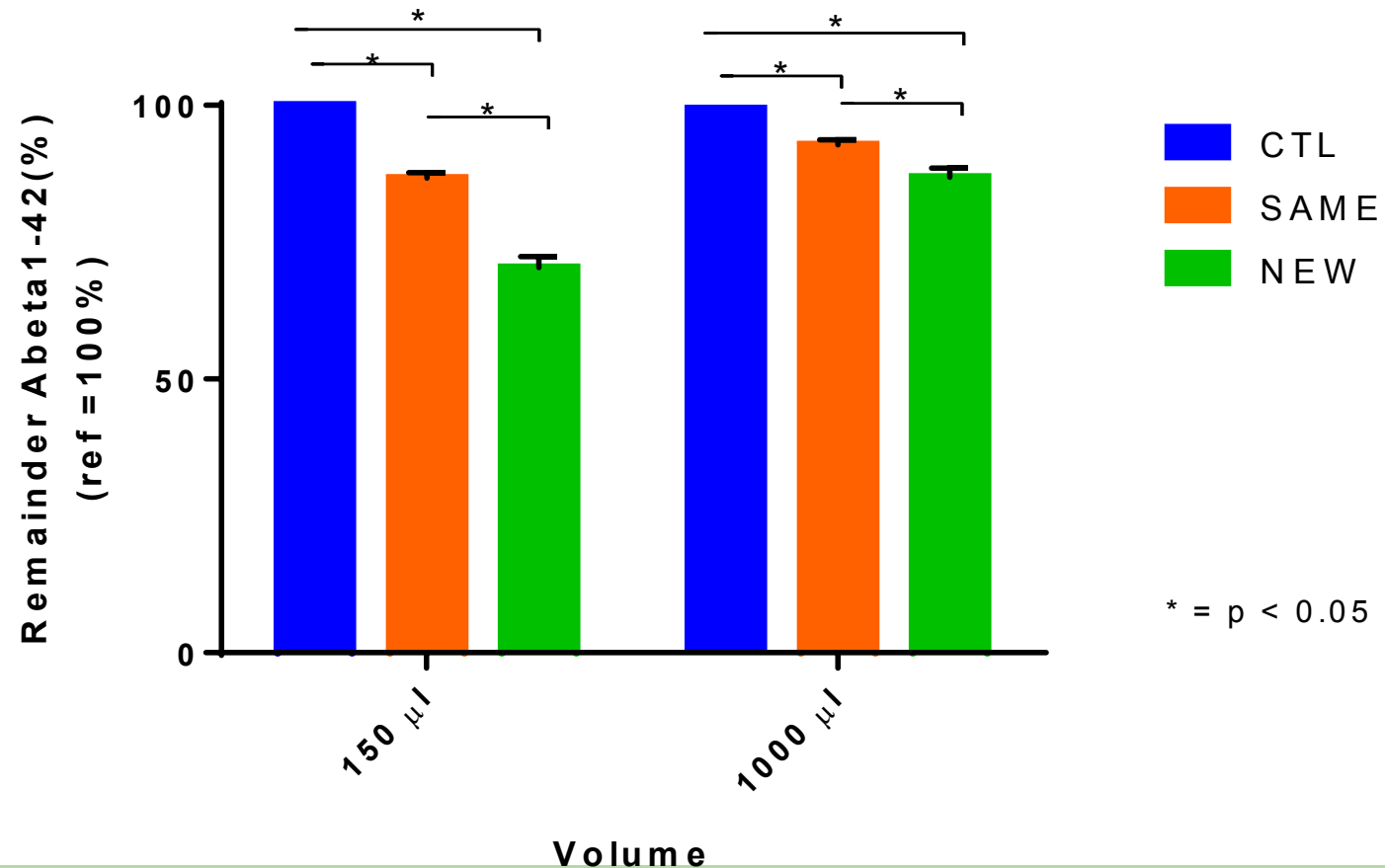
Targetting (pre-)analytical variation



*Willemse and Teunissen,
Book chapter in : CSF in clinical practise, ed. Deisenhammer, Teunissen, Tumani Sellebjerg*



A β 42 absorbed by pipette tip?





Consensus pre-analytical protocols for CSF



Critical issues in CSF analysis:

- Pre-analytic: Amyloid absorption to plastics
- Analytic: Variation between platforms:
 - ✓ reference materials/methods
 - ✓ automation

Central analysis of biomarkers

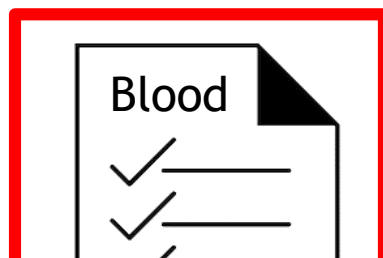


Consensus pre-analytical protocol for blood is lacking



Critical issues in CSF analysis:

- Amyloid absorption to plastics
- Variation between platforms:
 - ✓ reference materials/methods
 - ✓ automation



Critical issues in blood analysis:

- ✓ Collection tube?
- ✓ Time to centrifugation?
- ✓ Freezing/thawing?

Systematic evaluation of common pre-analytics



Project design



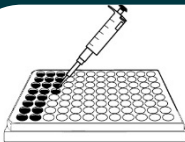
1) Survey among cohorts and diagnostic companies + expert opinion enquiry



2) Selection most relevant pre-analytical variables



3) Establish a biorepository of *mistreated* sample sets



4) Define pre-analytical effects on Alzheimer's blood-based biomarkers



5) Generate SOP



Summary

Body fluid biomarkers are a requirement in clinical trials in dementias - wide portfolio available

Detailed evaluation of trajectories needed to establish use as outcome measures

Good pre-analytical protocols CSF in place - blood under development

Analysis can easily be done centrally

You never work alone....

