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

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

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Long preclinical phase in dementias
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

Verberk et al, Annals of Neurology 2018
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%

Verberk et al, Alz Res Ther 2020
Inclusion

Plasma pTau181: Specifically increased in AD

- Thijssen et al, Nat Med 2020
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

Marta Del Campo Milan AAIC 2020
Standardisation

Targetting (pre-)analytical variation

Willemse and Teunissen,
Book chapter in : CSF in clinical practise, ed. Deisenhammer, Teunissen, Tumani Sellebjerg
Aβ42 absorbed by pipette tip?

Volume Remainder Aβ1-42(%) (ref = 100%)

- 150 µl
- 1000 µl

- CTL
- SAME
- NEW

* = p < 0.05

Willemse et al, Alzheimer's and Dementia 2017
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

Questions? Mail to: c.teunissen@amsterdamumc.nl
You never work alone.....