Keynote 3: Integration of Biomarkers and Quantitative Modeling - Plasma

October 27, 2020

Henrik Zetterberg, Professor University of Gothenburg & University College London
Biomarkers for A/T/N

- Amyloid = CSF Aβ42/Aβ40 ratio and amyloid PET
- Tau = Tau PET (CSF P-tau as a predictive marker?)
- Neurodegeneration = CSF neurofilament light, MRI, FDG-PET

Please email questions to ykarten@c-path.org
Can this be measured in blood?
Historically, plasma Aβ could show any result.
Nakamura - Nature, 2018

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Optimized method for plasma Aβ by IP-MS/MS

Levels of Aβ42 and Aβ40 in plasma can be measured in 250 uL of plasma with high precision. Also Aβ38 and Aβ 3 to 40 (APP 669-711) can be quantified.

- Recombinant 15N labelled Aβ42, Aβ40, Aβ38 as internal standard
- Plasma treated with Triton X100 to reduce matrix effects - binding to plasma proteins

IP using 6E10 + 4G8 (mid domain Mabs)

Coefficients of variation for Quality Control (QC) samples:

<table>
<thead>
<tr>
<th></th>
<th>pg/mL</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ1-38</td>
<td>21</td>
<td>5%</td>
</tr>
<tr>
<td>Aβ1-40</td>
<td>262</td>
<td>2%</td>
</tr>
<tr>
<td>Aβ1-42</td>
<td>25</td>
<td>12%</td>
</tr>
</tbody>
</table>

Please email questions to ykarten@c-path.org
Plasma Aβ in the Insight46 cohort

Study design: Insight46 - epidemiological study people born 1946 (n= 414 cognitively unimpaired)
APOE genotype, neuropsych testing, amyloid PET
Plasma Aβ42, Aβ40/42 using immunoassay (Simoa) and IP LC-MS/MS

Plasma Aβ42 and Aβ40/42 ratio by IP-MS/MS show high concordance with brain amyloidosis

ROC AUC for amyloid PET positivity:
- Simoa Aβ40/42: 0.61
- IP-MS Aβ40/42: 0.82

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Keshavan A et al., Brain, in press
The Elecsys prototype assay for plasma Aβ40 and Aβ42 - Diagnostic performance for detecting Aβ positivity (determined by CSF)

Palmqvist et al. JAMA Neurol 2019

Please email questions to ykarten@c-path.org
Plasma p-tau181 as a biomarker for tau pathology in AD

Plasma P-tau181 measured by a modified version of the Quanterix Simoa T-tau assay

Cohort: 15 controls
20 AD dementia

➔ Plasma P-tau181 a candidate blood biomarker for AD
➔ Good correlation between plasma and CSF levels - reflects brain pathophysiology
➔ Lack of analytical sensitivity to measure all samples (even in AD patients)

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Lilly Research Lab MSD method for plasma P-tau181

Plasma phosho-tau181 increases with Alzheimer’s disease clinical severity and is associated with tau- and amyloid-positron emission tomography

AUC 0.803 for amyloid PET+

MSD assay for P-tau181 show promise as a candidate blood biomarker for AD

Simoa assay for T-tau show poor discriminatory power (as before)

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P-tau181 assay differentiated AD from clinical (AUC 0.89) and autopsy-confirmed (AUC 0.88) FTD

Plasma P-tau181 identified amyloid PET positive cases regardless of clinical diagnosis and correlated with cortical tau deposition measured by flortaucipir (FTP) PET

Plasma P-tau181 may be a useful screening tool for AD-type tau pathology
Increased plasma P-tau181 with higher Braak stages
High baseline P-tau181 in controls and MCI cases predicts progression to AD dementia
Further support for the usefulness of plasma P-tau181 as a biomarker for AD-type tau pathology

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UGOTSimoa assay for blood p-tau181

In house Simoa assay

Karikari et al., Lancet Neurol, 2020

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TRIAD ‘discovery’ cohort
Plasma P-tau181 increased in MCI and AD

Karikari et al., Lancet Neurol, 2020
TRIAD validation cohort

P-tau181 in relation to clinical diagnoses

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Karikari et al., Lancet Neurol, 2020
TRIAD validation cohort
Plasma p-tau181 correlates with MK-6240 tau PET

$\rho = 0.6557, \ P < 0.0001$

$\rho = 0.6814, \ P < 0.0001$

$\rho = 0.6260, \ P < 0.0001$

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TRIAD validation cohort

P-tau181 correlates with AZD4694 amyloid PET

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Plasma P-tau181 in familial Alzheimer’s disease

O’Connor A et al., Mol Psychiat 2020

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Plasma P-tau181 in familial Alzheimer’s disease

Geometric mean plasma p-tau181 (pg/ml)

Estimated years to/from symptom onset (EYO)
Plasma P-tau181 in the 1946 cohort – plasma p-tau181 as a pre-screening tool for amyloid status

Keshavan et al., unpublished

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Plasma P-tau181 in Down syndrome

Fortea et al., 2020, unpublished

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Plasma P-tau181 - neuropathological validation

![Graph A](image1)

**Graph A**

- **Control**
- **AD (+CAA)**
- **AD (+Lewy Body)**
- **AD (+TDP43)**
- **CAA**
- **FTLD**
- **AR Tauopathy**
- **VaD**

Plasma p-tau181, pg/mL

**Graph B**

Neuropathologically confirmed AD pathology versus:

- Non-AD (AUC = 97.4%)
- Controls (AUC = 92.1%)
- Mixed AD (AUC = 57.3%)

**Graph C**

Neuropathologically confirmed mixed AD pathology versus:

- Non-AD (AUC = 90.1%)
- Controls (AUC = 84.1%)

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Discriminative Accuracy of Plasma Phospho-tau217 for Alzheimer Disease vs Other Neurodegenerative Disorders

Sebastian Palmqvist, MD, PhD; Shorena Janelidze, PhD; Yakeel T. Quiroz, PhD; Henrik Zetterberg, MD, PhD; Francisco Lopera, MD; Erik Stromrud, MD, PhD; Yi Su, PhD; Yinghua Chen, MSc; Geidy E. Serrano, PhD; Antoine Leuzy, PhD; Niklas Mattsson-Carlsson, MD, PhD; Olof Strandberg, PhD; Ruben Smith, MD, PhD; Andres Villegas, MD; Diego Sepulveda-Falla, MD; Xiyun Chai, MD; Nicholas K. Proctor, BS; Thomas G. Beach, MD, PhD; Kaj Blennow, MD, PhD; Jeffrey L. Dage, PhD; Eric M. Reiman, MD; Oskar Hansson, MD, PhD
Lilly MSD plasma P-tau217 across neurodegenerative diseases

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Palmqvist et al., 2020, JAMA
Lilly MSD plasma P-tau217 in Alzheimer's disease - compared with other markers, including P-tau181

Palmqvist et al., 2020, JAMA

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Plasma P-tau217 vs. P-tau181 - which one is the best?

JAMA paper (Palmqvist et al. 2020) favors P-tau217 over P-tau181 with higher AUCs for the former marker for clinical and biomarker-supported AD diagnoses.

Evidence that P-tau217 might be more CNS-specific and more specific to “pathological tau phosphorylation” (Barthélemy NR et al., J Exp Med. 2020)

But plasma P-tau181 may have similar or higher diagnostic performance against neuropathology:

- P-tau181 AUC for AD vs. non-AD pathologies: 0.97 (95% CI 0.94-1.00) (Lantero Rodriquez J et al., Acta Neuropathol. 2020)
- P-tau217 AUC for AD vs. non-AD pathologies: 0.89 (95% CI 0.81-0.97) (Palmqvist S et al., JAMA 2020)

P-tau217 a little bit harder to measure than P-tau181?

More head-to-head studies needed…

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NfL - ELISA vs. Simoa

LLoD = 0.26 ng/L; LLoQ = 1.95 ng/L

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Plasma NfL correlates with CSF NfL

$r = 0.872$
$p < 0.0001$

Gisslén et al., 2015
Plasma NfL in familial Alzheimer’s disease

![Box plot showing NfL levels in non-carrier, presymptomatic carrier, and symptomatic carrier groups.](image)

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Weston et al., Neurology 2017
Longitudinal plasma NFL in the ADNI study

- All ADNI patients: CU controls (n= 401), MCI (n= 855) and AD dementia (n= 327)
- Baseline + up to 11 year longitudinal data, in total 4326 samples

Plasma NFL can track neurodegeneration throughout the AD continuum
Serum NFL may be useful to monitor downstream drug effects on intensity of neurodegeneration

Mattsson N, et al. JAMA Neurol 2019
Biomarkers for A/T/N

- Amyloid = plasma Aβ42/Aβ40 ratio
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