AD CSF Biomarkers Team

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| **Covance** | Bob Martone |
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| **Eli Lilly & Company** | Peng Yu, Bob Dean, Janice Hitchcock, Brian Willis |
| **FDA** | Marc Walton, Jim Kaiser |
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| **Quanterix** | Andreas Jeromin |
| **ICON** | David Raunig |
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| **University of Göteborg** | Henrik Zetterberg, Kaj Blennow |
| **Washington University** | Anne Fagan, Betsy Grant |
| **University of Antwerp** | Sebastiaan Engelborghs |
Intended Application

Proposed context of use:

General Area: Clinical trial enrichment in “amnestic MCI” (aMCI)

Target Population for Use: Patients with aMCI.

Stage of Drug Development: All clinical stages of drug development, including dose-ranging, proof of concept and confirmatory clinical trials

Proposed biomarkers: cerebrospinal fluid (CSF) amino acid 42-containing isoform of amyloid beta protein (Aβ42); total tau (t-tau); and phosphorylated tau (p-tau)

The purpose is to exclude subjects that have a low probability of showing decline in cognition and function over two years and as such, increase the probability of identifying potential drug effects with therapeutic interventions in patients with amnestic MCI
CSF the sample of choice: Pros & Cons

• Cons:
  – Blood or urine most practical & acceptable
  – Risk of adverse events

• Pros:
  – Most reliable for assessing brain metabolism & function
  – Limitations to interpreting blood or urine derived markers
  – Perceived limitation of adverse events is not supported by evidence
  – More desired in some geog. areas vs PET for global clinical trials
  – Increased use in large-scale studies
    • ADNI: ADNI GO&II require CSF as part of enrollment
    • PPMI: all subjects required to provide CSF

Adapted from Elaine Peskind, with permission
**CEREBROSPINAL FLUID (CSF)**

![Diagram of the brain showing various structures related to CSF.](image)

**Assessments of complications after LP**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of cases</th>
<th>Post LP headache</th>
<th>Meningitis/hematoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blennow K, et al 1993</td>
<td>395</td>
<td>2.1%</td>
<td>0</td>
</tr>
<tr>
<td>Andreasen N et al, 2001</td>
<td>241</td>
<td>4.1%</td>
<td>0</td>
</tr>
<tr>
<td>Peskind ER, et al, 2005</td>
<td>342 (428 LP)</td>
<td>0.9%</td>
<td>0</td>
</tr>
<tr>
<td>Zetterberg H, et al, 2010</td>
<td>1089</td>
<td>2.6%</td>
<td>0</td>
</tr>
</tbody>
</table>

*Slide prepared by Kaj Blennow*
CSF biomarkers for AD

Background

- ↓Aβ_{1-42}, ↑t-tau & p-tau_{181} in CSF reflect amyloid plaque burden and tau pathology (tangles and neurodegeneration)
  - Brain amyloid load in autopsied brain
  - Tangles count
  - AD autopsy diagnosis
  - Brain amyloid load-PiB, florbetapir, flumetamol
  - More accurate than clinical diagnosis of AD in MCI & AD pts

- ↓Aβ_{1-42}, ↑t-tau & p-tau_{181} in CSF differentiate AD from HC and from other neurodegenerative diseases using RUO precision based immunoassays
CSF biomarkers for AD

Background cont’d

– $\downarrow A\beta_{1-42}, \uparrow t$-tau & p-tau$\text{\textsubscript{181}}$ in CSF predict progression: in cog decline and to AD dementia in MCI patients

• Multicenter studies demonstrate this
  – ADNI I and ADNI GO & II
  – Descripa
  – Swedish brain power

• Major single center studies
  – Wash Univ
  – Hansson, Buchave
  – Engelborghs
CSF Aβ₁₋₄₂ is Strongly Correlated to Plaque Counts in autopsied brains and Plaque Burden by PiB PET testing

Pittsburgh compound-B labeled positron emission tomography; SUVR = standard uptake value ratio

Rates of decline for CDRsob: Pathologic vs non-Pathologic biomarker CSF biomarkers (ADNI I dataset)

<table>
<thead>
<tr>
<th>Cutpoint</th>
<th>192 pg/mL</th>
<th>0.39</th>
<th>0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomarker</td>
<td>$A\beta_{42}$</td>
<td>t-tau/$A\beta_{42}$</td>
<td>riskTAA2i</td>
</tr>
<tr>
<td>CSF pathologic</td>
<td>+1.10/yr</td>
<td>+1.14/yr</td>
<td>+1.14/yr</td>
</tr>
<tr>
<td>CSF non-pathologic</td>
<td>+0.26/yr</td>
<td>+0.31/yr</td>
<td>+0.45/yr</td>
</tr>
</tbody>
</table>
CSF $\text{A} \beta_{1-42}$ alone has equivalent concordance to florbetapir t-tau/$\text{A} \beta_{1-42}$ for estimation of plaque burden in ADNI GO & II MCI patients.

<table>
<thead>
<tr>
<th></th>
<th>concordant</th>
<th>discordant</th>
<th>FBP-/Aβ-</th>
<th>FBP+/Aβ+</th>
<th>FBP-/Aβ+</th>
<th>FBP+/Aβ+</th>
<th>concordance</th>
<th>AUC</th>
<th>Test accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{A} \beta_{1-42}$</td>
<td>124</td>
<td>14</td>
<td>33</td>
<td>91</td>
<td>11</td>
<td>3</td>
<td>0.898</td>
<td>0.933</td>
<td>90%</td>
</tr>
<tr>
<td>t-tau/$\text{A} \beta_{1-42}$</td>
<td>123</td>
<td>15</td>
<td>37</td>
<td>86</td>
<td>7</td>
<td>8</td>
<td>0.891</td>
<td>0.954</td>
<td>87%</td>
</tr>
</tbody>
</table>
• The first treatment trial in pre-dementia (MCI) pts to use CSF AD biomarkers for patient selection; AAIC, 2012
• Immunoassay used after internal validation: AlzBio3
• Concomitant florbetapir in 77 patients

**Key Inclusion Criteria for the Randomized Study**
- Adults 45 to 90 years of age
- MMSE score between 24-30 (inclusive)
- CDR global score of 0.5 with memory box score ≥0.5
- Subjective memory complaints documented by patient or study partner
- Objective memory loss measured by education-adjusted scores on the LM-II or FCSRT
- Absence of dementia as clinically assessed using DSM-IV criteria
- No alternative causes of cognitive impairment based on MRI findings
- CSF Aβ42 levels <200 pg/mL or t-tau:Aβ42 ratio ≥0.39
- Comedication with stable dose of marketed cholinesterase inhibitor or memantine was permitted

**Conclusions:** CN156-018, the first clinical trial to recruit patients with PDAD defined by both Clinical phenotypic features and biomarker CSF criteria consistent with the presence of an amyloidopathy, demonstrates both the feasibility and challenges of studying PDAD. Efforts are warranted to refine entry criteria and decrease screen failures.
Advancing research diagnostic criteria for Alzheimer’s disease: the IWG-2 criteria

Bruno Dubois, Howard H Feldman, Claudia Jacova, Harald Hampel, José Luis Molinuevo, Kaj Blennow, Steven T DeKosky, Serge Gauthier, Dennis Selkoe, Randall Bateman, Stefano Cappa, Sebastian Crutch, Sebastiaan Engelborghs, Giovanni B Frisoni, Nick C Fox, Douglas Galasko, Marie-Odile Habert, Gregory A Jicha, Agneta Landtblom Andersson, Pasquale Galimberti, Gil Rabinovici, Philippe Robert, Christopher Rowe, Stephen Salloway, Marie Sarazin, Stéphane Epelbaum, Leonardo C de Souza, Bruno Vellas, Pieter J Visser, Lon Schneider, Yaakov Stern, Philip Scheltens, Jeffrey L Cummings


- CSF Aβ1-42, t-tau & p-tau, or PET amyloid imaging, indicate AD pathology in the brain regardless of disease stage-described as “pathophysiological’
- Indicated for inclusion in protocols of clinical trials

<table>
<thead>
<tr>
<th>CSF Aβ1-42, t-tau &amp; p-tau</th>
<th>Hippocampal volume, FDG PET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathophysiological marker</td>
<td>Topographical or downstream markers</td>
</tr>
<tr>
<td>Reflects in-vivo pathology</td>
<td>Poor disease specificity</td>
</tr>
<tr>
<td>Is present at all stages of the disease</td>
<td>Indicates clinical severity(staging markers)</td>
</tr>
<tr>
<td>Observable even in the asymptomatic state</td>
<td>Might not be present in earliest stage</td>
</tr>
<tr>
<td>Might not be correlated with severity</td>
<td>Quantifies time to disease milestones</td>
</tr>
<tr>
<td><strong>Indicated for inclusion in protocols of clinical trials</strong></td>
<td><strong>Indicated for disease progression</strong></td>
</tr>
</tbody>
</table>
Support of standardization efforts

• ADNI-longterm commitment to standardization of all methods
  — Open access to data generated following qc
  — Has been in operation for 10 years
  — Benefits from lots of interaction, peer review, with the scientific community in academia, industry, governmental sectors

• Alz Assn Global Biomarker Standardization Consortium
  — Analytical methods standardization--strong support for improved performance of existing and new immunoassays for CSF biomarkers, and automation
  — The Alz Assn-supported international CSF QC program provides continuing feedback on quality both short and long term
  — Support for mrm/tandem mass spectrometry for direct measurement of absolute Aβ_{1-42} concentration
  — IFCC/IRMM project to develop reference Aβ_{1-42} peptide material and using mrm/msms and large pools of CSF with accurately measured Aβ_{1-42}
  — Need same for t-tau

• CAMD(Coalition Against Major Diseases) has made a substantial commitment to support use of HV and CSF AD biomarkers in treatment trials
  — Hippocampal volume
  — CSF AD biomarkers
Clinical performance of AlzBio3 immunoassay compared to a validated mass spectrometry

**Analytical comparison**  
Clinical utility comparison

**ROC analyses**  
Clinical performance using 41 AD*, 41 cog normal controls for the *candidate reference mass spectrometry method*:

- Sensitivity: 92.7%
- Specificity: 85.4%
- PPV: 86.4%
- NPV: 92.1%
- Test accuracy: 89%
- AUC: 0.94**

Clinical performance using the same 41 AD and 41 controls for the *AlzBio3 Immunoassay: 2009 AoN*

- Sensitivity: 100% (96.4%)
- Specificity: 78% (76.9%)
- PPV: 82% (82%)
- NPV: 100% (95.2%)
- Test accuracy: 89% (87%)
- AUC: 0.90 (0.91)

*autopsy-diagnosis; **AUC’s, p=0.2

Korecka, et al, JAD, 2014
Proposed uses of CSF biomarker in Alzheimer’s disease research

I. Clinical diagnosis and management

- Improve diagnostic accuracy, especially in early stages of AD
- Combined with clinical exam results and further testing (blood tests, CT/MRI, PET)

II. Enrichment of AD cases in MCI treatment trials

- ~40-70% of MCI patients have prodromal AD
- CSF AD biomarkers can enrich the MCI treatment cohort with subjects at high risk for progression to AD; widely used RUO immunoassays have demonstrated their utility for this limited, but important, intended use.

III. Markers of biochemical drug effect

Assessment of specific biochemical effect of a drug:
- eg, CSF Aβ1-42 in trials of Aβ antibodies,
- CSF p-tau in trials of tau kinase inhibitors

Assessment of the effect of a drug on neurodegeneration:
- eg, CSF t-tau in trials of Aβ vaccine