AD CSF Biomarkers Team

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CAMD AD CSF Biomarker Team Members

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Biomarkable—Hugo Vanderstichele
Boerhinger Ingelheim– Mark Gordon
Cerora– Adam Simon
Covance—Bob Martone
Critical Path Institute—Diane Stephenson, Klaus Romero, Hemaka Rajapakse, Robin Shane
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Eli Lilly & Company—Peng Yu, Bob Dean, Janice Hitchcock, Brian Willis
FDA—Marc Walton, Jim Kaiser
Innogenetics—John Lawson
Janssen—Gerald Novak, Mahesh Samtani
Merck—Omar Laterza
Meso Scale Discovery—Bob Umek
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University of Göteborg, Henrik Zetterberg, Kaj Blennow
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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)

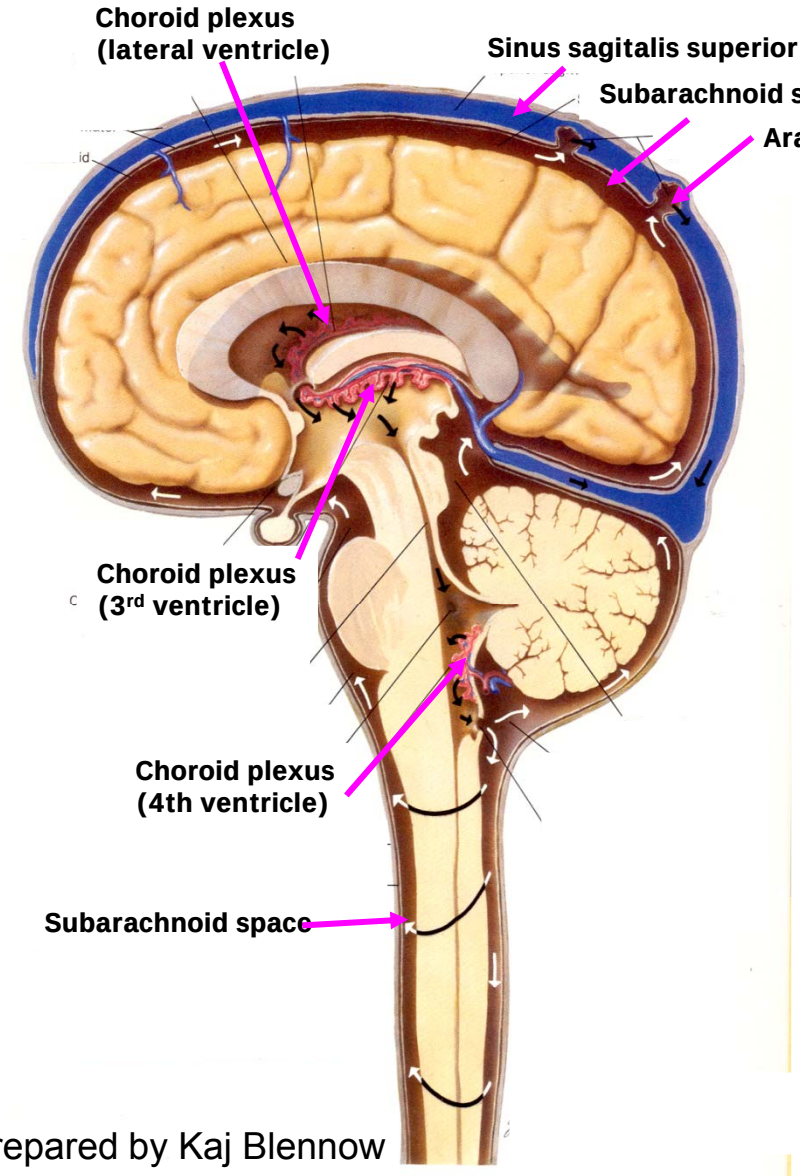
The purpose is to exclude subjects that have a low probability of showing decline in cognition and function over two years and as such, increase the probability of identifying potential drug effects with therapeutic interventions in patients with amnestic MCI

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)



Slide prepared by Kaj Blennow

Assessments of complications after lp

No. of cases	395
Post LP headache	2.1%
Meningitis/hematoma	0

Blennow K, et al 1993

No. of cases	241
Post LP headache %	4.1
Meningitis / hematoma	0

Andreasen N et al, 2001

No. of cases	342(428 LP)
Post LP headache	0.9 %
Meningitis / hematoma	0

Peskind ER, et al, 2005

No. of cases	1089
Post LP headache %	2.6
Meningitis / hematoma	0

Zetterberg H, et al, 2010

CSF biomarkers for AD

Background

- ↓$A\beta_{1\text{-}42}$, ↑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**
- ↓$A\beta_{1\text{-}42}$, ↑t-tau & p-tau_{181} in CSF differentiate AD from HC and from other neurodegenerative diseases using RUO precision based immunoassays

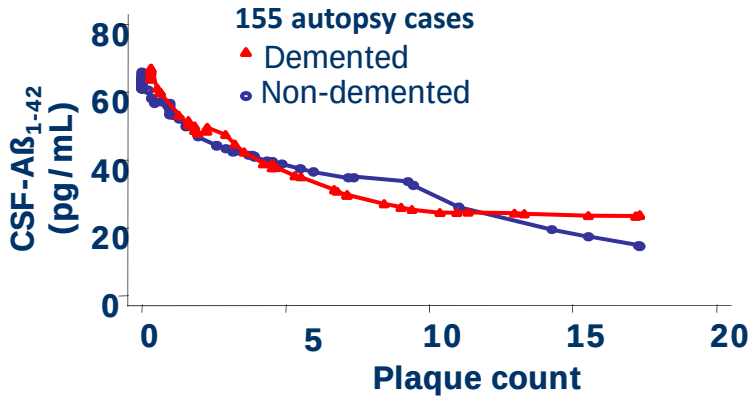
CSF biomarkers for AD

Background cont'd

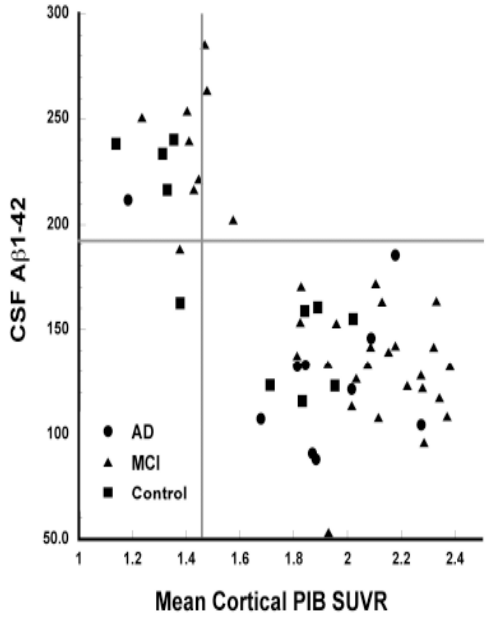
- ↓$A\beta_{1\text{-}42}$, ↑t-tau & p-tau_{181} in CSF predict progression: in cog decline and to AD dementia in MCI patients
  - Multicenter studies demonstrate this
    - ADNI I and ADNI GO & II
    - Descripa
    - Swedish brain power
  - Major single center studies
    - Wash Univ
    - Hansson, Buchave
    - Engelborghs

CSF $A\beta_{1\text{-}42}$ is Strongly Correlated to Plaque Counts in autopsied brains and Plaque Burden by PiB PET testing

CSF $A\beta_{1\text{-}42}$ vs plaque counts (neocortex and hippocampus)



CSF $A\beta_{1\text{-}42}$ vs mean cortical PiB SUVR

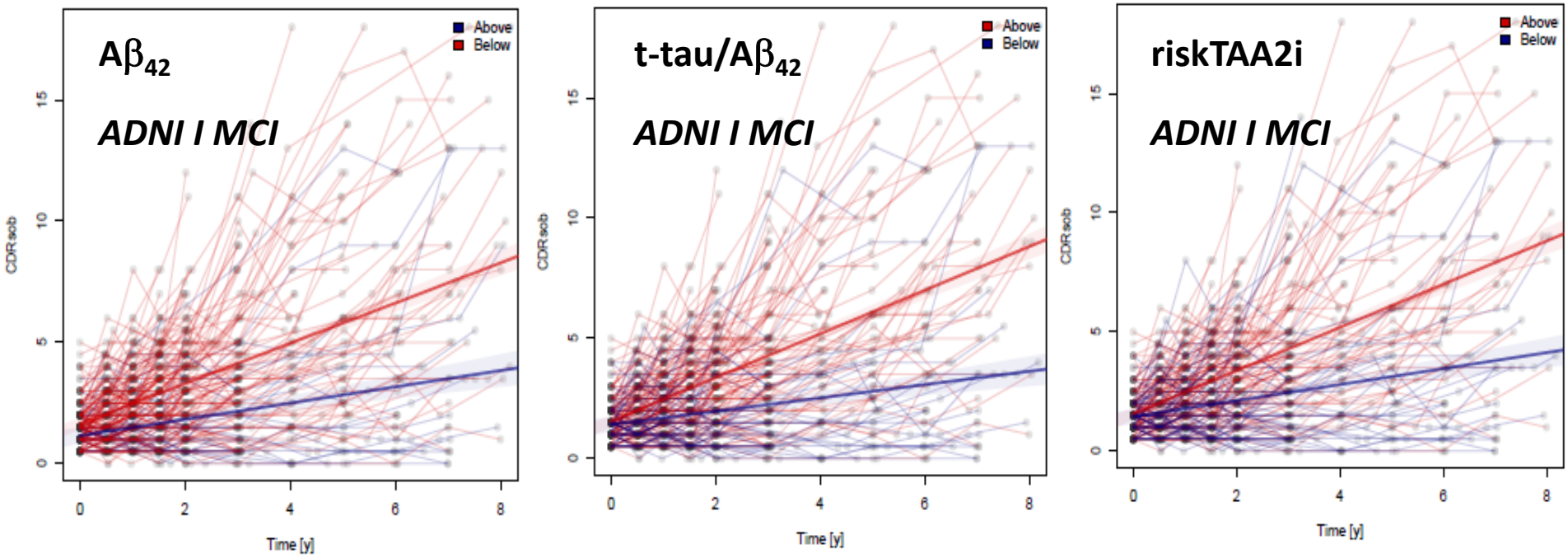


Pittsburgh compound-B labeled positron emission tomography; SUVR = standard uptake value ratio

Strozyk D, et al. *Neurology* 2003;60:652-656;

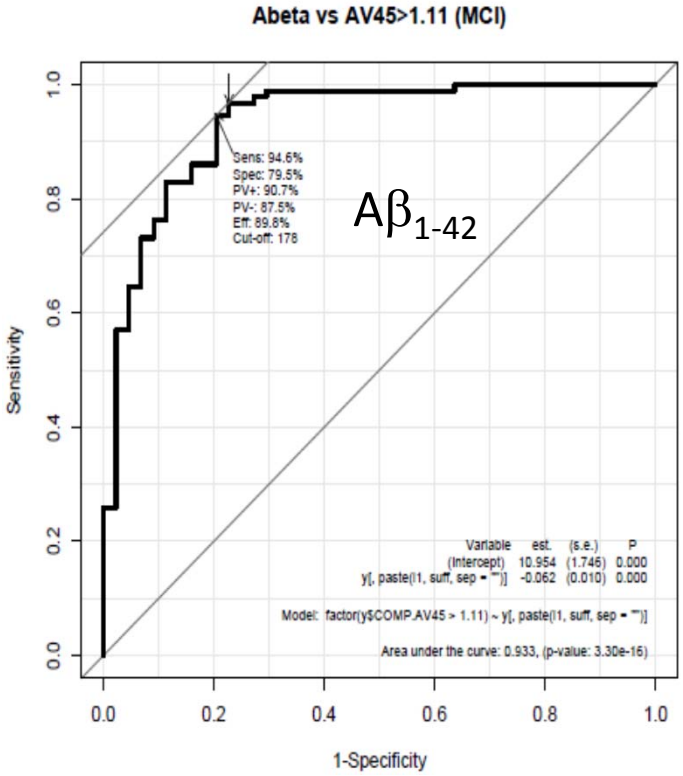
Jagust W, et al, *Neurology* 2009; 73:1193-1199

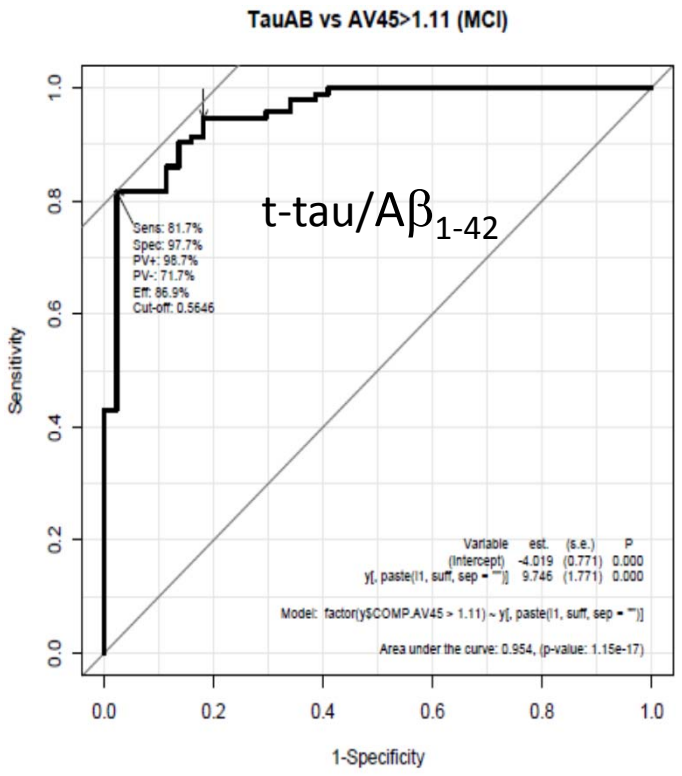
Rates of decline for CDRsob: Pathologic vs non-Pathologic biomarker CSF biomarkers (ADNI I dataset)



Cutpoint	192 pg/mL	0.39	0.5
Biomarker	$A\beta_{42}$	t-tau/$A\beta_{42}$	riskTAA2i
CSF pathologic	**+1.10/yr**	**+1.14/yr**	**+1.14/yr**
CSF non-pathologic	**+0.26/yr**	**+0.31/yr**	**+0.45/yr**

CSF $A\beta_{1-42}$ alone has equivalent concordance to florbetapir t-tau/$A\beta_{1-42}$ for estimation of plaque burden in ADNI GO & II MCI pati





MCI N=138	concord	discord	FBP-/Aβ-	FBP+/Aβ+	FBP-/Aβ+	FBP+/Aβ-	*concordance*	*AUC*	*Test accuracy*
$A\beta_{1-42}$	124	14	33	91	11	3	0.898	0.933	90%
t-tau/$A\beta_{1-42}$	123	15	37	86	7	8	0.891	0.954	87%

Avagacestat in Predementia Alzheimer's Disease: Methods and Baseline Results

Bristol-Myers Squibb

Vlad Coric,[1] Christopher van Dyck,[2] John Seibyl,[3] Susan Colby,[1] James Hazel,[1] Alan Lipschitz,[4] Stephen Kaplita,[1] Howard H. Feldman,[5] Tamara Bratt,[1] Stephen Salloway,[6] Robert M. Berman[1]

[1]Bristol-Myers Squibb R&D, Wallingford, CT, USA; [2]Yale University School of Medicine, New Haven, CT, USA; [3]ADD Molecular Neuroimaging, New Haven, CT, USA; [4]Bristol-Myers Squibb R&D, Princeton, NJ, USA; [5]University of British Columbia, Vancouver, British Columbia, Canada; [6]Brown Medical School, Butler Hospital, Providence, RI, USA

- 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 a 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 Nordberg, Florence Pasquier, 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

Lancet Neurol 2014; 13: 614–29

- CSF $A\beta_{1-42}$, 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

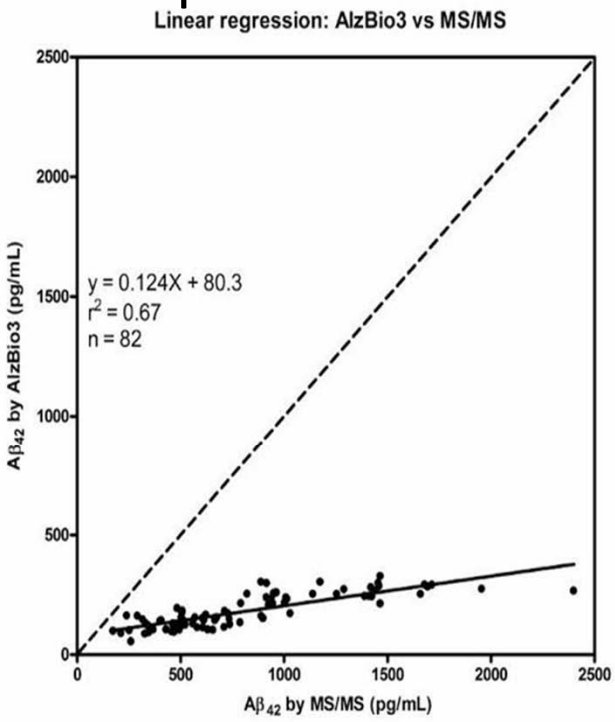
CSF $A\beta_{1-42}$, t-tau & p-tau	**Hippocampal volume, FDG PET**
Pathophysiological marker	Topographical or downstream marker
Reflects in-vivo pathology	Poor disease specificity
Is present at all stages of the disease	Indicates clinical severity(staging mar
Observable even in the asymptomatic state	Might not be present in earliest stage
Might not be correlated with severity	Quantifies time to disease milestones
Indicated for inclusion in protocols of clinical trials	Indicated for disease progression

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 $A\beta_{1\text{-}42}$ concentration
  - IFCC/IRMM project to develop reference $A\beta_{1\text{-}42}$ peptide material and using mrm/msms and large pools of CSF with accurately measured $A\beta_{1\text{-}42}$
  - 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



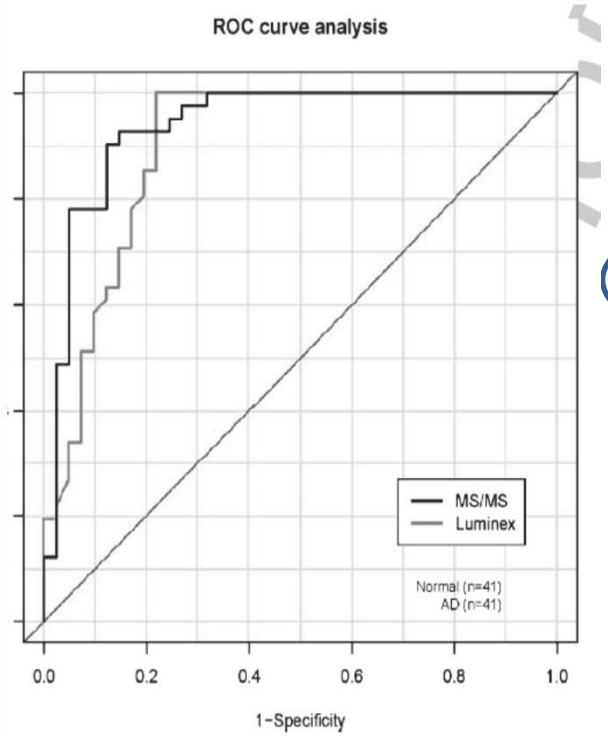


Fig. 4. Comparison of ROC curves for 2D-UPLC-MS-MS and AlzBio3 Luminex. The ROC AUC value for 2D-UPLC-MS-MS was 0.938, and for AlzBio3 Luminex immunoassay the AUC value was 0.900.

Korecka, et al, JAD, 2014

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

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, PE

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 g

for progression to AD; widely used RUO immunoassays have demonstrated th
for this limited, but important, intended use.

III. Markers of biochemical drug effect

Assessment of specific biochemical effect of a drug:
eg, CSF $A\beta_{1-42}$ 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