EVALUATION OF AD BIOMARKERS IN ABSENCE OF A GOLD STANDARD

Xiao-Hua Andrew Zhou; Zheyu Wang; Bud Kukull

National Alzheimer's Coordinating Center

October 6, 2012

NACC
www.alz.washington.edu

Outlines

- Background
- Mixture model approach and previous study
- Cautions on previous study
- Another analysis with data from Penn ADC
- Discussion and work in progress
- Acknowledgement

NACC
www.alz.washington.edu

Background

- The pathophysiological process of Alzheimer's disease (AD) is thought to begin many years before the diagnosis of AD dementia
- Various biomarkers are proposed for early AD diagnosis. -
  - CSF/blood amyloid beta and tau protein
  - structural MRI
  - PET-amyloid imaging
- Gold standard is hard to obtain
  - long "preclinical" phase of AD
  - limited data on autopsy
  - errors in clinical AD diagnosis, comorbidity

NACC
www.alz.washington.edu

Previous Study

- Geert De Meyer et al (2010) use a mixture model approach to assess the ability of several biomarkers in the early detection of AD

  - the analysis did not use clinical AD diagnosis

  - unobserved status related to AD pathology is considered as a latent variable

  - normality or multivariate normality assumption

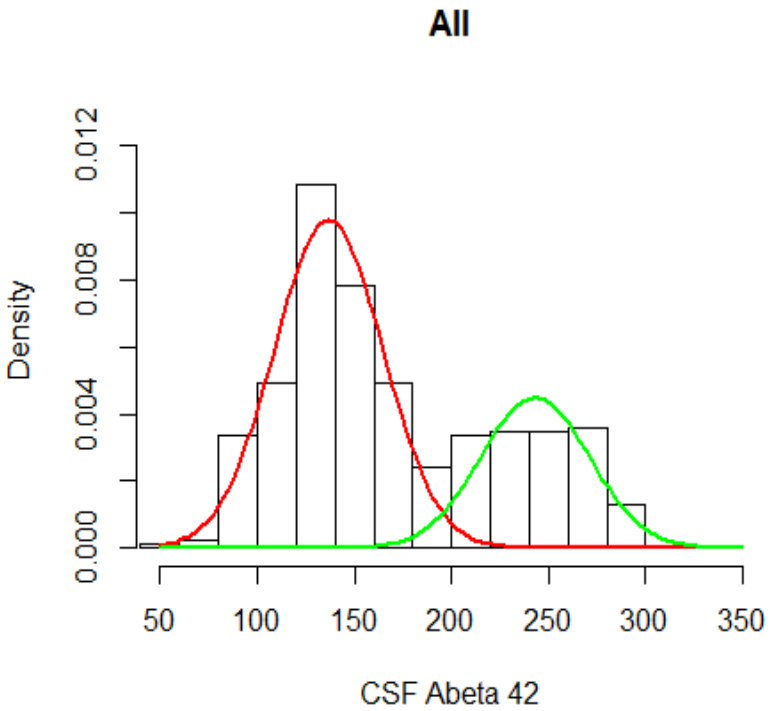
  - Aβ 1-42, total tau, P-tau$_{181P}$

- P(Biomarkers) = P(D=0) P(Biomarkers | D = 0)
  + P(D=1) P(Biomarkers | D = 1)

NACC
www.alz.washington.edu

Reproduced Results

- Data: Alzheimer's Disease Neuroimaging Initiative (ADNI)
- Results for CSF Aβ 1-42
- Two groups fitted by mixture model with normality assumption.
  - red line: group with AD feature
  - green line: group without AD feature

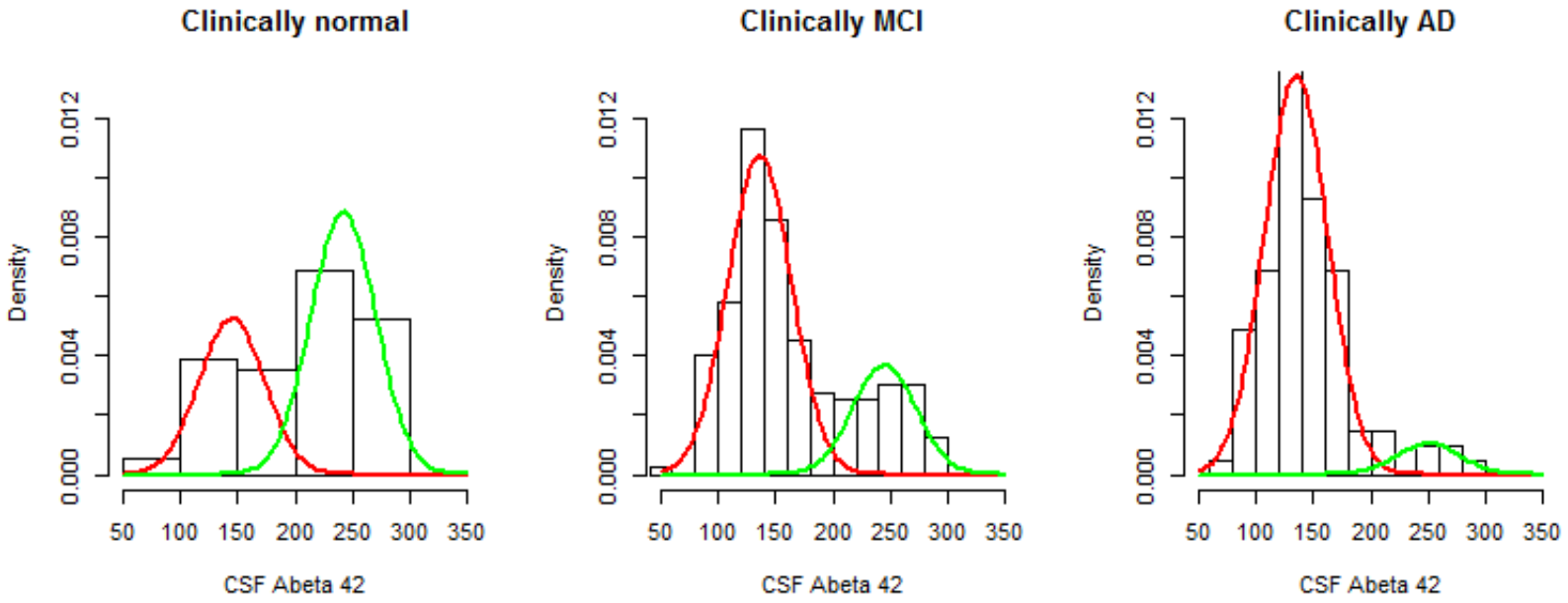


		Proportion	Mean	Sigma
All	Group with AD feature	0.68	136.5	27.5
	Group without AD feature	0.32	242.4	28.6

NACC
www.alz.washington.edu

Reproduced Results

- Results in subgroups based on clinical diagnosis



NACC
www.alz.washington.edu

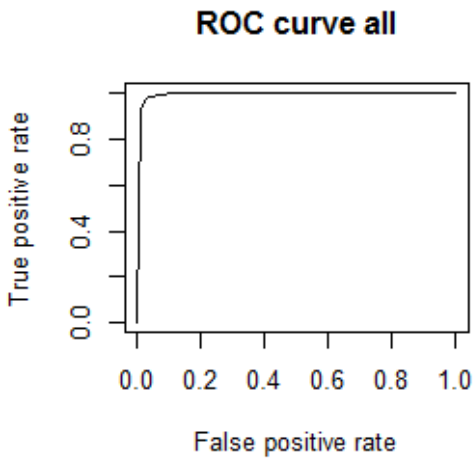
Reproduced Results

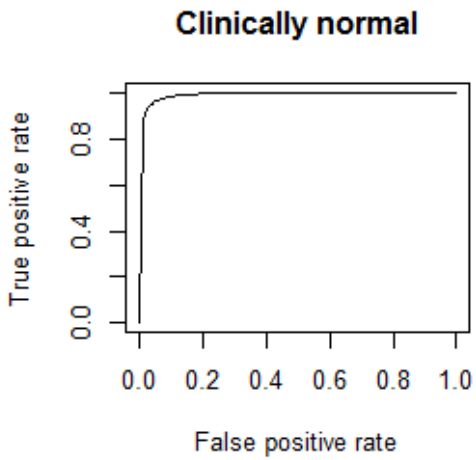
- Results in subgroups based on clinical diagnosis

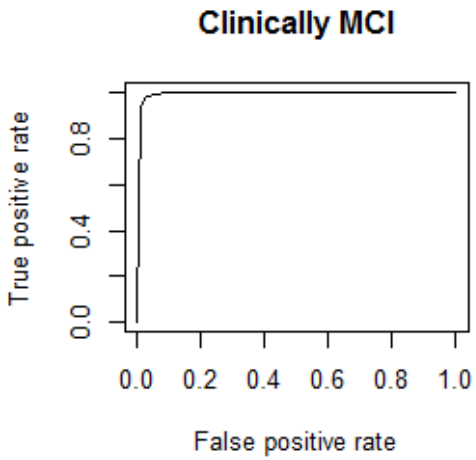
		Proportion	Mean	Sigma
All	Group with AD feature	0.68	136.5	27.5
	Group without AD feature	0.32	242.4	28.6
Normal	Group with AD feature	0.38	145.8	29.3
	Group without AD feature	0.62	242.5	27.7
MCI	Group with AD feature	0.74	135.8	27.4
	Group without AD feature	0.26	243.9	28.2
AD	Group with AD feature	0.92	134.3	27.0
	Group without AD feature	0.08	245.9	32.0

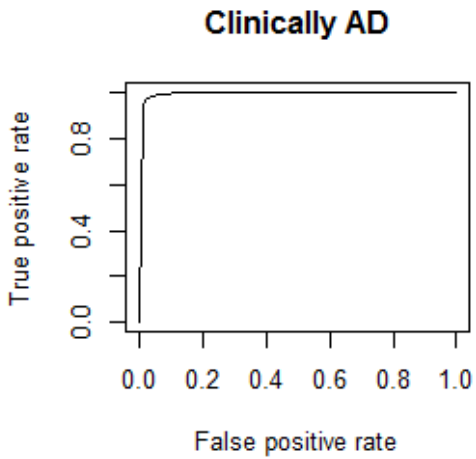
NACC
www.alz.washington.edu

ROC curves









NACC
www.alz.washington.edu

Caution

- Crucial assumption:
- 1. Biomarker values are normally distributed in each group, i.e., group with AD feature and group without AD feature

  - Normality assumption may not hold in practice

  - Log transform is used in their analysis for total tau, P-tau_{181P}
- 2. Disease prevalence and biomarker performance is homogeneous in the population

  - may depend on other covariates such as age, gender, etc.

Data

- Data from Penn's Alzheimer's disease Center
- **Inclusion Criteria**:

All data from Penn ADC that was uploaded to UDS subjects with at least one CSF biomarker measurement.

- As of May 14, 2012, there are 1058 unique subjects uploaded to UDS, of which 362 (34.2%) subjects have at least one CSF measurement.
- 6 subjects based on Elisa assay are excluded.

Assay type	Number (%)
Elisa	6 (1.7%)
Luminex	356 (98.3%)

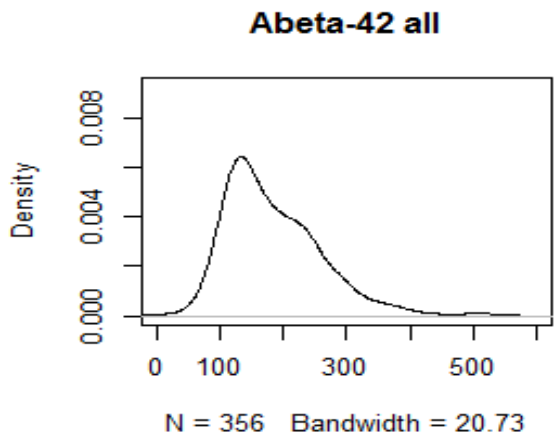
NACC
www.alz.washington.edu

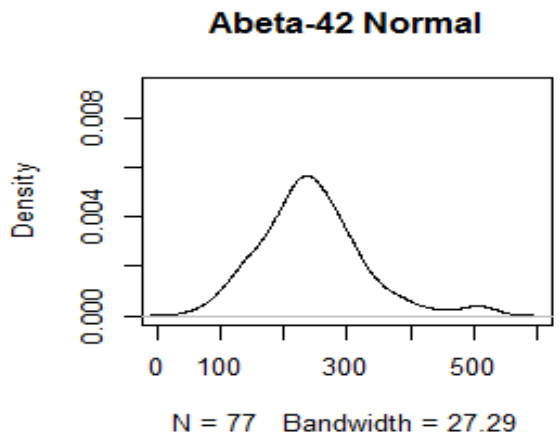
Descriptive Results

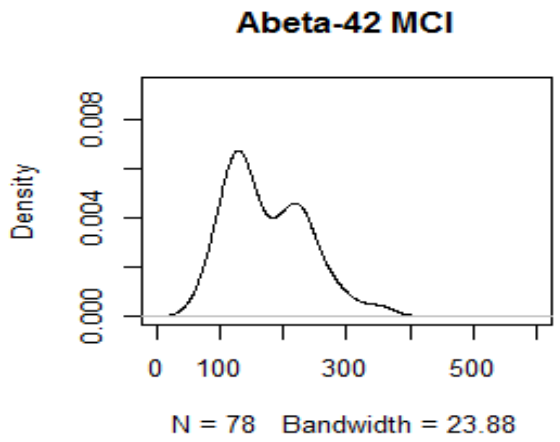
Characteristic		Mean (SD) or number (%) Visit closest to CSF sample
T-tau **P-tau** **A-beta42**		85.9 (±60.8) 34.9 (±24.7) 184.1 (±74.6)
Sex=Male		153 (43.0%)
Age (years)	at CSF sample at Assay at initial visit in UDS	72.3 (±9.1) 73.8 (±9.8) 73.1 (±9.3)
Race	White Black or African American Asian Other	293 (82.3%) 33 (9.3%) 3 (0.8%) 27 (7.6%)
Education (years)		15.0 (±7.5)
MMSE		23.85 (±7.2)
CDR-SB		3.57 (±3.65)
Clinical Diagnoses	Normal Amnestic MCI Any MCI Demented AD demented	73 (20.5%) 75 (21.1%) 85 (23.9%) 190 (53.4%) 141 (39.6%)
CDR	0 0.5 >0.5	69 (19.4%) 164 (46.1%) 123 (34.6%)

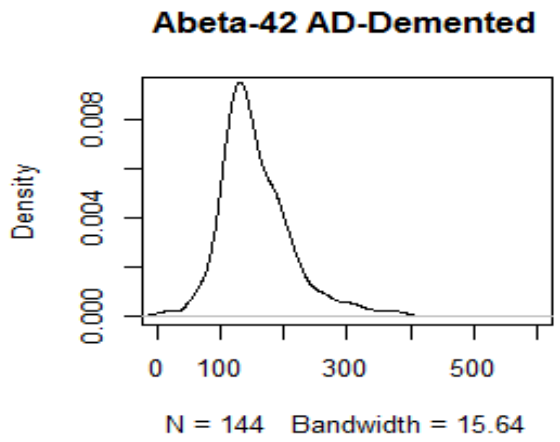
NACC
www.alz.washington.edu

Empirical Densities



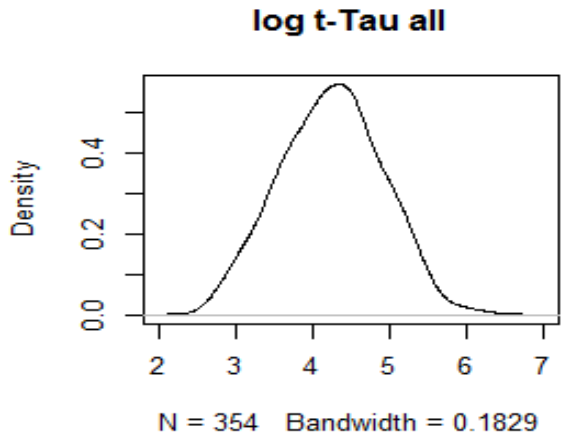


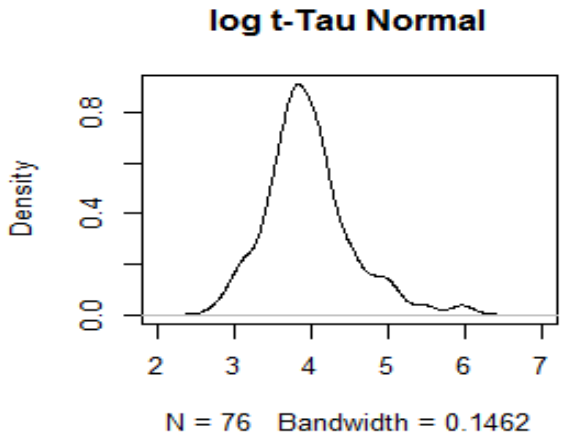


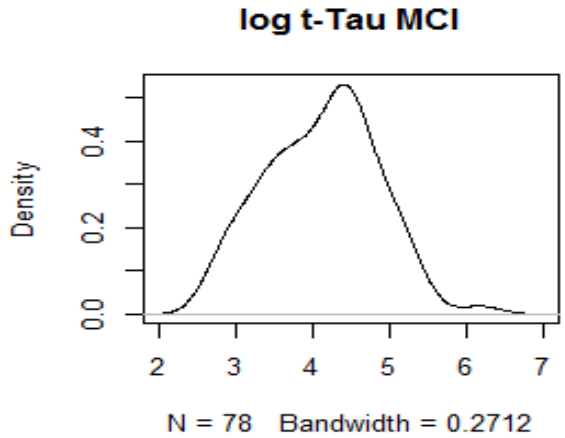


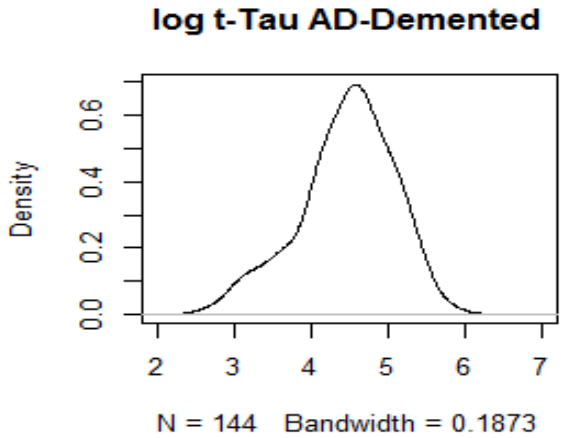
NACC
www.alz.washington.edu

Empirical Densities





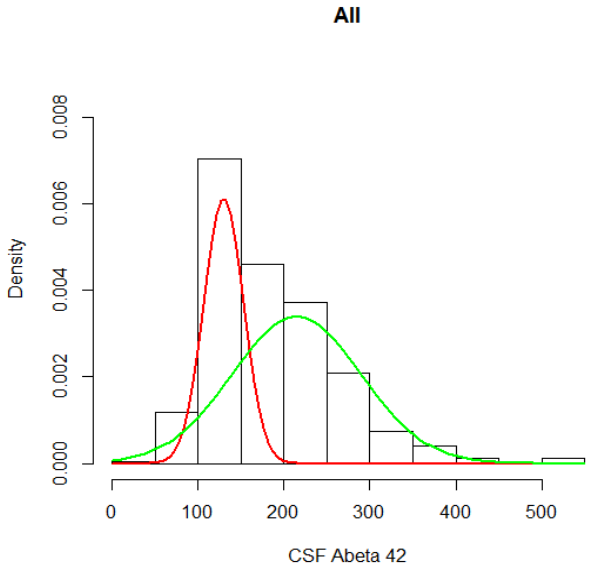


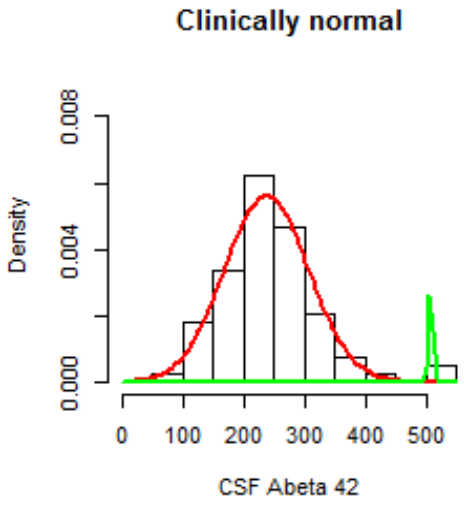


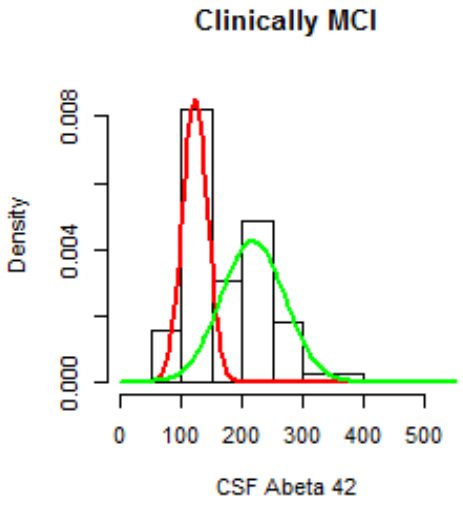
NACC
www.alz.washington.edu

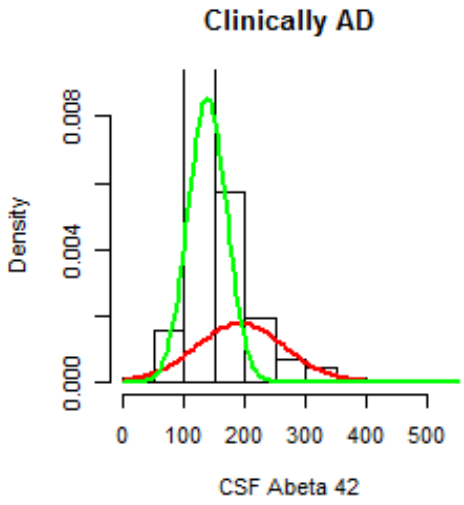
Results for Aβ 1-42

		Proportion	Mean	Sigma
All	AD feature	0.36	129.3	23.3
	Non AD	0.64	214.5	75.8
Normal	AD feature	0.97	237.8	69.4
	Non AD	0.03	507.5	3.67
MCI	AD feature	0.44	121.4	20.7
	Non AD	0.56	216.9	52.4
AD	AD feature	0.67	138.4	31.5
	Non AD	0.33	192.8	73.4

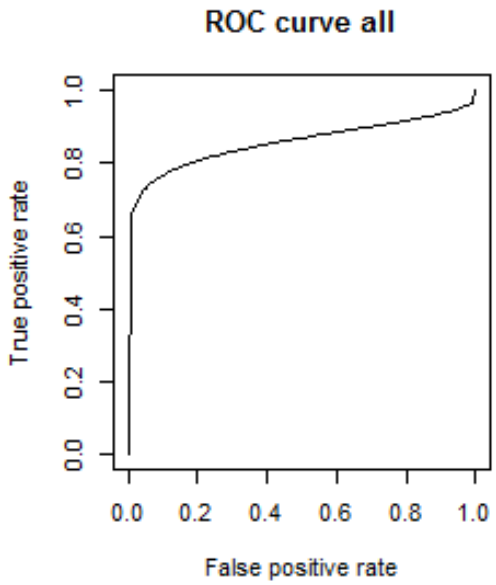


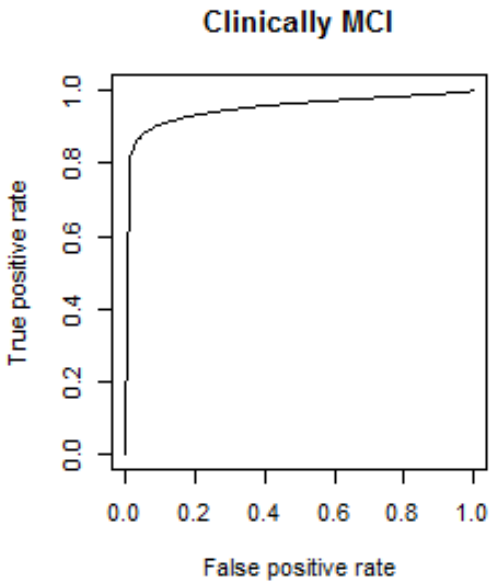


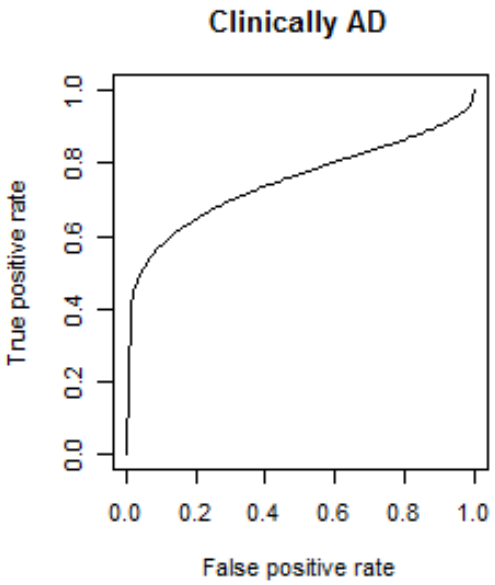




ROC curves

- 

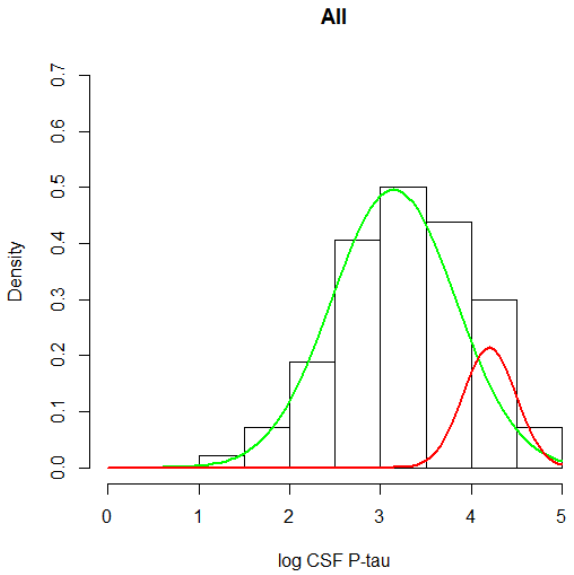


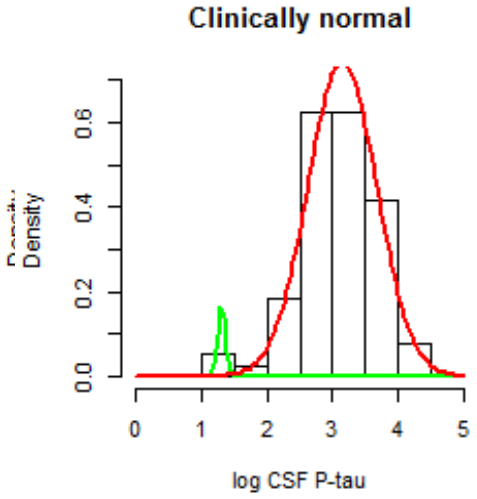


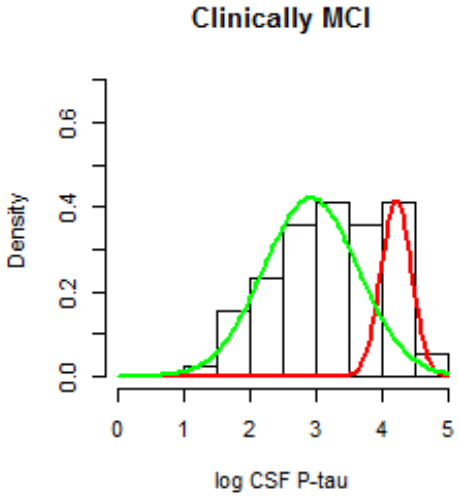
NACC
www.alz.washington.edu

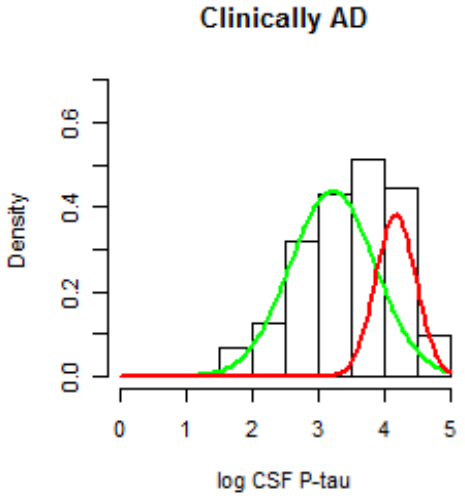
Results for P-tau$_{181P}$

		Proportion	Mean	Sigma
All	Non AD	0.84	3.14	0.67
	AD feature	0.15	4.22	0.27
Normal	Non AD	0.03	1.31	0.06
	AD feature	0.97	3.15	0.52
MCI	Non AD	0.76	2.92	0.72
	AD feature	0.24	4.21	0.23
AD	Non AD	0.71	3.23	0.64
	AD feature	0.29	4.18	0.31

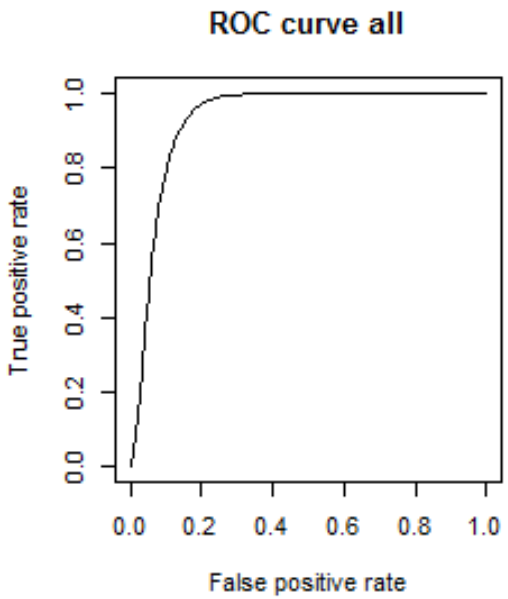


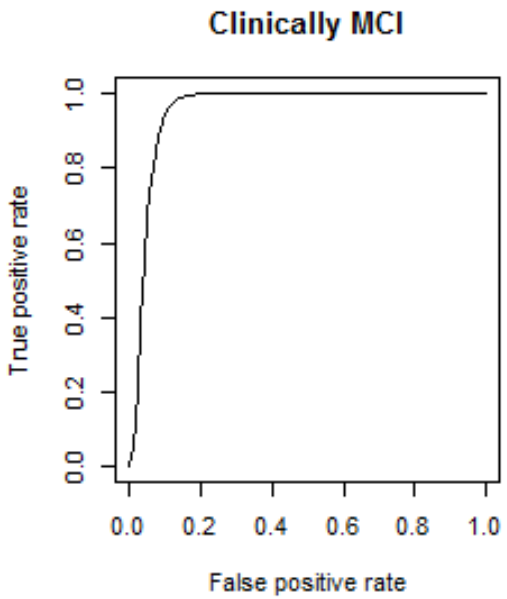


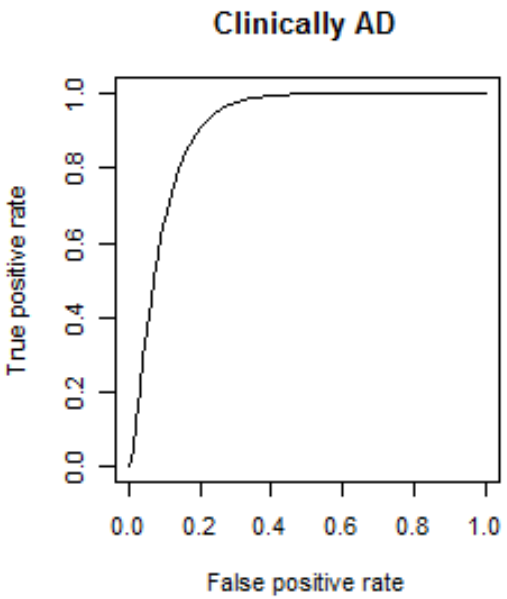




ROC curves



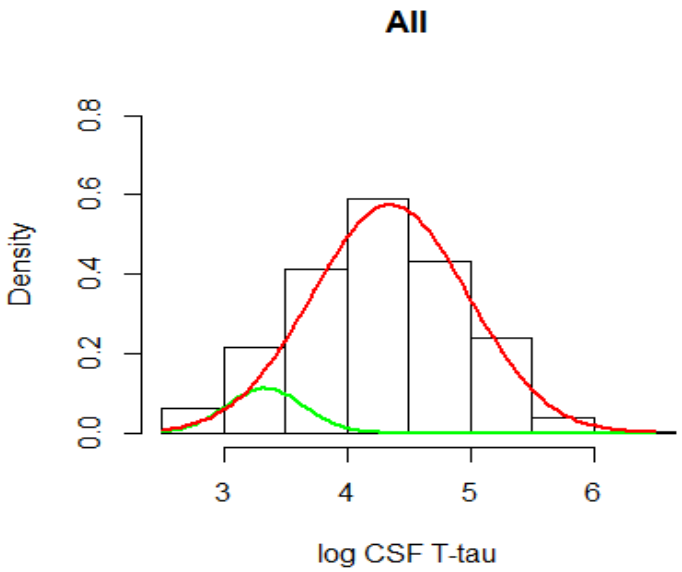


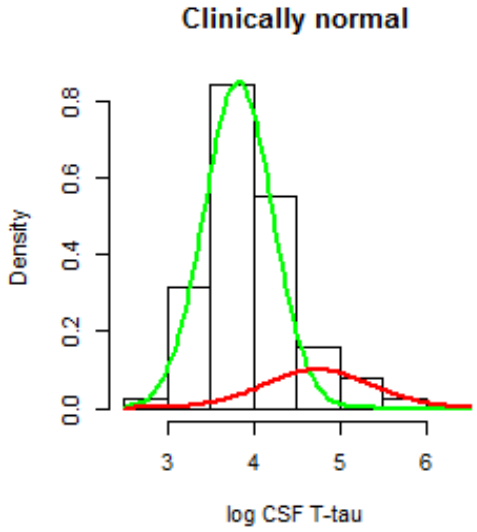


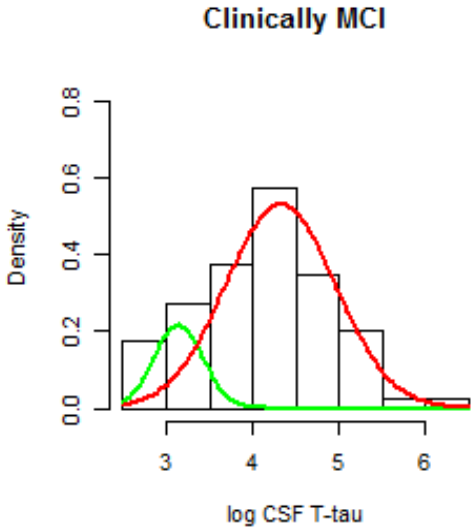
NACC
www.alz.washington.edu

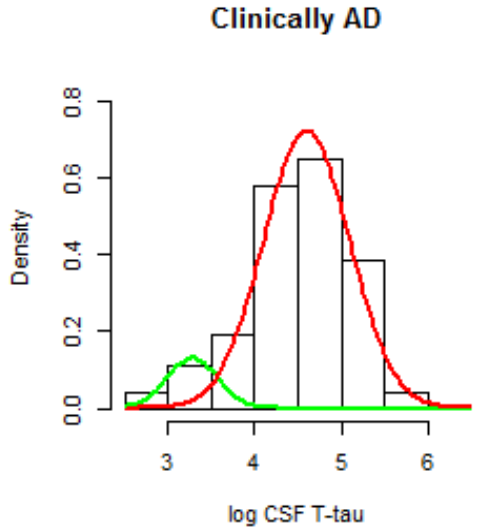
Results for total tau

		Proportion	Mean	Sigma
All	Non AD	0.13	3.37	0.34
	AD feature	0.87	4.37	0.59
Normal	Non AD	0.84	3.82	0.40
	AD feature	0.16	4.73	0.63
MCI	Non AD	0.19	3.18	0.30
	AD feature	0.81	4.34	0.60
AD	Non AD	0.11	3.31	0.31
	AD feature	0.89	4.60	0.47

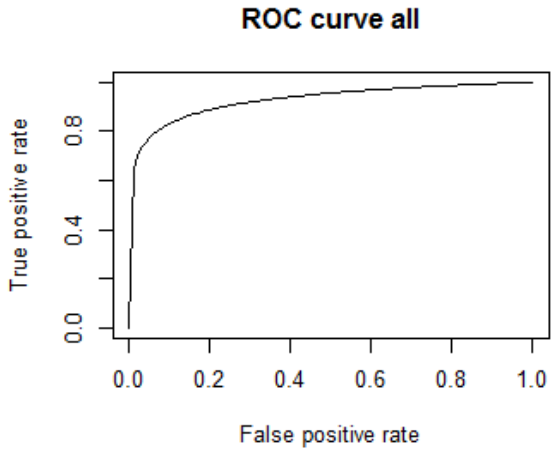


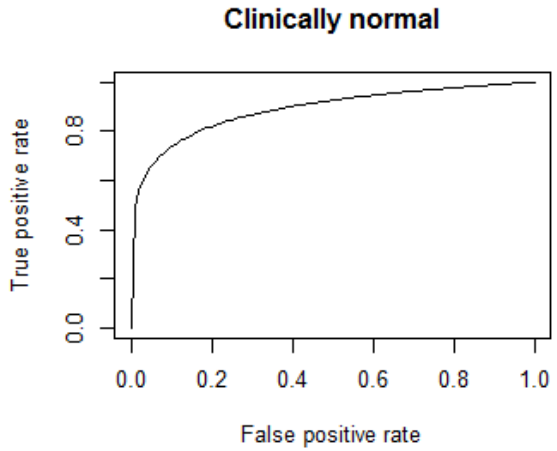


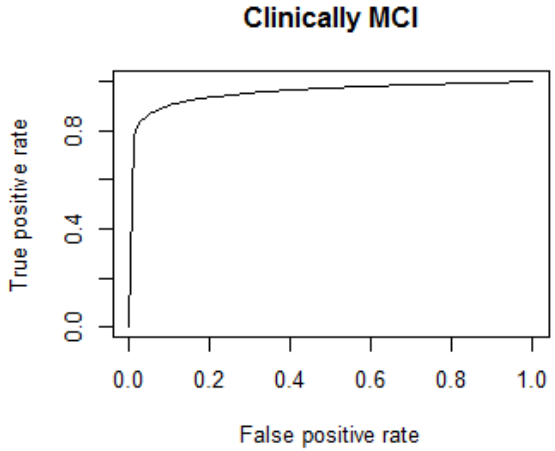


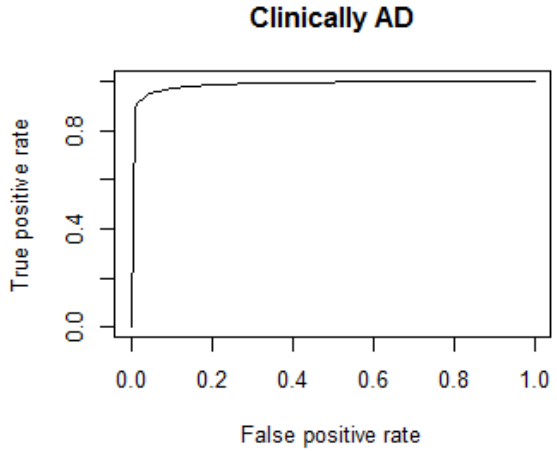


ROC curves









NACC
www.alz.washington.edu

Discussion

- In groups with clinical diagnosis of MCI or AD, group with AD feature occupied a bigger proportion comparing to group that is clinically normal.
- Changes in p-tau occur later in disease progress comparing to Aβ and t-tau (indicated by smaller proportion of subjects with AD feature), yet t-tau seems to be even earlier than Aβ based on the analysis results.
- Results about t-tau are the most similar to results of De Meyer, while results about Aβ and P-tau suggest some discrepancy.

NACC
www.alz.washington.edu

Discussion

- ADNI data has more strict inclusion and exclusion criterion, less outliners and less affected by comorbidity and other complications.
- Data from Penn's ADC may be closer to most data from practice
- Are the results reflect the data well? Do the assumptions hold in these data?

NACC
www.alz.washington.edu

Work in progress

- Allow transformation model on biomarker values to relax the normal or multivariate normal assumption
  - Box-cox transformation
  - non-parametric transformation

- Allow prevalence and biomarker values depends on patients characteristics

NACC
www.alz.washington.edu

Acknowledgments

- Penn’s Alzheimer’s Disease Center
- NACC Intramural Research and Data groups
- NIA

- No disclosures

NACC
www.alz.washington.edu

NACC is funded by the National Institute on Aging (UO1 AG016976) and located in the Department of Epidemiology at the University of Washington School of Public Health, Walter A. Kukull, PhD, Director.

National Institute on Aging

UNIVERSITY of WASHINGTON

NACC
www.alz.washington.edu