Biostatistics Core Report

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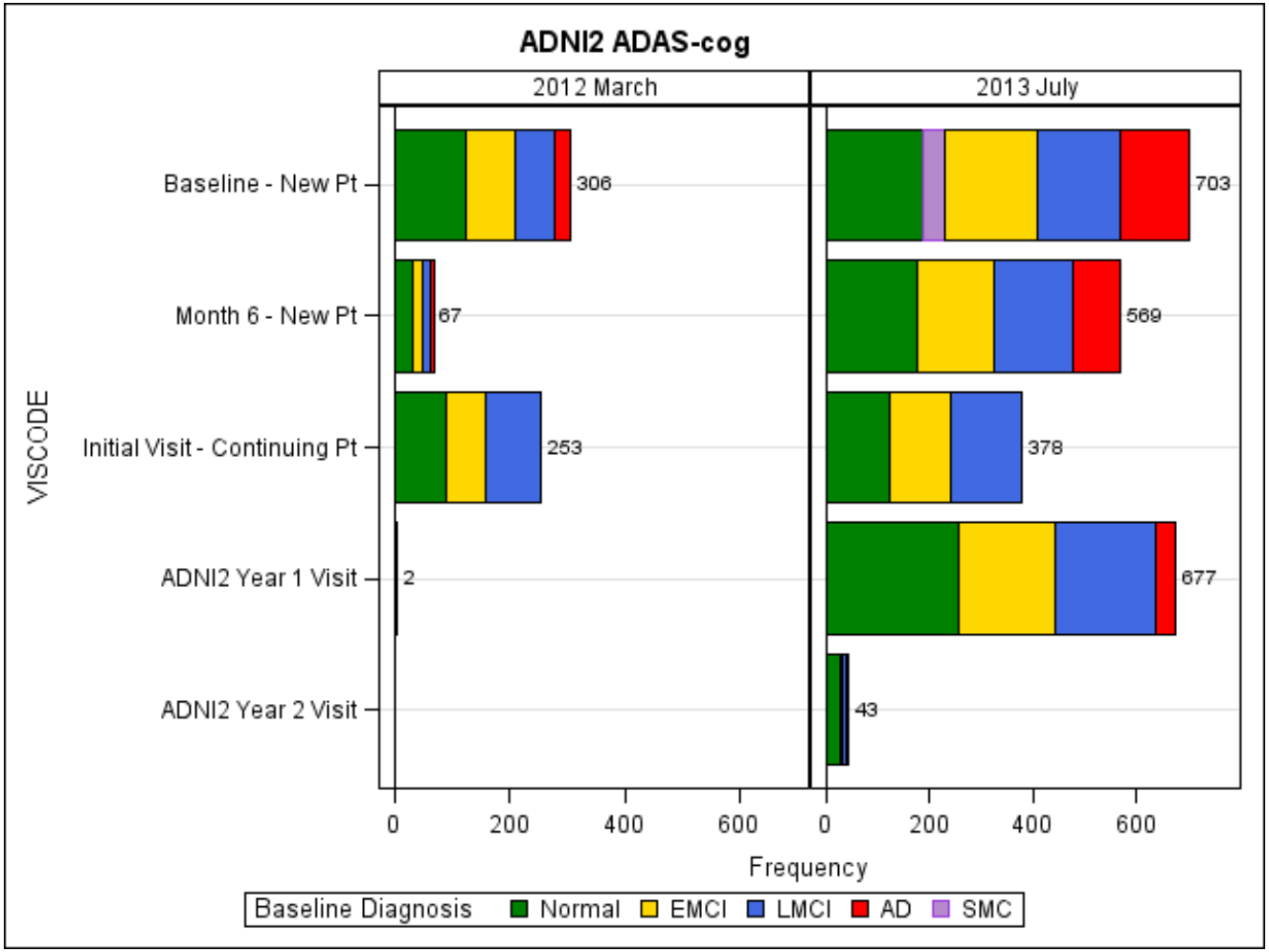
WW ADNI Meeting
Boston, July 2013

Outline: Biostatistics Core updates

- New data from ADNI-2: eMCI, amyloid imaging, new functional measures.
- Longer follow-up from ADNI-1, allowing more sophisticated assessment of trajectories.
- Development and application of statistical methodology for more insight.
- Upcoming: web conference on statistical analysis of ADNI data, August 1.

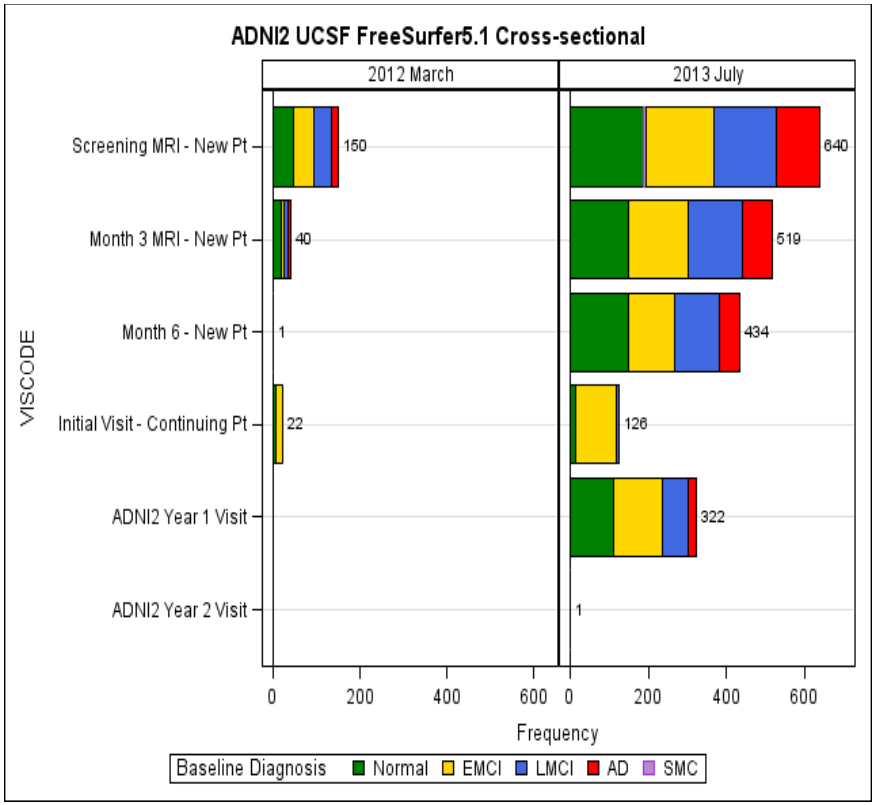
ADNI-2 progress since 2012: big increase in numbers of participants and of follow-up on new and continuing pts.

(Note: green=NC, yellow=eMCI, blue=MCI, red=AD, pink=SMC)

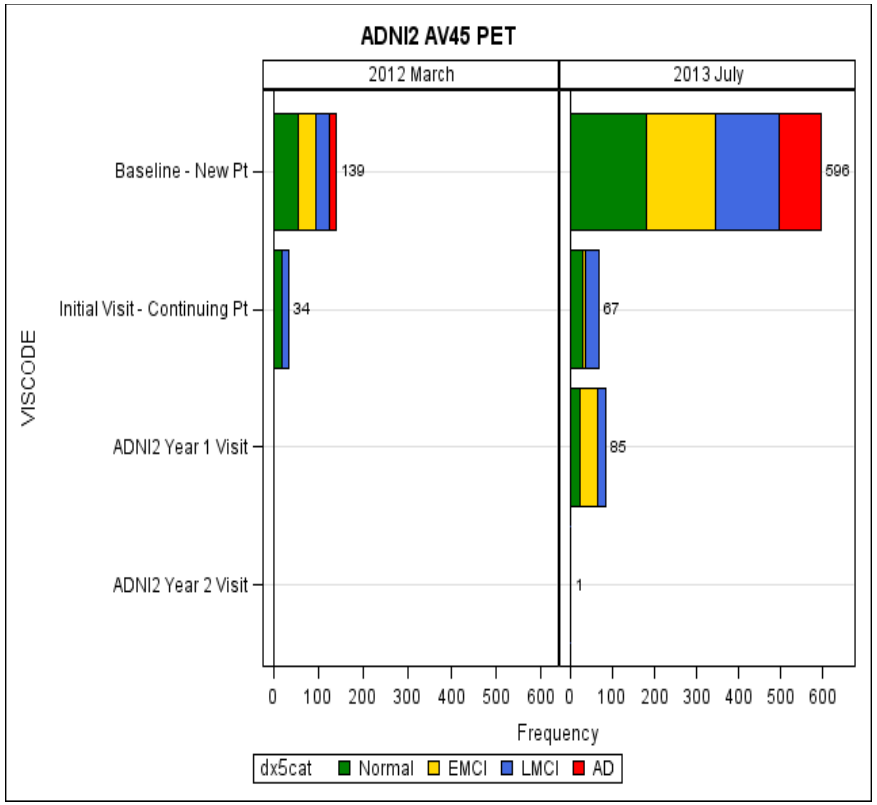


Lots more images processed and summaries posted.

Left: Freesurfer volumetrics, (UCSF)



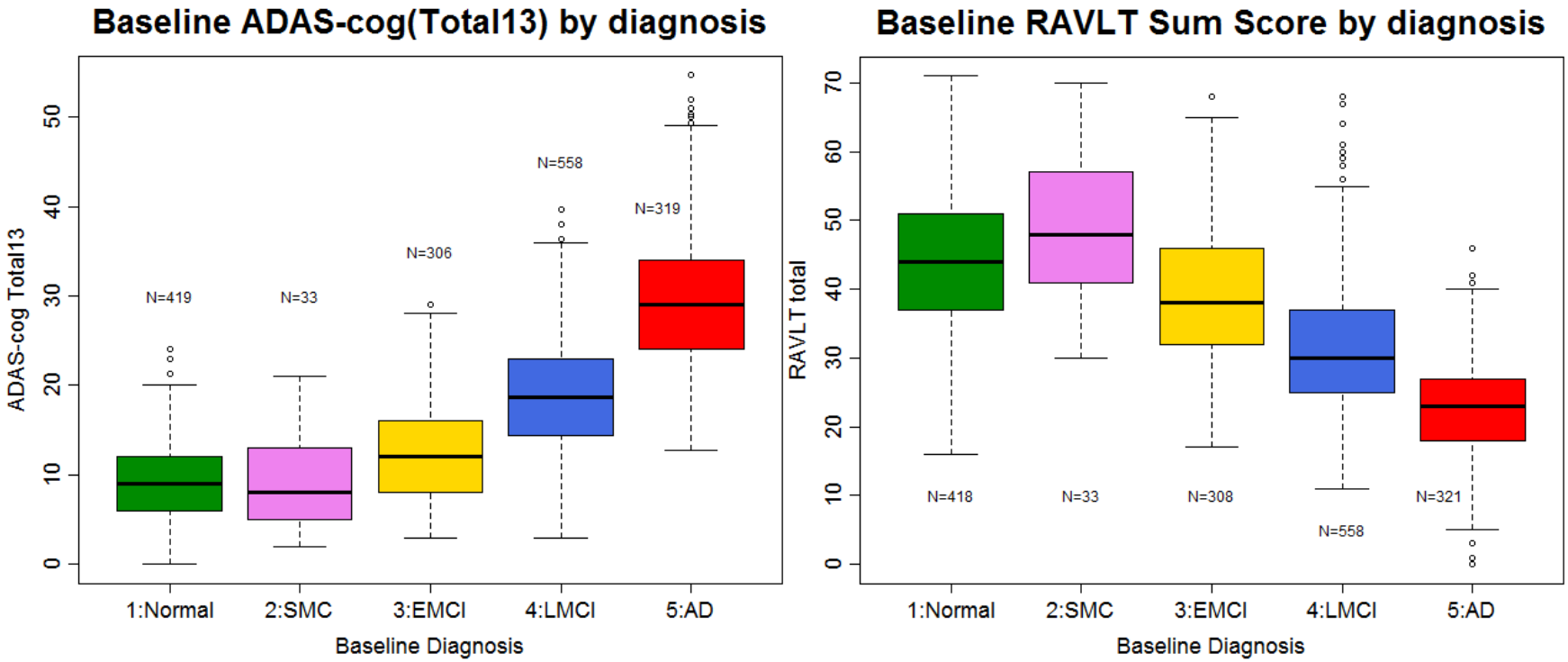
Right: AV45 summary (UC Berkeley)



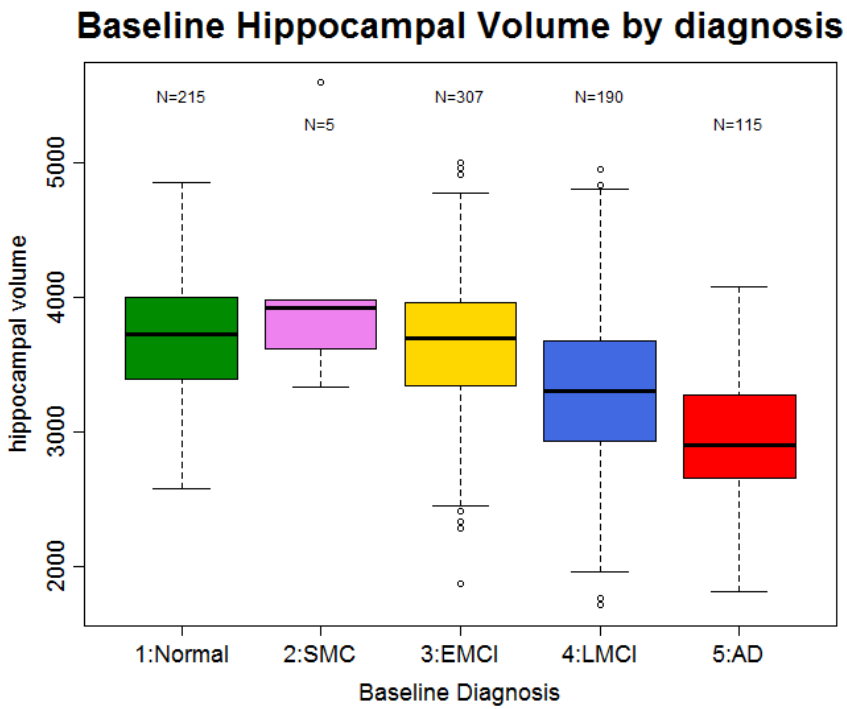
Where do new eMCI and memory complaint groups fit into baseline profile?

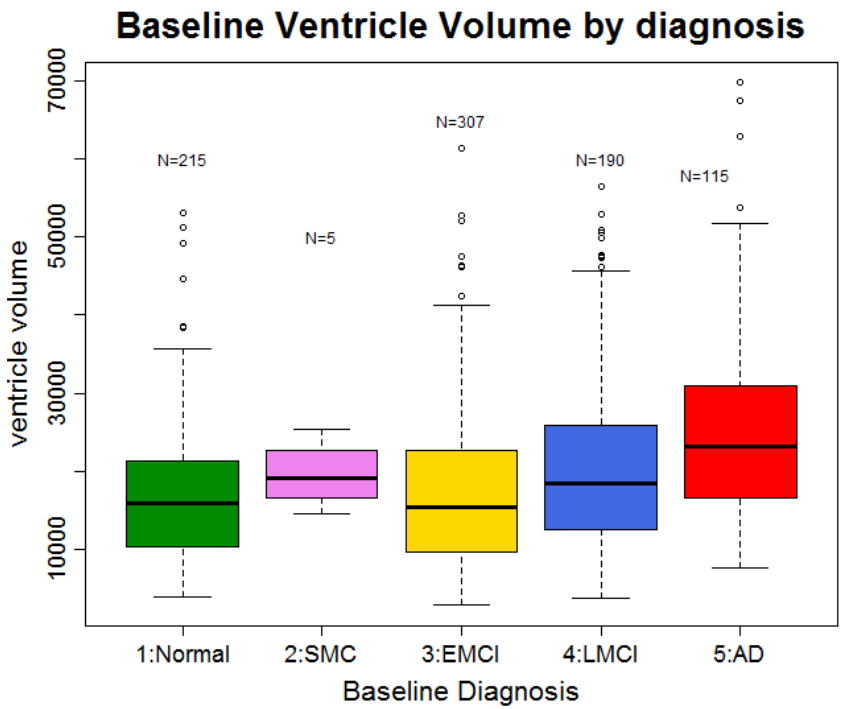
Clinically, about where we hoped:

eMCI between NC and MCI, SMC closer to NC.



Volumetrics: Hippocampal and ventricular volumes of SMC and eMCI are more like the NC (Freesurfer data).

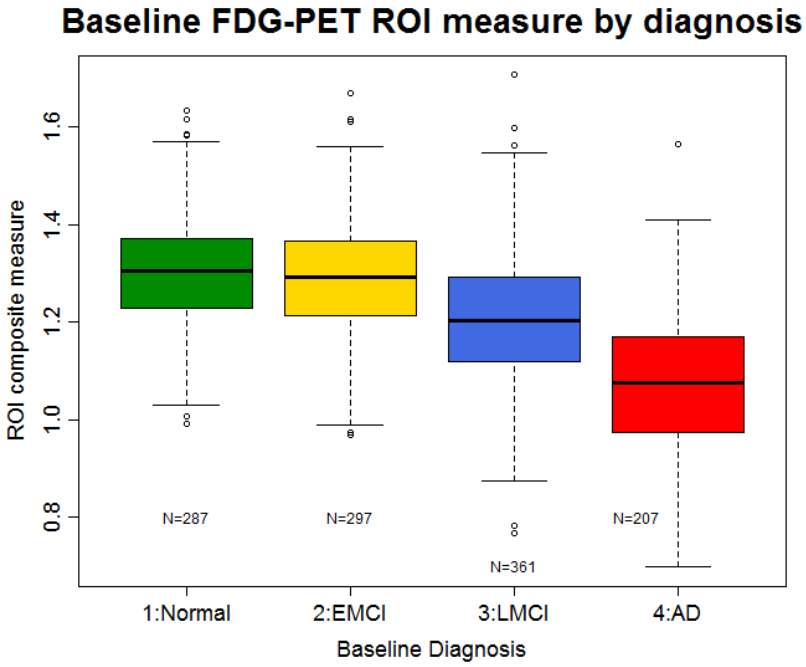


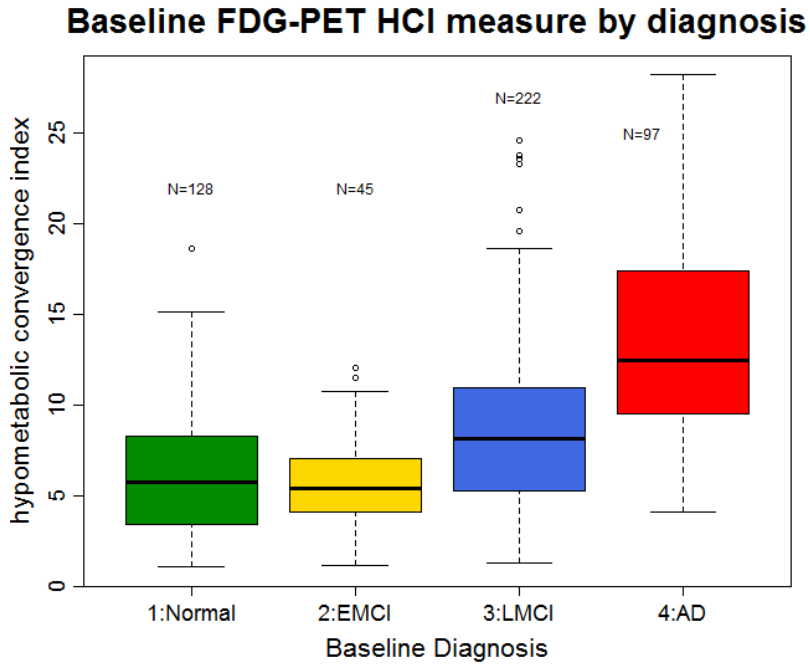


FDG-PET: eMCI are close to NC (too few SMC to show).

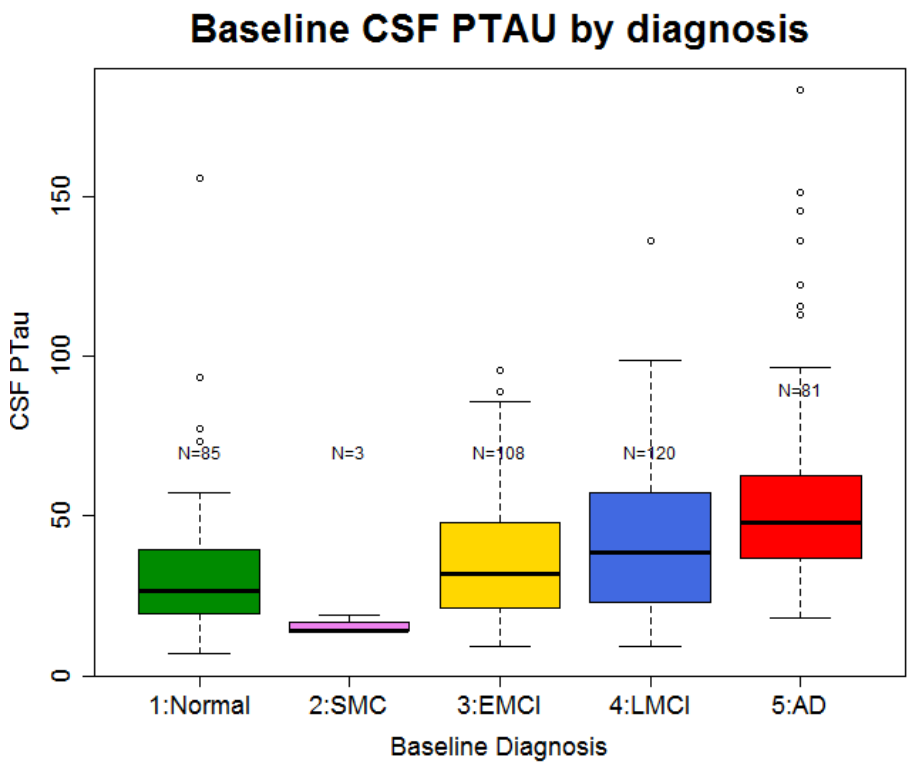
Left: Composite ROI, (UC Berkeley)

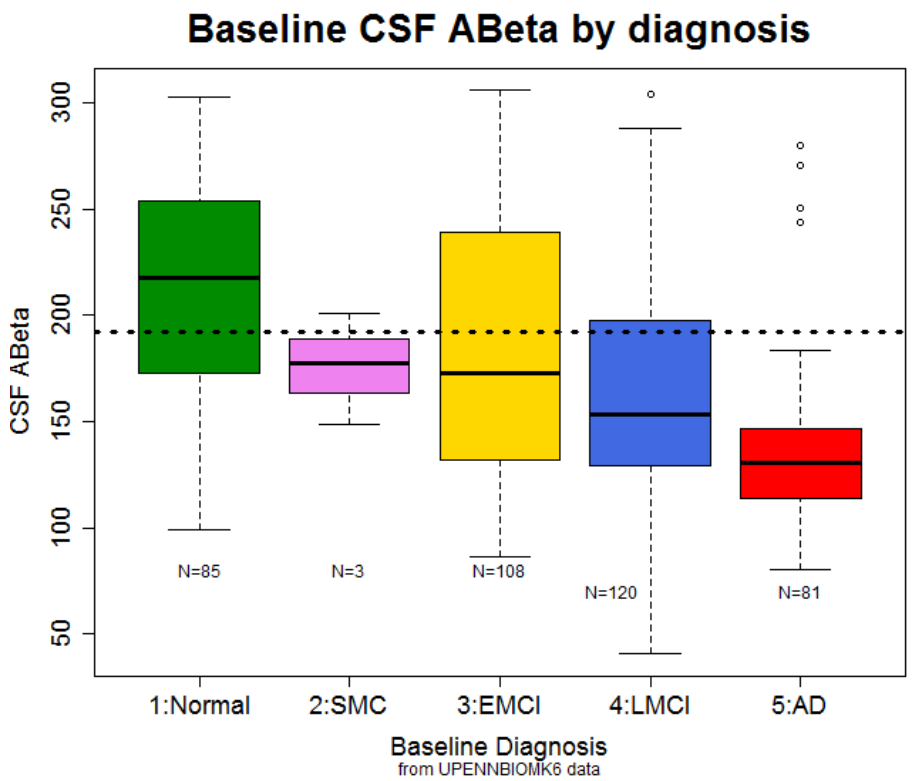
Right: hypometabolic convergence index (Banner)



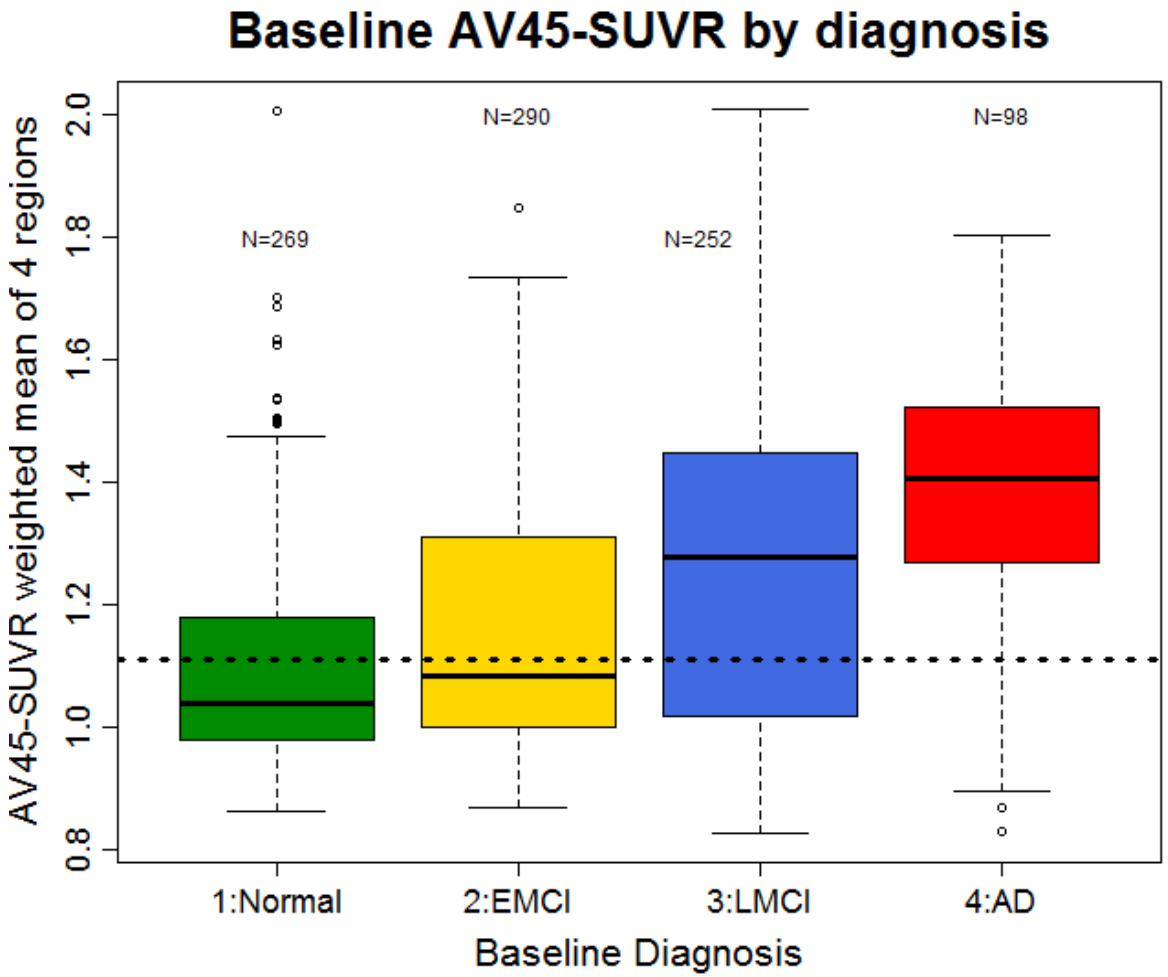


CSF measures: eMCI in between NC and LMCI; very small numbers of SMC so far.

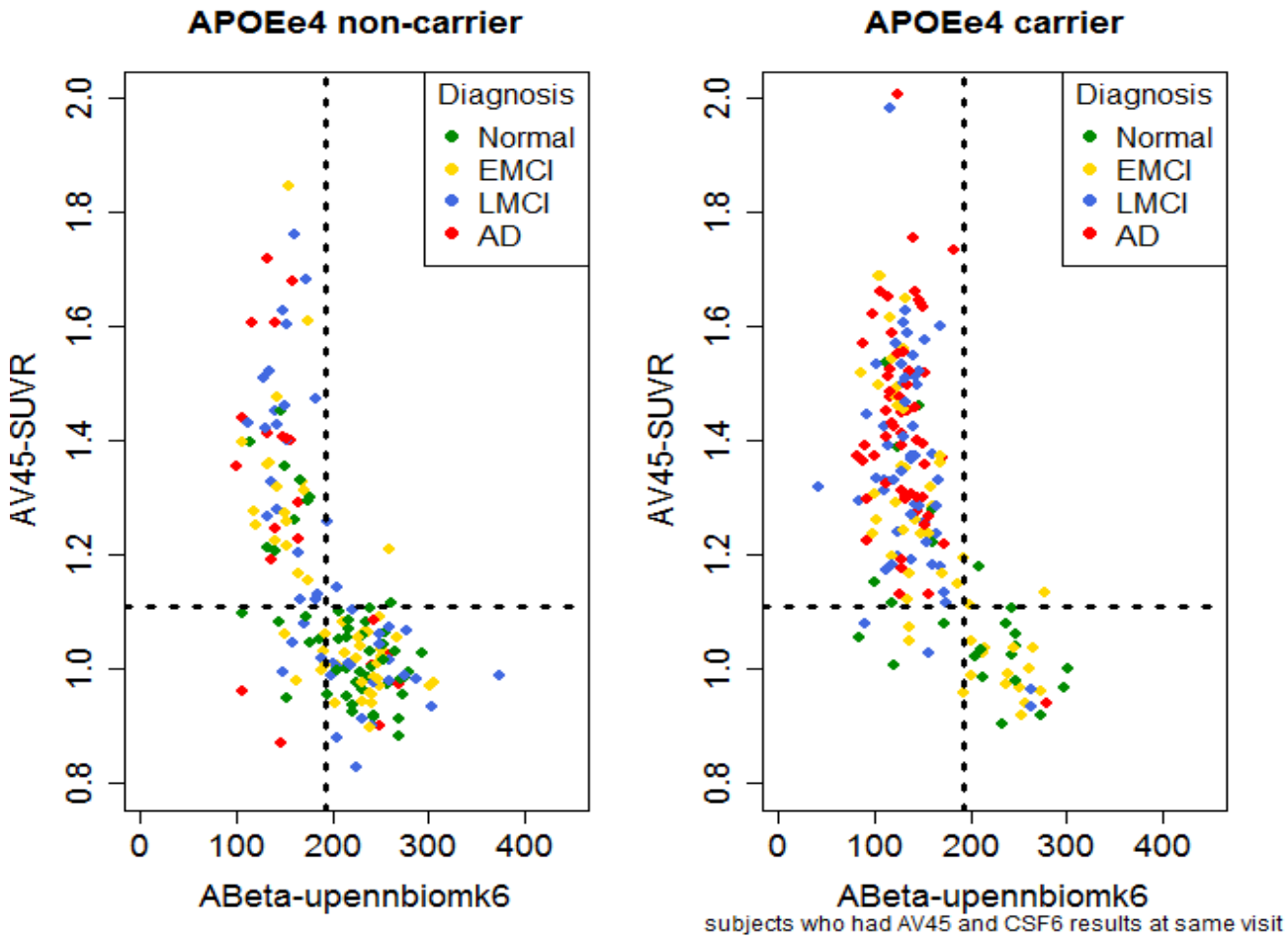




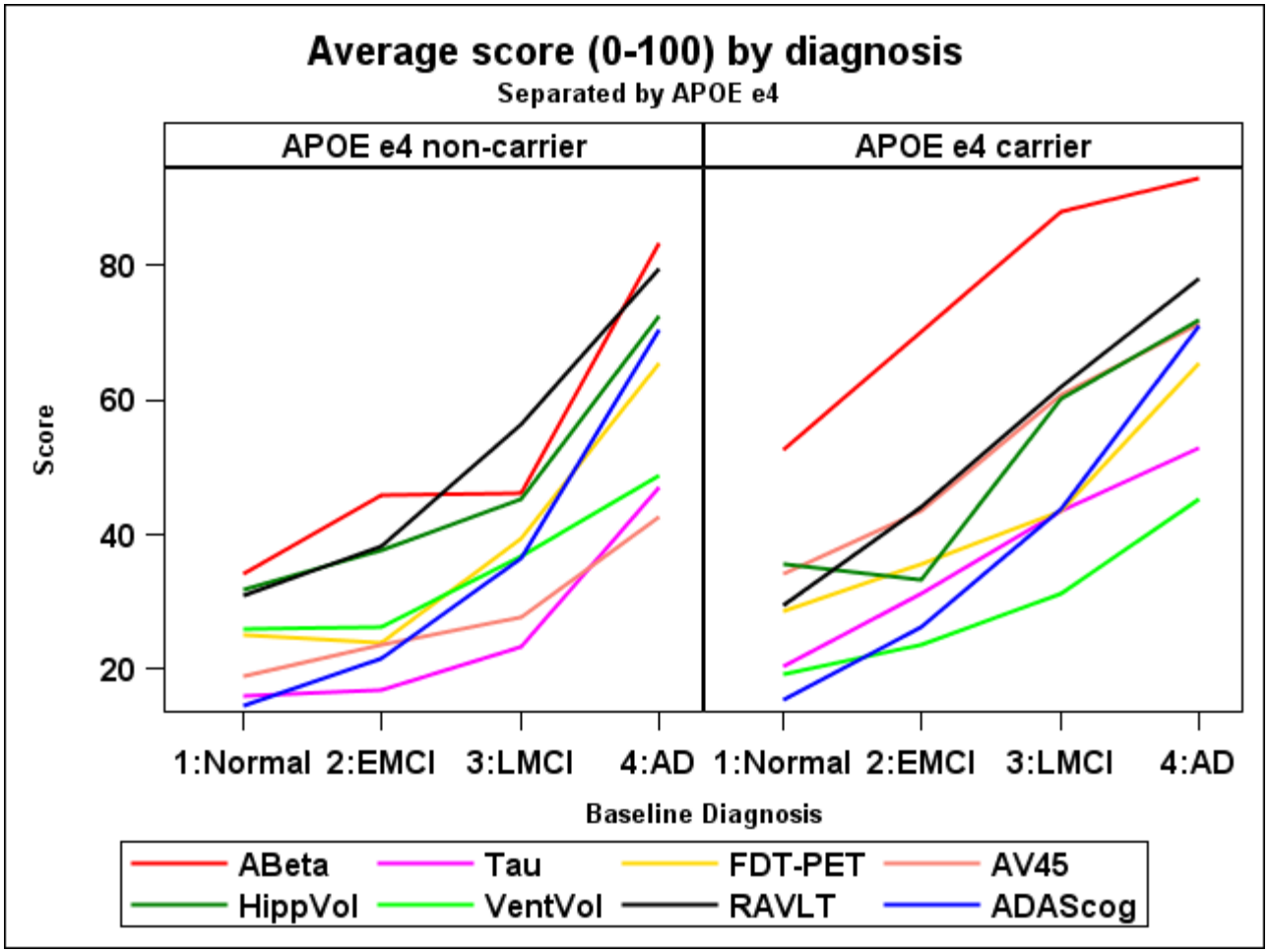
AV45 summary measure: about half the eMCI exceed the cutoff value (about 1/3 of NC).



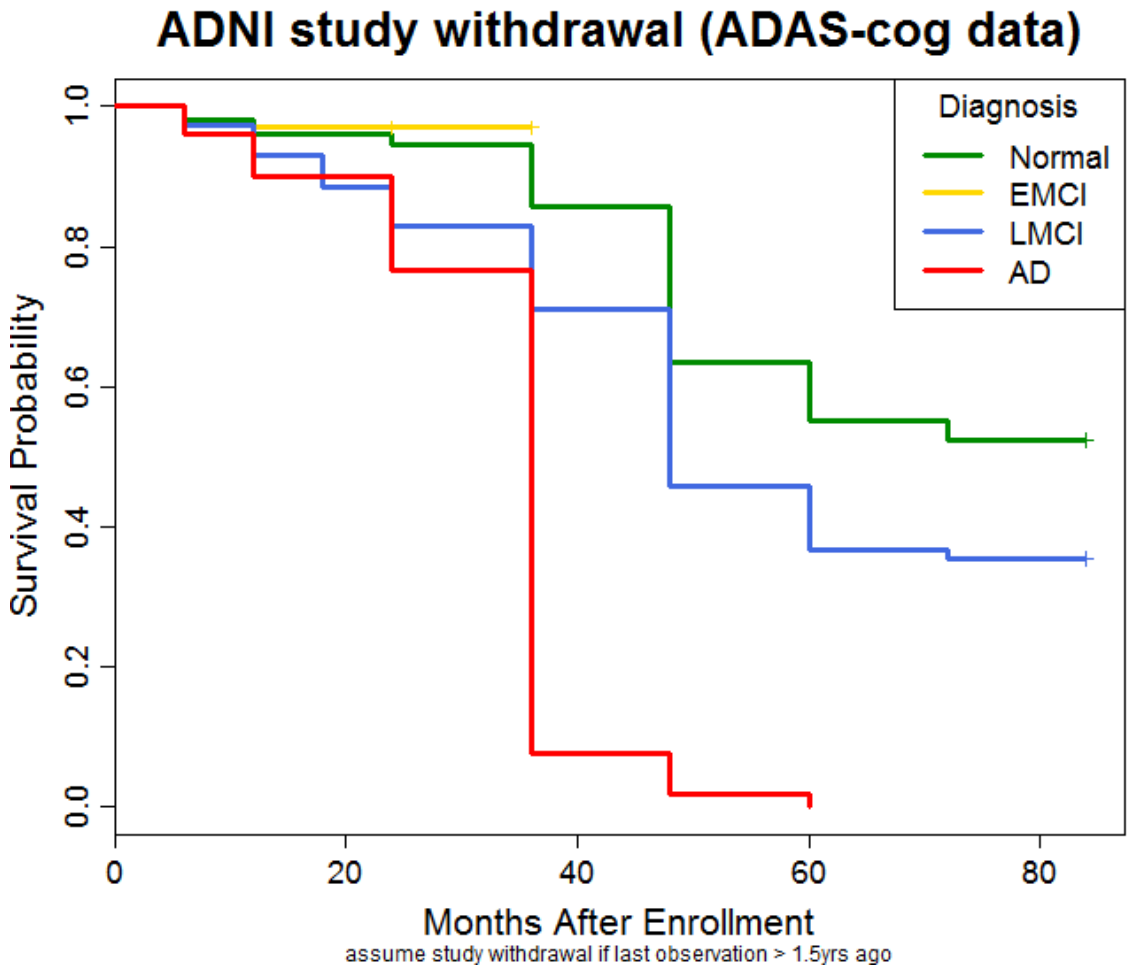
How closely do AV45 image and CSF Aβ agree? Generally quite well. Note more amyloid evident in the e4 carriers (right graph, upper left quadrant).



Means of key ADNI measures by diagnostic group, scaled from 0=NC “good” (best 10%) to 100=AD “bad” (worst 10%), separately for e4+ and e4-.



Now: much longer follow-up, allowing us to look at trajectories in more detail. Some clinical data out as far as 6 years in NC and MCI.



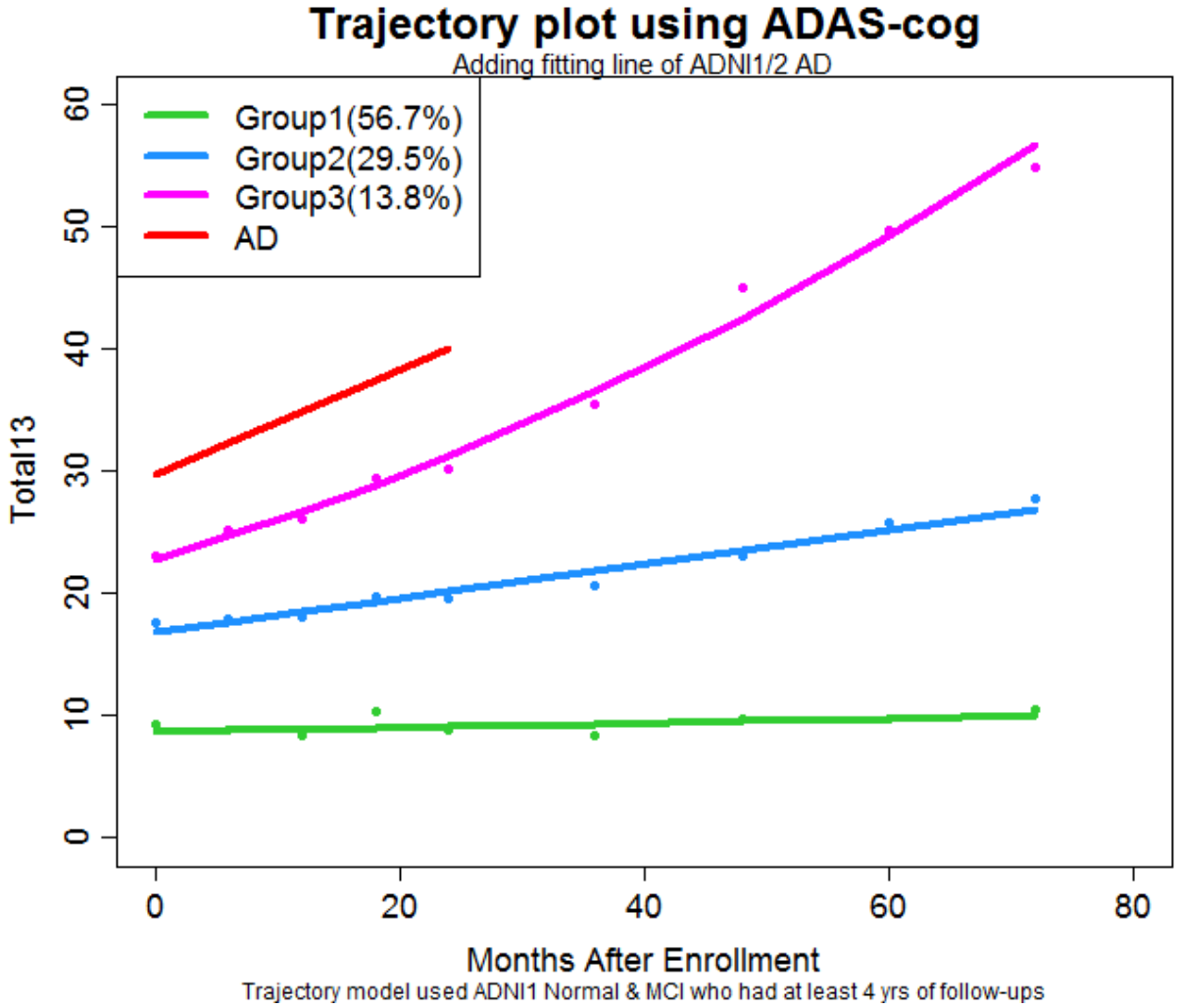
We fitted very flexible mixed models for trajectories to the combined NC and MCI participants.

- Allowed model to assign participants to latent groups according to similarity in trajectories.
- Allowed for more than 2 groups.
- Allowed mean trajectory for group to be non-linear if needed.

Generally 3 groups sufficed to capture variation.

Most measures showed linearity for all groups.

Results for ADAS-cog (only one with a hint of non-linearity), with AD path added for comparison.



Innovative work from biostatistics group

1. Examining relationships among ADNI measures.

2. Characterizing trajectories over time.

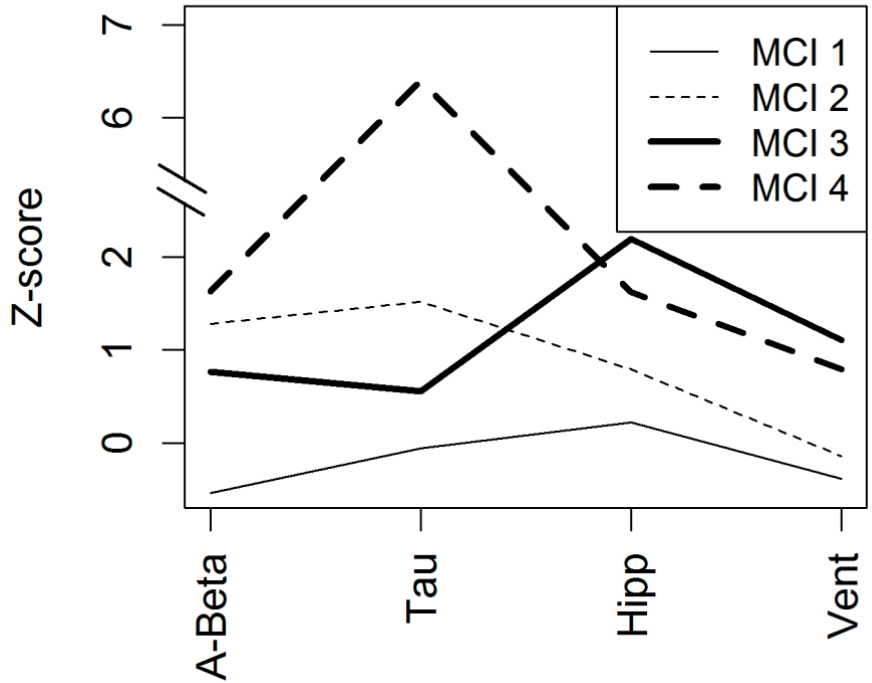
3. Quantifying the information captured by biomarkers.

1. Data mining via cluster analysis in ADNI-1 MCI to assess multivariate heterogeneity (Nettiksimmons, Beckett, Landau, DeCarli; Alz and Dement, in press).

We examined 11 baseline measures from MRI and CSF summaries and found heterogeneity suggesting 4 relatively distinct clusters.

Three of the groups looked like they might be at early, middle or late stages of an amyloid-driven sequence. The fourth looked quite different.

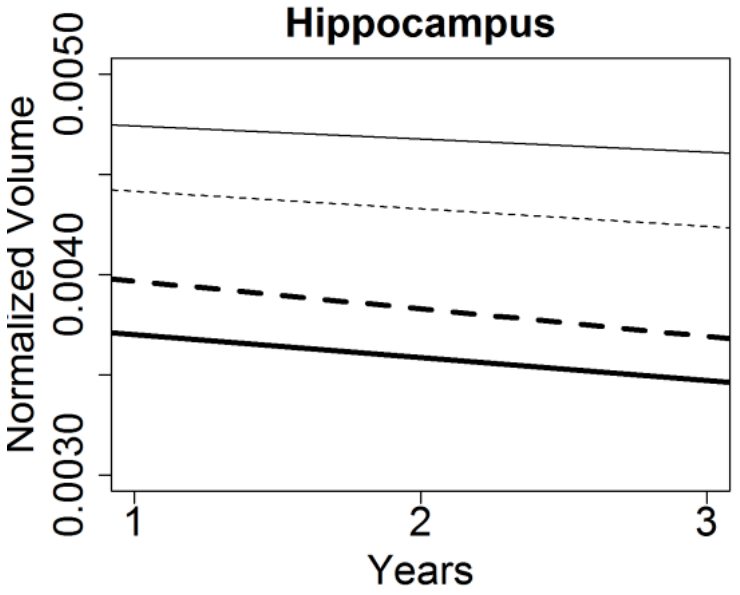
Profiles for groups represented by light solid, dotted and dashed lines follow a clear ordering for A-beta, Tau, HV and VV. But MCI3 (dark solid) is far worse in MRI measures relative to its CSF measures.

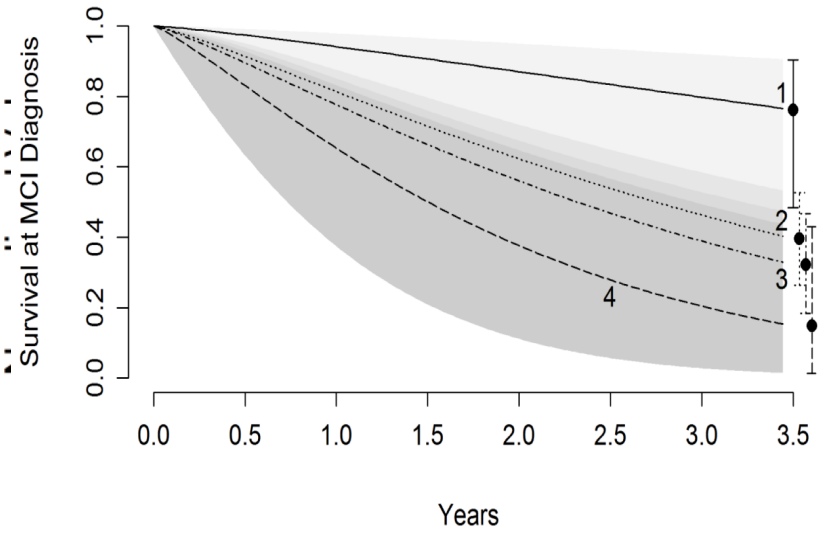


Profiles for 4 clusters (one line for each)
Showing Z scores for two CSF and two MRI measures.

High values on y axis are bad.

The groups also have different trajectories. Here are HV atrophy (left) and time to progression to AD (right).





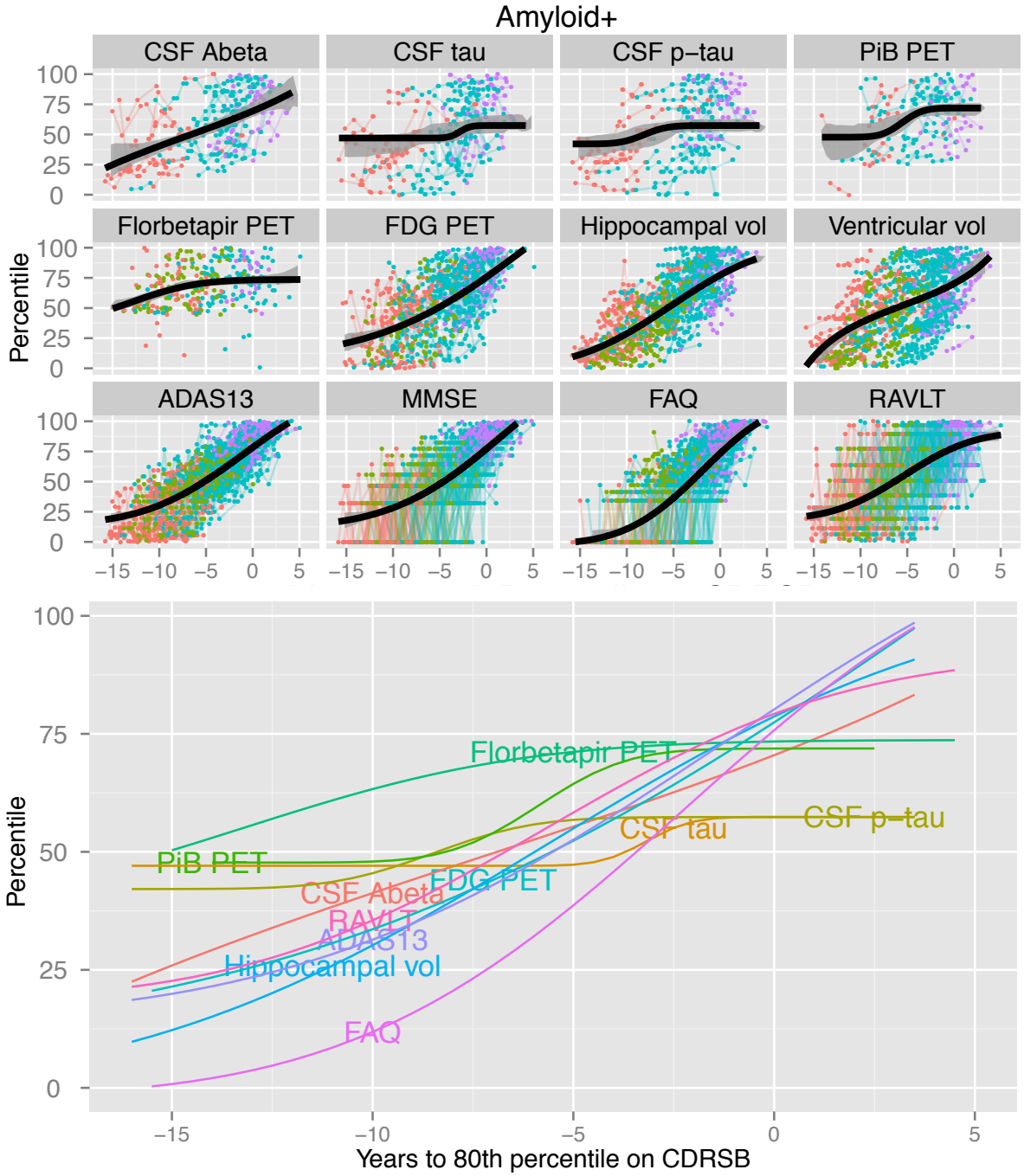
2. Modeling long-term progression from short-term trajectories: Donohue et al.

This paper uses ADNI-1 follow-up data to estimate long-term patterns:

- Timing of clinical progression, and
- Long-term biomarker trajectories.

Analyses were restricted to amyloid+ subset.

Pictures on next slide show how various biomarkers progress, relative to reaching 80th percentile on CDRSB.


Amyloid+
CSF Abeta
CSF tau
CSF p−tau
PiB PET
Florbetapir PET
FDG PET
Hippocampal vol
Ventricular vol
ADAS13
MMSE
FAQ
RAVLT
Percentile
100
75
50
25
0
−15
−10
−5
0
5
Florbetapir PET
CSF p−tau
CSF tau
PiB PET
FDG PET
CSF Abeta
RAVLT
ADAS13
Hippocampal vol
FAQ
Years to 80th percentile on CDRSB

3. Information-theoretic approaches to measuring and comparing how much biomarker predictors “catch” of progression outcomes (Dienes, Beckett).

Some measures commonly used include

Dichotomous P, Dichotomous O: - Sensitivity, Specificity, Positive and Negative Predictive Value

Continuous P, Continuous O - Coefficient of Determination (R^2)

The goal of our research is to create a unifying framework for validating and comparing biomarkers.

We developed an information measure that ranges from 0 (nothing more than chance, noise) to 1.0 (all possible information is captured).

Our approach is comparable across dichotomous or continuous, predictors or outcomes.

We looked at potential information about 2-year conversion from MCI to AD in ADNI-1.
We compared ADNI biomarkers at baseline and change in biomarkers. I will show results just for dichotomized predictors.

Variable	Cutpoint	POI	95% Confidence Interval
ADAS-Cog	10	0.057	$(0.024, 0.104)$
ADAS-Cog	12	0.065	$(0.029, 0.116)$
∇ ADAS	2	0.044	$(0.016, 0.088)$
CSF AB 142	192	0.054	$(0.032, 0.082)$
CSF AB 142	175	0.063	$(0.018, 0.134)$
Avg Hipp Vol	3200	0.053	$(0.021, 0.100)$
Avg Hipp Vol	3132	0.056	$(0.023, 0.104)$
∇ Avg Hipp Vol	-113	0.023	$(0.004, 0.056)$

Among ADNI patients diagnosed with MCI at baseline none of the biomarkers contain a large proportion of the information about 2 year conversion to AD.

Web conference: Analysis of ADNI data

August 1, 2013
8-10 AM Pacific Time

Focus will be on challenges of working with ADNI data: commonly used files, merging files, samples of Biostat Core code, ADNIMERGE packages, doing cross-validation.

Limited enrollment.
(Slides from first session on ADNI basics are on LONI site.)

Announcement and sign-up details will be forwarded to you soon.

Thank you from the Biostat Core!
Disclosures

- Laurel Beckett: NIH grants, C-Path consultant.
- Danielle Harvey: NIH, DOD grants.
- Mike Donohue: Institutional K12, Bristol-Myers Squibb consultant.
- Naomi Saito, Chun-Jung Huang, Huanli Wang: no relevant disclosures.