BIOSTATISTICS CORE ADNI 2 SUMMARY & ADNI3 PLANS

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ADNI2 Results: Highlights

- The Biostatistics Core integrates data from all Cores to address implications for clinical trial design:
  - Comparing candidate biomarkers for potential for inclusion/exclusion, stratification, adjustment
    - Predictors of disease progression (to MCI or to AD)
    - Predictors of cognitive and functional decline
  - Comparing candidate biomarkers as outcome measures of change
    - Signal-to-noise ratio of change over 1-2 years
    - Correlation of change in biomarker with cognitive or functional change
  - Characterizing sequence of change, especially in preclinical and early stages
  - Identifying important subgroups in MCI

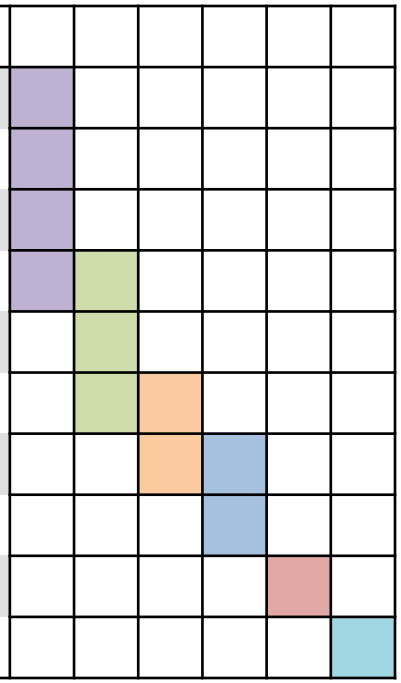
Predictors of progression from MCI to AD within 24 months

Marker	Effect Size			
FDG-R-UCB	1.19			
AV45-R-UCB	1.06			
Entr thickness	1.00			
Hpc vol	0.93			
CSF pTau	0.92			
CSF abeta	0.91			
CSF tau	0.87			
Entr vol	0.71			
Ventricles vol	0.38			
Whole brain vol	0.30			
W mat hyp	0.22			

- Measures with highest effect size for predicting progression are at top
- Effect size: how many SD separate the means for those that progress and those that do not
- Measures sharing colored bar are not significantly different after multiple comparisons

Predictors of change in ADAS-Cog in MCI (n=328)

Marker	Correlation	p-value
FDG-R-UCB	-0.32	<0.01
Entr thickness	-0.25	<0.01
AV45-R-UCB	0.22	<0.01
CSF pTau	0.19	<0.01
CSF tau	0.18	<0.01
CSF abeta	-0.15	<0.01
Hpc vol	-0.14	<0.01
Ventricles vol	0.12	0.02
Entr vol	-0.09	0.12
Whole brain vol	0.003	0.96



- Many baseline markers correlated with increase in ADAS-Cog
- The same top 3 as for progression to AD
- Measures sharing colored bar are not different after multiple comparisons

Promising biomarkers for prediction in MCI

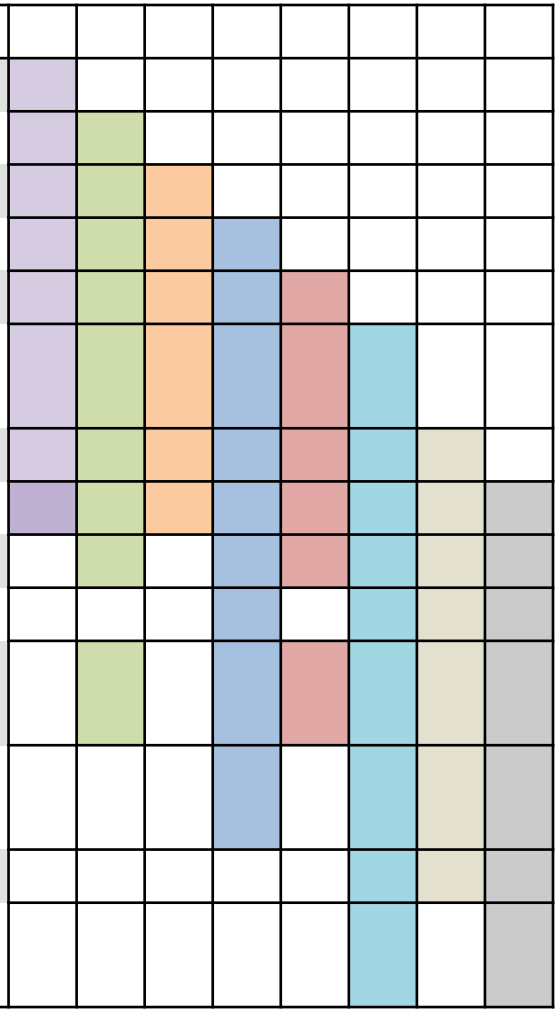
- Three different brain markers have at least a 1-SD difference between the baseline means for those that progress and those that do not and also correlate ($|r| \geq 0.2$) with ADAS-Cog change
  - FDG-PET summary measure (UC Berkeley)
  - AV45 cortical summary measure (UC Berkeley)
  - Entorhinal cortex thickness (UCSF, FreeSurfer)
- These markers, singly or in combination, could be used to improve clinical trial design by:
  - Inclusion of people more likely to progress
  - Exclusion of people more likely to stay stable, or
  - Stratifying by risk group

Assessing biomarkers in NC is harder

- Prediction of short-term progression to MCI is much weaker than MCI to AD
- Short-term change in ADAS-Cog is smaller and more variable, so harder to predict
- Instead, will see what does change

Signal-to-noise properties of 1-year change in NC

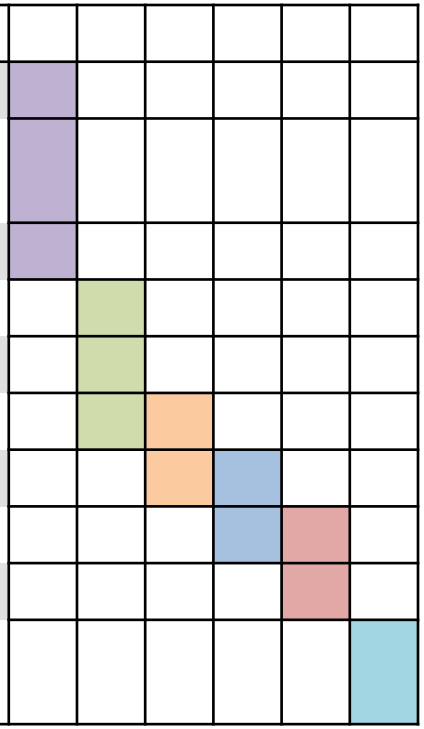
Marker	n/group
CSF Abeta rate	13546
WMHYP rate	7382
AV45 rate	6873
Entr volume rate	3810
TOTAL13 rate	3223
Hippocampal vol rate	3173
CDR-sb rate	2880
MMSE rate	1582
CSF Tau rate	1548
CSF PTau rate	1389
Entr thickness rate	1130
Whole brain vol rate	947
TBM rate	516
Ventricles vol rate	397



- Sample size required for 1-yr trial in NC to detect 25% reduction in change
- Best precision (smallest sample size) at bottom
- Measures sharing colored bar are not significantly different after multiple comparisons

Validating change in markers: correlation with ADAS-Cog change in NC (n=206)

Marker	Correlation	p-value
AV45-R-UCB	0.14	0.049
Entr thickness	-0.12	0.09
Entr vol	-0.12	0.10
CSF abeta	-0.08	0.25
CSF ptau	0.08	0.28
Hpc vol	-0.07	0.33
CSF tau	-0.06	0.41
FDG-R-UCB	0.05	0.46
Ventricles vol	-0.05	0.51
Whole brain vol	-0.03	0.64



- Increase in AV45 correlated with increase in ADAS-Cog
- No other association is significant
- Measures sharing colored bar are not significantly different after multiple comparisons

Promising markers for prediction in NC

- Less consistent than in MCI
- Some imaging measures have promising signal-to-noise ratios
  - Ventricular volume (FreeSurfer, UCSF)
  - TBM (Mayo)
  - Not as correlated with change in ADAS-Cog
- Baseline AV45 summary measure most correlated with change in ADAS-Cog
- Best marker to use in NC depends on goal

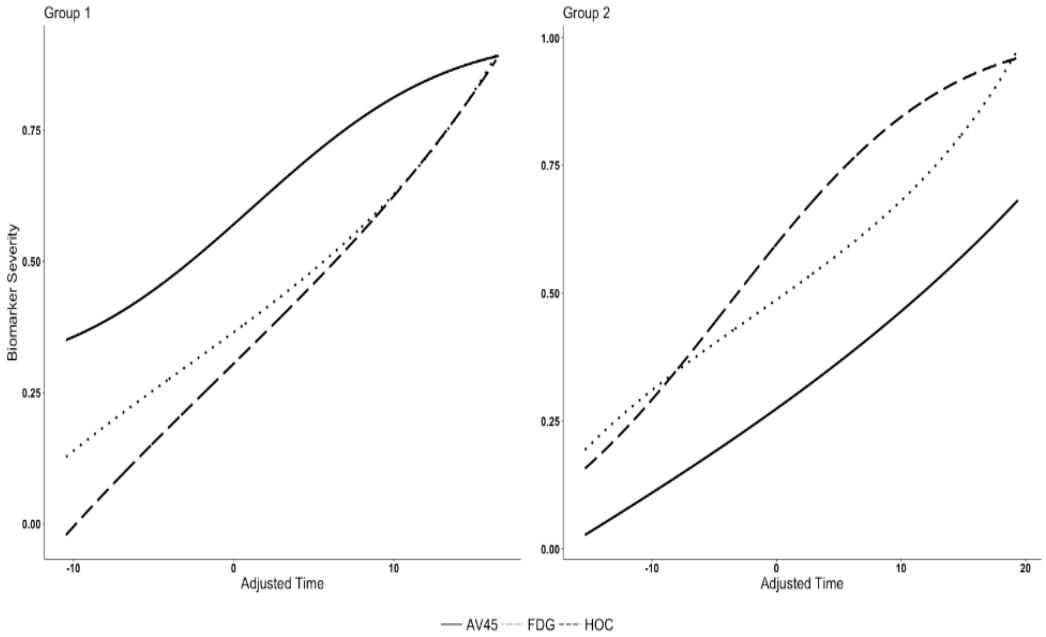
What about sequences of change in markers in NC and MCI?

- Clustering methods developed by Teresa Filshtein
- Utilizes longitudinal sequence of multiple markers to group “similar” people
- Applied to 339 participants (106 NC and 233 MCI) from ADNI-GO/ADNI-2
- Based on 3 markers
  - Hippocampal Occupancy (HOC; derived from UCSF FreeSurfer)
  - AV45 SUVR Summary Measure (UC Berkeley)
  - FDG-PET Summary Measure (UC Berkeley)
- Each measurement type transformed via weighted empirical distribution to get pseudo-centiloid measures (on 0 to 1 scale; 0=normal, 1=fully realized dementia)

Determining number of clusters

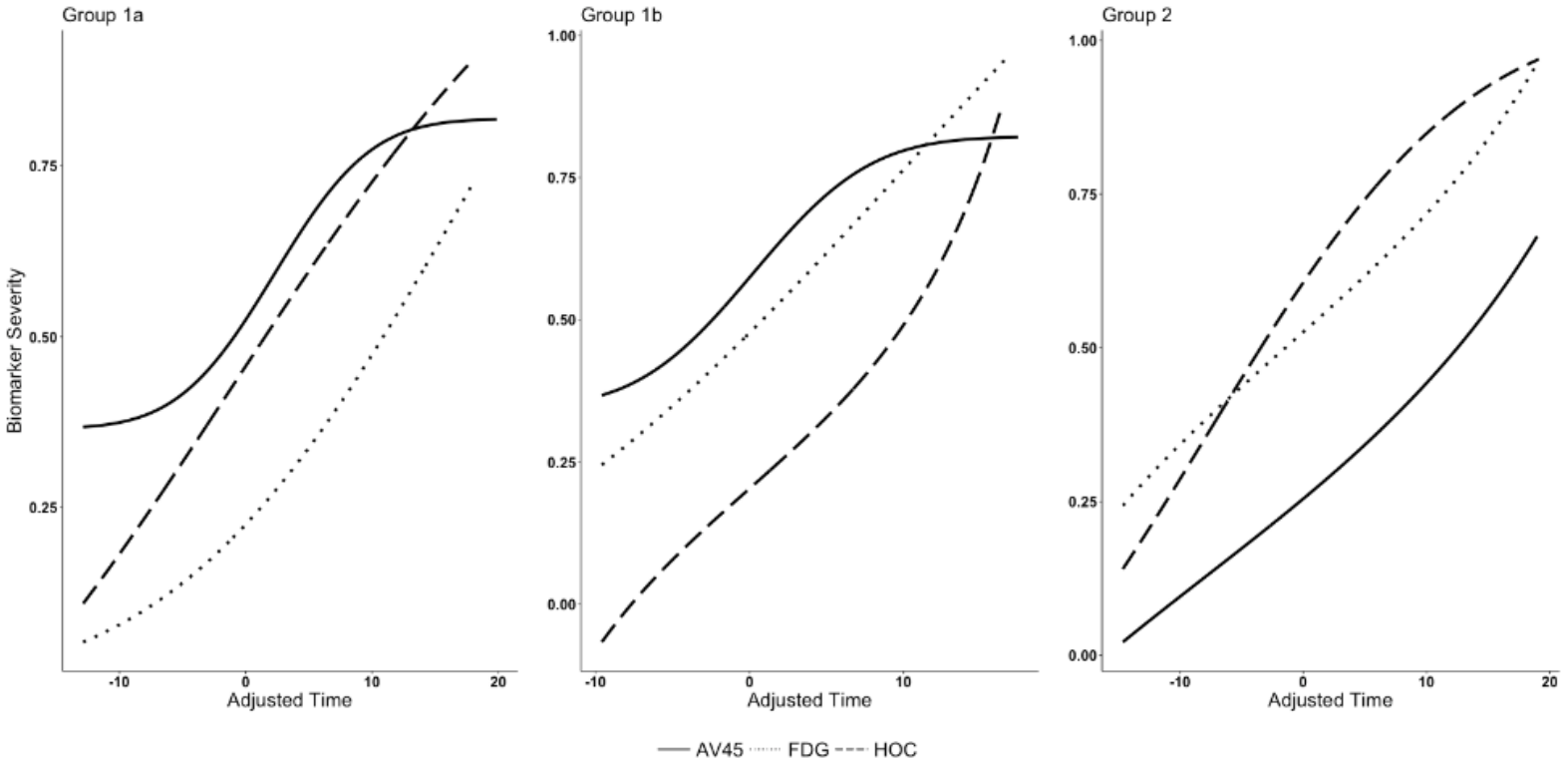
- Caliskin and Harabatz criterion – identified two syndromes
- Clinical relevance
  - Adapted a technique from Mike Donohue's approach for estimating trajectories within a single well-defined syndrome.
  - Technique identified 3 subgroups (essentially split one of the C-H groups)

Caliskan-Harabatz grouping



- Two syndromes
- Left side: amyloid 1st, then FDG, then HOC (54% of sample)
- Right side: FDG and HOC first, then amyloid (46% of sample)

Clinical relevance grouping

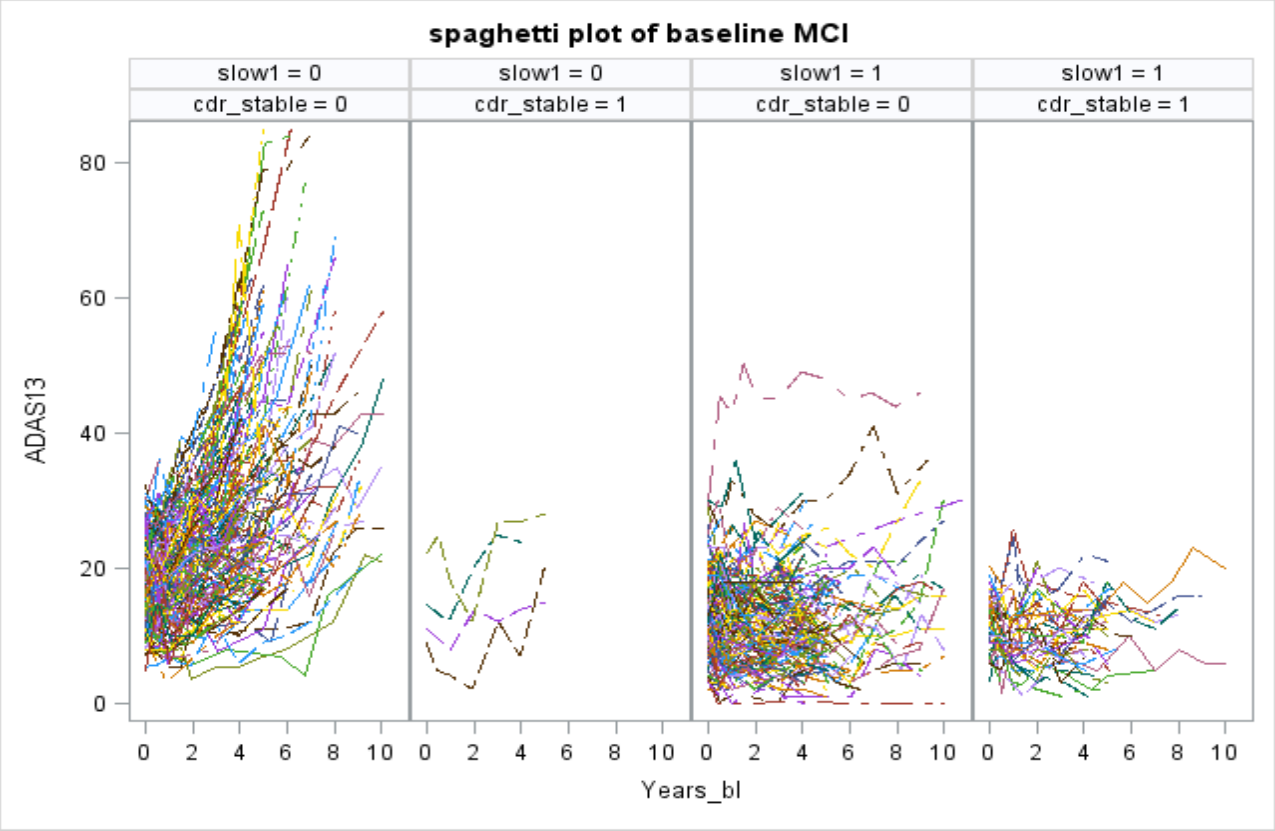


- Left side: amyloid first, then HOC, then FDG (31% of sample)
- Center: amyloid and FDG first, then HOC (29% of sample)
- Right side: FDG and HOC first, then amyloid (40% of sample)

What about subgroups in MCI?

- Interested in subgroup of MCI that remains stable
- Considered MCI (at baseline) from ADNI-1, GO, 2 (includes EMCI)
- Computed person-specific slopes in ADAS-Cog
  - Split according to slow changer (slope < 1) or not
- Further evaluated change in CDR Sum of Boxes (stable=1st and last score equal)

Spaghetti plots of ADAS-Cog

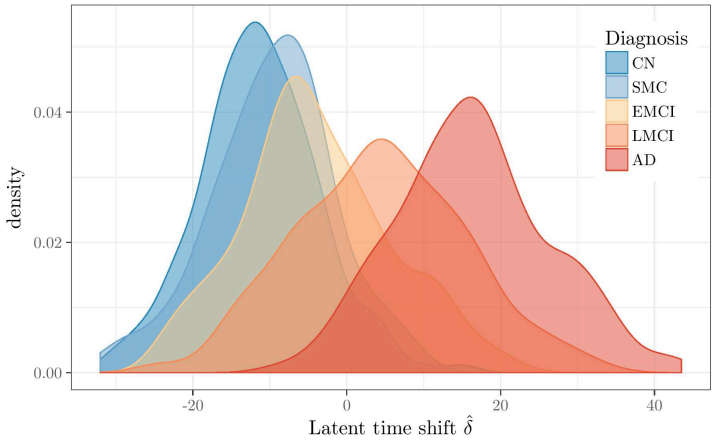


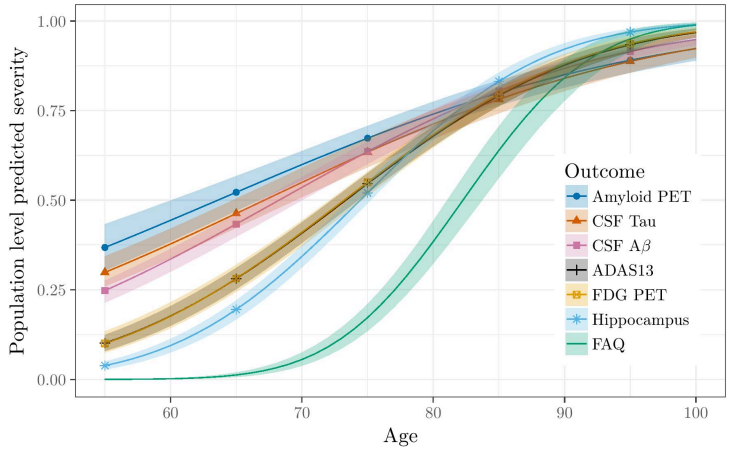
Which markers differ between those that remain stable and those that change? Something informative/protective in those that remain stable?

ADNI3: toward better clinical trials

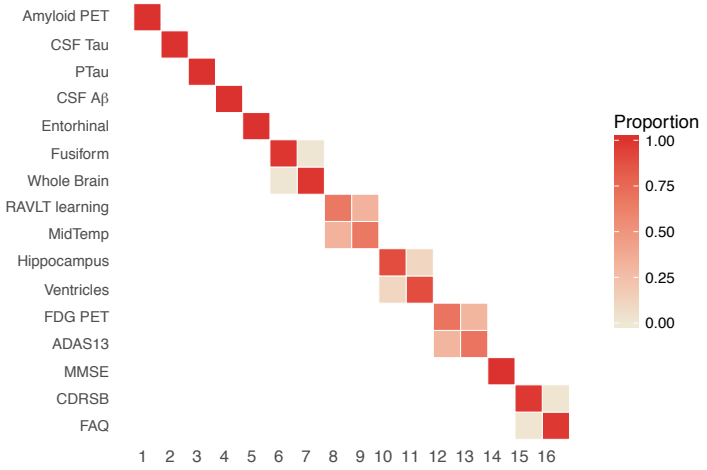
- We will assess new candidate markers (including from tau imaging), looking for markers with:
  - Sensitivity to change in early disease (at baseline, over time)
  - Good signal-to-noise properties
  - Correlated with relevant clinical change
  - Plausibility as surrogate marker and intervention target
- Also consider new clinical outcome measures (such as CogState) and how they might help in early disease
  - Sensitivity to early change
  - Good signal-to-noise properties

Bayesian Latent Time Joint Mixed-Models

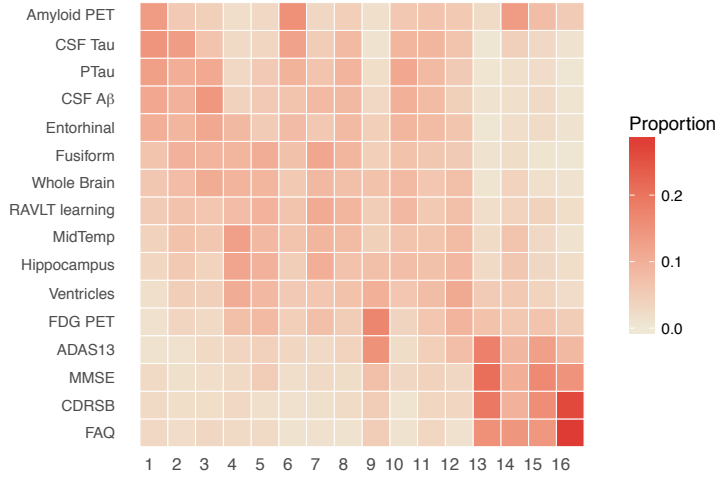




Population-level predicted order



Subject-level predicted order (*APOE*ε4+)



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https://arxiv.org/abs/1703.10266

AAIC Workshop on Clin Trials Methods

Friday July 14 8am-5pm

- Longitudinal data analysis, MMRM, Missing Data
  - Mike Donohue, USC
- Simulation and Trial Enrichment
  - Jeannie-Marie Leoutsakos, Johns Hopkins
- Adaptive Trial Design
  - Joyce Chang, University of Pittsburgh
- Expedition trial design: Delayed Start Analyses
  - Hong Liu-Seifert, Eli Lilly