ADNI Biostatistics Core: Results and Plans

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ADNI2 Results: Highlights and looking forward

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 (conversion to MCI, 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.
- Identifying subgroups in NL and MCI using multiple markers.
- Characterizing sequence of change, especially in preclinical and early stages.

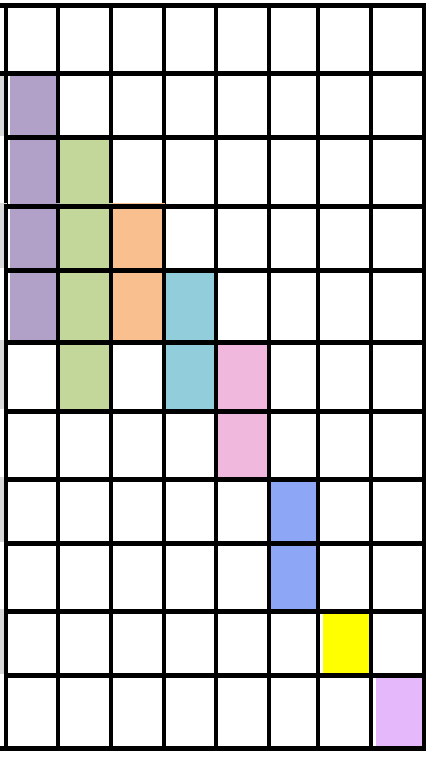
Predictors of conversion from MCI to AD within 24 m

Marker	EffectSize			
FDG-R-UCB	1.21			
CSF tau	1.07			
AV45-R-UCB	1.03			
Entr thk	1.01			
Hpc vol	0.92			
CSF pTau	0.89			
CSF abeta	0.87			
Entr vol	0.72			
Ventricles	0.41			
Whole brain	0.26			
W mat hyp	0.26			

- Measures with highest effect size for predicting conversion are at top.
- Effect size: how many SD separate the means for converters and non-converters.
- Measures sharing colored bar are not significantly different by multiple comparisons.
- Methods: Harvey (2016, in revision)

Predictors of change in ADAS-Cog in MCI (n=312)

MCI	Correlation	p-value
FDG-R-UCB	-0.30	0.00
Entr thk	-0.26	0.00
CSF tau	0.22	0.00
AV45-R-UCB	0.20	0.00
CSF abeta	-0.18	0.00
CSF ptau	0.16	0.00
Hpc Vol	-0.13	0.03
Ventricles	0.12	0.03
Entr vol	-0.09	0.12
Whole brain	0.01	0.88



- Many baseline markers correlated with increase in ADAS-Cog.
- The same top 4 as for conversion to AD.
- Measures sharing colored bar are not different by multiple comparisons.

Promising biomarkers for prediction in MCI

Four different brain markers have at least a 1-SD difference between the baseline means for converters and non-converters and also correlate ($|r| \geq 0.2$) with ADAS-COG change:

- FDG-PET average across regions of interest (Jagust, UCB)
- CSF tau
- AV45 region of interest (Jagust, UCB)
- Entorhinal thickness

These markers, singly or in combination, could be used to improve clinical trial design by:

- Inclusion of people more likely to convert,
- Exclusion of people more likely to stay stable, or
- Stratifying by risk group.

Assessing biomarkers in NL is harder

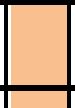
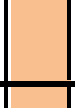
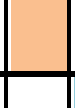
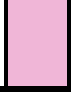
- Prediction of short-term conversion to MCI is much weaker than MCI to AD.
- Short-term change in ADAS-COG is smaller and more variable, so harder to predict.
- Instead, will see what does change, and look for key subgroups.

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

Normal	samplesize	1	2	3	4	5
WMHYPrate	5,669					
MMSCORErate	5,111					
cdrsumrate	4,501					
AV45rate	4,233					
etrvrate	3,225					
TOTAL13rate	3,170					
etrtrate	1,636					
hpcvrate	1,320					
wbrainrate	600					
TBMrate	453					
ventriclesrate	325					

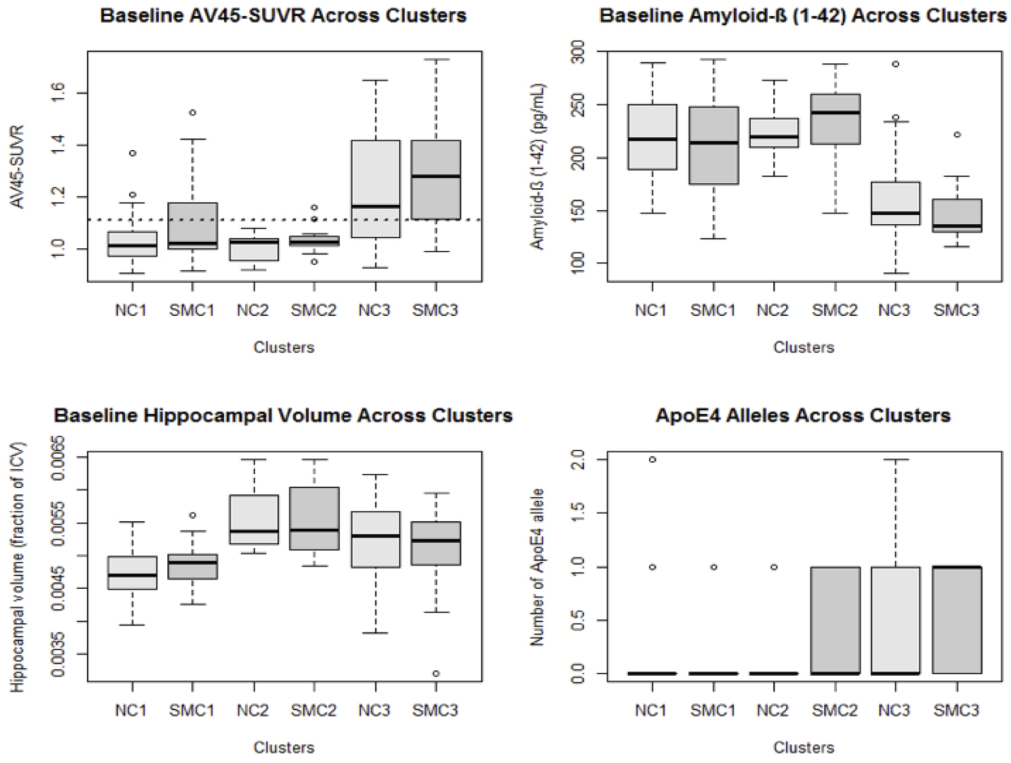
- Sample size required for 1-yr trial in NL to detect 25% reduction in change.
- Best precision (smallest sample size) at bottom.
- Measures sharing colored bar are not significantly different by multiple comparisons.

Validating change in markers: correlation with ADAS-Cog change in NL

NL	Correlation	p-value	
Hpc vol	-0.18	0.03	
AV45-R-UCB	-0.11	0.18	
Entr thk chg	-0.08	0.31	
Ventricles	0.08	0.32	
Whole brain	-0.08	0.36	
Entr vol	-0.05	0.58	
TBM	0.04	0.67	

- Decrease in hippocampal volume correlated with increase in ADAS-Cog.
- No other association is significant.
- Measures sharing colored bar are not different by multiple comparisons.

NL are heterogeneous: need to find high-risk subgroup



Cluster analysis in NL, SMC found 3 groups:

- No biomarker problems.
- Amyloid-characteristic problems.
- Atrophy but normal amyloid.

(C Wang, in revision)

Other new work helping focus on early disease

Current research from our Core provides more insight:

- Placing the Jack model for classic AD on 0-100 scale of severity and on time scale relative to diagnosis (Donohue 2014)
- Showing heterogeneity in patterns of trajectories: it's not all "amyloid first" (Filshtein, AAIC 2016)
- Earliest signs of problems in everyday function perceived by patients, typically before informants (C Wang, unpublished)

Next: looking deeper at amyloid+ NL as possible target for early-phase trials.

Potential biomarkers in amyloid+ NL

NL AMY+	mean	sd	samplesize
Ent Vol	-21.6	97.3	5,106
RAVLT	1.5	4.8	2,394
AV45-UCB	0.019	0.054	2,104
ADAS-COG	-0.61	1.55	1,637
Ent thk	-0.052	0.076	541
TBM	-0.005	0.006	410
Wh Brain	-6733	7696	329
Hpc vol	-57.0	53.3	219
Ventricles	844	618	135

NL AMY+	Correl	p-val
Ventricles	0.21	0.11
Entr thk ch	-0.20	0.12
Hpc vol	-0.17	0.19
Wh brain	-0.10	0.44
Entr vol	-0.08	0.53
AV45-UCB	-0.04	0.75
TBM	-0.02	0.85

- Analysis in 44 NL who were amyloid+.
- Signal-to-noise ratio for 2-year change (top table) is 1+ for ventricles, HCV.
- Change in ventricles, HCV, ER thickness, may correlate with ADAS-COG change (bottom table).
- Suggests there could be brain changes in this group that are relevant and consistent.

Hypothetical trial design in amyloid+ NL

We hope in ADNI3 to identify specific brain changes in high-risk subgroups that are:

- Relevant potential targets
- With signal-to-noise ratios for change at least 1
- Correlated with clinical change.

Consider a possible Phase II trial, with such a marker as an outcome:

- A 25% or greater reduction in change would be evidence worth further study.
- One-sided, level 0.05 trial, with 80% power
- Required sample size: n=25.

ADNI3: toward better clinical trials

We will assess new candidate biomarkers such as tau, 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.

New clinical outcome measures (CogState, Financial test) may also help in early disease: possibly more sensitive to early change, with better signal-to-noise properties, compared to dementia-focused measures.

Thank you!

Keep looking -
much more research to come, with ADNI3!