Discussion points:

Stratified medicine and targeted clinical trials for AD drug development in light of recent phase III trial results: Example apoE genotype

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No Disclosures, except:

"Canada, it's spelled with a 'can', not a 'can't'. Because when we're faced with adversity, we Look for a way, not a way out"

-Advertisement by Cenovus, industrial developer of Canadian oils sands project in Alberta: http://www.youtube.com/watch?v=j0vYTFve7tA

- What does stratification according to apoE genotype mean?
  - Are we looking for treatment affects stratified according to a pathway biology we don't understand?
  - Is this an example of a highly rational strategy applied to the wrong therapeutic agents?
- The elephant in the room: pre-MCI, MCI, early AD, etc. is highly heterogeneous
  - Natural variability in normal brain aging can mask as MCI, high prevalence of mixed dementias, differing trajectories of progression, variable pathology/pathogenesis
  - Are we stumbling out of the starting gate by conceptually homogenizing the disease?
- What is the feasibility of hypothesizing alternative/additional stratification measures from retrospective analyses of trial outcomes?
- How can we stratify rationally?

- There is much discussion that earlier=better for disease modification. Better is the thinking that we need to expose the right drugs to the right subjects at the right time in the course of their disease. How can stratification impact on this thinking?
- Recent trials suggest that we may be able to move biomarkers, but without impact on clinical outcomes. One obvious thought: were we in time?
  - Unproven is whether we can actually move clinical outcomes in any DM trial design. Should we open our thinking on co-varying clinical outcome measures with treatment responses to account for clinical variability?
  - Do we also need the right clinical outcome in the right subjects at the right time in the course of their disease, that may be variable among subjects who respond?
  - Perhaps not a good registration strategy, but potentially a good hypothesis generator for prospective evaluation

- What will we learn from the prevention studies regarding stratification and expectations for population-based outcomes?
- What can we learn from familial clusters that do not involve Mendelian dominant heritability?
  - Are there shared clinical and biomarker phenotypes that lend themselves to stratification analyses?
- EOAD and early treatment in “mainstream” AD reduce age-related confounding co-morbidities and allow for lifestyle modifications and non-pharmacologic approaches for impacting on outcomes.
  - Will, *e.g.* a baseline level of cardiovascular health be required for a positive pharmacological therapeutic outcome?
  - Are these also stratification measures to consider in trial design?
- Feasibility check: Will competition for subjects be a limiting factor?
  - How should we prioritize this precious resource?