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Designing the Ideal Alzheimer's Disease Prevention Trial

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Global Summary of Last Working Group

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Summary

- “Prevention” is too broad
- Divide into two papers:
  - Primary vs secondary prevention : Issues and Designs
  - Research designs for subjects who are biomarker positive

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First paper

- Primary vs secondary prevention in the AD spectrum
  - Can find amyloid in brain before cognitive change, but other changes usually coincide with cognitive changes starting
  - Can we identify very high “at risk” groups but no amyloid yet
  - tau
  - Detection method and outcomes to show efficacy = primary
  - Different definitions used by presenters
- How accurate does the non-biomarker (risk) profile need to be if the NNT is 20 or 2000? Benefit/risk of the drug. (relationship to the outcome needed & and length of the trial)
- Population old enough to have a risk in general, young enough that have limited impairment
- True primary prevention does not preclude trying to halt or to reverse damage in people with biomarkers a mild detectable cognitive change
- Pragmatics of treating people for 20 years (e.g., fluoride, cholesterol lowering agents, birth control pills)
- Risk identifiers, e.g.:
  - Genomic High Risk
  - Behavioral high risk: changes that predict the development of initial MCI (Oregon group – passive observation, Ecological momentary assessment (EMA) – active observation)
- Need to match the assessments to the group being tested and the intervention’s most likely point of impact to avert development of disease

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Another paper

- Impact of the diagnosis:
- Treatment v life style intervention
- Regulation of disclosure of genomic info?
- Is this a place for regulations for disclosure of non-genomic information?
- If in a trial, and will disclose, then the timing (beginning vs end of a study)

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Second paper

- Research design options for populations who are biomarker positive
  - Amyloid but no cognitive impairment
  - Parkinson's but no dementia
  - History of stroke, but without stroke-related dementia
  - Genomic-risk and some cognitive impairment (DIAN)
  - MRI evidence
  - ARCC (HIV+)
  - Down's syndrome
  - TBI (mild mod severe}
  - Family history
  - Vascular risk factors (DM, HTN, stroke) with cogn impairment
  - APOE4
  - CTE
  - Immune factor dysregulation
  - Socio-cultural factors (population specific, education-level//life span model)
- What are the design options when must measure amyloid or tau but your intervention is not amyloid or tau specific

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Potential Interventions for Secondary Prevention

Intervention strategy options

- Pharmacological targeted to biomarker (NfL)
- Pharmacological targeted at deactivating or circuit modification, compensatory intervention (immuno-therapy/modulation)
- Devices: Ultrasound (other brain stimulation), hyperbaric,
- Need to control for background life style interventions (exercise, nutrition etc)
- Genomic randomization (depression trial) using depression genomic risk; applicable to AD
- Having more than one intervention (everyone gets an intervention, randomize to which one is received)
- Different processes relevant to different stages of the illness (systems vs. brain disorder)
- REGULATORY hurdles
- Looking at the range of ages that genetically determined dementia develop cognitive impairment, is this relevant; onset for AD varies for identical twins too
  - what can we learn from these different designs
- Viruses & other health challenges with infection

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Outcome measurement goals

- Prove that:
  - Progression is stopped? Or, slowed? (e.g., Delayed for 5 y)
  - Biomarkers are reversed? (tau/amyloid “scar” v marker of active disease) (reversal or atrophy/ hypometabolism)
  - Reversal of functional changes? is there a way to lessen the severity of the functional decompensation of this disease (compensatory therapies)

- This happens with cancer immunotherapy (Keytruda)
- If successful, how long do you need to continue? forever as maintenance versus stop and surveil as in cancer tx
- It happens naturalistically in individuals who recover from attenuated psychosis syndrome
- Is there any reason to think that prodromes of dementia are different?
- (Don’t conflate a MMSE of 30 vs 10)
- Target of the trial will determine the outcomes monitored
- Hypertension , DM as moderators of progression and studying a fast progressing population (e.g., also age in Down’s)
- Wearables
- Is there an intermediary, like cholesterol for lipitor, in the causal pathway that can be used to monitor

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Objections / Challenges

- Speak to them in the paper (challenges)
- List:
- Paper 1: Primary – what is that; if biomarker positive but no symptoms, is that primary? Can biomarkers be reversed with future interventions? Ideal design if future interventions become available – designs if tau and amyloid are a consequence of the disease process or scar.
- Learnings from people protected or resistant to developing dementia (their biomarkers of protection)
- Think of the audience – methodological issues are a strength/ how do we measure/ handling multiple co-morbidity
  - Comment on lessons learned from current trials
  - Designs that work well for people still in the workforce. (digital measurement; passive assessment; wearables) – 2 way paging

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Primary v secondary

- Focus on attention on sporadic disease
- Instead of changing genes in genomic, remove that issue
- The familial forms help to inform this, but will focus on sporadic disease
- This is a cohort that one wouldn't know is at risk necessarily.
- Risk factors that impact/ modify age of onset in people predisposed as a modifiers.

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Plan

- List serve
- People volunteer to write up sections that we stitch together
- Regular teleconferences: monthly – 1 hour
- 30 min per paper
- Think of the audience – methodological issues are a strength/ how do we measure/ handling multiple co-morbidity
  - Comment on lessons learned from current trials
- Journal options:

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NOTES FROM LAST MEETING

Prevention? What's that?	Multiple population-based studies in different countries: Incidence of dementia, and AD specifically, is declining. Some studies suggest rising levels of education account for part of this. Neuropathology: AD pathology rarely occurs in isolation; often with vascular problems. More aggressive treatment of hypertension and hypercholesterolemia may be behind the decline. Can we learn anything about possible intervention studies from observation of this phenomenon?
Abstract **Intro** **Methods** **Results** **Discussion** **Recommendations**	
Intro	Series of ongoing prevention trials underway covering genetic and sporadic AD Offer great hope and at the same time, as a field we always need to think strategically and learn from everything we do so as to continually improve.
Review of current studies	Short review of current studies (maybe a table is best for this).
Main ideas: **What are we preventing?**	MCI? Dementia? A specific illness?
	Change in biomarkers? Amyloid deposition? Genomics? 1^0 relative with AD or MCI Performance-based metrics? High-risk populations? Genomics/dense pedigree
Who are the candidates for prevention trials? How do we select participants?	
What do we target?	
Eligibility criteria	
Enrichment of participants	? Preclinical AD
Other interventions	
Outcomes to assess?	Intermediate Endpoints. What is an "endpoint?" Diagnosis: MCI, mild AD, death?

Sample sizes	Progression from normal to MCI or MCI to AD takes very large sample sizes. Cognitive and functional measures also take large sample sizes. Small signal, lots of noise. Both between-person and within-person noise. Can frequent measures help? Can computerized testing (processing speed, e.g.) reduce noise? Need evidence that testing results are relevant to function.
Efficacy? Definition?	Something favorable and meaningful
Composite endpoints –	Functional questions generally interrogate a single construct either with individual questions or groups of questions, such that to what extent should the statistics that are applied to their analysis be left solely to the researcher who generated them versus considered and optimized by people conducting clinical trials, as long as the decision is pre-specified prior to database lock and unblinding. What is validated during a validation study, the construct the questions/answers represent or the statistics as well). There are many ways to combine endpoints in a composite and why not allow this to be specified for the individual trial.) The need to understand the assumptions underlying the components and decisions within studies.
Surrogate marker (ENDPOINT) criteria	High signal-to-noise ratio for change: between- and within-person noise. 2 Change in marker correlates with relevant clinical change. (Hard to show if clinical change noisy?).3 Change in marker differs for treated and untreated participants. 4 Hardest to show: Change in marker following treatment tracks with clinical impact.
Analysis and Stat models	
Change in a performance-based index / psychometrics that do not necessarily reflect impairment?	Worsening in the LASSI or UPSA? Other? Ropacki: ensure that the assessments are being used correctly. Ex. Only use logical memory 2 instead of alternate forms. Also, MMSE, global CDR. Should be a composite.
Progression to greater impairment, not necessarily diagnosable?	Episodic memory performance? ADL challenges?
Options for overall study designs?	Controls? Head to head? Some length of placebo?
Biomarker	Amyloid (too late?); TAU (too late?)
High risk conditions	Down syndrome
Industry and FDA perspective	
New ideas:	Down syndrome, other endpoints biomarkers vs cognition vs. combo of cognition and function/performance etc.

- What are the issues first
- Lon: write a relatively short paper that lays out some prevention guidelines
- Henry: Best practices are…
  - How would we do this right now?
- Larry Adler: How are you defining primary prevention?
  - Population-based approach
- How to define secondary prevention? This is a must to define the population we are talking about
  - Those with an identifiable risk factor.
- How define AD?
  - The criteria define a mixed criteria depending on what you use (small hippocampus). And, there may be other dementia pathophysiology of other ilks concurrently. And, are following the biomarkers that one started with.
- Raeanne: NIH is interested in what we can do for people starting at age 30
- Mike R: could have different papers on different stages. Need to specify the stage at the onset.
- The majority of studies now are secondary prevention unless talk about vaccine trials (primary prevention).
- Mads Lundbeck: the state of the art. The most advanced thinking. With the FDA guidelines etc. defining new more sens scales: beyond the MMSE, ADAS, and CDR etc.
- Primary prevention: family history / genetic risk

- Holly S. – are we really ready to conduct prevention trials? (Abbvie)
  - Pts may not have AD path. declining may be due to other issues & co-morbidity
  - Perfect world, tool would id the pathology: tau amyloid etc
  - Would need to follow the biomarker negative patients
  - Not just talking about AD.
- Lon: primary and secondary prevention can blur together
  - 60- 70 year 30-40% amyloid positive, over 5 years that 5-7% of the amyloid negatives. And other things are happening to people. Apply the intervention to all, and see who benefiting and how.
- Raeanne: need to define the population explicitly

- Lundbeck (Helle) : more to consider than interventional drug treatment. There are the lifestyle factors that impact rate of decline.
- Definitions are first: primary vs secondary (one or two papers)
- Those with the highest risk of developing AD.
  - High genetic load highest risk (Lon's table of life time risk for men and women from either general pop'n or had 1 or 2 apoE4 alleles. With one allele had a somewhat increased risk by age 75 is x % and higher than with no alleles.
  - This could be the main topic or at least a big message: Also confounds that in a 5 year study, the other risks that are modifiable, may well be getting modified by the participants. And, if other factors are influencing these modifiable. Things we don't recognize rae impacting and dooming our trials. How can new technology help? And, identifying them and accounting for them and designing for them in the paper

- Implicit requirements outlined by the two papers
- From what perspective are we coming into this.
  - What you should do!
  - Or, how to take the guidances that exist and how you use them in a trial

- Goal: of the paper
- Rosie C. (U Miami): Are we prevention AD or dementia?
- Lon:
- Lundbeck (Helle): which compounds is being taken into the trial also is a huge factor for how the study is designed.
- Targeting: modifiable risk factors vs. a target drug intervention, vs a more general intervention (hyperbaric o2, ultrasound guided…)
- Takeda TOMMOROW (Kathleen): what are the considerations going into a study being designed today. Where is the clinic to get normal people. What is the recruitment, what is the endpoint, how to enrich, risk and benefit or each age cohort's inclusion,
- Who is the audience of the paper: leverage what is known and go beyond the for the future.
- M Ryan: not yet ready to do a post mortem on the current trials. He also is a proponent of having multiple kinds of designs since knowledge of best practice can come from unexpected locations.
- generation trial: a portion of the alpha goes to Time to event outcome. Another portion of the alpha went to the cogn outcomes. Lon: it's an innovation for dementia trials, but not for interventional trials. This could be discussed in a position paper: don't use one outcome. Relooking at efficiency in a trial.

- M Ropacki: Advocacy for data sharing for improving future designs.
- (KAthleen): to Lon's question: what are we going to learn. The cohorts are so different. Heterogeneity will allow us to look at subgroups. The wealth of the data together will help drive the future
- Kim: Frequenist approach to Alzheimers trials. Moving away from p values and toward bayesian methodology. Models and predictions.
- M Walton: depends on having access to the patient level data from prior studies.
- Takeda: who is in the studies. Who stays in? Who are we really treating? Add in the tools (technology) to be able to capture the data for the subjects who left the study and maybe keep people in longer. (Not be left with the idiosyncratic group who made it through the trial).
- There are companies that pull data from EMRs.
  - Need to get consent for this and probably need to reconsent for this and some countries don't permit it regardless.
- There is often the statistical assumption that the drop out rate is random, but it is not.
- Lon: can comment on the system (health care) and what is a standard treatment? For oncology: they randomize to standard care or another treatment or add a new one on top.
- M Walton: this doesn't exist in primary care as much. In oncology one would go to the oncologist not the PC
- Tony (Sunovion): Resources: need to comment. N=3000, n=14,500 can't do this sort of n. So, how to design a study that can be done by smaller company? What would a study be that a smaller company can run?

- Tony , Sunovion: What do we need to know about the compound before put it into a bigger secondary prevention study?
- Kathleen (TOMMORROW): biggest reason for early termination: people feel threatened when they feel their cognition is slipping. Passively capturing this information would help. They planned from ADAPT. If can keep them in longer need fewer people.
- M Ropacki: IMI ePAD does this. Seamless adaptive trial with Bayesian modeling sharing risks. TTOny: we need to refer to this / touch on this.
- Before you do a prevention trial, show proof of concept. Question: what is the current state of the art on how to design a good proof of concept study.
- Alz Research Roundtable for proof of concept position paper exists: about 6 years ago.
- Mads: bapi trial – PET ab is coming close to being a surrogate. Working precompetitively to qualify a surrogate would be a tremendous step forward.
- Larry Adler: Repurposing a medication that is already out there. All of our discussion has applied to new chemical entities.
- Charles: Cognex, FDA asked to submit with phase 2.
- Lon - summary: talk to secondary prevention and deal with the issues involved in that. Touch on primary prevention in passing.

- Mads: maybe use the FDA stage 1 2 3 framework instead of secondary v primary prevention
- Travis: why not look at treatment responders vs non-responders. And, try not include the predictors of non-response.
- Kathleen: some of the goal of ePAD is for this. (ropacki)