Face-to-Face Meeting
AAIC 2018, July 20, 2018
Chicago, IL, USA

I. **Worldwide ADNI Updates**
    a. **AIBL – Chris Rowe**
        i. Started in 2006 – 10.5 review cycle nearly complete
        ii. Assessments
            1. Baseline assessments in 2314 (1476 CN, 394 MCI, 427 AD, 17 other). Still recruiting CN.
            2. MRI and Amyloid PET in 75%, but 95% of recruits since 2013. Conducted at 0, 18, 38 months, then every 3 years. All amyloid scans now with NAV4694. All results now available in centiloids (CL).
            3. Tau PET in 255 at baseline; 80 repeat scans. All tau PET scans now MK5240
            4. CSF in 250 participants – not serial
        iii. Current focus:
            1. Collaboration with J-ADNI on blood biomarkers (Nakamura et al Nature 2018)
            2. Pooling data with other large cohorts
            3. Supporting clinical trials in preclinical and prodromal AD
            4. Evaluating tau tracers
            5. Genetics
            6. Retinal scans
            7. CapAIBL – automated analysis package for MRI volumetric, amyloid and tau PET
            8. Will become part of ADNeT – the Australian Dementia Network, which was announced on July 1 and will include a registry, memory clinics, clinical trial sites, longitudinal and trial-ready cohorts.
        iv. Concerns
            1. Most amyloid-positive individuals going into clinical trials; thus it is hard to retain them in AIBL

    b. **Argentina ADNI – Ezequiel Surace**
        i. Started in 2012 with 56 participants (15 HC, 12 eMCI, 16 lMCI, 13 AD)
        ii. Baseline assessments – 100% neuropsychological assessments and MRI; 71% CSF Aβ and tau; 95% FDG-PET; 89% PiB PET
        iii. At 30 months – 12 HC, 6 eMCI, 15 lMCI, 2 AD
        iv. numbers incomplete for 60-month assessment, which will include PET tau and PET PiB for people who were PET negative at baseline.
        v. Concerns

1. High dropouts – reasons include death, hospitalization, or too far from center. Dropout rate at 1st year 14% now at the 60 month follow up only 14 people remain.
2. Small cohort generates difficulties in data analysis
3. Have not convinced other Latin American centers to participate

vi. Future plans
1. Will complete 60-month visit but do not anticipate extending further
2. Will try to apply to preclinical intervention based grants.
3. Will participate in WW-FINGERS, AA LATAM face-to-face, and Alzheimer's Prevention Initiative at AAIC 2018
4. Participating in Argentine Initiative for the Study of Down Syndrome and Alzheimer's (IASDA). , This is a 3 year longitudinal study with yearly clinical/neuropsychiatric evaluation, DNA/Plasma collection and PET.
5. Weiner urged continued participation in development of plasma assays.

c. **India ADNI – Naren Rao**
   i. Tata longitudinal study of aging in urban population age >50 years in southern India; will conduct baseline visit and follow up every 2 years including telephonic screening, clinical and cognitive assessments, blood, MRI, FDG-PET, carotid doppler, genotyping
   ii. Assessments: Baseline – 226 cognitive and clinical exams, 124 MRI, 44 PET; 1-year follow-up – 48 cognitive and clinical exams, 32 MRI; 2-year follow-up – 11 cognitive and clinical exams, 5 MRI, 2 PET
   iii. Using ADNI2 protocol for imaging studies, but will be shifting to ADNI3
   iv. Findings:
      1. Large number of comorbidities, especially hypertension and diabetes; also B12 deficiency, hypothyroidism, hypercholesterolemia
      2. Large number of white matter hyperintensities
   v. Srinivaspura Aging, Neuro Senescence and COGnition (SANSCOG) study in the Kolar district
      1. Collaboration of 4 groups
      2. Rural cohort >45 years
      3. N=10,000; MRI in 1000. Hoping to reach 1000 participants by next March.
      4. Using ADNI3 protocol – MRI, PET amyloid and tau
   vi. Concerns
      1. Struggling with amyloid and tau tracers in India
      2. Diverse environmental and socio-cultural factors
      3. Younger population than NA-ADNI (average lifespan in India is ~ 65 years)
      4. Many illiterates
      5. 2 predominant languages; will be doing cross-validation across 3 languages

d. **Japan ADNI – Takeshi Iwatsubo**

    i. Started in 2007 as 7-year study with 38 sites. Public funding from 3 governmental sectors
    ii. 537 participants enrolled (154 HC, 234 MCI, 149 AD)
    iii. Assessments – blood at every visit, CSF at baseline (37%), MRI, FDG-PET (63%), PiB PET (35%), clinical using Japanese translated Uniform Data Set.
    iv. J-ADNI database released on GAAIN for research use January 2016
    v. Comparison with NA-ADNI –
        1. Japanese AD group has more CDR 0.5 and fewer CDR 1.0;
        2. Japanese progress slightly faster in first year
        3. White matter disease not predominant (selection bias?); females tend to have less white matter disease
    vi. Articles published
        1. Iwatsubo T et al., May 2018. Japan and NA ADNI studies: Harmonization for international trials
        2. Iwata A et al. 2018 – *Alzheimer's & Dementia: TRCI* – cognitive decline faster in individuals with chronic kidney disease.

e. China ADNI – Kuncheng Li
    i. Plan to recruit 800-1000 participants at 90 sites (200-250 in four categories: NC, eMCI, lMCI, mild AD). So far have enrolled 146 participants including 62 in the past year.
    ii. Will collect data from: neuropsychological battery, blood and CSF biomarkers, APOE gene polymorphism, MRI, FDG-PET, and amyloid PET.
    iii. Research studies:
        1. Local-to-remote cortical connectivity in aMCI. (Zhang et al. 2017. Neurobiology of Aging 56:138-149.)
        2. 3-D ASL evaluation of AD – abnormal perfusion in AD may be a significant biomarker for early diagnosis.
        3. Epidemiological investigation in poor, rural area with high rate of illiteracy. Lower level of education and lower income correlated with higher rates of cognitive impairment.
        4. Traditional Chinese medicine –
            a. Four-gate acupuncture slowed progress of perfusion deficit
            b. Traditional Chinese Tuina improved mental state, cognition, flexibility of action, and sleep in AD patients.

    iv. **CAADI – Chinese Aging and AD Initiative - Yong Shen**
        1. Focus on AD, depression, autism; new technologies and big data. Multi-center program in Hefei.
        2. China Brain Initiative - Develop brain machine intelligence techniques, understand neural basis of cognitive function
        3. National Science Foundation of China projects:
            a. Mechanisms of Organ Aging and Degeneration (2016-2024).
            b. Mechanisms of cerebral small vessel diseases and clinical evaluation technologies.
        4. Chinese Academy of Sciences advanced medical research program in aging. Five directions: develop new technologies that can apply to

aging; dissect mechanisms of conversion of aging to degenerations; make early diagnosis and prevention of degeneration; Diseases

    f. **Europe ADNI – José Luis Molinuevo** presented on EPAD (Giovanni Frisoni unable to attend meeting)
- i. EPAD – public-private partnership is setting up infrastructure to perform proof-of-concept Phase 2 trials in prodromal and preclinical subjects.
  1. Longitudinal cohort study – originally aimed to enroll 6000 subjects, currently close to 1000. Now aiming for 3500.
  2. Risk score – probability spectrum of risk for AD
  3. Adaptive design with master protocol

II. Related project updates
    a. **WW-FINGERS – Miia Kivipelto**
- i. Multidomain trials aiming to prevent cognitive impairment and dementia.
- ii. Hope to learn from ADNI lessons related to data harmonization (genetics, biomarkers, biospecimens), harmonizing interventions and outcome measures and adapting them to different settings, introducing bioinformatics approach.
- iii. WW FINGERS was launched at AAIC 2017 along with US POINTER, new collaborating countries: UK FINGER, MIND China, FINGER, Maintain your Brain, SINGER, interested countries: Canada, Mexico, Argentina, Germany, Spain, Italy, etc.
- iv. US-POINTER – 2000 participants age 60-79 with normal cognition but at increased risk. 2-year intervention; global cognitive composite outcome.
- v. MIND-CHINA – will use cluster randomization by village. 3000 participants age 60-79. 3 groups: control, vascular intervention, multimodal intervention. Also doing MRI substudy.
- vi. MIND-AD moving from at risk target group is prodromal AD+vascular+lifestyle risk factors. Will combine multimodal intervention. with medical food to see if there is a synergistic effect.
- vii. SINGER in Singapore – 6-month feasibility study with 150 participants. Multidomain intervention.
- viii. European Dementia Prevention Initiative – FINGER, Pre-DIVA, MAPT
- ix. Diet harmonization will be an issue, healthy diets will be dependent on the country's respective food

    b. **Private Partners Scientific Board (PPSB) – James Hendrix**
- i. PET endpoints WG working with PET core to support execution of ADNI3; also looking at feasibility of early frame amyloid (EFA) PET. Proposal to assess EFA in ADNI3.
- ii. Blood Biomarker WG (BBWG) – 4 companies have requested residual samples; 3 of these have been approved.
- iii. Clinical Endpoints WG – has been working on implementing Cogstate brief battery.
- iv. PPSB contributions to Genetics Core – 3 companies came together to look at DNA methylation; results to be presented at AAIC.

     v.   Resource Allocation Review Committee (RARC) – Separate RARC required for genetic material; also a separate RARC proposed for postmortem tissue.

III.   ADNI 3 update – Mike Weiner

    i.   Now have over 1400 publications

    ii.   Now have substantial tau PET data but donation of AV1451 by Lilly has been curtailed; will pay Lilly for more production.

    iii.   Fixed ADNI Data sets – plan to establish additional fixed data sets (FDS) to ease use of ADNI data for researchers having difficulty figuring out how to select subjects.

    iv.   Blood tests becoming more important for developing: Polygenic risk scores. Time will come when blood samples will enable ATN classification. Now have 250K plasma samples in repository.

    v.   Rationale for ADNI4

        1.   Expand work with plasma samples – use to validate many assays

        2.   Perfect data set to identify which cognitive normal subjects will decline, who is at risk; very important for prevention trials.

        3.   Develop better markers of inflammation and microglia activation

        4.   Develop more robust PET ligand

IV.   ADNI3 Core updates

a.   Clinical Core – Ron Petersen & Paul Aisen

    i.   Have collapsed CN and MCI groups.

    ii.   New components for ADNI3 – MINT instead of Boston naming, Cogstate, Financial Capacity Instrument – short form (FCI-SF) (because FDA wanted functional test in unimpaired groups and FCI has shown some sensitivity). Brain Health Registry is co-enrolling and referring participants to ADNI.

    iii.   ADNI3 now has 615 participants: 375 rollovers + 240 new participants.

    iv.   Recruitment good: now ~.72/month/site; however minority enrollment still only 10% and slow enrollment of MCI and AD cohorts. Planning more incentives, recruitment funds, pulling back on CN enrollment, focus on diversity efforts.

b.   PET Core – Bill Jagust

    i.   Scan status: AV1451 – 486 total; florbetapir – 2573 total; florbetapen - 77 total; data very noisy. FDG scans only done in ADNI3

    ii.   Conversion to CL thresholds so that data can be compared across tracers and laboratories - done for florbetapen and florbetapir; need to see how they play out.

    iii.   AV1451 data – as expected, amyloid positivity increases as cognitive impairment progress; more tau seen in amyloid positives vs amyloid negatives.

        1.   In multivariate model, amyloid status, diagnostic status, and sex are greatest predictors of AV1451 positivity.

        2.   Exceptions being investigated:

        a. some impaired amyloid positive subjects have low tau and some amyloid negative subjects have high tau in medial/inferolateral ROIs.

        b. Between 25% and 45% of impaired amyloid positive subjects have tau in normal range. They are disproportionally male, less impaired, have more white matter hyperintensity, larger hippocampus, and less likely to be E4+.

        c. Amyloid negative impaired subjects – may be PART?

    iv. EFA - wash-in phase provides information about perfusion, while late phase shows binding. So EFA is a perfusion measure, correlates with glucose metabolism and cognition. Thus, it provides functional information and may be able to reduce variability in longitudinal studies.

c. **MRI Core – Cliff Jack**

    i. As ADNI has matured, data has become more heterogenous because of changes in vendors, hardware, operating systems, protocols, etc. One of goals of ADNI3 is to determine the effect of better technology on quantitative metrics, i.e., does it translate into better diagnostic performance.

    ii. Preliminary data suggests there is no effect from protocol change but significant effect from vendor change.

    iii. fMRI – developed network failure quotient (NFQ) as a marker of changes in functional connectivity. Using this metric, the degree of separation between CN, MCI, and dementia went down in ADNI3 vs. ADNI2 – may result from people moving to different systems.

    iv. Pulsed Arterial Spin Labeling (PASL) – compared 3D vs. 2D PASL – appears that newer and more complex measures result in better diagnostic performance.

d. **Biomarker Core – Les Shaw & John Trojanowski**

    i. Now have a total of nearly 250,000 serum and plasma samples and >60K CSF samples with increasing requests for these samples..

    ii. Aim in ADNI 3 to standardize measurement of CSF $A\beta_{1-42}$, t-tau, and p-tau$_{181}$ using Roche automated immunoassay platform, with LC/MSMS as the reference method. Also measure other Aβ species. Analyses in ADNI1, ADNIGO/2, and DIAN CSF samples.

    iii. Comparing Aβ42/Aβ40 ratio to Aβ42 alone for concordance with amyloid PET, ability to predict cognitive decline and progression to AD dementia in MCI participants, and for use in ATN pardigm.

    iv. Collaborating with non-ADNI cohorts.

    v. Evaluating other CSF proteins such as neurogranin as a biomarker for synaptic function. Seems to increase confidence in AD diagnosis versus other neurodegenerative diseases.

e. **Genetics Core – Andy Saykin**

    i. New biosamples collected in ADNI3 – PBMCs and RBCs.

    ii. Many publications using ADNI genetic data.

iii. Association of top IGAP AD candidates with imaging findings (Apostolova 2018).
iv. GWAS on key ADNI-2 endophenotypes (Jacobson presenting at AAIC) – many are HLA region genes associated with the immune system.
v. Stratification by polygenic risk score (Desikan RS 2017).
vi. Mapping bile acid ratios onto cortical phenotypes and FDG-PET.
vii. DNA methylation in known and novel genes.
viii. Telomere length study (Nudelman K) – possible aging biomarker shows small longitudinal difference between CN, MCI, and AD.
ix. Planning: additional whole genome sequencing; transcriptome and epigenetic profiling of ADNI's longitudinal DNA and RNA samples; systems biology research with AMP-AD/MOVE-AD, and others; collaborate with partners on molecular and functional validation studies; continue discussions with interested PPSB members on joint multi-omics analyses; collaboration with neuropath core on relating pathologic features to genetic variation.

f. **Biostatistics Core – Laurel Beckett**
   i. ADNI3 still mostly cross-sectional.
   ii. Evaluating Financial Capacity Instrument (FCI) in 384 people. AD subjects much worse; MCI subjects closer to CN than to AD. However, on timed performance, MCI subjects about half way to AD, suggesting that time may be the important metric.
   iii. Assessing agreement among different amyloid measures (AlzBio3, Roche, florbetapir). Good agreement for the most part.
   iv. Study non-linearity in the CSF-PET imaging relationship.
   v. Other activities: finishing analyses of ADNI2 data; assessing added value of baseline imaging and fluid biomarkers to predict cognitive decline; collaborations with Japan ADNI, DIAN, and ATRI; working to update website to make more user friendly.

V. **DIAN/ADNI Comparison Study – John Morris**
   a. ADAD (DIAN cohort) and LOAD (ADNI cohort) get to amyloidosis by different mechanisms but both have altered Aβ homeostasis. Purpose of the study is to determine if downstream mechanisms are similar and thus, if they would respond to therapies in the same way.
   b. Biomarkers similar except PiB PET in ADAD shows amyloid in cortex plus basal ganglia, versus only cortex in LOAD.
   c. Neuropathologically – LOAD associated with many pathologies; ADAD generally free of other pathologies other than synucleinopathy.
   d. To compare cohorts, anchored on dementia progression using CDR-SOB.
   e. Results – Both LOAD and ADAD have long asymptomatic period. Endophenotypes seem to be identical at symptom onset – increased amyloid, tau, hippocampal atrophy, cog decline. Once symptoms appear, DIAN participants have accelerated cognitive decline, more rapid hippocampal volume loss, possibly more rapid amyloid PET burden. Other biomarkers are similar.

f. Conclusions – suggest that biomarkers reflect similar mechanistic changes; therefore, if a compound shows efficacy in ADAD, it may extrapolate to LOAD.

VI. **Comments**
a. Weiner cited the need to coordinate plasma assay efforts between consortia; need consensus on how this is done, how to report data, and how to build a common database. Hendrix noted that the ADDF/Gates Foundation is investing in research in this area; Carrillo added that we need to get ahead of these projects in terms of standardization and harmonization.