WW-ADNI

Minutes of meeting – July 11, 2014

Copenhagen, Denmark

1. Welcome and introduction – Michael Weiner
2. WW-ADNI Core Presentations
   1. NA-ADNI Overview – Michael Weiner
      1. Naturalistic study of AD progression involving 57 sites and 1700 subjects:
         1. 350 Normal controls
         2. 150 subjective memory complaint
         3. 850 MCI
         4. 350 AD
      2. Assessments: clinical, blood, spinal fluid (CSF Aβ and tau), cognition, imaging (MRI, FDG-PET, Amyloid PET), genetics, neuropathology
      3. Contributions:
         1. Standardized methods
         2. First large multisite study using amyloid imaging
         3. Wider acceptance of lumbar puncture
         4. MRI across vendors
         5. Data sharing model
         6. Led to WW ADNI, GWAS, whole genome sequencing, US Department of Defense (DOD) tau PET imaging,
      4. Other ADNI-like projects – DOD ADNI, DOD MCI ADNI (PTSD and TBI), tau imaging study, Depression ADNI, Parkinson’s Progression Markers Initiative (PPMI), TRACK TBI, DIAN
      5. Predictive power of florbetapir and PIB imaging across disease stages, impact of ApoE4 status.
      6. Planning for ADNI 3 (2016-2021)
         1. Add tau PET
         2. Continue multimodality MRI
         3. Mass spectrometry for CSF analysis of Aβ
         4. Computer-based neuropsychological testing; pilot with CogState
      7. Emerging importance of tauPET – (to be studied with DOD funding) – many autopsy pathology studies show that tau tangles correlate with synapse loss, neuron loss, memory loss, cognitive decline. Hope is that longitudinal tau deposition will correlate with progression and that slowing of tau deposition would indicate disease modification (i.e. surrogate endpoint).
      8. ADNI data sharing is a model for future science - all raw and processed data are shared on internet with no embargo.
      9. The Brain Health Registry – addresses the high cost of trials as an obstacle to effective treatments; uses the internet to recruit, assess, screen, and monitor subjects – 8,000 subjects in San Francisco Bay area already enrolled; have obtained cognitive data on 2500 within just a few months.
      10. Funding – NIA; PPSB partners through FNIH also major contributors
      11. Comment on allegations about quality of Japan ADNI data – investigation showed no evidence of fraud or fabrication. Japan ADNI has been extremely successful.
   2. Clinical Core – Ron Petersen
      1. Now have hit or exceeded targets in all 5 groups (CN, SMC, early MCI, late MCI, AD):
      2. Baseline clinical characteristics, demographics, and cognitive measures reinforce continuum from normal to AD dementia.
      3. Added ECog (everyday cognition) assessment – both self and partner subjective impressions. Shows that in normal and early MCI, participants view severity worse than study partners, but this flips in late MCI and AD.
      4. Planning for ADNI 3 – trying to balance scientifically interesting questions with how we can best inform drug development/clinical trials. Need to think about where clinical trials are likely to be 3-4 years in the future, e.g., do we need to look at new groups, etc. and should we be addressing gaps in understanding how AD progresses. Ran ideas by the PPSB. One idea was that we may have learned all we need to know about dementia and should focus on earlier stages, but there was a clear and resounding “no” from the PPSB – we still need to learn more about the dementia stage. Other things being considered are dropping the early MCI/late MCI distinction, enriching enrollees with various biomarkers and genetic marker, and enrolling younger subjects and if we do that, identifying appropriate markers to follow.
   3. Biomarker Core – Les Shaw
      1. Studies reported using ADNI biofluids: mrm/tandem MS study of 567 tryptic peptides associated with 221 proteins
      2. Newly approved studies using ADNI biofluids: YKL40 and Vilip1, metabolic pathways and networks, DDE (breakdown product of DDT), Neurogranin, Tau in plasma, phosphorylated α-synuclein.
      3. 2014 ADNI2 batch analyses of CSF completed and uploaded data on ADNI/LONI website in June 2014:Test-retest performance – R2: tau .986, Aβ42 .924, ptau181 .988; %CVs range from 4.9% to 7.2%
      4. ADNI1 and GO+2 baseline comparison
      5. Progress report on mrm/tandem MS reference method for Aβ1-42 – published two papers on the round robin study; pilot assessment of IRMM standard is underway
      6. Supporting other standardization efforts with GBSC, CAMD, Japan ADNI
      7. Planned analyses
         1. Continued systematic documentation of performance of AlzBio3 and mrm MS assays
         2. Document that CSF biomarker-based incidence in ADNI2 subjects replicates that seen in ADNI1
         3. Establish clinical utilities of qualified mrm/MS methods
         4. Assess potential for new biomarkers to add sensitivity for detection of neuropathology and add predictive ability for progression of disease (e.g., VILIP-1, YKL40, proteins or peptide profile, neurogranin, Aβ42 oligomers, serum or plasma proteins including DDE and t-tau)
         5. Longitudinal CSF biomarkers
   4. MRI – Cliff Jack
      1. MR measures vary across different labs (Mayo, UCD, UCL, UCSF/VA, USC) – sMRI, cerebrovascular disease, ARIA-H, ASL, hippocampal subfields, DTI, TF-fMRI
      2. sMRI conclusions –
         1. no consistent differences between accelerated and unaccelerated
         2. when changing from unaccelerated to accelerated, no effect with Siemens or Philips, but effect with GE.
         3. Therefore, recommend using accelerated consistently.
         4. Sample size estimates 12 months, 25% effect size – CN and eMCI – n~200/arm, late MCI n~100/arm, AD n~50-100/arm
      3. CVD conclusions –
         1. Normals have less white matter hyperintensities (WMH) than others but no WMH group differences among cognitively impaired groups
         2. WMH increase in volume with time
         3. Individuals with greater WMH at baseline have greater cognitive decline over time.
      4. Microhemorrhages – prevalence in ADNI cohort 25%, increase with age and amyloid load. Greater number at baseline associated with greater annualized rate of additional microhemorrhages.
      5. ASL – decreasing perfusion at baseline associated with greater impairment and greater rate of decline associated with greater impairment
      6. Hippocampal subfields – no clear advantage over standard hippocampal volume measurement
      7. DTI – provides additional biological information
      8. Resting state fMRI – best performance measure for group-wise discrimination – see progressive decline in connectivity except in normals.
      9. ADNI3 considerations:
         1. Perform all sequence types on all scanners/subjects to the extent possible.
         2. Favor fragmented vs. standardized experimental sequences. Some systems can do this but not all, however the rationale is that by the end of the study what is now state of the art will be routine and unless we test these advanced techniques in the context of multi-site environments we won’t know if they have anything to add.
         3. Core sequences and experimental sequences proposed; however if we did all these sequences the scan would be over an hour (capped at 30 minutes in ADNI1) so it still has not been determined which sequences will make it into protocol.
   5. PET – William Jagust
      1. Over 1400 FDG scans done on nearly 700 subjects; about 300 have had more than four scans.
      2. About 384 subjects have had florbetapir scans at two time points and by the end of the year about 100 subjects will have more than 3 scans.
      3. Number of positive florbetapir scans among normal and SMCs is similar.
      4. Longitudinal florbetapir data – using cerebellum as a reference region does not work very well so we are using a composite region. Conversion is slow and very early in the progression of AD.
      5. ADNI3 – why tau imaging?
         1. Correlates with severity – can be an outcome marker
         2. Can be used for subject selection
         3. May be helpful in studies of tau targeted therapies.
      6. Tau imaging – 3 potential families of compounds; 2 ADNI pilot grants proposed using AV-1451 (also called T807)
      7. FDG scan opposite of tau scan
      8. We are very excited; beginning to see thing that make sense. With dynamic data we will have a good handle on how to analyze this when it becomes an ADNI staple.
   6. Genetics – Andrew Saykin
      1. Many papers published using ADNI genetic data – mixture of ApoE and GWAS studies.
      2. ApoE genotyping complete on all ADNI subjects (n=1720)
      3. Impact of diagnosis and ApoE status on regional amyloid deposition, CSF amyloid and tau measures, medial temporal lobe atrophy, and regional glucose metabolism – (oral presentation at AAIC on 7/14) – profiles are different in terms of the gene effect and diagnostic presentation effect, and complementary information by combining modalities and combining genetics with clinical presentation.
      4. Whole genome sequencing data analysis – very challenging in part due to huge files. We are processing on giant supercomputer at Indiana University for 10 months. Reconstructing data using Broad Institute’s public pipeline. Now will compile results into a usable file for analysis and make available in coming weeks or months.
      5. Preliminary Illumina-generated results being presented at this meeting, including rare ApoE variants, PSEN1 variants and relationship to LOAD, PLD3 variants correlated with imaging phenotypes, butyrylcholinesterase variants as predictors (along with ApoE) of florbetapir variants.
      6. Other directions: RNA studies by BMS, metabolomics
      7. ADNI 3 planning:
         1. Collect DNA longitudinally to look at epigenetic changes
         2. Sequential RNA studies to look at changes in transcriptome as a function of stage.
         3. Nature of cell lines that have been collected and considering possibility of collecting other kinds of cells (e.g., PBMCs or fibroblasts) that could be useful for stem cells.
         4. Investigating ways to integrate/analyze/leverage different omics data.

* 1. Neuropathology – Nigel Cairns
     1. So far 63 deaths of participants and 40 autopsies
     2. Average age 80.7; clinical diagnosis 78% with AD, 10% MCI, 12% still waiting. Neuropathologic diagnosis – vast majority have AD as primary diagnosis but a significant number have mixed diagnosis or other diagnosis. Most cases have insignificant cerebrovascular disease.
     3. Clinical and multimodal biomarker correlates in 22 cases – see JB Toledo et al paper 2013 (Acta Neuropathol Commun 2013 1:65). Clinical diagnosis of DAT or MCI due to AD was supported by pathological diagnosis of AD in all cases. Other pathologies also seen: TDP, SVD, DLB, AGD, HS
     4. Semi-quantitative neuropathologic “heat map” grading of ADNI cases shows difference between AD and AD+DLB pathology.
     5. Core also serves as the DOD ADNI NP core and DOD MCI ADNI NP core.
     6. For ADNI3 – continue to promote donations, provide standardized neuropathological assessment, maintain repository of fixed and frozen tissue, and conduct neuropathologic correlative studies with biomarkers and imaging measures of molecular pathology of AD.

1. Worldwide partners
   1. AIBL – Chris Rowe
      1. In AIBL, have been using PiB for a long time; also other ligands in some subjects (florbetapir, flutemetamol). 4.5 year data release coming soon.
      2. Major results:
         1. Last year showed data on natural history of Aβ deposition in sporadic AD.
         2. 3-year clinical progression rate vs. PiB SUVR, with about a 30 year accumulation period for amyloid; even more informative when combined with ApoE4 status, hippocampal volume, and episodic memory (CVLT).
         3. Looking at accumulators: Initial Aβ burden better predictor of progression from MCI to AD than rate of Aβ accumulation, but both amount of amyloid in the brain and the rate of accumulation drives the rate of decline.
         4. Also have looked at other factors that can improve prognostic ability – cerebrovascular disease, executive function, educational attainment, genetics (apoE seems to be the biggest driver), SMC, BDNF Val66Met. Overall: high Aβ combined with ApoE4+ and BDNFMet predicts higher rate of memory decline.
      3. Other studies:
         1. Retinal amyloid fluorescence imaging – correlates with neocortical SUVR
         2. Investigating blood-derived exosomes as biomarkers for AD – 17 exosomal miRNAs dysregulated in AD compared to HC.
         3. Blood based biomarkers – correlation with neocortical amyloid burden (will be oral presentation on July 14 by Burnham et al)
         4. Role of diet and physical activity
      4. Future directions:
         1. Further refine prognostic value and comparative effectiveness of imaging and blood biomarkers
         2. Examine genetic and environmental influences
         3. Add tau imaging
         4. Create new pool of amyloid positive HC and MCI for early intervention studies
         5. Use AIBL infrastructure to support A4 and DIAN therapy trials.

* 1. European ADNI/PharmaCog WP5 – Giovanni Frisoni
     1. PharmaCog WP5 includes 13 centers across Europe with planned enrollment of 150 MCI subjects assessed with ADNI protocols. Enrollment was slow in the beginning but is now complete (147 subjects)
     2. Several papers published or in press:
        1. Biomarker validity in tracking disease progression at MCI stage (Drago et al JAD 2011)
        2. Multisite reproducibility of atrophy rates (Jovicich et al Neuroimage 2013)
        3. Review of animal models for AD drug discovery (Marizzoni et al Drug Discovery Today 2013)
        4. Multisite longitudinal reliability of TBSS in DTI (Jovicich et al Neuroimage 2014 in press)
     3. Papers in progress:
        1. Descriptive study of baseline biomarkers
        2. Multisite reproducibility of rest fMRI
        3. MR diffusion study in TASTPM Tg mice
        4. Entorhinal cortex structural study in mouse models
     4. Other projects/products:
        1. Healthy volunteer dataset
        2. Data sharing with IMI EMIF-AD
        3. EPAD – largest project funded by European Commission to develop infrastructure in Europe to carry out primary prevention clinical trials
        4. HarP – harmonized hippocampal protocol
  2. Korea ADNI – Seong Yoon Kim
     1. Now in 2nd year of 6-year project
     2. Established infrastructure in 2013; 14 clinical sites; hope to have 10-11 more.
     3. Subject recruitment (n=500) scheduled for 2013-2015 has been delayed because of several factors (trimming of extensive neuropsychological evaluation, establishment of eCRF and LORIS networking, approval of flutemetamol by Korea FDA, IRB processes, etc. First subject to be recruited in August.
     4. Targeted enrollment: 50 HC, 200 aMCI, 100 MCI with WMH (50 moderate/50 severe), 150 mild AD (50 each with mild/moderate/severe WMH).
     5. Other national projects to parallel K-ADNI:
        1. Biomarker National Centers
        2. Development of dementia prediction map
  3. China ADNI – Zhigang Qi
     1. Plan to enroll 800-1000 subjects at 80 sites: 200-250 each of HC, early MCI, late MCI, mild AD
     2. Neuropsychological battery, biomarkers (blood, CSF, genetics, PET, MR
     3. Slow enrollment – now have a total of 41 cases
     4. Genetics study in a family with ADAD – APP K724M gene mutation identified
     5. MR and FDG-PET studies (no AV-45 PET)
     6. Epidemiologic research study in southwest China – 10049 cases older than 40 years. 228 (2.269%) suspected cognitive impairment including 199 AD and 29 VaD. (Paper is published in English in *Alzheimer's & Dementia*)
  4. Argentina ADNI – Gustavo Sevlever
     1. First part of study in a single center (FLENI) – 60 subjects screened, 50 enrolled and followed for 1 year. (HC=10, eMCI=15, late MCI=16, AD=9.
        1. ADNI protocols plus cognitive reserve inventory and PiB PET scan.
        2. CSF on 76%, PET-FDG on 98%, PET-PiB on 86%
     2. Main project will be a multicenter cohort from 2015-2018
     3. FLENI houses nly brain bank in Argentina; ADNI participants are asked to consent to brain donation at the time of death.
     4. Papers published and submitted
     5. Participating in DIAN study
  5. India ADNI – Viji Ravindranath
     1. Not yet part of ADNI, but poised to join.
     2. Diversity in India – demographic, language, cultural; very little known about ApoE and other genetic factors
     3. High prevalence of cardiovascular risk factors
     4. Research studies:
        1. Bilingualism delays age of onset of dementia independent of education and immigrant status (Alladi et al, Neurology)
        2. Investigating traditional medicine for discovery and development of rational therapy for brain disorders – purified extract containing 5 compounds and hope to take to preclinical trials. LRP1 down-regulation reverses therapeutic effect of this extract.
     5. New funding:
        1. Tata Trusts US$15 million for 5 years to Center for Neuroscience to study presymptomatic AD (mouse to humans)
        2. Endowment from Pratksha Trust (US$37.5 million) for Centre for Brain Research
  6. EMA Perspective – Maria Isaac
     1. EMA give support to 28 countries
     2. Centralized evaluation by the Committee for Human Medicinal Products (CHMP), Scientific Advice Working Party (SAWP)
     3. Qualification of novel methodologies - qualification advice and opinions
     4. Work in parallel with FDA – increase dialogue, exchange views, but each agency issues a separate response.
     5. Examples of advice/opinion:
        1. Qualification opinion on low hippocampal volume by MRI for use in clinical trials for regulatory purpose in pre-dementia stage of AD. Worked with CAMD on this.
        2. Qualification opinion of a novel data driven model of disease progression and trial evaluation in mild and moderate AD (worked with CAMD)
     6. Many stakeholders; vision is to speed up/optimize drug development and utilization and improve public health.

1. Big data and data sharing
   1. EMIF – Johannes Streffer
      1. Vision is to be a trusted hub in Europe
      2. 56 partners - academic, patient organizations, SMEs, Efpia (pharma)
      3. EMIF-AD – use existing datasets through data platform
         1. use extreme phenotypes as an outcome (e.g., amyloid pathology, ApoE status, hippocampal atrophy, cognitive decline)
         2. fingerprint data
         3. working with electronic health records – how to leverage data.
         4. Linkage of many cohorts – diverse data ownership and availability.
      4. One example: AddNeuroMed – 697 total subjects (normal, AD, MCI) from 27 AD cohorts – clinical, MRI, blood based biomarkers; 3-8 year follow-up. Resulted in 45 publications 2006-2014.
      5. AD Big Data DREAM challenge – new analyses of existing datasets:
         1. Subchallenge 1 – predict the change in cognitive scores 24 months after initial ssessment – using ADNI as training set with ancillary data from AddNeuroMed; then Rush, ROS/MAP as test set.
         2. Subchallenge 3 – classify individuals into diagnostic groups using MR imaging – using ADNI as training set, AddNeuroMed as Test set.
      6. Data aggregation and access – US and Europe – (GAAIN/EMIF) - challenges with making data sharable and accessible and with patient consent issues.
      7. Exploring different funding models to ensure sustainability
   2. GAAIN and LONI – Arthur Toga
      1. Diversity of data – structural and functional; protein to behavioral; integrating in a common framework presents challenges.
      2. Models, databases, tools
      3. Centralizing data is a challenge that does not scale well (e.g., ADNI, LONI, Human Connectome project)
      4. GAAIN uses a federated rather than centralized approach – network of machines allows more efficient distribution.
      5. Problems for investigators: what data exist, how to get it, what are rules, how to combine
      6. Problems for data holders – ownership, privacy, control of data, assigning credit
2. ADNI-inspired/leveraged studies
   1. White matter disease study (Canada) – Sandra Black
      1. Medical Imaging Trials NEtwork of Canada (MITNEC) - four themes; one is imaging trials in neurology.
      2. Rationale for study –
         1. small vessel disease often coexists with AD and can contribute to cognitive decline.
         2. Longitudinal imaging using cerebral amyloid labeling to understand additive/interactive effects of AD and small vessel disease.
         3. Elders with white matter disease (WMD) at risk for amyloid; may be a target group for prevention
         4. Management of vascular RFs could slow progression to dementia?
      3. Aims of study:
         1. Determine in patients with significant WMD the prevalence and degree of uptake of amyloid on PET relative to baseline clinical and other brain imaging measures; and whether baseline WMD predicts increased amyloid uptake
         2. Evaluate changes in amyloid uptake and correlation with changes in other clinical, structural, functional measures
      4. Primary hypotheses: patients who have a high burden of periventricular white matter hyperintensities (pvWMH) will have a higher likelihood of positive amyloid scans; the volume of pvWMH will correlate with standardized measures of florbetapir uptake; patients with a high burden of pvWMH volumes will show greater increases in amyloid deposition.
      5. Secondary hypotheses: patients with abnormal florbetapir uptake ratios on PET at baseline will have lower cognitive scores, hippocampal and brain volumes, metabolism (FDG-PET), and larger ventricular volumes than people with amyloid negative PET scans; baseline positive florbetapir uptake will predict greater cognitive and functional decline at one year..
      6. 120 patients – with NC, MCI, AD subjects as control group.
      7. 3T MRI, FDG-PET, florbetapir PET, neuropsychological testing, blood sampling at baseline and one year.
   2. Women’s Healthy Ageing Project (Australia) – Cassandra Szoeke
      1. Rationale: early detection needed and prodrome is several decades, therefore need to study people earlier in disease. Midlife vascular risk factors strong impact on late-life disease; therapeutic window in midlife? Need 20 years longitudinal prospective study with RF, confounders, cognitive trajectories.
      2. N=438 in 1991; 67% retention at 15 years, 58% retention at 22 years
      3. Assessments:
         1. Cognition – 4 times over 15 years
         2. Clinical/psych – 12 times over 22 years
         3. Lifestyle/physical activity – 11 times over 22 years
         4. Biomarkers and stored specimens – 11 times over 22 years
         5. Nutritional and BMD – 3 times over 22 years
         6. Imaging – 2 times (2002, 2012)
      4. Compared with AIBL BL cohort – no statistically sig diff in age, vascular RFs, education, but statistically significant difference in proportion of ApoE4 positive participants (AIBL>WHAP)
      5. Data lock 2014 – presentation of data later this week. Research questions:
         1. Lifespan risk on late life cognitive trajectories and amyloid
         2. Cognitive trajectories and amyloid accrual over 65
         3. Cognitive trajectories and functional decline
      6. Findings:
         1. Subjects who refused PET scan recalled fewer words on CVLT; acceptance of PET scan associated with higher education
         2. Episodic memory at baseline negatively correlated with amyloid PET
         3. High vascular risk associated with elevated amyloid PET, especially in ApoE4+
         4. CVLT-delayed scores decline a decade before amyloid scan
         5. No association between SMC and amyloid accrual, except a question about confusion was significant for amyloid accrual
      7. Work plan:
         1. Earlier detection for those at risk of cognitive decline – investigate hormone levels and hormone therapy
         2. Lifespan approach to risk of cognitive decline – is there a therapeutic window?
         3. Impact on QOL and functional measures
         4. Lifespan biobank
         5. Imaging biomarkers

* 1. ADNI Veterans study (U.S.) – Michael Weiner
     1. Many studies (including autopsy) show association of TBI and PTSD with AD, but none use biomarkers
     2. 200 normal veterans and 200 Vietnam veterans with MCI, all over age 65 with history of TBI, PTSD, or controls
     3. Assessments almost identical to ADNI (except no FDG-PET and no perfusion MRI); also added tau PET with this cohort plus 50 controls, 50 MCI, and 50 AD subjects from ADNI
     4. Recruitment challenges – slow recruitment (85 subjects baselined so far); also difficulty enrolling African Americans despite the large numbers that served in Vietnam.
     5. Florbetapir scans – two subjects among the 9 TBI subjects showed asymmetric scans.