ADNI and Worldwide ADNI (WW-ADNI) Update Meeting
Minutes – July 12, 2013
Boston, Massachusetts

Attendees:

Maria Carrillo	Jessice Payne	Denise Ferraiolo
Keith Fargo	Jonh Hall	Shirley Lasch
Dean Hartley	Hiroyuki Arai	Ken Marek
Meredith McNeil	Takashi Asada	Neil Buckholtz
Heather Snyder	Hayashi Toshihiro	Richard Hodes
William Thies	Ryoko Ihara	Creighton Phelps
Salvador Guinjoan	Takeshi Ikeuchi	Martin Bednar
Chahin Pachai	Kenji Ishii	Ana Catafau
Pachai Amaravadi	Atsushi Iwata	Antonella Favit-Van Pelt
Alvy Mikulskis	Takeshi Iwatsubo	Susanne Ostrowitzki
Jesse Cedarbaum	Ryozo Kuwano	Celine Risterucci
Feng Luo	Shigeo Murayama	Misty Long
Holly Soares	Ikuhisa Sawada	CK Liu
Brucki Sonia	Morihiro Sugishita	Barry Greenberg
Ricardo Nitrini	Robert Brashear	Les Shaw
Diane Stephenson	Enchi Liu	William Jagust
Kuncheng Li	Richard Margolis	Laurel Beckett
Lance Macauley	Gerald Novak	Paul Aisen
Giovanni Frisoni	Geon-Ho Jahng	Michael Weiner
June Kaplow	Kwangseok Jeong	John Trojanowski
Susan Abushakra	Jong-Min Lee	Sandra Black
Adam Schwarz	Won-Jin Moon	Art Toga
Stacie Weninger	Sang Won Seo	Nigel Cairns
Paris Moore	Jae Seung Kim	Tae Sung Lim
Erika Tarver	Simon Lovestone	Annette Merdes
Zivjena Vucetic	Megan Pritchard	Maria Pueyo Ferenc
Igor Grachev	Andy Simmons	Martenyi
Francois Nicolas	Seong Yoon Kim	Andreas Meier
Susan DeSanti	Cliff Jack	Howard Fillit
Robert Green	Ron Petersen	Ralph Martins
Pravat Mandal	Michael Egan	Chris Rowe
Andrew Saykin	Stacey Wing	Cassandra Szoeke
John Lawson	Johan Luthman	Ara Khachaturian
Manu Vandijck	Bob Umek	Zaven Khachaturian
Asker Ahmed	Mark Frasier	

I. Welcome from Maria Carrillo, Alzheimer's Association

II. Comments from Neil Buckholtz, NIA - gratifying to see what has happened especially with respect to the database and access by researchers around the world. This is the way of the future.

III. Comments from Mike Weiner
   a. Korea has been funded and will start enrollment in 2014. Plans to follow ADNI model that data will be available without embargo; also in English.
   b. Summarize US ADNI (1, GO, and 2):
      i. Total enrollment – 413 normal, 49 SMCE + 40?, 565 late MCI, 3013 early MCI, 323 AD.
      ii. Important findings
         1. Patients with clinical AD who are APOEε4+ are 99% likely to be amyloid positive, vs. 55-75% of clinically diagnosed patients are APOEε4 negative and amyloid positive.
         2. Amyloid status is significant driver of brain atrophy
         3. Tauopathy in normal aging is accelerated by presence of amyloid.
         4. Arterial spin labeling (ASL) – cerebral brain flow (CBF) significantly reduced in AD subjects. Regional differences: in some regions, CBF with amyloid (by florbetapir) but the opposite in the posterior cingulate. Different patterns in normal, eMCI, lMCI, and AD. We conclude that Aβ pathology has strong effects on ASL-CBF. Structural MRI of entorhinal cortex and hippocampus is more sensitive than ASL-CBF to detect effects of Aβ pathology in late stage disease. ASL-CBF in some brain regions may be more sensitive than structural MRI to detect early effects of Aβ pathology.
         5. Now have funding to study veterans and the effects of TBI and PTSD on AD.
         6. Data sharing from ADNI study has resulted in 636 manuscripts, 329 have been published. WW-ADNI has extended around the world; would like to see more efforts in India and Africa.

IV. Core presentations
   a. Clinical (Ron Petersen and Paul Aisen)
      i. ADNI 2 enrolled 704 new subjects; also includes 273 continuations from ADNI1 and 120 from ADNI GO, for a total of 1097 subjects total at 59 sites in US and Canada: includes >300 controls, early MIC and late MCI, 49 SMC, 135 AD.

ii. eMCI is meant to capture individuals who are normal but leaning towards progression. SMC meant to capture at risk group. We are going to stop recruiting SMCs because of financial concerns.

iii. Baseline data (CDR-SB and ADAS 13) show these groups do represent the spectrum of cognitive impairment, although instruments do not appear sufficiently sensitive in early stages. However, they are more highly educated than general populations.

iv. Transitions: normal to MCI – about 16-20% per year with only about 4% backwashes.

v. A major advance has been the release of draft guidance from FDA, which embraces concept of prodromal AD defined as MCI plus biomarker evidence. Built to a great extent on ADNI data.

vi. This year will be launching A4 trial that will enroll amyloid positive normal population. Surprising design will use cognitive measure as outcome because WWADNI, AIBL, etc. have allowed us to determine early effects of amyloid on cognition.

vii. Major issue at FDA is role of patient symptoms and PROs in preclinical AD. ADNI has also been moving in that direction.

viii. Mike Weiner asked if anyone has calculated WW incidence of AD based on the observation that 1/3 of normals in their 70s have AD pathology; Paul agreed, saying WW numbers could triple or quadruple based on understanding that AD starts as a preclinical state, not with dementia or cognitive impairment.

b. MRI (Cliff Jack)

i. Major efforts over past year: ingest and organize methods, documents, data dictionaries, and numeric data to make accessible to public.

ii. Testing whether accelerated scans have equivalent or better performance compared to unaccelerated scans. Looks like they are equivalent. Further study warranted.

iii. Data are available at four sites: UCL, UCSF/VA, UCLA, Mayo

iv. FLAIR for cerebrovascular disease grading – shows eMCI may be more vascular/more heterogeneous. Also shows graded relationship between number of microhemorrhages and clinical severity.

v. Experimental sequences

1. ASL (Siemens) – eMCI slightly decreased perfusion in temporoparietal regions; more severe in AD. "ASL may turn out to be better than we thought".

2. T2 scan to measure hippocampal subfields (also using Siemens scanners; ADNI1 add-on project)

3. DTI (GE) – MD increases with clinical severity.

4. Task free MRI (Phillips) – little relationship to clinical severity.

vi. Protocol changes under evaluations:

1. Optimize high performance sites
2. Add DTI with better spatial/angular resolution to GE sites with SRM gradients
3. May add tfMRI and DTI to Phillips sites; and advanced tfFRI to GE sites.
4. Change phantom scanning to site requalification.

c. PET (William Jagust)
  i. Now have over 1,000 baseline florbetapir scans; 174 follow-up scans, 39 early frame datasets.
  ii. Have 2920 FDG scans.
  iii. Analyzing florbetabir data to identify inflection points – around 1.1 value.
  iv. Longitudinal data – looking at quality of data, plotting as function of age.
  v. APOEε4 study – only 56% of e4- subjects are florbetapir+, compared to 98% of e4+ are florbetapir+. CSF not that different. So a substantial number of e4- do not seem to have amyloid.
  vi. Relationship between florbetapir and CSF – Kappa = 0.779; no clear signal as to which becomes abnormal first.
  vii. CSF change by florbetapir status – good correspondence.
  viii. New initiatives:
    1. "early frames" add on – does early uptake reflect perfusion?
    2. Centiloid project (not ADNI) – an effort to standardize the reporting of PET amyloid tracer retention and clearly define thresholds.
    3. Tau imaging – may incorporate into ADNI; need to solve complicated issues.

d. Biomarkers (Les Shaw) – highlights from 2012-13
  i. α-synuclein correlates with tau & p-tau$_{181}$ but not with Aβ$_{1-42.}$ (Toledo et al)
  ii. Longitudinal data set analysis – supports Cliff Jack's progression model where Aβ$_{42}$ changes are earlier event than p-tau and tangle development.
  iii. Recently uploaded full analytical report –
    1. Showed reasonable precision and test-retest performance.
    2. Raw 2013 and raw 2012 – good concordance despite different lots, etc.
    3. Anchored 2012 compared to anchored 2013 – differences seen making mixing data difficult; not recommended.
  iv. Anchoring CSF biomarkers to "gold standard" – using a reference set of samples and will be reporting this.
  v. Protocol for developing and validating the UPenn/ADNI UPLC-srm/tandem MS method. Compared with AlzBio3 immunoassay – high degree of concordance although different values.

      vi. 4 labs testing samples in round robin to develop reference material that can anchor measurements across different labs, methods, etc. Working with IFCC.

e. Richard Hodes commented on how important ADNI has become to AD research and beyond, as an icon for data sharing, combining cutting edge intellectual, scientific, technologic efforts with commitment to share to maximize progress.

f. Neuropathology (Nigel Cairns)
      i. There have been 54 ADNI deaths; missed a few autopsies in the early years but now have 31 autopsies.
          1. Mean age 80
          2. Clinical diagnosis - 87% with AD dementia; 12% MCI amnestic
          3. All had AD – 52% e4+, 26% also had Lewy bodies.
          4. Other comorbid pathologies may contribute to variation in biomarkers
      ii. Data on LONI website, uploaded in format of NACC Neuropathology data element dictionary (version 9.1, Sept 2008).
     iii. FDG PET and CSF Aβ and α-synuclein distinguishes between ADNI participants with AD and DLB (Toledo et al).
     iv. This and other studies suggest that multidimensional data analysis of CSF biomarkers, functional and structural imaging, and neuropathology may detect comorbid (Lewy body) disease in at-risk subjects.

g. Biostatistics (Laurel Beckett)
      i. There will be a second web-based biostatistics unit on August 1. Will focus on challenges of working with ADNI data.
      ii. Since last year, big increase in numbers of participants as well as follow-ups on new and continuing subjects. Thus, more images processed and summaries posted. Being posted with increasingly sophisticated documentation, so easier to find and more complete.
     iii. Data suggest that, as expected, eMCI fit between NC and MCI. SMC closer to NC.
     iv. Rich set of longitudinal data – beginning to see more sophisticated longitudinal patterns and trajectories. This allows us to examine relationships among ADNI mesures.
      v. Measuring and comparing how biomarkers capture progression – goal is to create a unifying framework for validating and comparing biomarkers with a common metric.

h. Genetics (Andrew Saykin) – highlights from 2013
      i. Many publications using ADNI GWAS and APOE data

    ii. Genes that have emerged include cell adhesion molecules, inflammatory, others.

    iii. Gene network analysis – systems biology approach, putting signals in context

    iv. Role of APOEε4 in early MCI; also looking at role of APOEε3

    v. GWAS related to amyloid PET burden

    vi. Whole exome sequencing – applying to other datasets (AddNeuroMed, MIRAGE).

    vii. Relationship of SPON1 gene to rate of decline – working with GENAROAD Consortium

    viii. GWAS of memory and aging with other NIA datasets.

    ix. Ongoing projects:
1. Whole genome sequencing
2. RNA working group

i. Data and Publications (Robert Green)

    i. Through June 30, 2013, 4401 investigators have sought access, 4104 approved

    ii. Many countries with ADNI data applicants – USA, UK, China, Japan, and Canada lead the way.

    iii. 1.3 million images in this academic year have been downloaded

    iv. Manuscript management – as of yesterday, 740 manuscripts have used ADNI data; 442 have been published and 9 are in press.

    v. ADNI has been acknowledged at White House – Stephen Friend was one of 13 "Champions of Change" honored for vision and commitment to open science on June 20th, 2013.

j. WGS (Robert Green) – ADNI Sequencing Working Group

    i. Partnership with Brin Wojcicki foundation and Alzheimer's Association

    ii. $2 million to sequence 818 samples using next gen sequencing (Illumina).

    iii. 200 terrabytes of data – LONI, Broad Institute, and Indiana Univ donated storage space.

    iv. VCF files will be available shortly.

    v. Brin Wojcicki Foundation offered additional $300K challenge grant; PPSB requested matching funds from 26 members.

k. Canada ADNI (Sandra Black and Howard Chertkow)

    i. 5 sites across Canada (University of British Columbia, University of Western Ontario (2), Sunnybrook Health Sciences Centre, University of Toronto and McGill University)

    ii. ADNI-2 received partial funding from CIHR.

        iii. Medical Imaging Trail Network of Canada (MITNEC) – Protocol "Amyloid and glucose PET imaging in Alzheimer and Vascular Cognitive Impairment patients with significant white matter disease."
1. Stratify patients by APOEε4 status
2. Evaluate changes in amyloid uptake and correlate with changes in clinical and structural/functional brain measures over 1 year.

        iv. Other Canadian cohort studies at Ontario Brain Institute, CIHR, Canadian Consortium on Neurodegeneration in Aging and Brain Canada.

V.   GAAIN (Art Toga) (Global Alzheimer's Association Informatics Network)
   a. Portal to share data
   b. Federated platform
   c. Global network of analysis and workflow software and tools
   d. Currently partners – ADNI, AIBL, CAMD, EMIF, NeuGRID
   e. Facility moving in entirety to USC – will have new data center, storage, equipment.
   f. Challenges –
      i. privacy protection across international boundaries
      ii. complexitiy of data
   g. Progress
      i. Initial set of standard terminologies
      ii. Subset of data exchanged
      iii. Mapping tool prototype
      iv. Federated database infrastructure
   h. Genetic data will also be available through GAAIN
   i. Plan to use lend-lease approach – users buy drives, we load data on them and ship back to user.

VI.   WW-ADNI Presentations
   a. AIBL
      i. Imaging (Chris Rowe) –
         1. 3 yr data available. Has been requested by 540 research groups from 35 countries.
         2. Now have 6 yr follow up PIB PET data
         3. Amyloid – 12 years from completely negative to SUVR 1.5; so entire process seems to be about 30 years.
         4. Predictive value of low vs intermediate vs high PIB finding – being strongly amyloid positive carries much worse prognosis.
         5. Initial Aβ burden is a much better predictor of progression from MCI to AD than the rate of accumulation.
         6. 13% of healthy older controls progressed over 3 years to MCI or AD - strongest predictor was subtle memory impairment plus positive amyloid scan.

       7. Plan to add tau imaging and replaced PIB with ^{18}F-NAV4694

   ii. Biomarkers & Lifestyles (Sam Burnham and Stephanie Rainey-Smith)
1. Blood based biomarkers
2. Extend to multimodality, including ocular imaging and clinical and cognitive measures.
3. Lifestyle programme aims to identify lifestyle and dietary modifications that can prevent AD.
4. MeDi associated with improved performance on verbal memory, executive function, language, and visuospatial function.
5. Prudent diet associated with improved performance on visual memory, language, and visuospatial function.
6. Western diet associated with increased cognitive decline
7. Physical activity data – suggest increased PA associated with decreased amyloid in APOEε4+ individuals only. Different story in periphery, where high PA associated with decreased Aβ in APOEε4 – individuals only.

   iii. WHAP Update (Cassandra Szoeke)
1. We have now put a number on the time for amyloid evolution of 20 years
2. Women's Healthy Aging Project (WHAP) looked at disease evolution from age 50 to 70.
3. Results will be presented at AAIC.
4. Started in 1990; we now have 20 years of data on more than 200 people. Looking for collaborators.

b. Japan ADNI (Takeshi Iwatsubo)
   i. 7 year study as of 2013, 38 clinical sites
   ii. Conversion of MCI to dementia - 19% at 12 months (higher than NACC)
   iii. Conversion CN to MCI – 1.4% at 12 months
   iv. Progression in CN e4 carriers – lower total brain volume than non-e4 carriers, also faster progression of atrophy in posterior cingulate, precuneus, and left temporoparietal cortex.
   v. J-ADNI2 launching in July 2013; will be focusing on earlier stages (preclinical, early and late MCI)
   vi. J-ADNI working on sharing data on LONI

c. Europe ADNI - PharmCog (Giovanni Frisoni)
   i. PharmaCog is IMI project
   ii. Studying humans and animals with homologous markers
   iii. Papers in press describe harmonization of methods
   iv. Characterization of MCI patients – by CSF Aβ42 status; correlated with structure, diffusion, EEG power density, cortical thinning. (data to be presented at AAIC)

        v. Upcoming: fMRI, peripheral markers, longitudinal markers, F18 amyloid PET. Also animal structural/diffusion MR imaging and histology.

d. Korea ADNI (Seong Yoon Kim)
        i. Now in year 1 – working to set up infrastructure.
        ii. Database to be aligned with ADNI if possible
        iii. Will be recruiting subjects for 2 years at 25 clinical sites; follow for 36 months.
        iv. Neuropsychological, clinical, MRI, PET (amyloid and FDG), biosample repository provided by national bio bank.
        v. Government requires that we upload data as soon as it is acquired.

e. Argentina ADNI (Salvador Guinjoan)
        i. Argentina has greatest percentage of at-risk individuals (those age 65 or older).
        ii. Recruited 60 adults age 66-90 for single center pilot study – 15 AD, 30 MCI, 15 HC
        iii. PET-PIB, FDG-PET, cognitive, CSF biomarkers,
        iv. Data in LONI
        v. Future – will begin using flutametamol (from GE); also starting to recruite prospective candidates for DIAN site. Plan to study adult children of AD patients with ADNI-like protocol plus autonomic and circadian abnormalities.

f. China ADNI (Zhigang Qi)
        i. Plan to enroll 800-1000 subjects at 80 sites in 4 groups: normal, eMCI, lMCI, mild AD.
        ii. Neuropsychological tests, biomarkers, MRI, PET (FDG and F18-AV45)
            1. MRI will include 3D T1 volumetric, DTI, resting state fMRI, MRS, Susceptibility weighted imaging
        iii. 16 new subjects enrolled since July 2012.

g. India ADNI (Asker Ahmed) –
        i. we have protocol in place but now need funding.
        ii. Targeted enrollment – 740 subjects; 5 year study

h. Taiwan ADNI (CK Liu)
        i. Under IRB review
        ii. Two stages: 1st stage six centers in Taipei area; 2nd stage in other parts of Taiwan
        iii. Expect to start recruiting by 2014 for 3 year longitudinal study.

i. Brazil ADNI (Ricardo Nitrini)

      i. Prevalence of dementia 5.1-19% in those over age 65; 55% due to AD.
     ii. Objectives common to other ADNI centers – establish biomarkers norms, study genetic polymorphisms.
    iii. NC, SMC, early and late MCI, AD
    iv. Similar measures as other countries – will be using flutametamol for amyloid imaging. Also have brain bank in Brazil.
     v. Hope to start in 2014.

VII. AddNeuroMed Imaging Update (Andrew Simmons & Simon Lovestone)
  a. 6 European sites, 385 subjects studied with MRI (1.5T structural at baseline, 3 months, 1 year), also clinical cognitive assessment, blood/plasma/RNA,
  b. Focus strongly on MRI, proteomics, genomics, lipidomics, metabolomics
  c. Bring together AddNeuroMed with other data from ADNI, AIBL, others
  d. Have been rewriting imaging database. New design scalable to tens of thousands of subjects, flexible in terms of integration with imaging pipelines, lots of features for automated data upload.
  e. EMIF – the European Medical Information Network – incorporates E-ADNI and AddNeuroMed. A public private consortium for reutilization of data for health research. More than 60 partners; more than €56 million,
      i. Vision: to enable and conduct novel research into human health by utilizing human health data at an unprecedented scale.
     ii. When completed, will have electronic health records on 40 million Europeans, AD data on more than 100,000 research participants, 50,000 blood samples, 10,000 subjects with MRI, >3,000 CSF samples, 1500 amyloid PET scans. Also data on diabetes and metabolic disorders on over 20,000 subjects.
    iii. Data platform similar to GAAIN.
    iv. Will do fingerprinting – high level description of cohorts.
     v. For EMIF-AD we are looking for markers using extreme endophenotype approach.
    vi. Incorporating many preclinical AD studies and population studies, also clinical cohorts of subjects with MCI or subjective complaints and single center biomarker studies.

VIII. Industry Perspective - PPSB (Adam Schwarz)
  a. fNIH is the glue that holds everything together
  b. PPSB comprised of 30+ institutions/companies – pharma, CROs, imaging companies
  c. Forum for industry members to come together and discuss issues of common interest.
  d. Have direct line to ADNI, liaisons to ADNI cores
  e. Activities related to ADNI driven by the PPSB: e.g., Biofluid Biomarkers WG, Clinical Endpoints WG, PET Endpoints WG, ADAS-Cog + WG.

      f. Open to new members

IX.   Parkinson Progression Marker Initiative (PPMI) Update (Ken Marek)
   a. Goal is to develop progression biomarkers to answer questions that we face when we try to develop disease modifying drugs for PD
   b. 3 pillars: develop specific biomarkers dataset, standardize acquisition and analysis of data, share data.
   c. Have enrolled 400 PD patients, 200 age and gender matched HCs, 70 SWEDD. DAT imaging required for enrollment. SWEDD do not have abnormal DAT imaging.
   d. Not yet enrolled (but planned): 100 prodromal, genetic cohort (LRRK2), 100 synuclein.
   e. Follow with motor assessments, neurobehavioral cognitive testing, autonomic, olfaction, sleep, DaTSCAN, VMAT, amyloid imaging, DTI and resting state MRI, biologic (DNA, serum, plasma, CSF).
   f. 24 sites – 18 in Europe and 1 in Australia
   g. Public private partnership - Michael J. Fox Foundation sponsors study and provides significant funding.
   h. All data available on website along with application for samples.
   i. Thinking about ho PPMI and ADNI can inform each other through data mining, other collaborative projects.