**Worldwide ADNI Update – July, 2012**
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**Introduction**
When the Alzheimer's Disease Neuroimaging Initiative (ADNI) was launched nearly ten years ago, the idea of a collaboration between academia, industry, the federal government and non-profit organizations seemed revolutionary. Now, however, ADNI serves as a model of a public-private partnership and has expanded far beyond its original six-year funding period, its focus on a single disease entity, and its residence in the United States. Worldwide ADNI (WW-ADNI) now brings together and harmonizes neuroimaging and biomarker initiatives in North America, Europe, Japan, Australia, Taiwan, Korea, China, and Argentina. Biomarker profiles are being generated for other forms of dementia and research is expanding into genetics with the rapidly emerging technologies that enable whole genome sequencing. Sharing of data with minimal restrictions has resulted in an unprecedented level of collaboration and the publication of over 350 manuscripts. Most importantly, providing access to more scientists has helped the whole field to move to better understanding and utilization of biomarker for AD and related dementias.

WW-ADNI is an umbrella organization created and managed by the Alzheimer's Association. In July, 2012, investigators from WW-ADNI projects met in Vancouver, Canada to share progress from their individual sites and to discuss concerns with regard to harmonization, standardization, and the conduct of clinical trials. This report summarizes that meeting.

**Substantial progress, but challenges remain**
Since its inception, the goals of ADNI have been to reveal cognitive, clinical and biomarker trajectories across the entire spectrum of AD in order to inform the design of clinical trials and accelerate the development of drugs. U.S. and international ADNI data have indeed led to changes in trial designs; however substantial challenges remain in the effort to transform hypothetical trajectories proposed by Jack et al [1] into data-driven trajectories. These challenges include:

1. Better analytical methods are need to capture, extract, and synthesize data from all subjects and across all clinical, cognitive, and biomarker measures
2. Longer-term follow-up of ADNI participants is needed to capture longitudinal data reflecting what is now believed to be a 15-year process.
3. Biomarkers are needed that reflect the earliest changes/actual onset of AD, now thought to be in the 50s and 60s, so that the search for treatments can move to the initiating phases of the disease. This younger cohort has not been captured in ADNI and funding to extend ADNI into this group has remained elusive.

ADNI-2 has begun enrolling subjects for continuing studies particularly in the earlier stages of disease. At the time of the Vancouver meeting, 57 sites had been approved and 826 subjects screened, with 226 screen failures. Recruitment of mild AD subjects has lagged somewhat

because of competition with treatment trials for this population. There are also plans to add a new clinical group, i.e., those who are clinically normal (CDR 0) but with subjective cognitive concern.

**Core Progress**
The eight ADNI Cores have continued to optimize their protocols and adapt to both changing technologies and the need to capture additional information that reflects brain changes across the disease trajectory.

<u>MRI Core</u>
The MRI Core has continued to evaluate both core and experimental protocols. The goal of experimental protocols is to identify a biomarker that becomes abnormal before amyloid. Signals in network dysfunction may provide such a biomarker.

- *Accelerated vs. non-accelerated.* An analysis of eMCI subjects by Paul Thompson's group showed essentially no difference between accelerated and non-accelerated protocols at 6 months and 12 months. Both protocols provide similar sample size estimates and maps of cumulative brain atrophy look nearly identical. However, Nick Fox's group looked a cross-sectional measures and showed significant differences for brain but not ventricles. Accelerated scans take about half as long, but more study is needed to confirm equivalence, particularly across different vendors. A reasonable atrophy signal appears to be present at 3 months in all groups, and sample size estimates based on TBM-SyN in selected ROIs for eMCI groups range from ~400/arm at 3 and 6 months and ~150-200/arm at 12 months.
- *Analysis of vascular factors using FLAIR.* DeCarli's group reports that eMCI group has greatest load of cerebrovascular disease. This speaks to greater heterogeneity among eMCI subjects. A software application developed by Jeff Gunter at Mayo for grading of ARIA-H indicated that the prevalence of one or more microhemorrhages (MH) is about 25% in ADNI cohort and increases with age and Aβ load. ApoEe4 and e2 carriers had greater numbers of MH compared to e3 homozygotes. Topographic densities were highest in occipital lobes and lowest in frontal lobes and deep/infratentorial. A greater number of MHs at baseline was associated with higher incidence of subsequent MH.
- *Diffusion tensor imaging (DTI) assessment at GE sites only.* Paul Thompson's group showed that diffusivity measures (DM) other than fractional anisotropy (FA), in particular mean diffusivity and axial diffusivity, seem to be better at identifying axonal damage.
- *Arterial Spin Labeling (ASL) perfusion assessment at Siemens sites only.* Norbert Schuff's group has been assessing regional differences between eMCI, MCI, and controls. They have put together a classifier, trained the classifier, and then done a cross validation. Discrimination metrics indicated AUCs in the 71-78% area (eMCI vs. control and MCI vs. control).
- *Task free fMRI at Phillips sites only.* Mayo investigators have been trying to compress data into a single metric that could be used as an outcome measure in clinical trials. They have identified a detectable signal but the relationship with disease severity is complex, non-linear, and non-monotonic, indicating that more work needs to be done to identify optimal ways to analyze data in a clinical trial context.

PET Core

The PET Core reported studies comparing florbetapir to PiB and the use of different data processing methods [2]. In comparing different reference regions and different processing approaches (freesurfer vs. Avid processing) they concluded that the reference region affects the correlation coefficient but not the slope, enabling conversion of results from one approach to another. Results were very robust despite different processing methods including smoothing of the data. Threshold values for florbetapir ranging from 1.10 to 1.13 depending on the processing method were capable of differentiating positives from negatives and correlated well with PiB and Avid autopsy data. While these data are encouraging, more data are needed especially from autopsy studies. Moreover, at this point these thresholds are only meant for research applications and not clinical use.

Comparing results from FDG-PET to florbetapir-PET studies, agreement as defined by Kappa coefficients was poor, indicating that the two biomarkers have different meanings. Even among subjects with clinical AD diagnoses, there were many discordant cases (e.g., hypometabolic but no amyloid). More longitudinal follow up on these cases is needed to better understand the meaning of these findings. One factor that appears to be important is ApoE genotype.

Data were also reported from a longitudinal subgroup analysis of cognitively normal and MCI subjects [3]. In healthy controls, florbetapir but not FDG positivity was associated with cognitive decline assessed by the ADAS-cog. In subjects with MCI, both FDG and florbetapir were predictive of decline. These data fit with the hypothesis that amyloid status is useful in recognizing the prodromal stages of the disease when there are minimal signs of neurodegeneration; and that as the disease progresses into MCI, neurodegeneration markers predict of the rate of progression. FDG is not specific for AD however, and will pick up changes related to aging and other forms of dementia.

Biomarker Core

The biomarker core has continued efforts to improve the precision and performance of CSF biomarker assessment while also expanding efforts to develop sensitive plasma biomarkers. The core has collected CSF, serum, and plasma from over 400 ADNI participants at baseline, and plasma and serum from 190 participants at 6 months, and 123 at 12 months. These specimens have enabled comparison of CSF to plasma biomarkers as well as assessment of the precision of a robotized Luminex immunoassay platform for plasma analysis. While the precision of the method has improved and correlations were seen between plasma and CSF biomarkers, these correlations were not strong enough to support the use of plasma biomarkers for diagnostic screening [4]. Longitudinal studies of plasma Aβ1-42 and 1-40 did not reach clinical significance although studies in the DIAN cohort suggest that early changes may turn out to be important and significant.

Clinical utility analyses to determine whether eMCI CSF profiles differ from late MCI suggest that CSF profiles in the early stages of MCI look more like normals than like late MCI. Comparisons have also been made between CSF Aβ1-42 and PET imaging results with florbetapir using a cutpoint of 1.11. The correlations were excellent for subjects with AD, and "good enough" for normal controls and those with early and late MCI, despite the fact that the two methods are measuring different things, i.e., soluble vs. insoluble Aβ.

The international AD biomarker community has also been working collaboratively to improve standardization and harmonization of techniques and develop an independent reference method and calibrator.

Data and Publications Core
The Data and Publications Core reported that applications for data access are now averaging about 600 per year, the vast majority of which are accepted. Downloads of imaging files has increased dramatically to about 900,000 in 2011-12. About 515 manuscripts have been reviewed and close to 300 have been published [5].

Genetics Core
Several major studies emerged from the genetics core in 2012, including results from the ADNI-GO/2 ApoE study, ENIGMA and CHARGE Consortia GWAS [6-9], a copy number variation (CNV) analysis [10], and candidate and discovery pathway-based analyses [11-14]. Data from many of these studies were presented at CTAD.  These studies suggest a convergence of diverse –omics sources (e.g., genomics, proteomics, transcriptomics, metabolomics, etc.) utilizing novel bioinformatics strategies. Efforts are also ramping up to develop blood-based tests for AD utilizing these technologies, and investigators are also beginning to look at gene expression. Ultimately, increased computing power will be needed to manage the massive amount of data and enable analysis of gene-gene interactions, gene-expression interactions, and epigenetic mechanisms.

Neuropathology Core
In 2011-12, the Neuropathology Core reported an autopsy rate of 100%, bringing the overall autopsy rate to 60% since the Core was established in 2007. These neuropathological studies indicate a high rate of mixed pathologies, including AD, Dementia with Lewy bodies (DLB), Agyrophilic grain disease (AGD), hippocampal sclerosis, TDP-43, and mild small vessel disease. The Core thus helps explain the variation seen in other cores by correlating pathological data to the variance in clinical diagnosis, biomarkers, and neuroimaging.

Biostatistics Core
The biostatistics core has compiled data from close to 1400 individuals at baseline with as many as 7 years of follow up, and plotted change over time for various biomarkers and neurocognitive tests. Then, in order to predict sample sizes needed for clinical trials of amyloid-based therapies, they used the ability to detect a 50% group difference between amyloid-positive and amyloid-negative subjects as an estimate of the amyloid effect. As expected, these analyses reveal that as the disease progresses, sample sizes decline for most measures. More importantly, they show which particular measures may enable reasonable sample sizes in different populations. For example, in individuals with eMCI, a sample size of ~300 is predicted to detect a 50% difference in hippocampal volume in a 24 month study with 80% power, assuming a 20% dropout rate. A more detailed biomarker modeling session was presented at CTAD.

In addition to using these data to predict sample sizes, the Core has plotted biomarker data over time. Superimposed, these curves validate to some extent the hypothetical curves proposed by Jack et al [1].

**ADNI Sequencing Initiative**
The ADNI Sequencing Initiative, a collaboration of the Alzheimer's Association and the Brin Wojcicki Foundation will enable whole genome sequencing of over 800 ADNI subjects. This constitutes the largest number of individuals in any single disease related study to undergo whole genome sequencing. Within ADNI, the Initiative takes advantage of the Genetics, Data and Publications, and Biostatistics Cores. All data will be available on LONI, providing access to researchers around the world who may utilize novel methods of analysis to glean pertinent information.

**Updates from worldwide ADNI sites:**
E-ADNI
The European Union established the PharmaCog consortium to facilitate drug development for AD. E-ADNI is one of PharmaCog's four main modules, and workpackage (WP) 5 of PharmaCog aims to validate and qualify biomarkers that are sensitive to disease progression. Subjects with MCI are enrolled and undergo serial assessment of clinical, MR, blood, and neuropsychological measures every six months for three years, with CSF assessment at baseline, 18, and 36 months. Baseline assessments have been done on 150 subjects, half amyloid positive and half amyloid negative. By following the NA-ADNI recruitment protocol, E-ADNI has built a cohort remarkable similar to the ADNI cohort. Volunteer enrollment has been slow but appears to be gaining strength.

Qualification procedures for MR studies include assessments (using a phantom) of the stability of cortical thickness estimation (FSsurf), stability of volume estimate via automated segmentation (FSsurf), stability of fractional anisotropy (FA) and mean diffusivity (MD), stability of correlation between nodes, and stability of spatial activation. Neuropsychiatric measures using EEG and P300, CSF and blood assays of $A\beta$1-42, tau, and phospho-tau are also undergoing qualification. Within-site reproducibility for structural MR has revealed errors in line with those reported in the literature [15]. Test-retest reliability using diffusion MR has been acceptable, and for fMRI studies of the resting state default mode network, despite the use of different scanners and different subjects, functional correlation between key nodes has been very stable, although the DMN nodes are sensitive to amyloid burden [16]. The spatial reproducibility of DMN activation patterns has been >80%, which is consistent with results reported in the literature [17].

AddNeuroMed is another cross-European public-private partnership developed for AD biomarker discovery that uses ADNI protocols and phantoms and has merged datasets with ADNI. AddNeuroMed encompasses 6 sites in Europe for a total of 716 subjects. Their goal is to get as much information as possible from blood through the use of proteomics, metabolomics, genomics, and transcriptomics; and to combine these data with imaging data. In one study, they confirmed that plasma concentrations of 5 proteins, along with age and sex, explain more than 35% of the variance in whole brain volume in individuals with AD, suggesting that complement activation and coagulation play important roles in AD pathogenesis [18]. In another study, plasma levels of transthyretin were shown to be reduced in rapid decliners [19]. And in yet another study, combining MRI with measures of cytokines proved to be a better predictor of progression than either alone [20]. Combining multiple MRI measures also has been shown to

improve prediction accuracy [21], and combining MRI with CSF measures improves the ability to distinguish AD from controls and MCI from controls [22]. Combining MRI with measures of different vitamin E forms also improved the ability to discriminate AD from controls.

Future studies will investigate extreme clinical phenotypes though the European Medical Information Framework, which links ADNI, AddNeuroMed, and other large studies to provide access to clinical and omics information on more than 40 million individuals.

Japan-ADNI
Japan-ADNI initiated a 5-year study in 2007 at 38 sites with a combination of public and private funding. A two-year extension was granted, making this a 7-year study. At the time of this meeting, 543 of 600 subjects had been enrolled. All subjects undergo clinical assessment and MRI using the same protocols as those used in NA-ADNI; and all contribute blood for collection of immortalized lymphoblasts and ApoE testing. A subset undergoes FDG-PET and amyloid PET imaging. Results of these assessments are compared to those in NA-ADNI. J-ADNI data for 12 month decline in FDG-PET score in MCI suggest that a 20% effect size can be achieved by recruiting 266 subjects per arm. This is somewhat lower than the sample size calculated using NA-ADNI data.

CSF biomarker studies show a good correlation between NA and J ADNI, but with different cutoffs. A harmonization study is underway with University of Pennsylvania, Niigata, and Innogenetics to minimize the differences. A unit for early/exploratory clinical development of AD/CNS drugs has been established at the University of Tokyo as a joint project with J-ADNI. The BACE-1 inhibitor TAK-070 was licensed to U Tokyo in June 2012 and will be the test case for this unit.

A proposal for J-ADNI 2 will be submitted in August 2012. This project will focus on late and early MCI and preclinical AD.

AIBL/Australian ADNI
Australian ADNI, also known as The Australian Imaging Biomarkers and Lifestyle Flagship Study of Aging (AIBL) has been following a cohort of over 1000 volunteers since 2006 with a variety of methods.

Converters from MCI to AD were somewhat higher than expected: 30.5% at 18 months and 80% at 36 months. Conversion from healthy to MCI was seen in about 2.5% at 18 months and 5.7% at 36 months. A number of studies have been conducted examining the conversion from healthy to MCI. A bimodal distribution was seen, with higher performers less likely to convert in comparison to low performers. Another factor that influenced the likelihood of conversion included ApoEe4 carrier status: the transition group included more ApoEe4 carriers than the stable group and carriers also had an increased magnitude of decline over the initial 18 months. Amyloid PiB positive subjects also showed more decline over a number of cognitive tasks including several memory tests, paired associate learning, and pattern separation. Studies have also been conducted looking at the influence of physical activity, which appears to have beneficial effects on cognitive function, plasma biomarkers and amyloid imaging [23-25]. A study of adherence to the Mediterranean diet also points to possible benefits [26].

At the 4.5 year follow-up point, AIBL is trying to image all participants with MRI and one of three amyloid imaging ligands (flutemetamol, AV-45, or PiB). They have also added new participants from the Women's Healthy Aging Program (WHAP) and plan a cohort of Vietnam veterans through AIBL-DOD.  Longitudinal data confirm that amyloid accumulation is a slow process, occurring at a similar rate in healthy controls and MCI subjects but plateauing with advanced dementia [27]; that amyloid-positive individuals have increased rates of hippocampal atrophy and a greater rate of episodic memory decline; and that combinations of biomarkers provide better prediction of a progression, for example, PiB positivity combined with hippocampal atrophy has 85% accuracy for predicting progression and a positive predictive value of 78%.

Canada ADNI
Canada is part of North American ADNI (NA-ADNI), which has enabled the incorporation of five Canadian sites into ADNI-2. ADNI is just one part of Canada's International Collaborative Research Strategy for Alzheimer's Disease (ICRSAD), which is one of CIHR's roadmap signature initiatives. ICRSAD aims to strengthen innovative and collaborative research efforts on neurodegenerative disease, both nationally and internationally through outreach to the EU, Asia, and the U.S.

China ADNI
China ADNI plans to begin Phase 1 at 7 medical centers in Beijing this year. More centers throughout the country will be added. The study team has translated plans, procedures, standards, and scales into the Chinese language with appropriate cultural adaptations. They have also completed specialized training and qualification of researchers for the clinical core. The Biomarker, Genetics, PET, and MRI cores are following the protocols provided by ADNI. However, testing of the PET and MRI phantoms was delayed because the phantom was damaged in an accident.

China ADNI has received research funds from Beijing Municipal Science and Technology and the National Science and Technology Support Program. In addition, two new studies have been approved and funds should be allocated in 2013.

Argentina ADNI
Argentina ADNI, also known as Fundacion de Lucha contra las Entermediades Neurologicas de la Infancia (FLENI) had, at the time of the meeting, recruited 15 subjects of the 60 total expected to be recruited over a 3-year period.  Protocols and supplies are in place for clinical and neurocognitive assessments, collection of biospecimens for blood and CSF analysis, imaging studies, and a brain bank. First limited data should be available next year.

Korea ADNI
Korea ADNI is a six year project supported by the Korean Ministry of Health and Welfare and industry collaborators. The planned 2011 start of the project has been delayed and so far the focus has been on infrastructure development. Recruitment of 500 subjects at more than twenty nationwide dementia centers will begin in 2013 and subjects will be followed for three years. A subcortical ischemic vascular dementia sub-cohort will be included.

Other worldwide sites
Taiwan ADNI did not make a presentation at the 2012 update meeting, although the project there is underway. Inquiries have also been received from India and Greece about setting up WW ADNI projects.

**Offshoots from ADNI**
ADNI has spawned research on neurodegenerative diseases not only throughout the world but also across a number of different diseases. For example, the Parkinson's Progression Markers Initiative (PPMI) modeled on ADNI is a public private partnership with the goal of promoting biomarker discovery, standardization and validation that will enable disease modifying PD trials. Other goals are to establish a specific cohort and make data and biospecimens easily available to the research community.

With regard to CSF biomarkers, all subjects in PPMI are required to have a lumbar puncture at baseline, 6 months, and yearly thereafter. Although there were concerns this could limit enrollment, it has not turned out to be a problem. As with ADNI, PPMI is seeking to develop means of identifying PD in its presymptomatic stages through the use of biomarkers, including many similar to those used in ADNI as well as a unique imaging technique called dopamine transporter imaging and assessment of olfactory loss. As subjects are recruited at earlier stages, it may become more efficient to assess subjects jointly for more than one neurodegenerative process, e.g. PD and AD. Thus, this may be an opportunity for PPMI and ADNI to interact.

GAAIN, the Global Alzheimer's Association Interactive Network is another project that has spun off from ADNI as the need for a diversity of methods for collecting and sharing data became apparent. GAAIN is a cloud-enabled infrastructure spanning centralized computational facilities in North America and Europe. It will link the LONI and neuGRID networks into one federated network, providing researchers with free-of-charge access to a vast repository of data – most importantly to high-resolution, time-varying, multidimensional data sets of the brain. In addition to establishing the research data repository and an AD research registry, GAAIN will enable sharing of data analysis tools.

**Industry perspective**
The Private Partnership Scientific Board (PPSB) of ADNI was established to provide a pre-competitive forum for industry partners to discuss scientific issues related to ADNI, interact with regulators and the ADNI leadership, network with other organizations such as the Alzheimer's Association and the Coalition Against Major Diseases (CAMD), which support the ADNI project in various ways, and provide input to related initiatives such as the National Alzheimer's Plan. Workgroups formed with PPSB tackle a variety of issues including biofluid biomarkers, plasma proteomics, informatics, PET imaging, clinical endpoints, and global standardization. PPSB is also tackling issues beyond the ADNI project, such as convincing the FDA to accept different and perhaps less well validated measures.

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