July 15, 2011

Minutes from World-Wide ADNI Meeting; Paris, France

Attendees:

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Jack Watters
Michael Weiner
Mark Weinstein
Dirk Wouters
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ADNI Updates

Scott Campbell , President and CEO of the FNIH, welcomed all attendees and thank you to those who contribute to the ADNI endeavor. ADNI is one of the premier activities of FNIH.

ADNI, ADNI Go, ADNI 2 Overview (Michael Weiner)

Mike gave overview of the ADNI, ADNI Go and ADNI 2 activities:

- 240 eople from ADNI are rolling over to ADNI 2
- In ADNI 2, they will enroll:
  - 300 eMCI
  - 150 new control
  - 150 late MCI
  - 150 AD
- Require LP at enrollment – the importance of CSF was apparent during ADNI
- What has ADNI given to the scientific community (outcomes):
  - Standardized methods
  - Rate of change in MRI
  - Predictors through MRI, FDG-PET, CSF
  - Earlier diagnosis is supportive of MCI/preclinical stage of AD
  - Data has assisted clinical trial design
  - Data sharing without embargos
  - Led to WW-ADNI and world wide collaborations
  - Over 200 publications, >80 submitted

Clinical Core (Ron Petersen, Paul Aisen)

Review of the clinical core activities, including ADNI, ADNI Go and ADNI 2 recruitment. Update on ADNI 2 activities:

- 44 sites approved
- Enrolled 40 people
- Working on strategies to improve enrollment

Discussed impact on clinical trials – for controls, there is a group with no change in cognitive function according to clinical measures; however, if we select on biomarkers, we can be predictive of cognitive decline and potentially link this group to therapeutic intervention clinical trial design

MRI Core (Cliff Jack)

Review the protocols for the 3T MRI (ADNI Go and ADNI 2). Review of protocol changes in response to initial information and preliminary analysis looking for results within the eMCI group (note: not sufficient numbers of individuals to make specific inferences). Summary of results:

- Acceleration is not harmful – reasonable x sect and long results

- Susanne Mueller from USCF received AA Funding to perform hippocampal sub field analysis in ADNI 2. Will be incorporated into 26 sites.
- WMH – reasonable longitudinal consistency
- DTI – reasonable correlation with age, longitudinal consistency
- ASL – reasonable initial results; made changes to the ASL sequence in January 2010 to adjust timing parameters and add a product phase map.
- Resting state fMRI
    - Became aware of an issue regarding fat aliasing does not appear to be significant – working in conjunction with Phillips. Made changes to increase SI coverage to 159 mm (now 7 minutes). Distributed in April 2011.
    - Reasonable initial results

PET Core (Bill Jagust)

Major accomplishments – F18 florbetapir add on

For PET, there are two mechanisms to look at processing: free surfer processing (automatic, in native space) and SPM processing (template for region of interest).

- Review of data for the comparison between these two methods – not significant differences, conversion possible
- To date, do not know appropriate cutoffs yet (need more data)
- Issue of standardization essential – not difficult to standardize across methods, but is difficult to standardize across tracers b/c need individuals with duel scans (ADNI provides this).
- Cut off – do you want sensitivity or specificity? Cut off essential for the "normal" group
- Break out groups by (+) or (-), depending on cut offs. If use, 1.22:
    - Normal controls: 25-30% positive
    - eMCI: 55% positive
    - MCI: 67% positive
- Five publications in recent months result from PET core
- Next phase:
    - Investigate additional Amyloid PET ligands (Flurbetaben, Flutemetamol)
    - Target patients of clinical importance who are currently excluded from ADNI
    - Focus on MCI with a vascular etiology
    - Demonstrate the importance of AB in progression to AD in MCI patients with vascular pathology.
    - All data treated identically to ADNI data

Biomarker Core (Les Shaw)

- Proteomics Study – measured 190 plasma proteins and peptides in 600 participants from two independent clinical cohorts at Penn and Wash U. Identified 17 analytes associated with diagnosis of late MCI or AD (early and later AD).
- Four of these are: APoE, B-type natriuretic peptide, CRP, pancreative polypeptide (poster presentation during AAICAD, Monday, July 18)
- Follow up study in CSF samples – looking at same analytes
- Compare the analytical platforms for CSF metrics to look at differences between platforms compared to AB and tau related to PiB PET imaging. Two methods (Innolyst

and AlzBio3) are similar – both comparative in predicting amyloid plaque buildup in brain).
- Incorporated automatic processing (up to 17 steps) – contributed to reproducibility
- Evidence in plasma about what is in brain and modest correlation between CSF AB1-42. There are other sources of AB in the circulation, so still pending whether this is useful biomarker.
- Summer-fall, 2011:
    - PPSB/FNIH/ADNI RBM study in 328 baseline CSF samples – will analyze more than 40 RBM proteins (i.e. Picam, etc)
    - Merck/ADNI BACE in ADNI CSF samples
    - Finish production of CSF pools from residual ADNI CSF
    - AlzBio3 immunoassay of AB1-42, t-tau, p-tau181 in ADNI Go CSF samples (over 120 samples)
    - Continue QC studies of AlzBio3 xMAP immunoassay – special focus on sample processing
- Discussion regarding the need for further study regarding plasma detection – important for the industry perspective to ascertain differences in amyloid modulation; also see trends in plasma AB and CSF AB which is highly repetitive.

Genetics Core (Andrew Saykin)

Over 25 papers to date using genome data from ADNI – including two large GWAS papers
- Identified 5 new candidate genes: MS4A4/ MS4A6E, CD2AP, EPHA1, CD33, CD2AP. Independent replication of these candidates
    - MS4A family – role in immune function
    - EPHA1 – role in immune function
    - CD2AP – role in endocytosis
    - CD33 – role in endocytosis and immune function
    - ABCA7 – role in lipid processing and immune function
- On going investigations to look at the associations between identified genes and brain function:
    - Collaboration between ADNI and AddNeuroMed group – resulted in publications related to genes associated with entorhinal cortex. CSF powerful phenotype to compare genetics and CSF data.
    - Another gene identified – EPC2: mapped in drosophila. Map to the hippocampal region of the brain.
    - Genetic variants that predict rate of change - links between Cadherin gene influence in annual percent change in hippocampal volume.
    - Candidate genes related to biological processes – amyloid pathway and deposition on PiB-PET – identified gene that helps to explain differences
- On-going collection of samples (DNA, RNA) to look at expression and epigenetic (requires serial DNA); targeted DNA and RNA re-sequencing

Data and Publications Update (Robert Green)

Update on the use data use and the publications – policy on access to ADNI data and publication policy for use of ADNI data:
- Approval of access for each user (turn away people that cannot fill out a form)

- Maintain table of users and their goals (allows identification of users, collaborators, etc)
- Annual renewal for each user
- Trouble shoot data access for users
- Require minimalistic review of publications for ADNI data – ADNI investigators acknowledgement in authorship (one issues is the NLM adds all ADNI investigators to the authorship in PubMed)
- Track all publications
    - 2,463 investigators; 1,802 requests for data; 154 denied
    - On-going growth in image downloads – other data, over 90,000 downloads
    - 352 manuscripts utilized ADNI data (199 published)
    - In independent search, found 50 not submitted through Committee – 13 compliant; 37 non-compliant
- What if anything should researchers be sharing with their subjects/ patients/ individuals regarding the on-going findings
    - Return of incidental findings from research is a hot topic – forming a workgroup in ADNI to look at this issue.

Neuropathology Core Update (Nigel Cairns):
To date, 31 deaths of ADNI subjects (9/1/2005 through 2/1/2011); 13 autopsies – the core was not in establishment at beginning, reflecting discrepancy.

- Diagnostic accuracy of cases that have come to autopsy is 100% accurate – AD pathology at autopsy;
- In addition to amyloid and tau, other pathologies are present: most commonly alpha synuclein and Lewy Body Dementia. Two other pathologies – Hippocampal Sclerosis present; Argyrophilic Grain Disease (4R Tauopathy)
- 40% of cases have co-existing LB pathology

Biostatistics Core Update (Michael Donohue):
Overview of the Biostatics core activities since April ADNI meeting:

- Many biomarkers predict rate of decline, when looked at individually. When you take into account baseline cognitivie and functional performance, individual biomarkers add somewhat less:
    - In MCI, hippocampal volume, Tau and Tau/Abeta
    - In AD, hippocampal volume, FDG PET ROI, Abeta, Tau/Abeta
- Results of biomarkers predicting conversion, consistent with other studies
- Looking at analysis of explained variation (age, education, apoE4 status, cognitive change) – look for continuous measures of decline vs. rate of change

WW-ADNI Updates

E-ADNI Update (Giovanni Frisoni)
Current emphasis on the data collection - smaller effort relative to the US ADNI. A component of PharmaCog network. Review of activities from clinical, MRI, PET and Informatics Cores:
Clinical Core: pharmaCog/EADNI. At enrollment, data to be collected for analysis.
MRI Core: Alzheimers Association EACD ADNI harmonized protocol for hippocampal volume.
PET Core: Head to head comparison of FDG-PET metrics.

Informatics Core: neuGRID – unprecedented data management. At this year's AAIC2011, the first study where three datasets have been used together will be presented. In the coming years, we will have significant increase in the number of images and data available. Vision of a cloud network to allow for integration and migration of data from neuGrid, Canarie, LONI – will be known as OutGrid. This is not going to be enough. Will organization workshop in Geneva – global workshop (February 2012) to develop global network for cloud.

J-ADNI (Takeshi Iwatsubo)

Review of Japanese ADNI on-going activities:

- 7 year study – since 2007
- 38 clinical sites
- 600 subjects (150 early AD; 300 MCI and 150 NC)
- 1.5T MRI, 55% FDG-PET, 41% amyloid PET, blood and ApoE 100%, CSF 38% and 14 compatible test batteries

Current status of recruitment – 500 (152 NC, 235 MCI, and 113 AD enrolled) – approaching goal of 600 subjects. The demographics are not dissimilar to the USA. Exclusion rate is 22.1% (compared to 43% in the USA) – and 34/500 discontinued (5.9%) . Last entry of MCI (sept 2011); last AD (March 2012). 2011is the 5th year of follow up; J-ADNI anticipates follow up will be completed in 2014.

Cognitive battery similar – MMSE nearly same; CDR lower in J-ADNI than US ADNI
See CSF trends for AB1-42 levels, Total tau and pTau that are consistent with Alzheimer's vs. Normal Controls – nice correlation with US data in a follow up study
Comparison of CSF and PET amyloid signature data in J-ADNI –
CSF data:

1. AD 2 32 (94%)
2. MCI 21 50(70%0
3. AD 41 12 (23%

Other comparative analysis to date:

- PiB vs. CSF – able to separate out NC, MCI and AD (n-45 total)
- Initial autopsy findings – death by pneumonia; 78y male with early AD; enrolled in 2009., apoE3/apoE4
- Conversion rates to date: 67 aMCI cases out of 201 converted to AD – 28% conversion rate
- CDR global score upon conversation 0.5, 62.2%
- ApoE4 positivity rate: 56.8% in converters
- CSF AB1-42, t-tau, p-tau: intermediate of AD and MCI

Database construction – will be done in collaboration

AIBL Update (Chris Rowe)

Update on AIBL activities including recruitment:

- 366 participants – neuropsych, MRI, PET and analysis (PiB, MRI using 3 tissue segmentation maximization probability maps)

In addition, they use a single operator for all PiB scans.

Enriched ApoE4 carriers – 41% (compared to 20-25% expected from random population)

Cut off at 1.5 – 31% positive (normal controls)
If you have the traditional ApoE4 make up, then you reduce to 25% positive (normal controls)
See doubling of PiB PET positivity based on ApoE4 carrier state vs year of age (80+ yoa, 80% positive PiB scan vs. 45% non positive PiB scan) – No evidence that older AD patients have more amyloid in brain (based on amyloid imaging).
11% + in 60s, 32% in their 70s, 51% in 80s - able to convert to accuracy b/c issue of specificity:

1. If in 60s, positive scan is 92% (based on individual having cognitive issue)
2. If in 70s, 84% specific
3. If in 80s, 78% specific

In reviewing data, see correlation between amyloid and hippocampal volume in normal controls, MCI but not in AD. On the five year follow up, see that individuals that are positive, slowly accelerating; if you have AD, you will initially increase in plateau. ApoE4 is a strong predictor of progression – hippocampal atrophy is moderate predictor; combination of hippocampal atrophy and PiB PET leads to approximately 86% accuracy

AIBL and CSIRO Update (Cassandra Szoeke)
3 year follow up nearly complete
87% retention
Aibl study – structure of CSIRO has been in flux last 12 months. Have distinct sectors (biomarkers, clinical, imaging, tissue, etc) –
Identified at risk healthy group – of the 704 healthy controls, found 59% performed significantly better on 4 tests than the other 41%
Those in the other 41% had increased risk of AD – of the converters, 17/20 were in this group.
AIBL – better performers converter rate 0.5% (HC – MCI) and 0.3% (HC-AD)
For the others group, 5.6% (HC-MRI) and 1.2% (HC-AD)
Found 10x increased risk for conversion

Biomarkers work – similar results to ADNI

Next 3 years –
Complete 3 and then 4.5 year follow up
Add 200 women from a cohort previously – Women's Healthy Aging Project
Add prevention study
Develop funding strategy for 6 and 7.5 year follow up.

AddNeuroMed (Andrew Simmons)
AddNeuroMed Study is focused on 6 European sites (~400 subjects); clinical/cognitive assessment, blood/plasma/RNA, 1.5T structural MRI to be combined with nearly 825 datasets from ADNI, 200 cohort from London, and 130 subjects from Memory Clinic, and 2000 healthy controls (young) .

- ADNI partnerships –
  - Multivariate analysis comparing ADNI and AddNEuroMed data
  - Performed genome wide scoring – most significant is PICALM
- Looked at proteins associated with severity, pathology and progression of AD - Clusterin. This is coordinated with animal word. Plasma Clusterin is associated.

- In silico identification for potential markers for AD – looks through literature to identify published descriptions of proteins or factors that may be linked to potential AD - candidate biomarker = not associated with MMSE but highly significantly correlated to baseline of AD.
- Next steps – RNA analysis studies, continuing collaborations with ADNI, proteomic studies, vitamin E forms, combined imaging-omics MCI conversion

C-ADNI Update (Kuncheng Li)
Update on progress on the C-ADNI set up. The Advisory Committee is established. Clinical core includes neurologists, psychologists and geriatricians from five hospitals in Beijing area constitute the clinical core. Currently, working on thetraining of standard operating procedure and workflow, especially the battery of Neuropsychological examinations.
Recruitment will include four types of new subjects – cognitively normal, eMCI, late MCI, AD. Groups will be recruited accordingly:

- Cognitive normal and eMCI recruited from community investigation of epidemiological research.
- Late MCI and AD recruited from memory clinical at the Dept of Neurology, Psychiatry and Geriatrics

MRI and PET core are in process of being established. PET scan will be completed in one site. Funds – funds from the Sciences and Technology Committee of Beijing to initiate the project in Dec2010. The group is preparing to apply for more funding from the Chinese government.

K-ADNI (Duk NA)
Korea was unable to participate.

Arg-ADNI (Silvia Vazquez)
FLENI organization – on 2/7/11, the Argentine Ministry of Science agreed to support of Argentina ADNI and create and support future national initiative. They are proposing to establish initiative in Buenos Aires. Goal is to recruit 60 Argentine adults – age 55-90 (inclusive) over 3 year period – 15 MCI, 15 normal, 20 AD.

T-ADNI (CK Liu)
Start from north Taiwan with 6 medical centers. Starting work for three year longitudinal study – neuropsychological tests, biomarkers (blood, apoe, amyloid, tau, csf) imaging. MRI/ Neuroimaging Core – DTI, RSFC, MRS, SWI and 3D 1.5T amyloid imaging – will not only include current measures, but additional measures for imaging techniques. Will have on-going training workshops to standardize neuropsychological tests (may and august 2011), other procedures, as well as standardized procedure manual.

Industry Perspective of WW-ADNI (Enchi Liu)
Enchi Liu is this year's PPSB Chair and is representing this group.

Who is the PPSB: Collaborate with ADNI2 Steering and Executive Committees and core leader. Identify areas of gaps: database working group; PET imaging endpoints; and AB as a Biomarker working groups.

Major hurdles facing AD Drug development:

- Is it the target? Is it the mechanism? Is it the clinical trial design? Other
- Clinical trial design for disease modifying therapeutics is difficult – importance of standardization.

Examples of collaborations – PPSB collaborations with ADNI cores in discussion or ongoing; Biomarkers Consortium ADNI Plasma Proteomics Project, etc.

ADNI has some "unexpected" benefits – the ability to understand shifts in AD disease progression and placebo response over time; more regularly attention to Alzheimer's disease (FDA and EMA); engagement of the global community; and a sense of shared responsibility in understanding AD etiology, improving clinical trial methodology and helping patients (unprecedented level of cooperation and engagement between industry, academic, and federal sectors in the US as well as other countries).

Future directions:

- ADNI Go and ADNI 2 – inclusion of more patients in the eMCI and late MCI to help us understand this disease in the earlier sections of the continuum.
- Treatment earlier in disease continuum: parallel thinking of the field and the industry (i.e. two companies in early trials – BMS and Roche)
- Individual patient vs. group prognosis – utility in clinical practice as well as for drug development in the pre-symptomatic phases

Remaining Gaps:

- Drug development tools
    - Need to be able to monitor disease in the earlier stages
    - Clinical scales
- Biomarkers
    - Need to align with regulatory agencies regarding use of biomarkers for clinical use
    - Lack of F18 amyloid imaging acceptance to use in patient sectors
- Other
    - Address emerging safety issues
    - Need for common data base

PPMI (Ken Marek)

Parkinson's Progression Marker Initiative (PPMI) – another example of an initiative spawned by ADNI. Asks audience to think about ways PPMI may help to inform ADNI and vice versa, based on patient population.

- Study was developed by the Scientific Advisory Board of the MJ Fox Foundation (primary sponsor) – collaboration of academic, industry and government advisees
- Identify cohort of individuals and focus on standardization of data collection/ analysis, and ensure data available and open to the community.
- Project design is similar to ADNI format – LONI houses the database (similar to ADNI)
- Commitment to making data and bio-specimens available
- 400 subjects with PD and 200 age matched controls to be evaluated over 4 years (Cognition, behavioral, autonomic -i.e. constipation, bladder, sexual, cardiac-, olfaction,

sleep, Motor analysis, imaging, biologicals, RNA profiling, and genetics – i.e. alpha synuclein, LRRK-2, tau, DJ1
- Validating biochemical markers (tau, alpha synuclein, LRRK-2, tau, DJ1, and amyloid beta).
- Enrollment on-going. 21 sites (16 in US and 5 in Europe) and will be developing 3 sites in Australia. Unlike ADNI, all recruit under same protocol and send info to the same repositories.

Discussion
Success of all we have heard has led to a persistence movement forward – despite the economy, there is a tremendous commitment from NIA, the PPSB, etc. and it is nearly equivalent to the commitment several years ago.

How to "sell" ADNI to senior management? There is a fine line between being on the cutting edge or getting ahead of yourself in therapy development. ADNI is only choice in being meaningful and committed helping achieve goal that we are all striving for – therapeutic development

Each company has internal processes and decisions organized at central level. Spend significant administrative time regarding funding decisions within corporations, and see this reflected in the Foundation of NIH (i.e. established as a result of biomarkers consortium). Example is one of the projects to analyze CSF samples is triple the price estimated, so as a result, only able to analyze small fraction of the samples planned. It is an impact of the economic realities.