The Alzheimer’s Disease Neuroimaging Initiative (ADNI): A Public-Private Partnership

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National Institute on Aging

National Institutes of Health
Department of Health and Human Services
Need For Validated Biomarkers For Alzheimer’s Disease (AD) Trials

• Current trials use clinical/cognitive outcome measures:
  – slow rate of change over time, do not easily determine disease modifying effects of treatment
  – trials require large sample size, are time intensive and costly

• Imaging and Biochemical Biomarkers – hope to improve speed and efficiency of clinical trials
The Alzheimer’s Disease Neuroimaging Initiative (ADNI)

National Institute on Aging
GOALS OF THE ADNI:
LONGITUDINAL MULTI-SITE OBSERVATIONAL STUDY

• Major goal is collection of data and biological samples to establish a brain imaging, biomarker, and clinical database in order to identify the best markers for following disease progression and monitoring treatment response.

• Determine the optimum methods for acquiring, processing, and distributing images and biomarkers in conjunction with clinical and cognitive data in a multi-site context.

• “Validate” imaging and biomarker data by correlating with cognitive and clinical data.

• Rapid public access of all data.

• Access to biological samples.
Neuroimaging Initiative Development

- March, June, 2002 - Informational and advisory meetings
- Fall, 2002 - Working groups:
  1. MRI
  2. PET
  3. Study Design
  4. Biological Measures
- July, 2003 - Meeting with industry representatives, advocacy groups, FDA, Foundation for NIH (FNIH)
Neuroimaging Initiative
Development

• October, 2003 - RFA issued

• May, 2004 - Review of applications

• Sept, 2004 - Funding

• Spring/Summer, 2005-Preparatory Phase

• September, 2005-Start of recruitment
Study Design

- Transition from normal cognition to AD: Markers of disease progression

- Subjects:
  - Mild Cognitive Impairment (MCI, n=400): 0, 6, 12, 18, 24, 36 months
  - AD (n=200): 0, 6, 12, 24 months
  - Controls (n=200): 0, 6, 12, 24, 36 months
Study Design

• Measures:
  – Clinical/Cognitive, MRI (1.5 T) at all time points
  – FDG PET at all time points in 50%
  – 3 T MRI at all time points in 25%
  – PET-PIB (amyloid imaging: Pittsburgh Compound-B) substudy on 120 subjects
  – Cerebral spinal fluid (CSF), blood, urine
Biomarkers

- Blood and urine at all timepoints
- CSF at baseline, 1 yr., 2 yr (subset): 50% of subjects
- DNA and immortalized cell lines
- Measurements of tau, amyloid, isoprostanes
Structure

• **Administrative Core:** Mike Weiner

• **Clinical Core:** Paul Aisen, Ron Petersen, Marilyn Albert, Pierre Tariot, David Salmon, John Morris, Steve DeKosky, (Leon Thal, deceased)
  - Based at ADCS at UCSD; Clinical Data Base

• **Neuroimaging Core**
  - **MRI:** Cliff Jack, Norbert Schuff, Anders Dale, Nick Fox, Charles DeCarli, Matt Bernstein, Joel Felmlee
  - **PET:** Bill Jagust, Norm Foster, Eric Reiman, Bob Koeppe

• **Informatics Core:** Art Toga UCLA/Laboratory of Neuroimaging (LONI); Imaging data base
Structure

- **Biomarker Core**: John Trojanowski, Les Shaw

- **Neuropathology Core**: John Morris

- **Statistics Core**: Laurel Beckett, Anthony Gamst

- **Industry Scientific Advisory Board (ISAB)**: Eric Siemers, Pat Cole

- **57 performance sites**: PIs and Study coordinators
Funding

• $12 million/yr, 5 years

• Total funding $60+ Million
  – $40 Million provided by NIH (NIA, NIBIB)
  – Over $20 Million provided by industry and other partners

• Cooperative agreement (UO1)
Academic Partners

Industry Partners

Philanthropic Partners

Foundation for the National Institutes of Health

National Institute on Aging

ADNI

Academic Partners
ISAB Contributions to ADNI

- Nearly $25 million has been raised by the Foundation for NIH from 17 organizations (15 companies and 2 non-profits)
ISAB Participation in ADNI

ADNI Industry Sponsors
• All have representation on ADNI ISAB/Steering Committee

ADNI ISAB Chairs
• Peter Snyder, Pfizer (2004)
• William Potter, Merck (2005-2006)
• Eric Siemers, Lilly (2007)
• Patricia Cole, Eisai (2008)
• Holly Soares, Pfizer (2009)

Liaisons to ADNI Cores
• Multiple ISAB representatives to each ADNI Core
ISAB Contributions to ADNI (continued)

Cerebrospinal Fluid (CSF)

- Implemented “round robin” between 3 ISAB companies, academic labs and the ADNI biomarker core to further define analytical methods for CSF analyses

- Additional funds being raised for the extension of CSF collection in years 2 and 3 (not currently part of the ADNI grant)
  - commitments to date from the Alzheimer’s Association, AstraZeneca, Cure Alzheimer’s Fund, Merck, Pfizer, and an anonymous foundation

PET with Pittsburgh Compound B (PIB) Supplement

- An additional $2.6 million supplement (sponsored by the Alzheimer’s Association and GE Healthcare) is exploring this neuroimaging tool, which has the potential to aid in detecting Alzheimer’s Disease by visualizing how $^{11}$C-PIB binds to amyloid plaque in the brain
ISAB Contributions to ADNI (continued)

Genome-Wide Genotyping (ADNI Add-On)

- Blood collected from all ADNI subjects being utilized for genome-wide genotyping that promises to provide the most extensive and robust dataset of this kind for AD; work being conducted by T-Gen
  - funds for the genome-wide genotyping provided by Gene Network Sciences, Merck, Pfizer and an anonymous foundation

Genome-Wide Genotyping Genetic Analysis (ADNI Add-On)

- Statistical analysis of the whole genome genotyping (which will identify genes associated with AD and explore new methodological approaches) being conducted by the University of California, Irvine (Steve Potkin, Member, ADNI Genetics Core) and University of Indiana (Andrew Saykin, Chair, ADNI Genetics Core)
  - funds for the genome-wide genotyping analysis provided by Merck, Pfizer and an anonymous foundation
  - additional funds being provided by NIBIB
Biochemical Biomarkers (ADNI Add-On)

• Proposals for targeted and whole proteome profiling approaches using ADNI CSF and plasma samples developed by the ISAB

• The targeted proposal is currently under development through The Biomarkers Consortium (www.biomarkersconsortium.org), a Foundation for NIH pre-competitive public-private partnership, which will:
  – utilize ADNI CSF and plasma (approved by the ADNI RARC)
  – use an existing multiplex assay of approximately 100 analytes and mass spectroscopy analysis of multiple A beta and phosphorylated tau species

• The whole proteome/discovery proposal delayed -- approval for use of the samples has not yet been approved by the ADNI RARC

• ISAB lead: Holly Soares (Pfizer)
A Public-Private Partnership

• Common, specific goals --- clearly defined

• Pooling resources

• Not just $$ --- direction, ideas, interaction through Industry Scientific Advisory Board
Data and Sample Sharing

• Rapid public access of *all raw and processed data*

• Central repository for all QA’d MRI and PET (LONI)

• Clinical data base at UCSD is linked to LONI

• Databases- in the public domain, available to all qualified investigators

• No special access

• Data Sharing & Publication Committee
  - ADNI Data Use Agreement, User Table

Biological sample sharing
  - Resource Allocation Review Committee
Resource Allocation
Review Committee (RARC) – Biological Samples

• Review applications
  – Significance
  – Scientific quality
  – Doesn’t duplicate
  – Commitment to sharing
  – Investigator & environment

• Decide allocations
  – NIA makes final decisions
Current Status

- 822 subjects enrolled in 57 sites

- We expect all studies to be completed by summer of 2010, and most analyses to be completed by end of 2010
## Baseline Summaries

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<th>n</th>
<th>Age</th>
<th>Education</th>
<th>% Female</th>
<th>% LP</th>
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<tr>
<td>NL</td>
<td>229</td>
<td>75.86 (5.02)</td>
<td>16.04 (2.87)</td>
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<td>MCI</td>
<td>405</td>
<td>74.71 (7.40)</td>
<td>15.69 (3.03)</td>
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<td>AD</td>
<td>188</td>
<td>75.26 (7.55)</td>
<td>14.66 (3.14)</td>
<td>47.34%</td>
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<td>62.23%</td>
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<td>Overall</td>
<td>822</td>
<td>75.16 (6.86)</td>
<td>15.56 (3.05)</td>
<td>41.85%</td>
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mean (sd)
Alzheimer’s Disease Assessment Scale – Cognitive Subscale (ADAS-Cog)
Average Differences in Cortical Thickness

- AD - NC
- MCI - NC

-0.5mm (cyan) to +0.5mm (yellow)

Fennema-Notestine, Karow, McEvoy, Dale
Mean Cortical Thickness Change over 12 Months

Holland et al.
PET: Regional Hypometabolism

Kweei Chen, Ph.D., Eric M. Reiman, M.D.
Banner Alzheimer’s Institute
Translational Genomics Research Institute
University of Arizona
Arizona Alzheimer’s Consortium
Phoenix, Arizona, USA
12 month CMRgl Decline in AD

12 month CMRgl Decline in MCI

Kewei Chen, Ph.D., Eric M. Reiman, M.D.
Banner Alzheimer's Institute
Translational Genomics Research Institute
University of Arizona
Arizona Alzheimer's Consortium
Phoenix, Arizona, USA
CSF Baseline Samples

- 102 AD
- 114 controls
- 200 MCI

- 56 centers (anywhere from 1 to 22 CSF samples/site)

- Analyses
  - CSF
    - Tau, pTau$_{181p}$, Ab$_{1-42}$ (completed, final review underway)
    - Homocysteine (completed, MRL)
    - Isoprostanes (recently completed)
Original Scan Archival

• Over 27,000 original MR and PET scans archived
• ~26,000 MR scans
• ~1,600 PET scans
Downloads

• Twenty-two months since first data use application approved

• Over 270,000 image downloads by 265 investigators:
  • Original scans: 203,000
  • Pre-processed images: 68,000
  • Post-processed images: 1,400

• Clinical data downloaded by 203 investigators

![Image Downloads Graph]

[Graph showing image downloads by month and type (PET, MRI)]
ADNI Data Use Applications

400% increase in Pharmaceutical usage
1) ADNI is meeting or exceeding expectations

2) The data will be flowing in during the next year

3) Huge opportunities for analysis and writing papers

4) Designing studies, using ADNI data as controls or for comparison
Expected Final Result

• Establish methods for multi-site AD clinical trials

• Identify the best imaging and biomarker methods with high rates of change, small SD, and high power, which correlate with clinical measures.

• These imaging and biomarkers will be used in Phase 2 and 3 studies, and will be validated in the treatment setting.

• Ultimately, a ‘validated’ biomarker; i.e., a surrogate marker, will be identified
Maximizing The Impact of ADNI

- Industry will use ADNI methods and sites

- Many investigators will process and analyze ADNI data

- ADNI results may allow “use of prior information” in design and analysis of AD trials, increasing statistical power

- FDA may give greater weight to ADNI-evaluated imaging and biomarkers
Maximizing Impact Of ADNI

• Hope is that ADNI will facilitate the development of effective disease modifying therapies for:
  – Treatment of AD
  – Delay of Disease Progression
  – Prevention of AD