ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

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National Institute on Aging/NIH

NEED FOR VALIDATED BIOMARKERS FOR AD TRIALS

- **Biomarkers useful in Phase 2 to make decisions about Phase 3 (e.g. doses)**

- **Biomarkers useful in Phase 3**
  - **Provide additional evidence to support primary outcome findings**
  - **Provide evidence for "disease modification" and not simply symptomatic improvement**

GOALS OF THE ADNI: LONGITUDINAL MULTI-SITE OBSERVATIONAL STUDY

- Major goal is collection of data and 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 neuropsychological data in a multi-site context

- "Validate" imaging and biomarker data by correlating with neuropsychological and clinical data.

- Rapid public access of *all* data and access to samples

Mild Cognitive Impairment

Normal

MCI

AD

ADNI 2
(EMCI)

ADNI 1
(LMCI)

0

0.5

1

CDR

New Diagnostic Criteria

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on workgroups on diagnostic guidelines for Alzheimer's disease.

McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR Jr, Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH.
Alzheimers Dement. 2011 May;7(3):263-9.

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.

Albert MS, Dekosky ST, Dickson D, Dubois B, Feldman HH, Fox NC, Gamst A, Holtzman DM, Jagust WJ, Petersen RC, Snyder PJ, Carrillo MC, Thies B, Phelps CH.
Alzheimers Dement. 2011 May;7(3):270-9.

Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease.

Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, Iwatsubo T, Jack CR Jr, Kaye J, Montine TJ, Park DC, Reiman EM, Rowe CC, Siemers E, Stern Y, Yaffe K, Carrillo MC, Thies B, Morrison-Bogorad M, Wagster MV, Phelps CH.
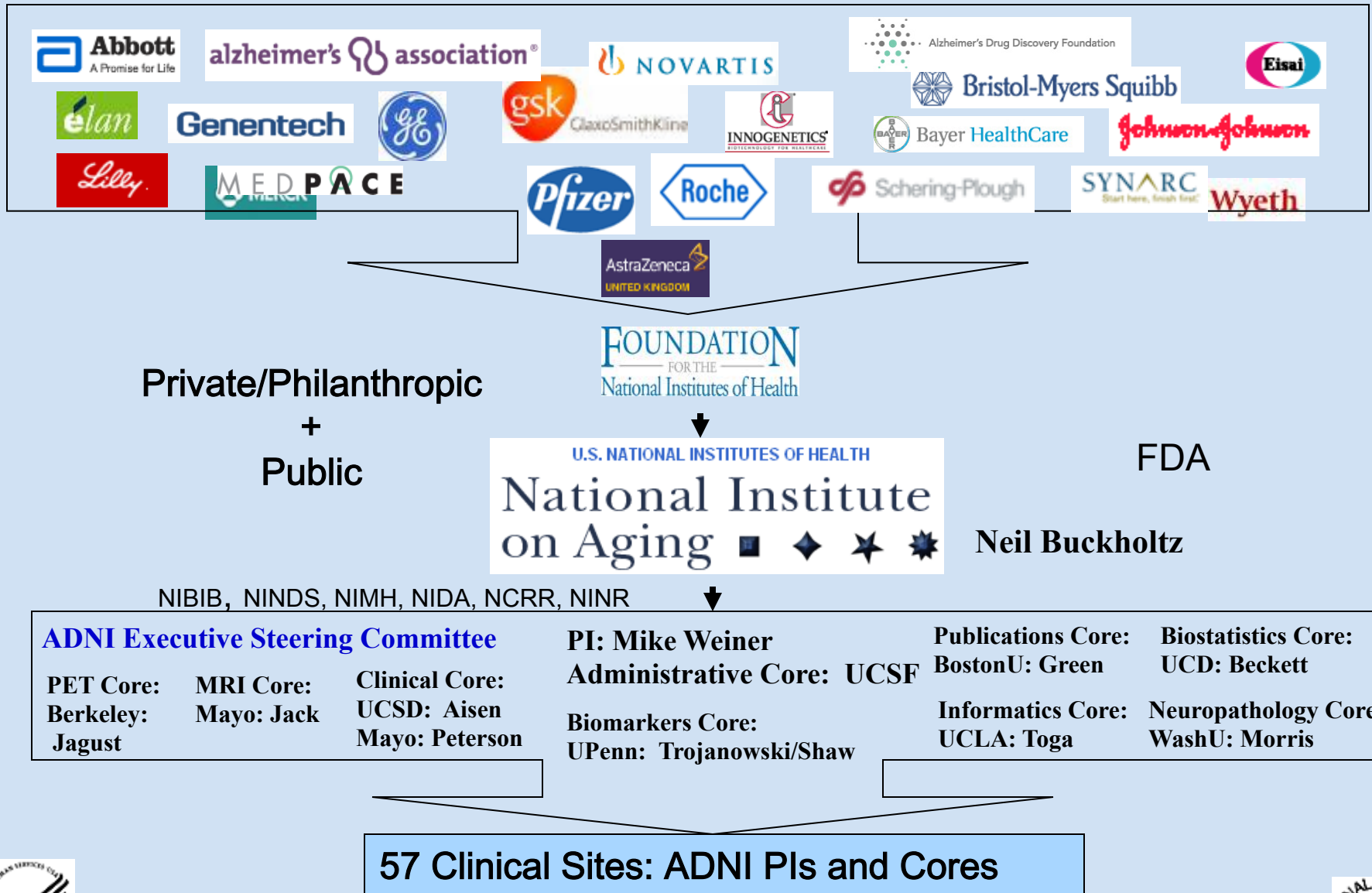Alzheimers Dement. 2011 May;7(3):280-92.

STUDY DESIGN-ADNI1

- 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
- Clinical/neuropsychological evaluations, 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%
- PIB sub-study on 120 subjects
- Blood and urine at all time points from all subjects; CSF from 50% of subjects 0, 1 yr, 2 yr (subset); DNA and immortalized cell lines from all subjects
- GWAS study

ADNI Public-Private Partnership Structure

Abbott — A Promise for Life | alzheimer's association® | NOVARTIS | Alzheimer's Drug Discovery Foundation | Bristol-Myers Squibb | Eisai

élan | Genentech | GE | gsk GlaxoSmithKline | INNOGENETICS BIOTECHNOLOGY FOR HEALTHCARE | Bayer HealthCare | Johnson-Johnson

Lilly | MEDPACE | MERCK | Pfizer | Roche | Schering-Plough | SYNARC Start here, finish first. | Wyeth

AstraZeneca
UNITED KINGDOM

Private/Philanthropic

+

Public

FOUNDATION
FOR THE
National Institutes of Health

FDA

U.S. NATIONAL INSTITUTES OF HEALTH
National Institute on Aging ■ ◆ ✦ ❋

Neil Buckholtz

NIBIB, NINDS, NIMH, NIDA, NCRR, NINR

ADNI Executive Steering Committee			**PI: Mike Weiner**	**Publications Core: BostonU: Green**	**Biostatistics Core: UCD: Beckett**
PET Core: Berkeley: Jagust	**MRI Core: Mayo: Jack**	**Clinical Core: UCSD: Aisen Mayo: Peterson**	**Administrative Core: UCSF** **Biomarkers Core: UPenn: Trojanowski/Shaw**	**Informatics Core: UCLA: Toga**	**Neuropathology Core: WashU: Morris**

57 Clinical Sites: ADNI PIs and Cores

ADNI 2 Private Partner Scientific Board

23 companies, 1 government entity and 2 non-profit organizations

Data and Sample Sharing

- Goal is rapid public access of *all raw and processed data*
- Central repository for all QA'd MRI and PET [Laboratory of Neuroimaging, UCLA (LONI)]
- Clinical data base at UCSD is linked to LONI
- Databases- in the public domain, available to all qualified investigators
- Sample sharing-Resource Allocation Review Committee
- No special access
- Data Sharing & Publication Committee (DPC)
  -ADNI Data Use Agreement

ADNI Demographics

	Normal controls (n=229)	MCI (n=398)	AD (n=192)	P
Age, mean (SD)	76.4 (5.0)	75.3 (7.5)	75.8 (7.4)	0.15
Female (%)	48.0	35.4	47.4	0.002
Years of education, mean (SD)	15.6 (3.1)	16.0 (2.9)	14.7 (3.1)	<0.001
Apolipoprotein E e4: Positive (%)	26.6	53.5	65.6	<0.001

Subject Evaluation

- Baseline/screening eval and q 6 mo.
  - Labs, Apo E
  - Hamilton(S)
  - Beck
  - MMSE
  - ANART
  - ADAS-cog
  - NPI
  - CDR
  - ADL

- Neuropsyc(B and q 6 mo)
  - Logical Memory(S)
  - AVLT
  - BNT
  - Trails A &B
  - Symbol digit
  - Clock drawing
  - Category fluency

ADAS Cog 11
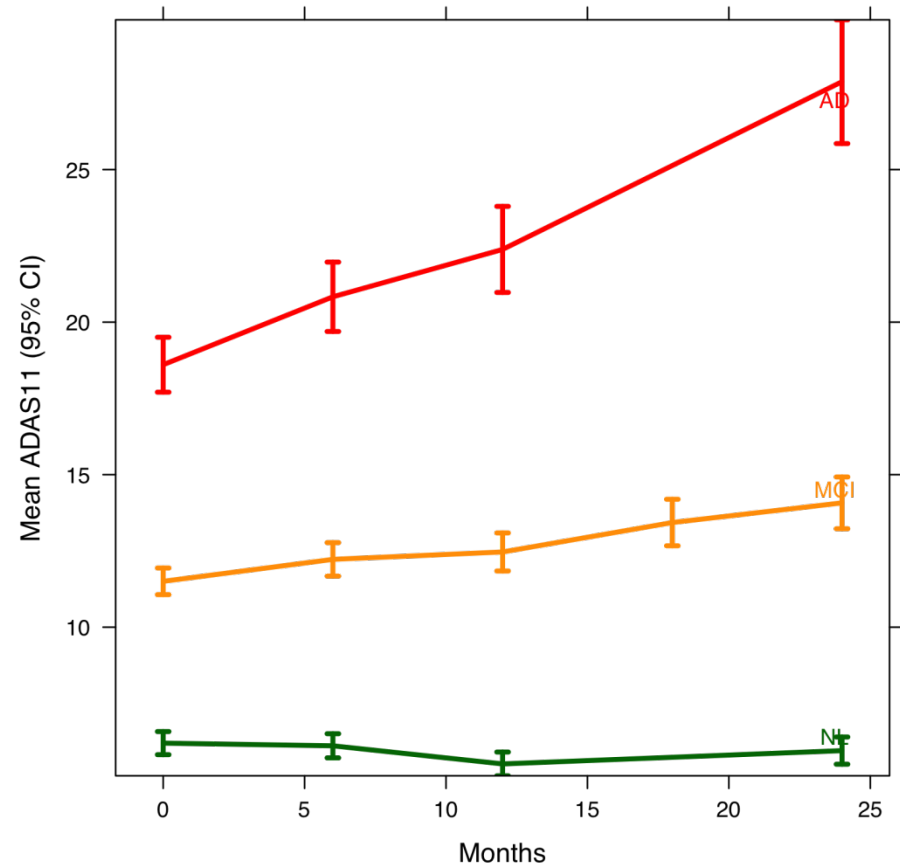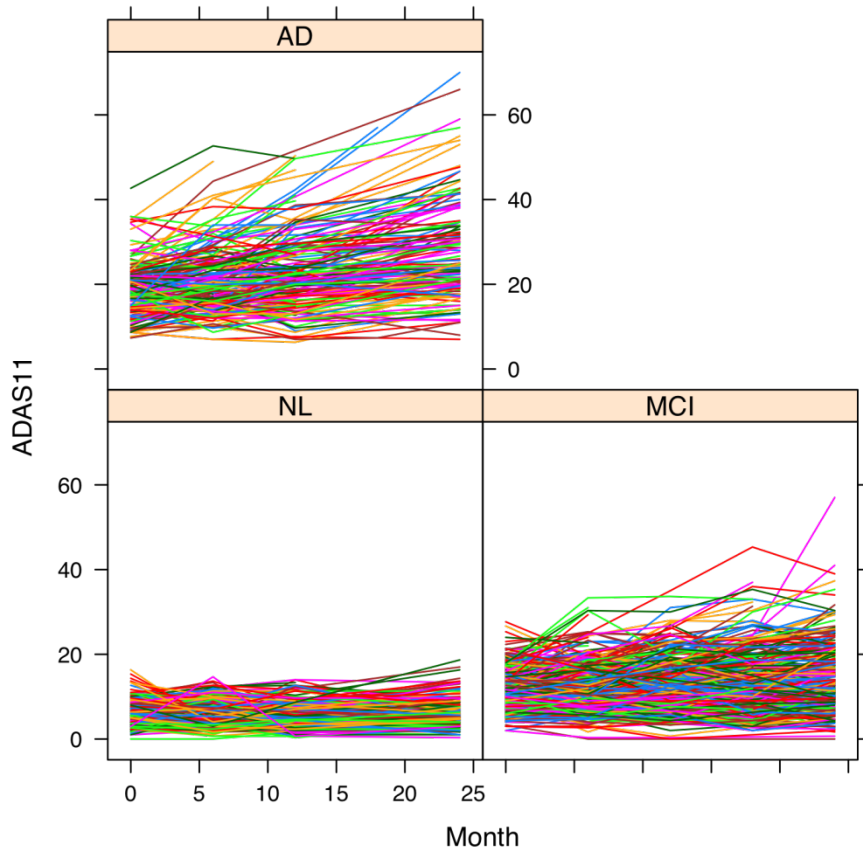
MMSE
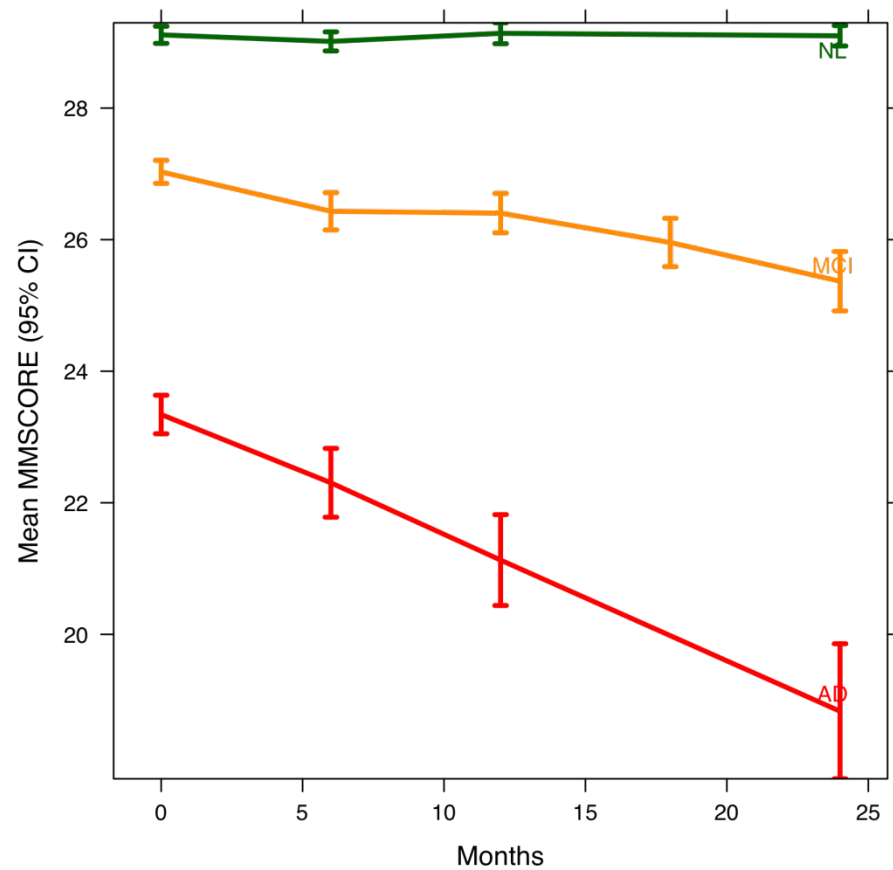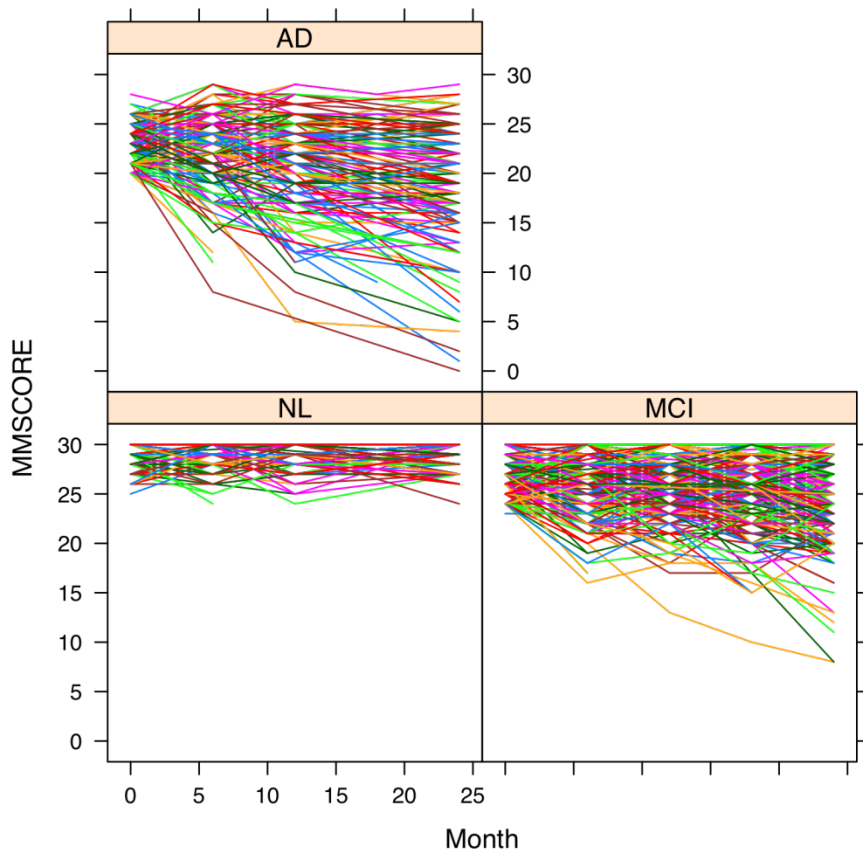
AD Subjects: Hippocampal Volume (mm3)
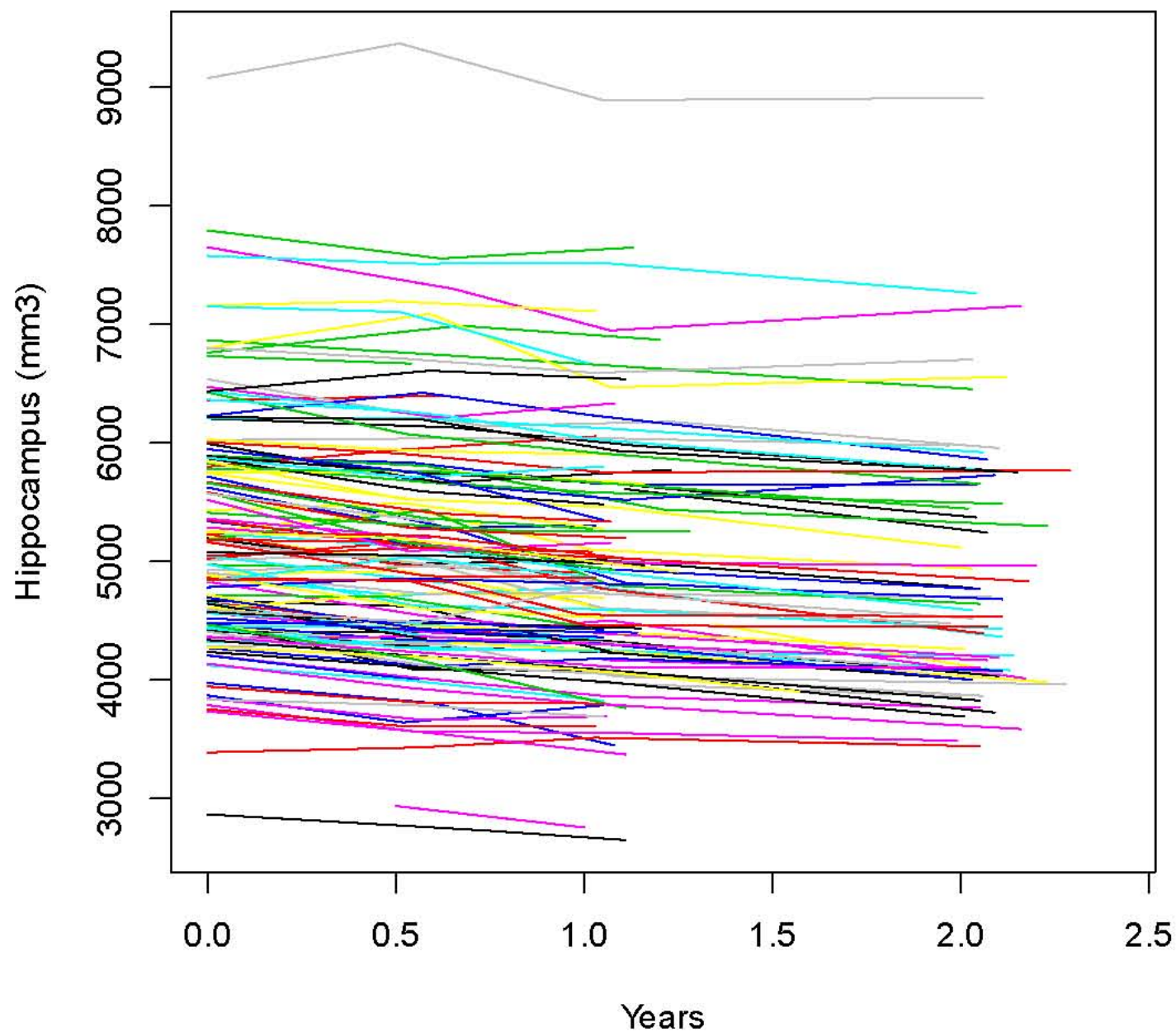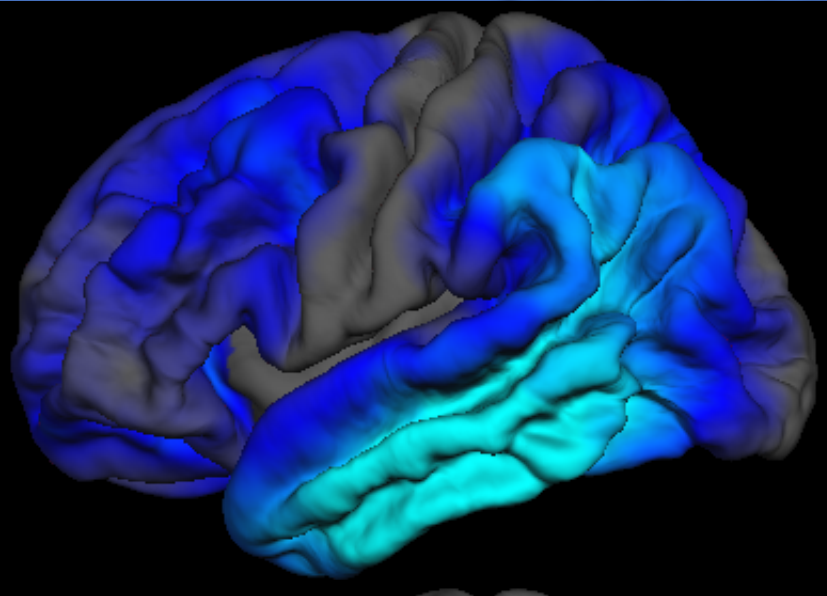
ADNI Progression Rates
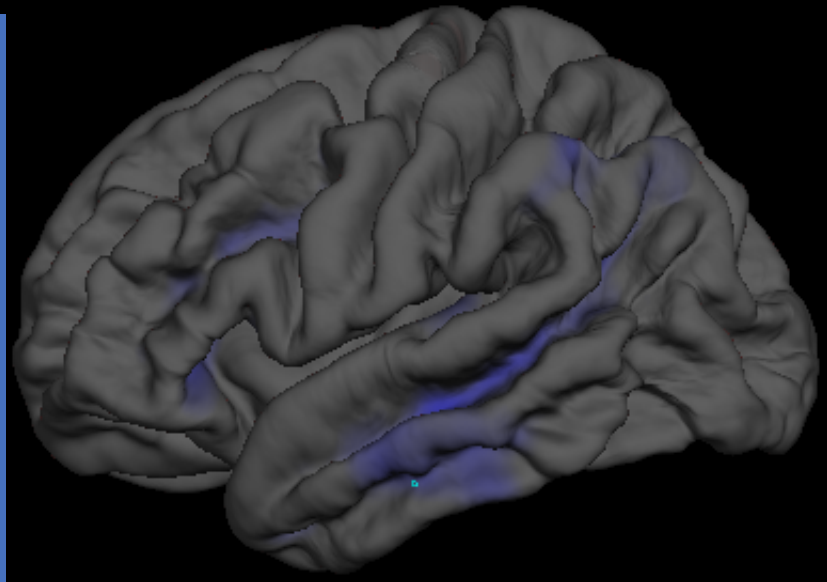
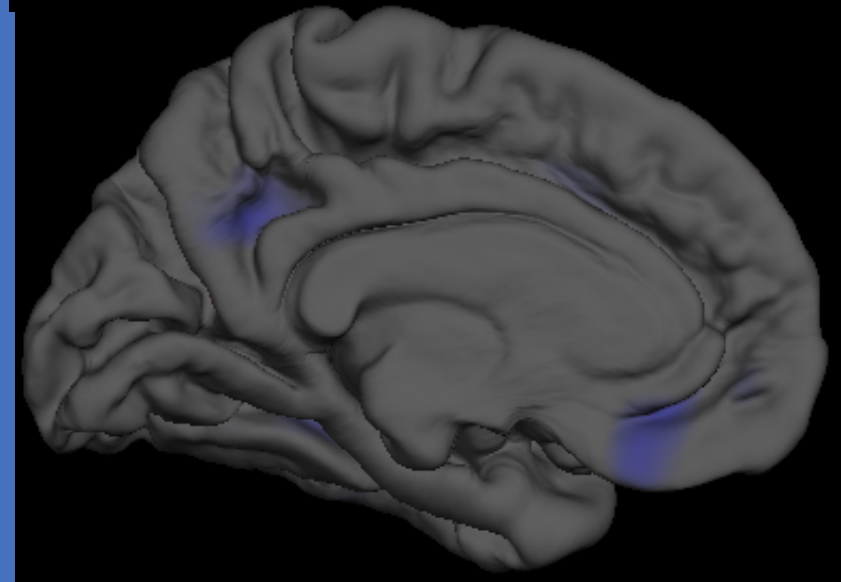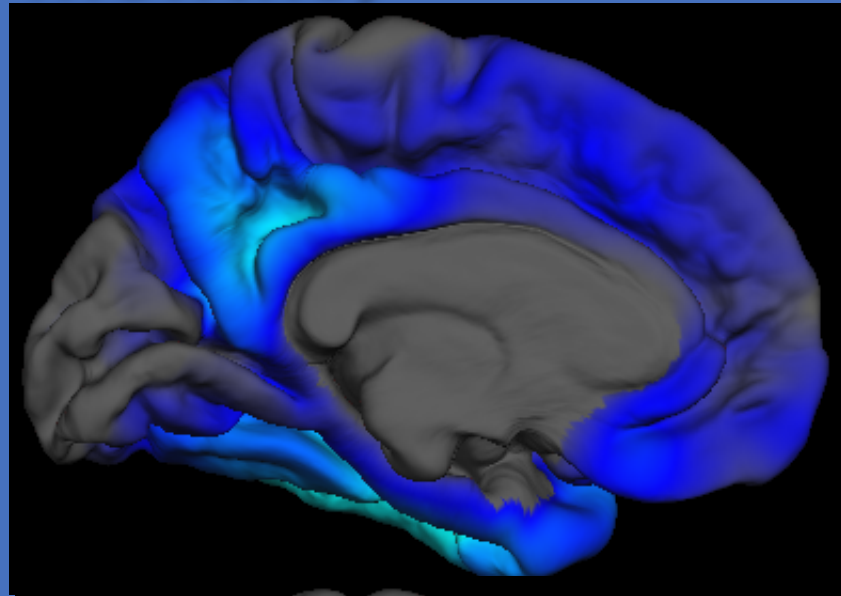| Year	Normal ➜ MCI	MCI ➜ AD
0-1	1.4% (0.0-3.2)	16.0% (11.3-20.4)
1-2	2.4% (0.0-4.7)	23.9% (19.0-29.5)
2-3	0.0% (0.0-3.4)	9.1% (5.8-13.5)

Mean Cortical Thickness Change
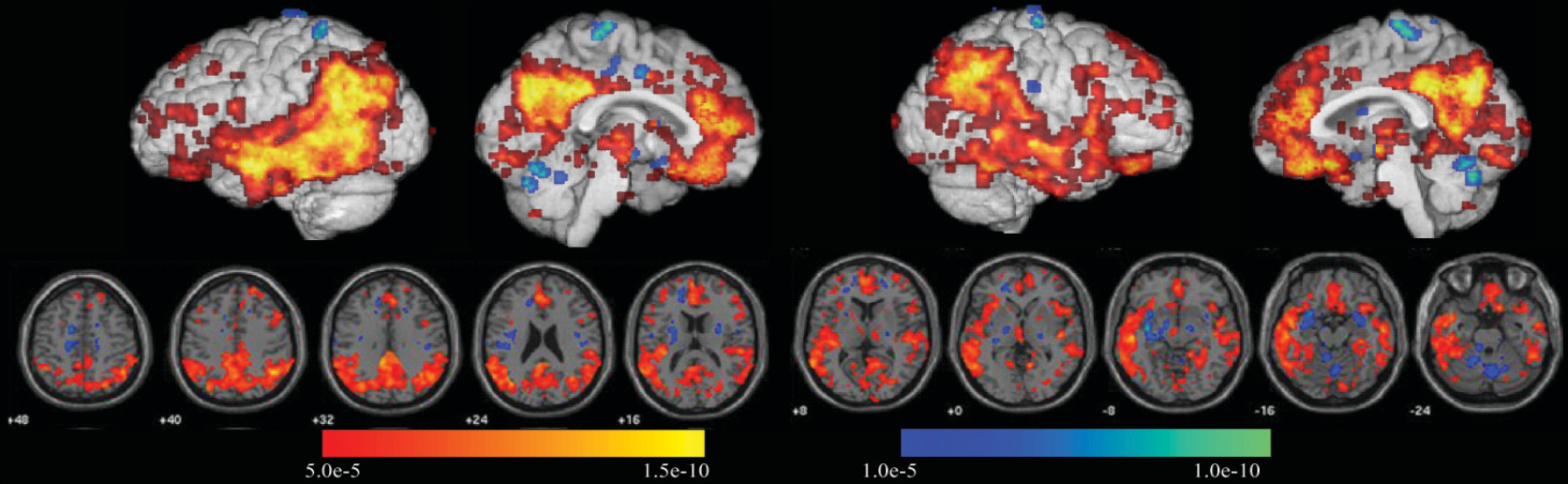## (over 12 months)

Diagnosed as AD

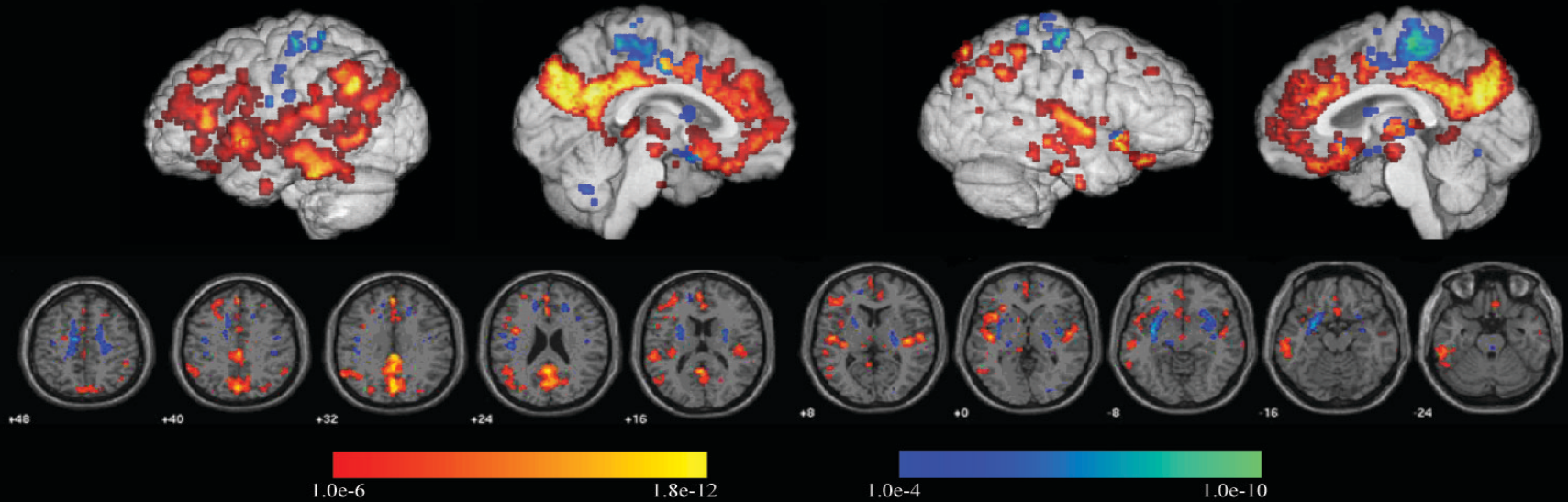**Diagnosed as NC**

Lateral View

Medial View

+2%

-2%

Holland et al.

Statistical ROI's of 12-Month CMRglDecline

ADNI 1 Baseline PIB data (N=101)

Mean Cortical SUVR

Cutoff > 1.46
PIB+
(Berkeley Data)

Normals
9/19 (47%)
PIB+

MCI
47/63 (68%)
PIB+

AD
17/19 (89%)
PIB+
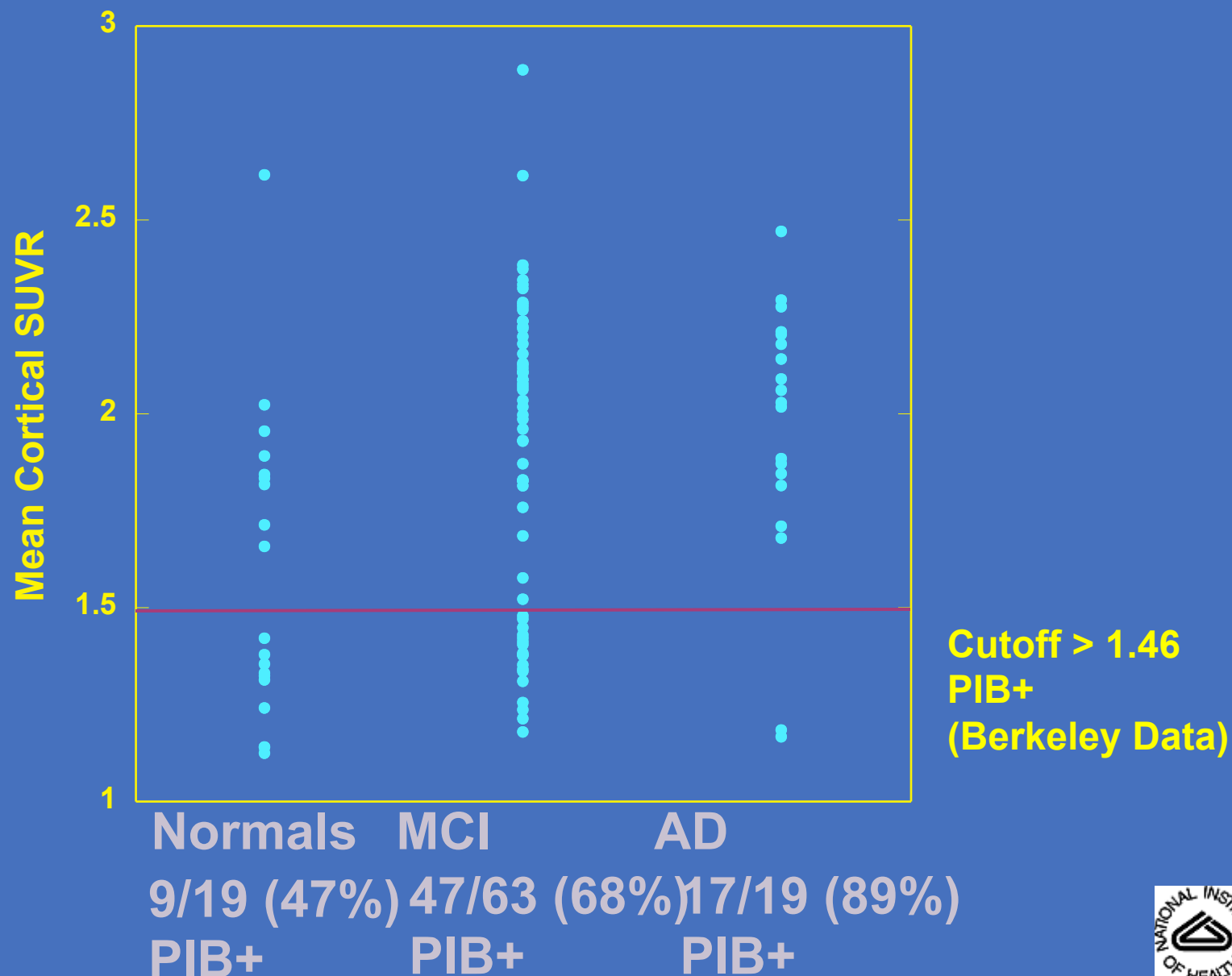
Follow-Up of PIB-Positive ADNI MCI's

ADNI PiB MCI's
N = 65, 12 mo. follow-up

PiB(-)   18

Converters to AD   3

PiB(+)   47

Converters to AD   21

ADNI BASELINE CSF biomarker concentrations show the expected average differences between AD and MCI and NC

AD (n=102)	Tau	$A\beta_{1-42}$	P-Tau$_{181P}$	Tau/$A\beta_{1-42}$	P-Tau$_{181P}$/$A\beta_{1-42}$
Mean±SD	122±58	143±41	42±20	0.9±0.5	0.3±0.2
MCI (n=200)					
Mean±SD	103±61	164±55	35±18	0.8±0.6	0.3±0.2
NC (n=114)					
Mean±SD	70±30	206±55	25±15	0.4±0.3	0.1±0.1

$p < 0.0001$, for each of the 5 biomarker tests for AD vs NC and for MCI vs NC.
For AD vs MCI: $p < 0.005$, Tau; $p < 0.01$, $A\beta_{1-42}$; $p < 0.01$, P-Tau $_{181P}$; $p < 0.0005$, Tau/$A\beta_{1-42}$; $p < 0.005$, P-Tau $_{181P}$/$A\beta_{1-42}$.
Mann-Whitney test for statistical differences used for these non-normally distributed data sets.

MCI progressors to AD at YEAR 1(n=37)
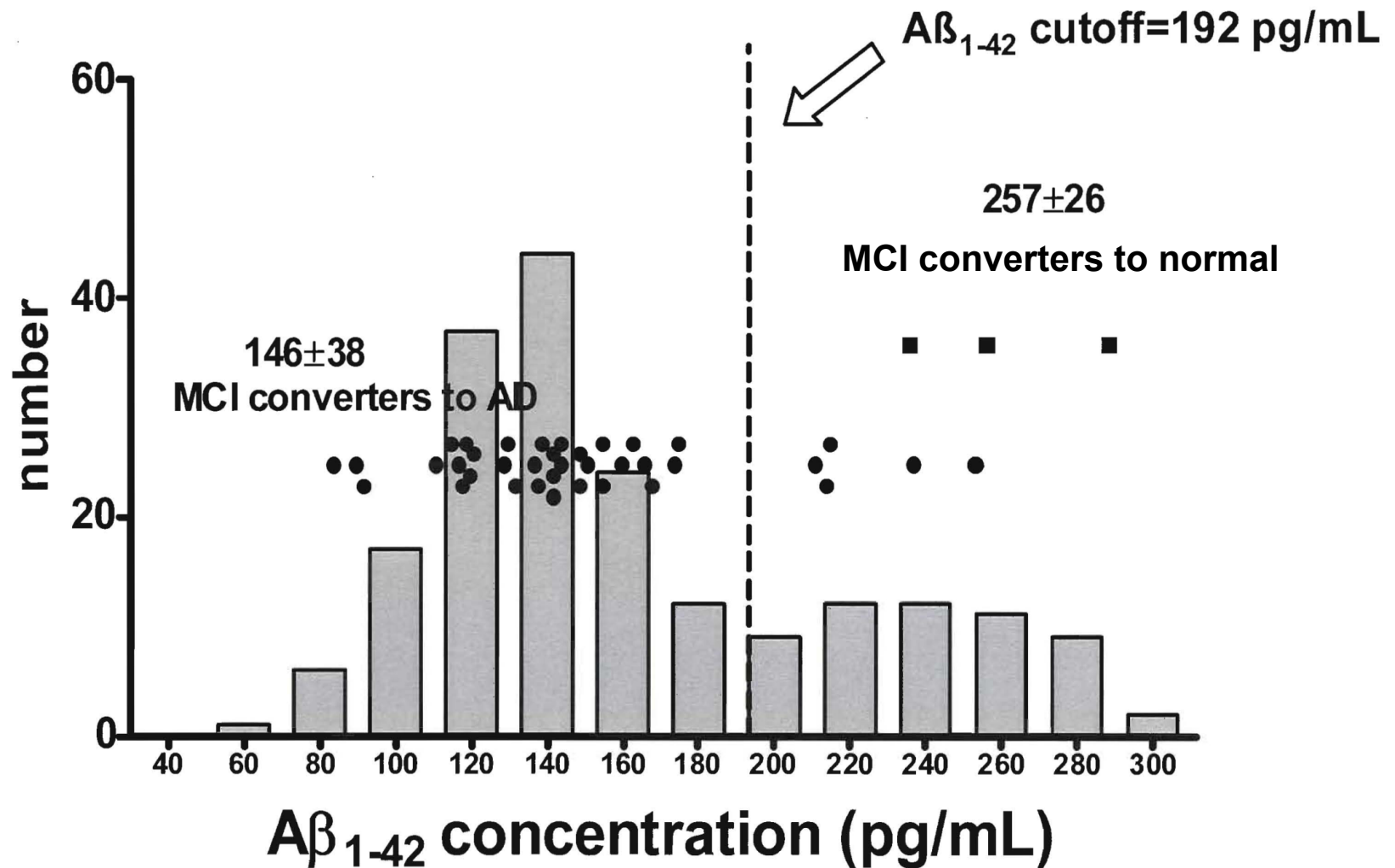
Aβ₁₋₄₂ concentrations in CSF, collected at the baseline visit, of 37 ADNI MCI subjects who at their one year visit converted to a diagnosis of probable AD. The data points for the MCI→AD converters are presented as a horizontal dot plot with the x axis scale identical to that of the Aβ₁₋₄₂ frequency plot for the entire ADNI MCI group. The vertical line indicates the Aβ₁₋₄₂ cutoff concentration obtained from ROC analysis of an ADNI-independent cohort of autopsy-based AD subjects' CSF.

ADNI Plasma
and CSF Proteomics Studies

**GOAL:** Leverage ADNI Plasma and CSF samples to assess the utility of existing AD biomarker panels studies.

PLASMA STUDY:

- Baseline and 1 year ADNI plasma samples analyzed using RBM190 analyte multiplex immunoassay platform (Luminex xMAP) containing proteins previously reported in the literature to be altered as a result of cancer, cardiovascular disease, metabolic disorders, inflammation, Alzheimer's disease

- All data posted to ADNI website and available as of Nov, 2010

- Project Team - completed statistical analyses; finalizing manuscript

CSF STUDY:

- ADNI CSF samples to be sent to RBM for analysis (July, 2011)

- Additional studies planned to to qualify a Multiple Reaction Monitoring (MRM) Mass Spectrometry panel and to examine Beta-Site APP Cleaving Enzyme (BACE-1) levels and enzymatic activity in CSF.

Hippocampal atrophy rates (L+R) – free surfer data – in ADNI subjects with CSF $A\beta_{1-42}$ >192 pg/mL or <192 pg/mL
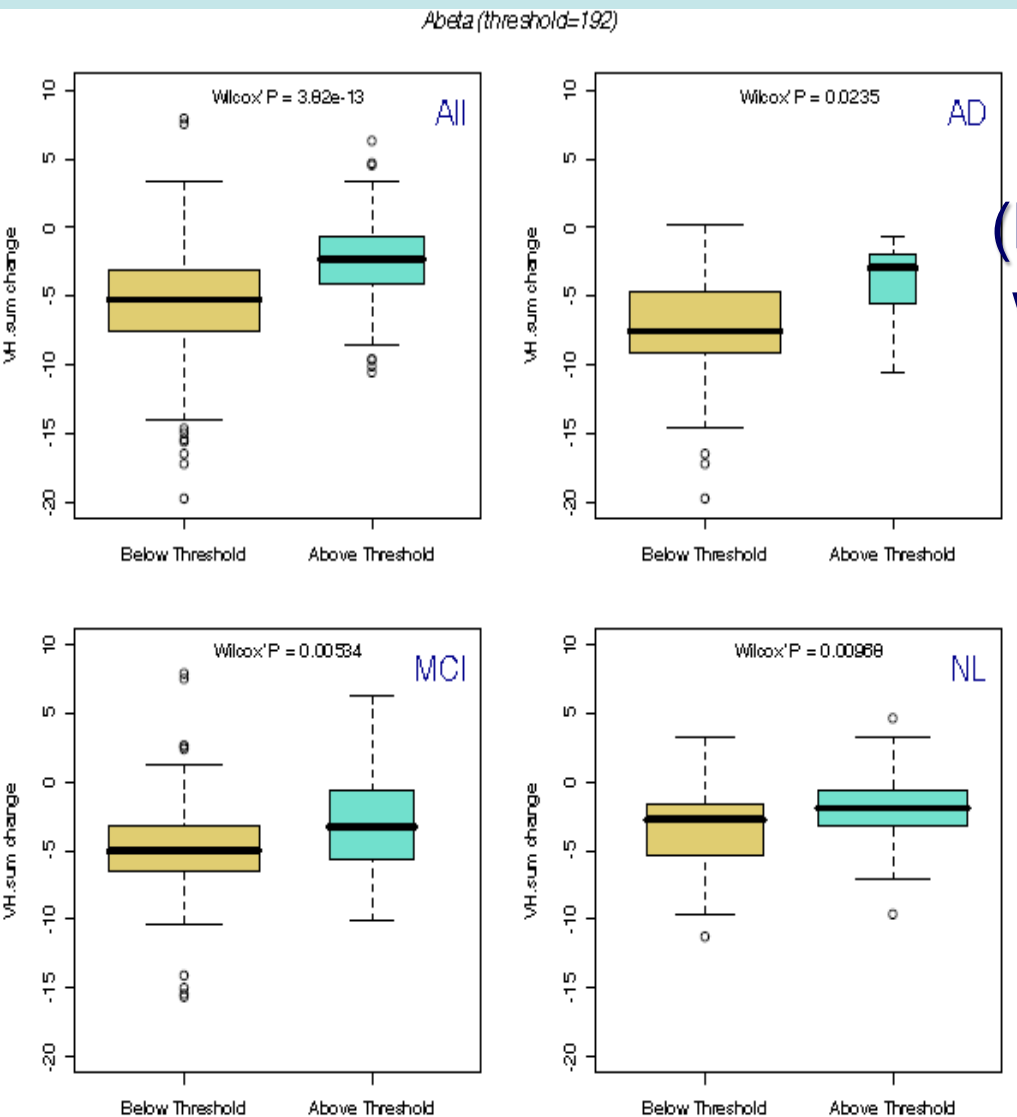
Hippocampal % atrophy rates (BL→12 mos), for ADNI subjects with $A\beta_{1-42}$< 192 or >192 pg/mL

	$A\beta_{1-42}$ <192pg/mL	$A\beta_{1-42}$ >192pg/mL
ALL	-5.6±4.7	-2.6±4.1
AD	-8.0±5.9	-4.2±3.5
MCI	-4.8±3.6	-2.9±3.7
NC	-3.6±3.2	-2.2±4.3

These data show that in ADNI AD, MCI and NC subjects the rate of hippocampal atrophy increases at a significantly higher rate in subjects with Ab_{1-42} <192 pg/mL cutoff concentration compared to those >192 pg/mL

POWER OF CLINICAL/COGNITIVE TESTS
25% CHANGE 1YR STUDY (2 ARM) :
AD

Test	Sample Size		
MMSE	803		
RAVLT	607		
ADAS	592		
CDR SOB	449		

1.5T MRI Comparisons - AD (n=69)

| Lab	Variable	SS/arm		
Alexander	L. Hippo. Formation	334	🟩	
Dale	Whole Brain	207	🟩	🟪
Schuff – FS	Hippocampus	201	🟩	🟪
Dale	Ventricles	132	🟩	🟪
Dale	Hippocampus	126	🟩	🟪
Studholme	Temporal lobe % change	123	🟩	🟪
Schuff – FS	Ventricles	119	🟩	🟪
Studhome	CV – % change	106	🟩	🟪
Fox	VBSI % change	105		🟪
Fox	BSI % change	71		🟪
Thompson	CV – % change	54		🟪

ADNI Genotyping

- Initial goal: high density genome wide scan
  - Identified major microarray platforms for GWAS
    - Compared marker selection strategies, HapMap coverage of genome, performance & reliability, as well as cost/sample
  - Illumina platform was selected by consensus of the Genetics Committee & ISAB for this project
  - TGen (Phoenix, AZ) was selected to perform the assays
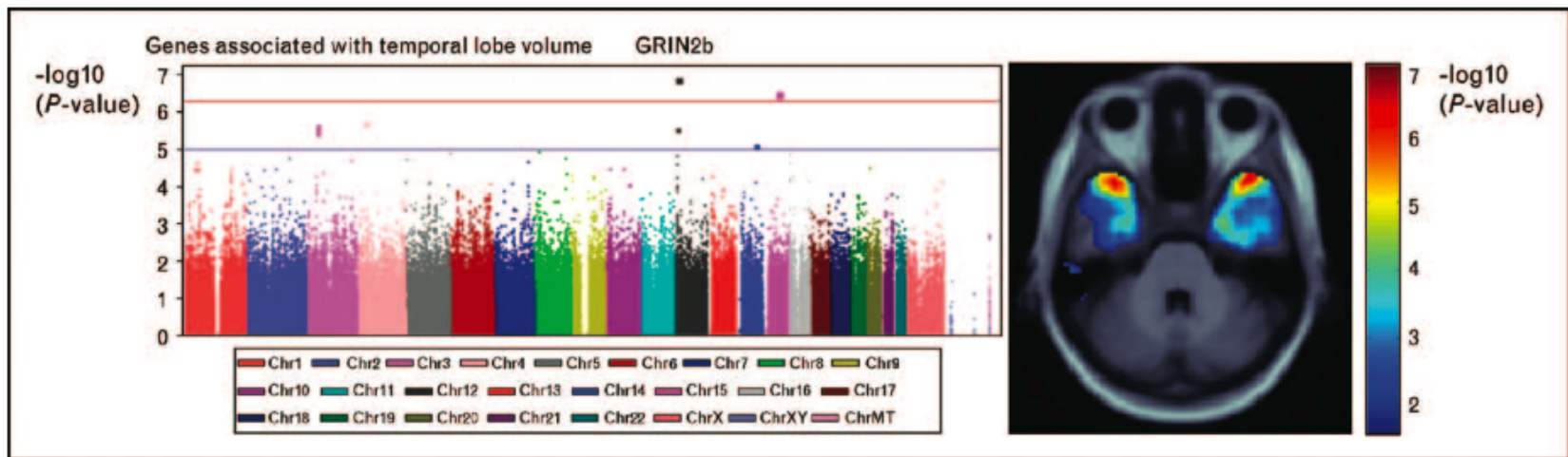 - Illumina Human 610-Quad
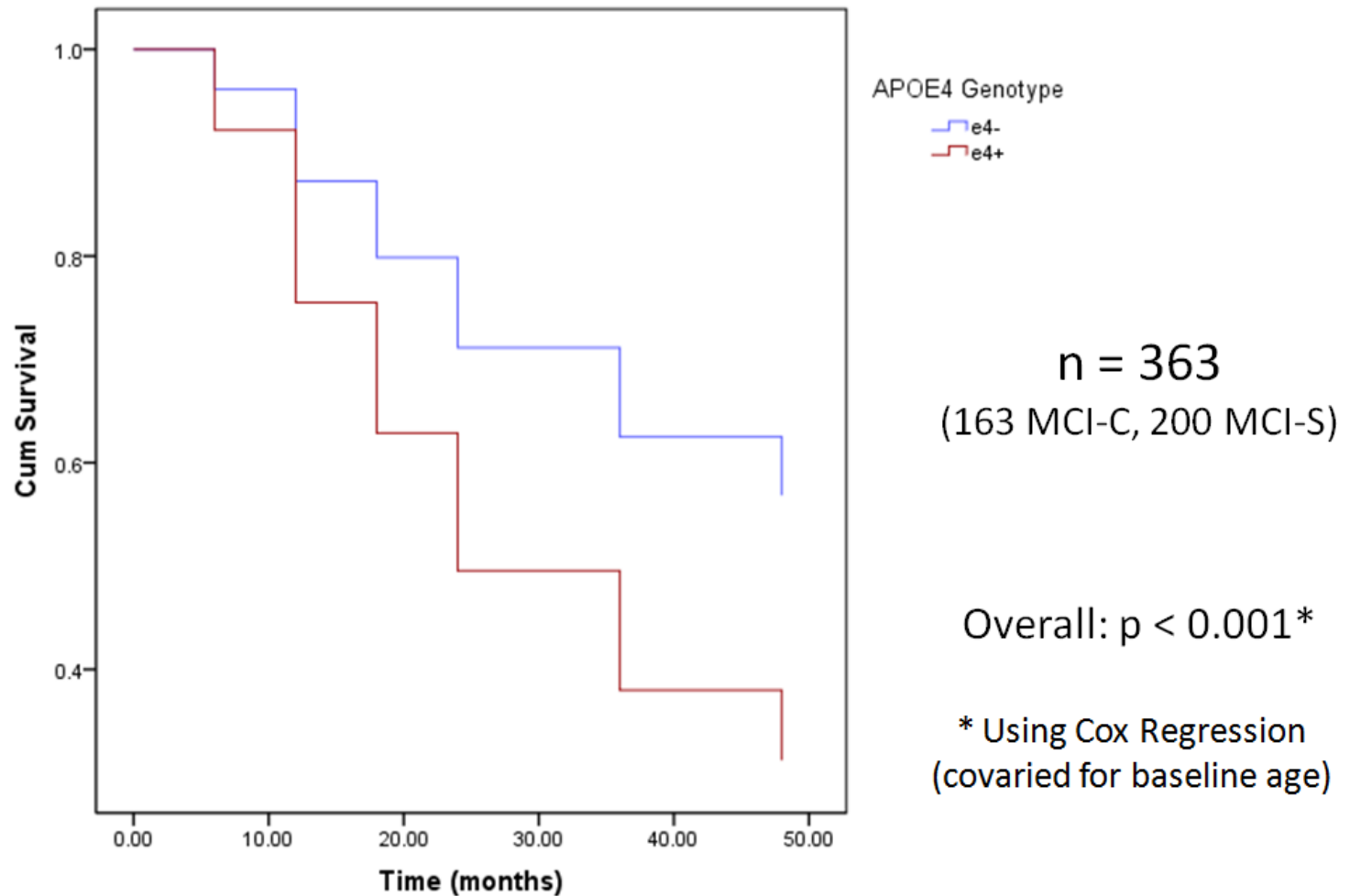
Shen et al 2010: Overview
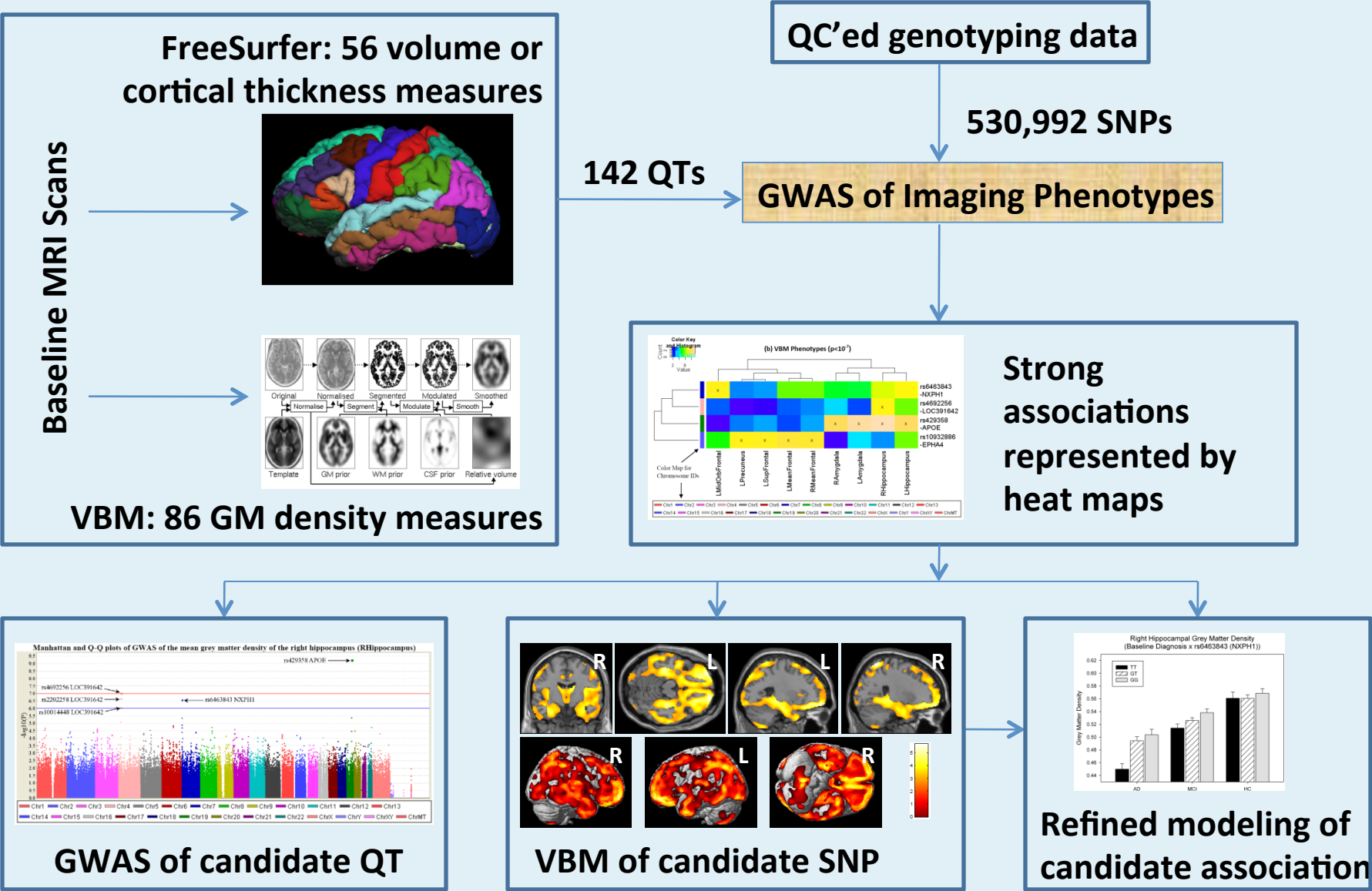
Conclusion: Imaging Gene Discovery

Gene Identification with Imaging "Deep Phenotypes": GWAS

Structural MRI + 600k SNPs =
GRIN2b as Novel Risk Factor for MTL deficits in Alzheimers

Stein et al 2010; ADNI

Survival Plot for MCI to AD Conversion by APOE Genotype (comparing ε4 negative to ε4 positive)

APOE4 Genotype
- e4-
- e4+

n = 363
(163 MCI-C, 200 MCI-S)

Overall: p < 0.001*

* Using Cox Regression
(covaried for baseline age)

163 MCI-C (50 ε4 negative, 113 ε4 positive)   200 MCI-S (112 ε4 negative, 88 ε4 positive)

ADNI Genetics: Next Steps

- ADNI-GO/2
  - Ongoing DNA, RNA, cell line sample collection
  - Planning for genotyping of new samples
- ADNI-1 data analysis
  - Baseline and rate of change
  - Copy number variation
  - Candidate genes & pathways, GWAS approaches
  - Associations with PET & CSF/plasma biomarkers
  - Collaborative projects, replication, other cohorts
- Future:
  - Targeted DNA and RNA resequencing – identify key regions for intensive scrutiny
  - Epistasis, Transcriptomics/expression, microRNA
  - Epigenomics (DNA methylation, etc)

AD Progression

ABNORMAL

CSF Aβ 42

FDG-PET

MRI hipp

Amyloid imaging

Cog

CSF tau

Fxn

NORMAL

Pre-Symptomatic | eMCI | ʟMCI | Dementia

TIME

— CSF abeta42	— FDG PET	— Function (ADL)
— Amyloid Imaging	— MRI Hippocampal Volume	
— CSF Tau	— Cognitive Performance	
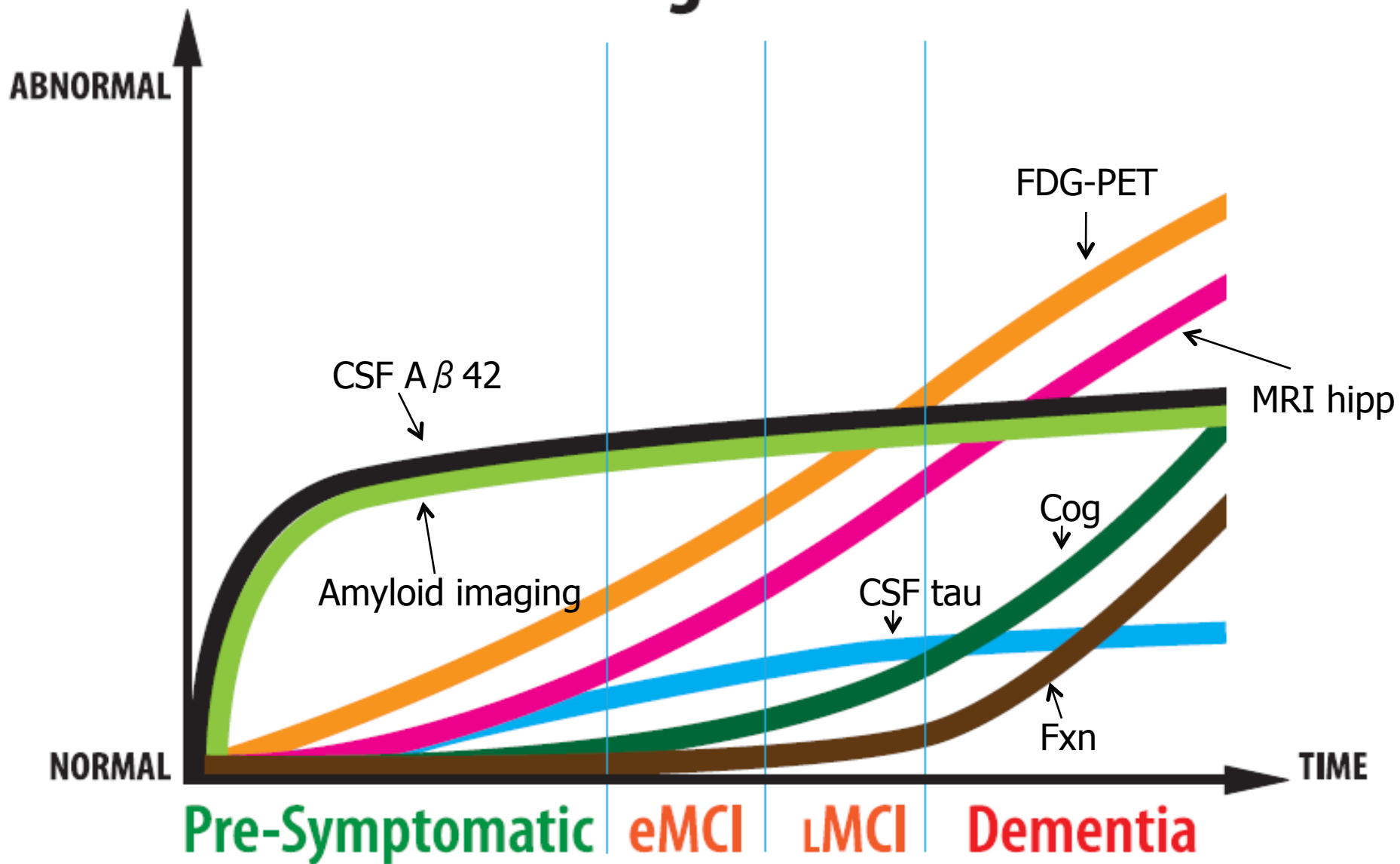
ADNI 2

- Continue to follow all EMCI, LMCI and NC from ADNI 1 and ADNI GO for 5 more years
- Enroll:
  - 100 additional EMCI (supplements 200 from GO)
  - 150 new controls, LMCI, and AD
- 3T MRI at 3, 6, months and annually
- F18 amyloid (AV-45)/FDG every other year
- LP on 100% of subjects at enrollment
- Genetics

Summary: ADNI

- <u>Standardization</u>: imaging, biomarkers
- <u>Neuroscience</u>: relationships among biomarker trajectories elucidate neurobiology
- <u>Trials</u>: new understanding of biomarkers has facilitated interventional studies in very early AD
- <u>Data sharing</u>: ADNI has demonstrated the power of real-time public data sharing
- <u>Collaboration</u>: academia, industry, non-profits, regulatory agencies world-wide

# ADNI Data and Publications Committee: Key Charges

- Creation and revisions as needed or data application and publication policy

- Approval of data applications

- Review and standardization of manuscripts-administrative review
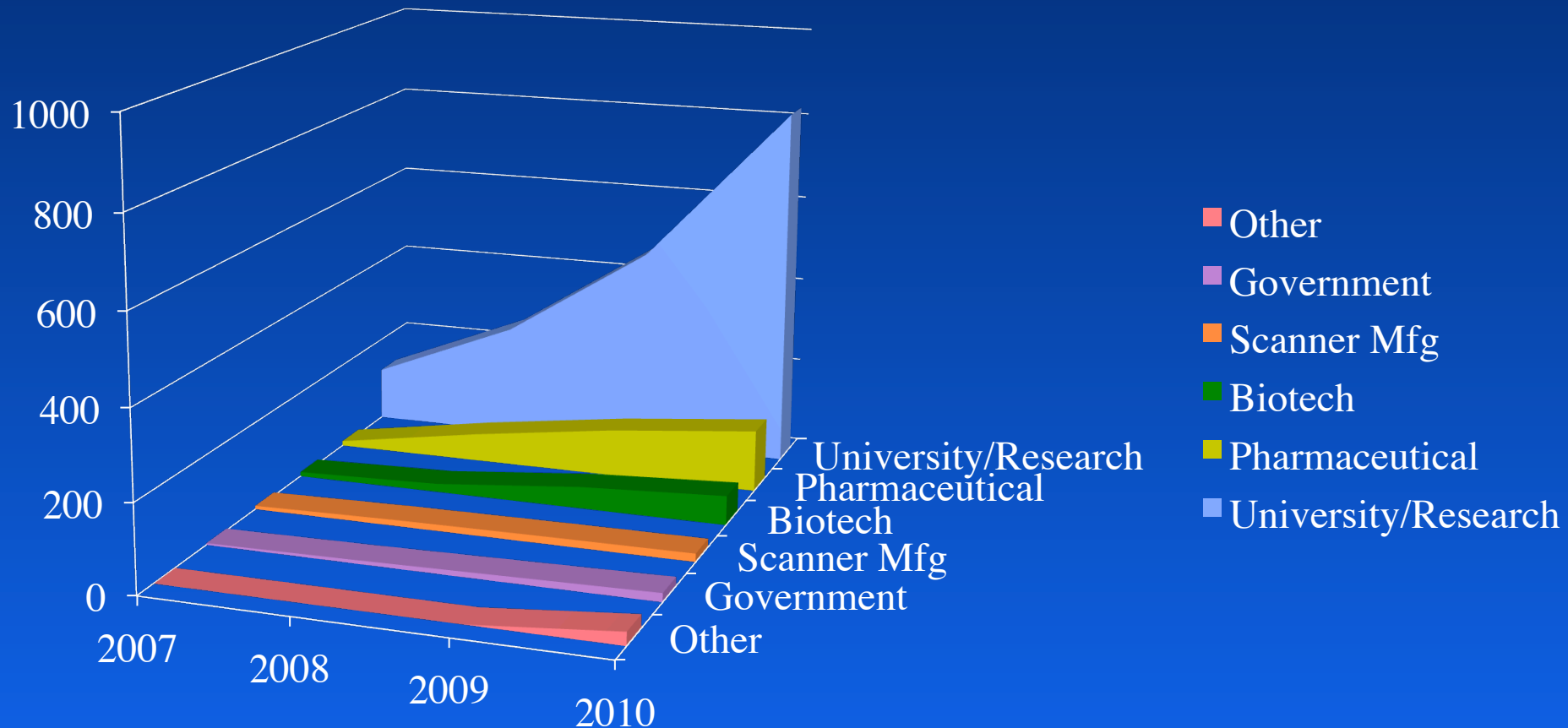
ADNI Data Applications

Total Applications	1,590
Initially Approved	1,463
Challenged	127

ADNI

ADNI Data Applications

Challenged Applications (127)

- Asked to clarify
- Nonsense users

14

113
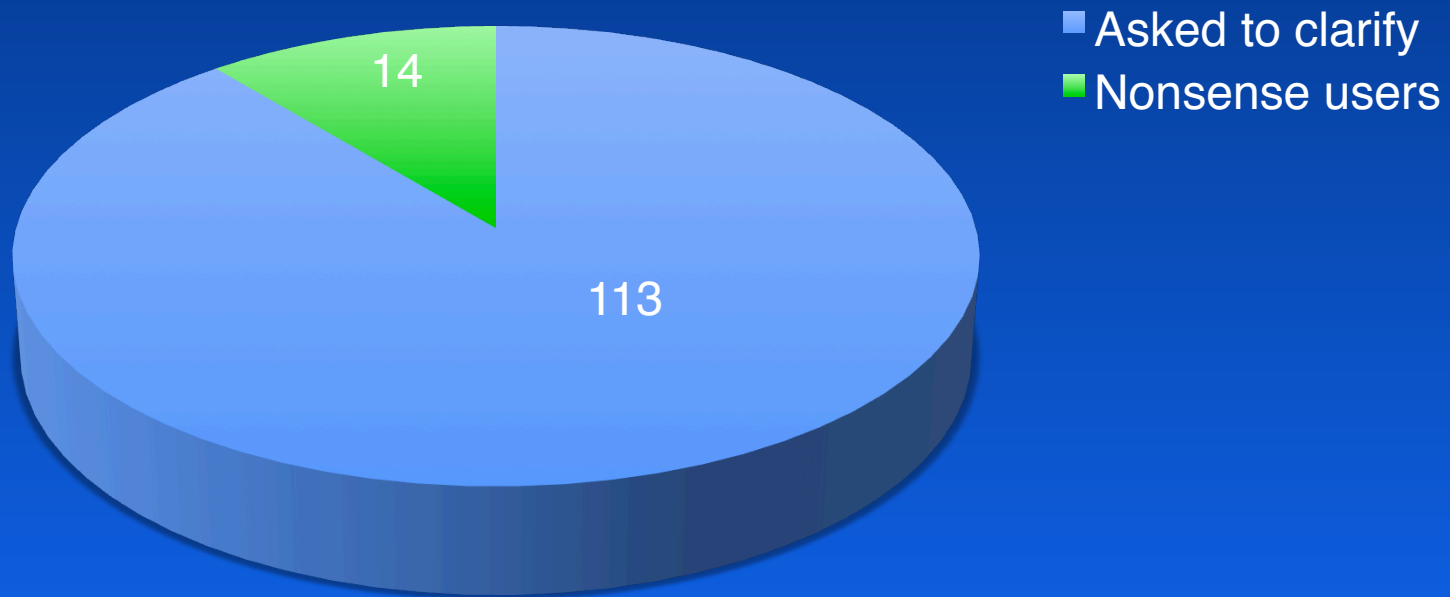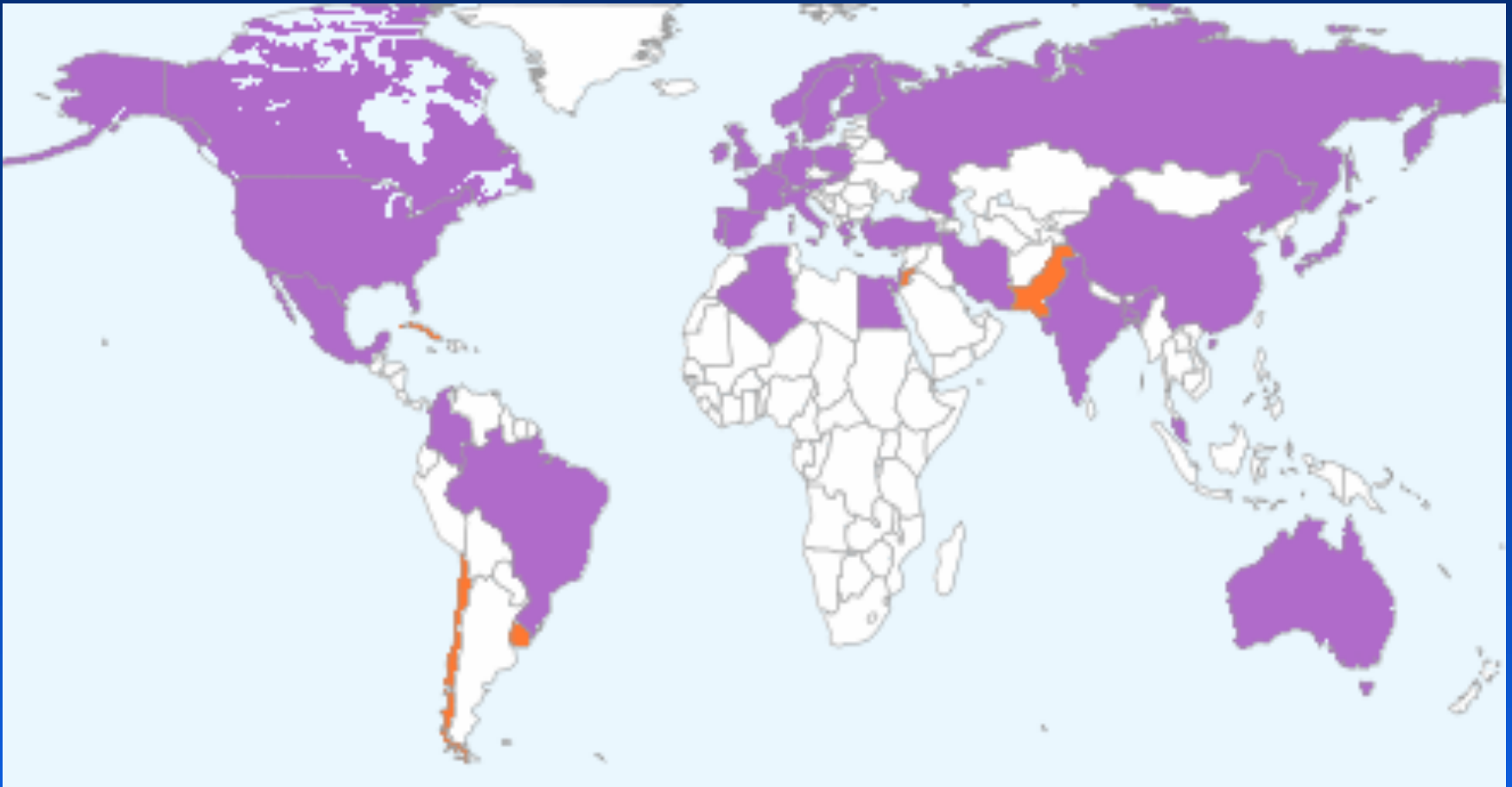
ADNI

ADNI Data Applications by Sector (cumulative)

Countries with ADNI Data Applicants

Countries with ADNI data use applicants
New countries since last meeting

ADNI Manuscripts

305 manuscripts utilized ADNI data

Published	175
Epub ahead of print	26
In Press	3
Under revision	10
In submission	86
Withdrawn	2
Under review by ADNI	3

ADNI

Data Archived and Downloaded

- 140,000 images archived (raw and processed)

- 1.2 million image downloads

- 90,000 downloads of non-image data (clinical, genetic, proteomic, summary) from 36 countries

Websites Maintained by LONI with Input from DPC

REVISED DATA USE AGREEMENT:

http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_Data_Use_Agreement.pdf

PUBLICATION POLICY:

http://adni.loni.ucla.edu/wp-content/uploads/how_to_apply/ADNI_DSP_Policy.pdf

ACTIVE ADNI INVESTIGATORS WITH KEYWORDS:

http://adni.loni.ucla.edu/research/active-investigators/

PUBLICATIONS:

http://adni.loni.ucla.edu/publications/

ADNI

WW-ADNI

NA-ADNI

E-ADNI

C-ADNI

K-ADNI

J-ADNI

T-ADNI

A-ADNI

ADNI as a model for other diseases

- Parkinson's disease
- FTD

http://www.adni-info.org
http://www.loni.ucla.edu/ADNI

Manuscript Submission Procedure