ALZHEIMER'S DISEASE NEUROIMAGING INITIATIVE

FUNDED BY NATIONAL INSTITUTE ON AGIN
NIMH, NINR, NINDS, NCRR, and NIDA

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Industry Scientific Advisory Board (ISAB)

And Site PIs, Study Coordinators and 821 subjects enrolled in 58 Sites in US and Canada

NEEDS OF OUR FIELD

- Of course we need a treatment that works!
- Diagnose AD pathology in the brain with certainty, in subjects with symptoms or complaints
- Detect AD pathology in the brain in subjects without symptoms or complaints
- Measure change of AD in the brain

GOALS OF ADNI

- Validate biomarkers as measures of change
- Validate biomarkers as diagnostics or predictors: symptomatic and presymptomatic
- Optimize biomarker methods
- Standardize biomarker methods
- Establish a world-wide network for clinical AD studies and treatment trials

ADNI

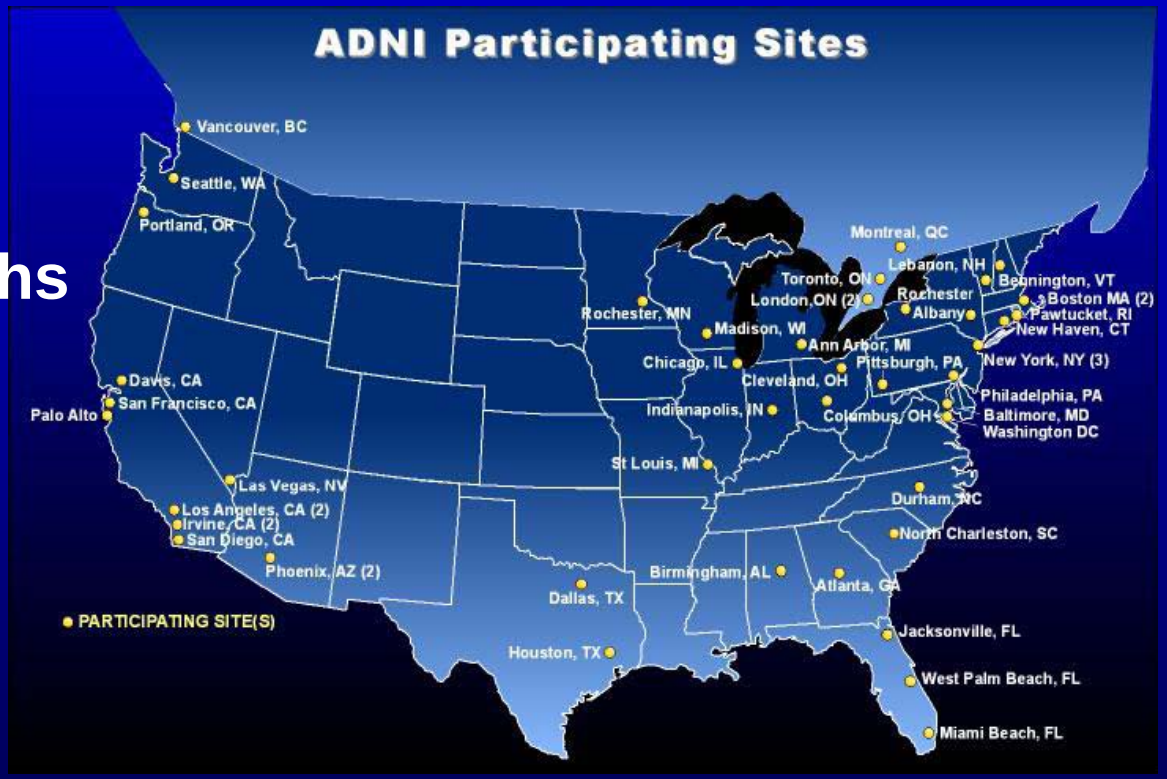
Naturalistic study of AD progression

- **200 NORMAL 3 yrs**
- **400 MCI 3 yrs**
- **200 AD 2 yrs**
- **Visits every 6 months**

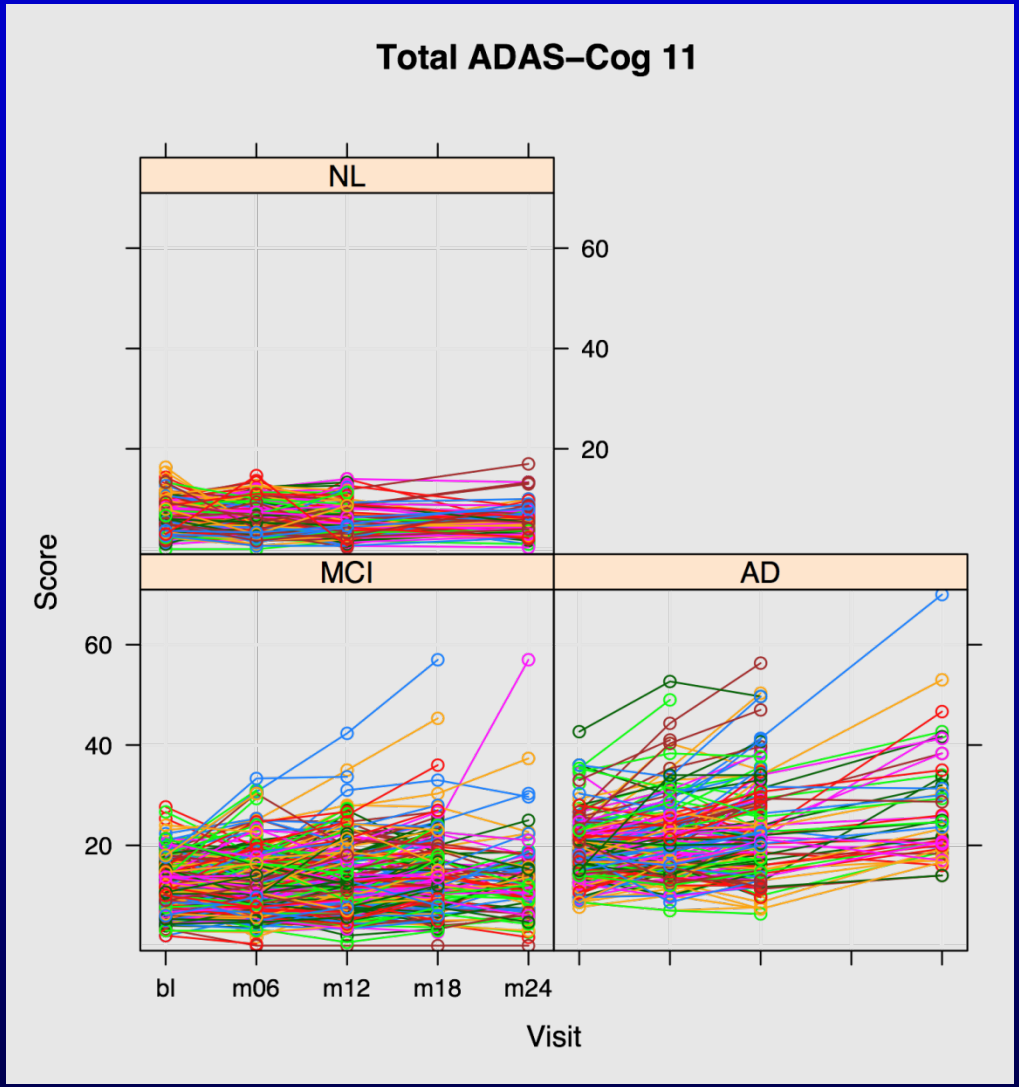
- **57 sites**
- **Clinical, blood, LP**
- **Cognitive Tests**
- **1.5T MRI**

Some also have

- **3.0T MRI (25%)**
- **FDG-PET (50%)**
- **PiB-PET (approx 100)**



All data in public database: UCLA/LONI/ADNI: No embargo of data


Total ADAS–Cog 11
NL
MCI
AD
Score
60
40
20
bl
m06
m12
m18
m24
Visit

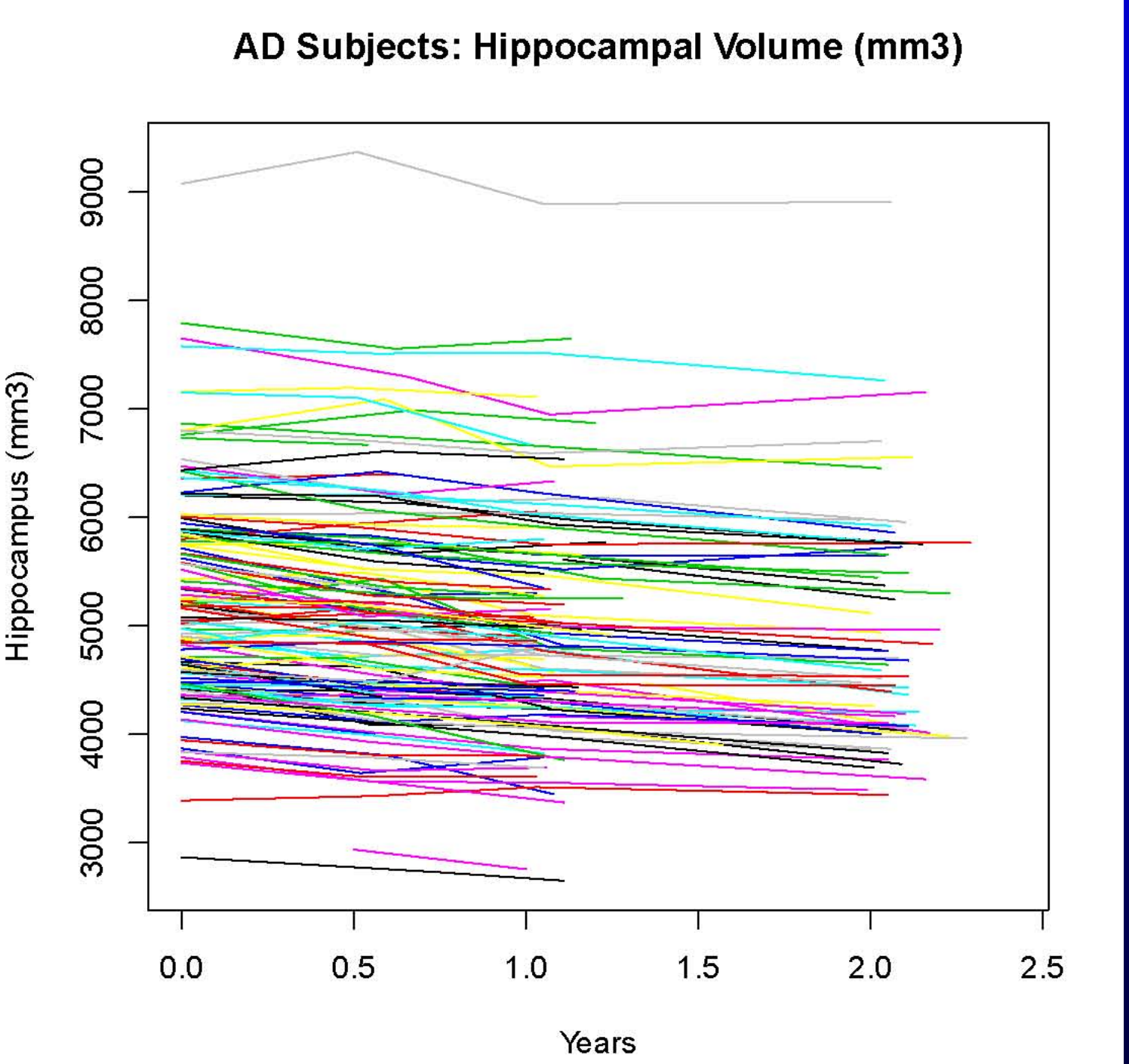
CONVERSION RATES

- MCI-AD
  - 1 YR 16%, 2 YR 40%
- Control – MCI
  - 1 YR 1.4%, 2 YR 3.9% (about 8 subjects)

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

AD (155 Subjects)

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


AD Subjects: Hippocampal Volume (mm3)
Hippocampus (mm3)
3000
4000
5000
6000
7000
8000
9000
0.0
0.5
1.0
1.5
2.0
2.5
Years

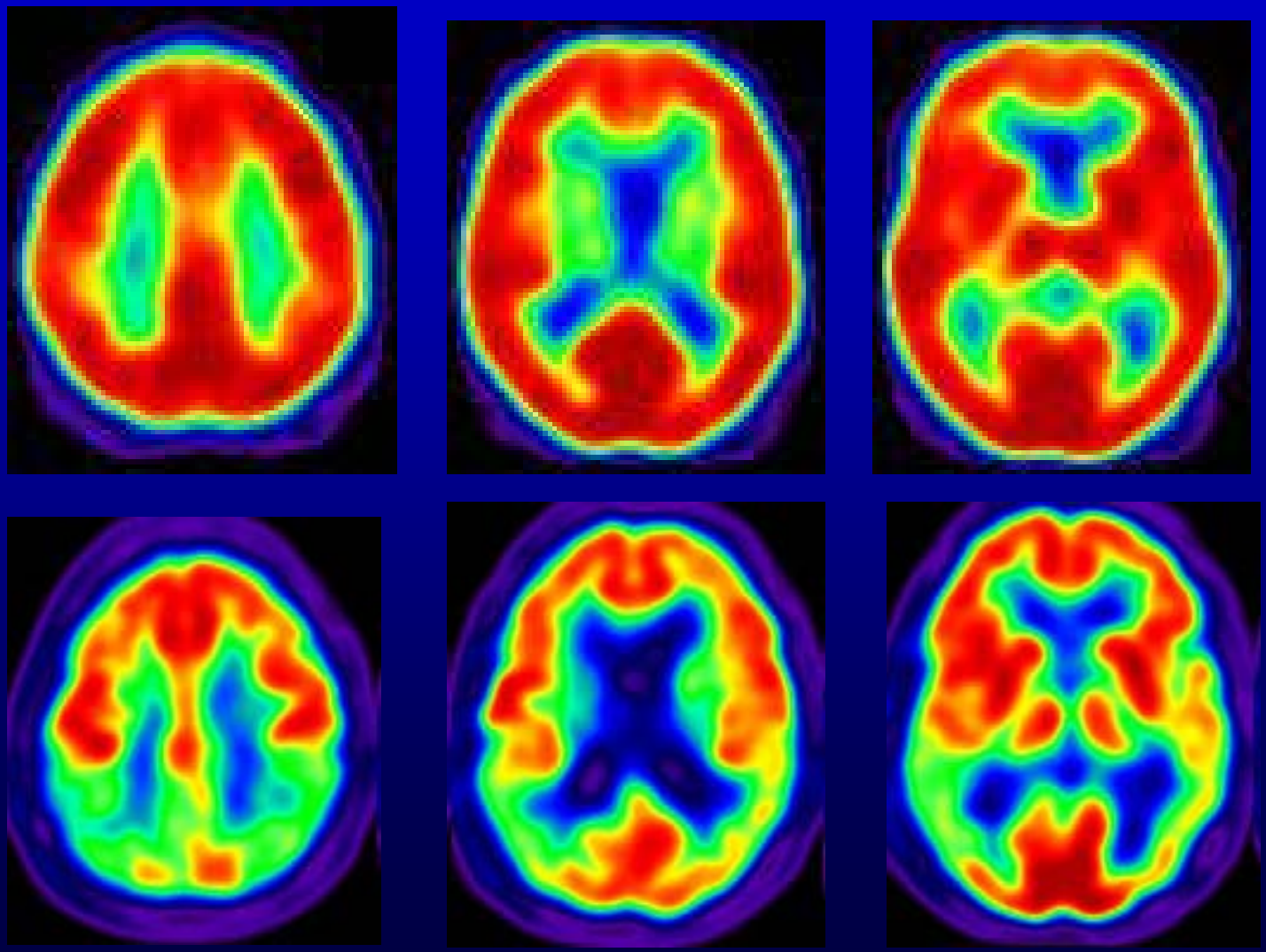
1.5T MRI Comparisons - AD (n=69)

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		

Normal Aging vs. Alzheimer's Disease
FDG PET

Normal

AD



1.5T vs PET Comparison in AD (n=30)

Lab	Modality	Variable	SS/arm				
Foster	PET	hypometabolism1	593				
Foster	PET	hypometabolism2	508				
Jagust	PET	ROI-avg	396				
Schuff - FS	MRI	Hippocampus	173				
Schuff - FS	MRI	Ventricles	95				
Reiman	PET	CV - fROI	91				
Fox	MRI	VBSI % change	87				
Thompson	MRI	CV - % change	53				
Fox	MRI	BSI % change	50				

1.5T MRI vs PET Comparison in MCI (n=69)

Lab	Modality	Variable	SS/arm
Jagust	PET	ROI-avg	4605
Foster	PET	hypometabolism1	2176
Foster	PET	hypometabolism2	1629
Fox	MRI	VBSI % change	284
Schuff - FS	MRI	Ventricles	277
Reiman	PET	CV - fROI	249
Schuff - FS	MRI	Hippocampus	202
Fox	MRI	BSI % change	177
Thompson	MRI	CV - % change	73

First Conclusion

- In general atrophy, measured by MRI is a more sensitive and robust measure of rate of change
  - Hippocampus, ventricles, not that different
- With the exception of Eric Reiman's statistically generated ROI, PET measures have less statistical power to detect a slowing of change than MRI
- BUT PET may be more sensitive to detect a treatment effect which improves function!!!

IDENTIFYING PREDICTORS

- A “predictor” is a measure which correlates with some future change
- The future change could be
  - Change of a cognitive or functional measure
  - Conversion from MCI to AD
  - Change of a biological measure
- Provides information on sequence, improves power

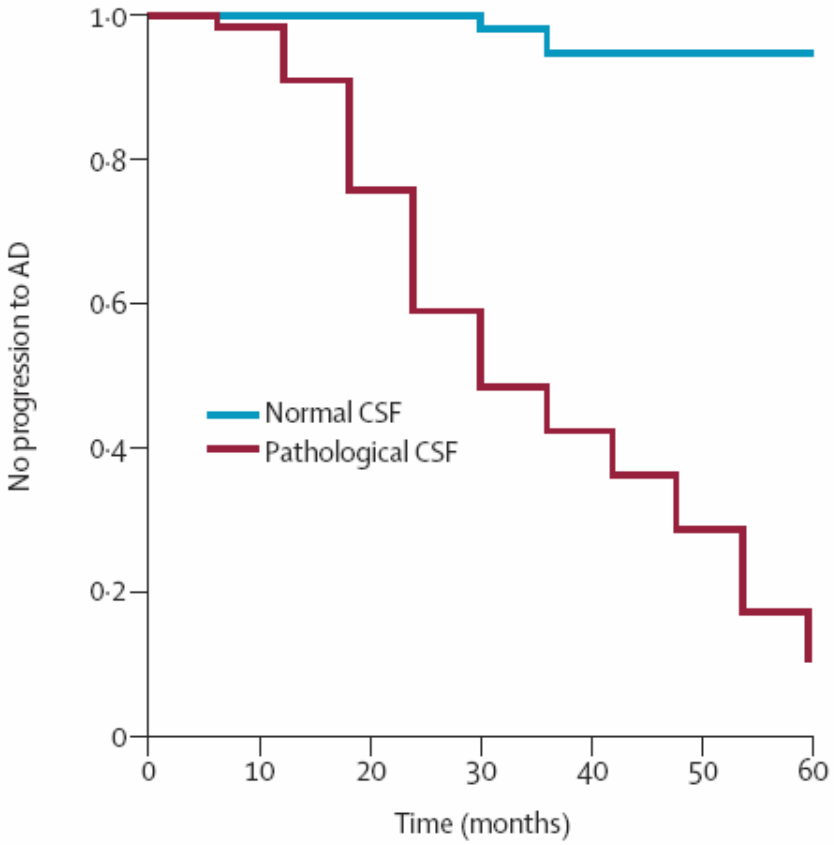
BIOMARKERS

John Trojanowski, Les Shaw, U Penn.

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



Numbers at risk							
Total	134	131	111	87	74	55	31
Normal CSF	67	66	62	56	47	40	28
Pathological CSF	67	65	49	31	27	15	3

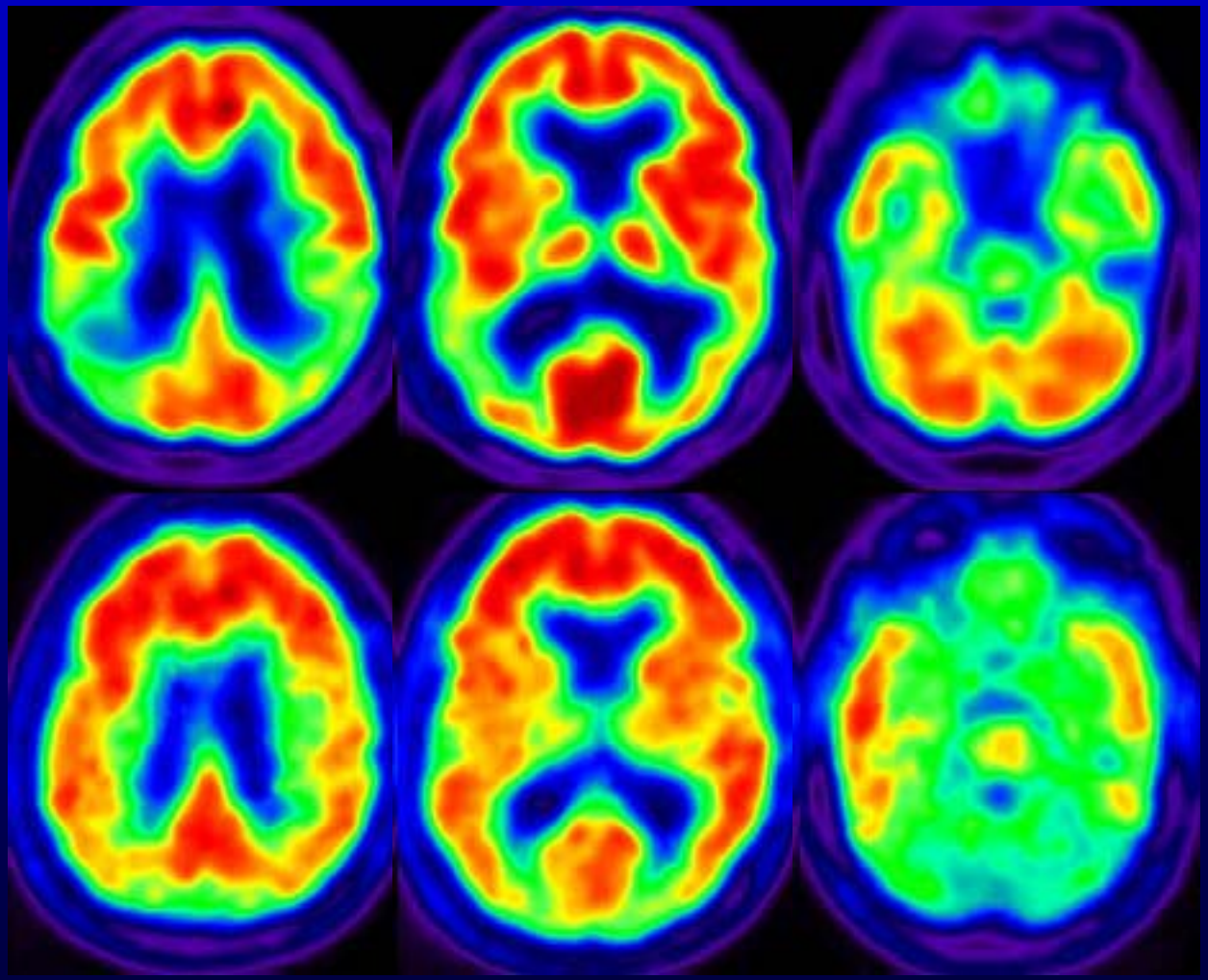
***Figure 2*: Kaplan-Meier estimates of the rate of progression to Alzheimer's disease in patients with MCI who have either normal CSF or pathological CSF at baseline**

Numbers at risk are the number of patients with MCI at each time point who had not developed any type of dementia and for whom clinical follow-up was still ongoing. Cut-off values for pathological CSF were >350 ng/L for T-tau and <530 ng/L for Aβ42. The incidence of Alzheimer's disease in patients with MCI who had pathological CSF (n=67) was 27% per year compared with 1% per year in patients with normal CSF (n=67).

PIB Imaging: Alzheimer's Disease

FDG

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	14

Follow-Up of ADNI PiB Controls

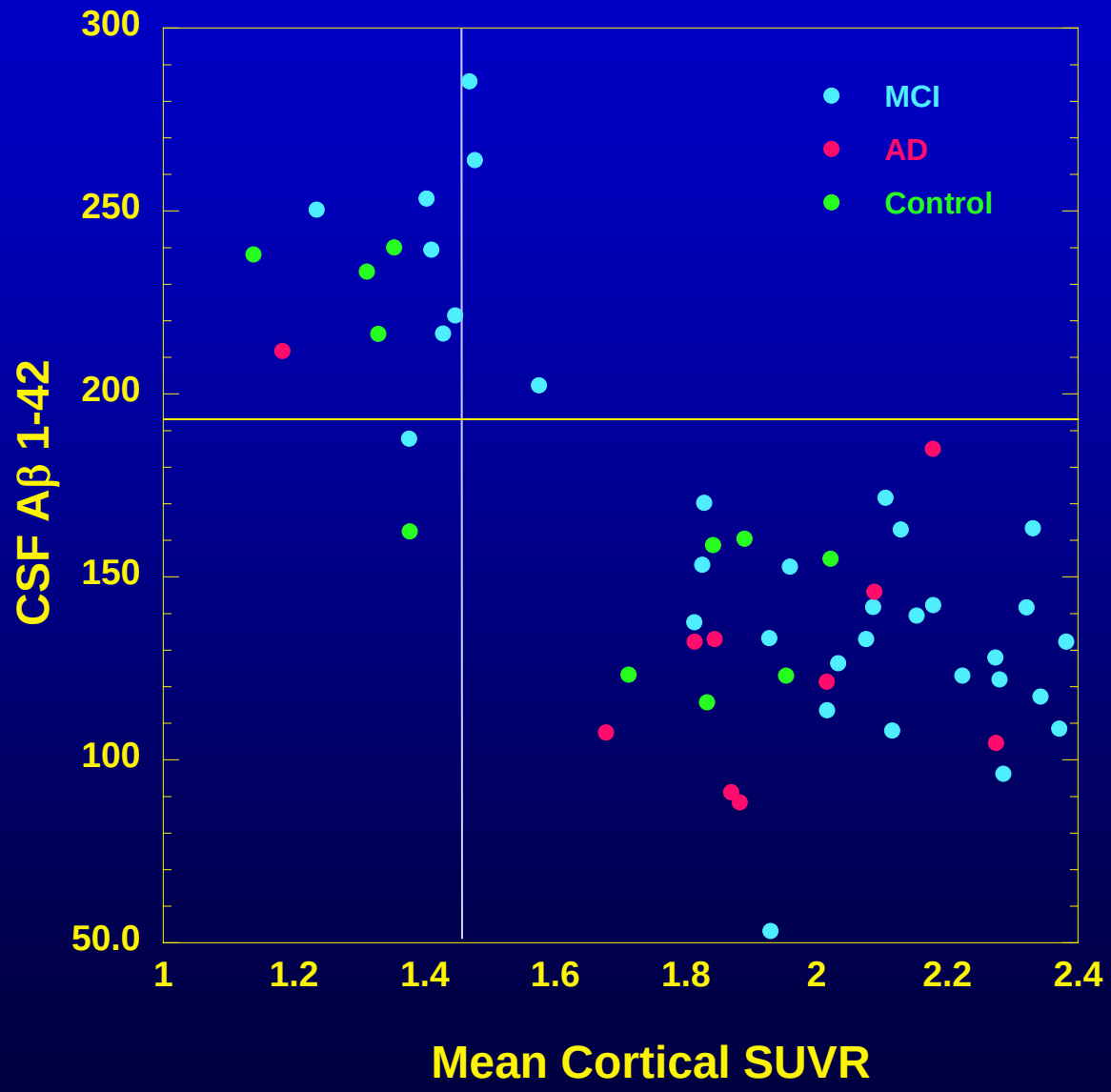
ADNI PiB Ctrl's

N = 19, 12 mo. follow-up

PiB(-)	10
Converters to MCI	0
PiB(+)	9
Converters to MCI	2

PIB vs CSF Biomarkers: Aβ

Total N = 55 (11 Control, 34 MCI, 10 AD)



Penn Autopsy Sample (56 AD, 52 Cog normal)

192 pg/ml

PREDICTING FUTURE RATE OF HIPPOCAMPAL ATROPHY

- Controls: CSF AB and tau
- MCI: APOE, CSF AB and tau, FDG PET
- AD: CSF AB and tau

Second Conclusion

- Cognitive measures,APOE, CSF, MRI are predictors
- FDG PET is also a good predictor
- But much more analysis of the ADNI data is needed with longer followup

ADNI data in support of early AD trial: proof of concept Phase II

- 2 year trial, MCI subjects with CSF $A\beta_{42}$ <193 pg/ml
- Analysis: linear mixed effects modeling, MRI covariate,

  CDR-SB single primary outcome
- 40% effect
- now only require **101 subjects** per group

ADNI: HC atrophy and CSF Aβ

	$A\beta_{1-42}$ <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

SAMPLE SIZE/ARM TO DETECT A 25% SLOWING OF HIPPOCAMPAL VOL IN 2 YRS

		Hippocampus	
	ADASc	Full Sample	Reduced Sample
			No Adjustment (A-Beta Adjusted)
All NL Subjects	No Decline	423	582 (569)
ApoE4+	6949	583	1047 (1100)
ApoE4-	No Decline	339	385 (298)
Low Beta Amyloid	59882	223	–
High Beta Amyloid	No Decline	1152	–

A prevention trial on normals could be designed with an interim analysis of hippo vol, and continue with clinical/cognitive endpoints

ADNI Neuropathology Core

- **Protocols and Support Documents Online:**
  - https://adcs-adni.bbl.ucsd.edu/docs/studydocs/Neuropath%20Core
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    ADNI Neuropathology Core Coordinator

Table 1. ADNI Autopsy Rates

09-01-2005 to 03-29-2010

ADNI Funding Period	ADNI-NPC	Deaths	Autopsies	Autopsy Rate (%)
09-01-2005 to 08-31-2007	N0	6	0	0
09-01-2007 to 08-31-2008	YES	10	4	40.0
09-01-2008 to 08-31-2009	YES	9	5	55.5
09-01-2009 to 03-01-2010	YES	3	1	33.3
Total (2005-2009)	-	28	10	35.7
Total since NPC established	-	21	10	47.6

Note: The ADNI-NPC was established on 9/1/2007. During the initial stage of ADNI1 the NPC had not been established and no autopsies were performed on the 6 ADNI participants who expired during 2007 and the first half of 2008.

Autopsy rate = number of brain autopsies/total number of ADNI participants who died.

Table 2. Clinical and Neuropathologic Diagnoses at Expiration

Clinical diagnosis	Neuropathologic diagnosis [N (%)]					TOTAL (%)
	AD	AD + DLB	AD + AGD	AD + TDP-43	AD + HS + AGD + TDP-43	
DAT	2 (20)	3 (30)	1(10)	1 (10)	1 (10)	8 (80)
MCI	2 (20)	0 (0)	0(0)	0 (0)	0 (0)	2 (20)
Normal	0 (0)	0 (0)	0(0)	0 (0)	0 (0)	0 (0)
TOTAL (%)	4 (40)	3 (30)	1(10)	1 (10)	1 (10)	10 (100)

Note: N, number of ADNI cases. AD, Alzheimer's disease; AGD, argyrophilic grain disease; DAT, dementia of the Alzheimer type; DLB, dementia with Lewy bodies; MCI, mild cognitive impairment; TDP-43, TDP-43 proteinopathy in the medial temporal lobe.

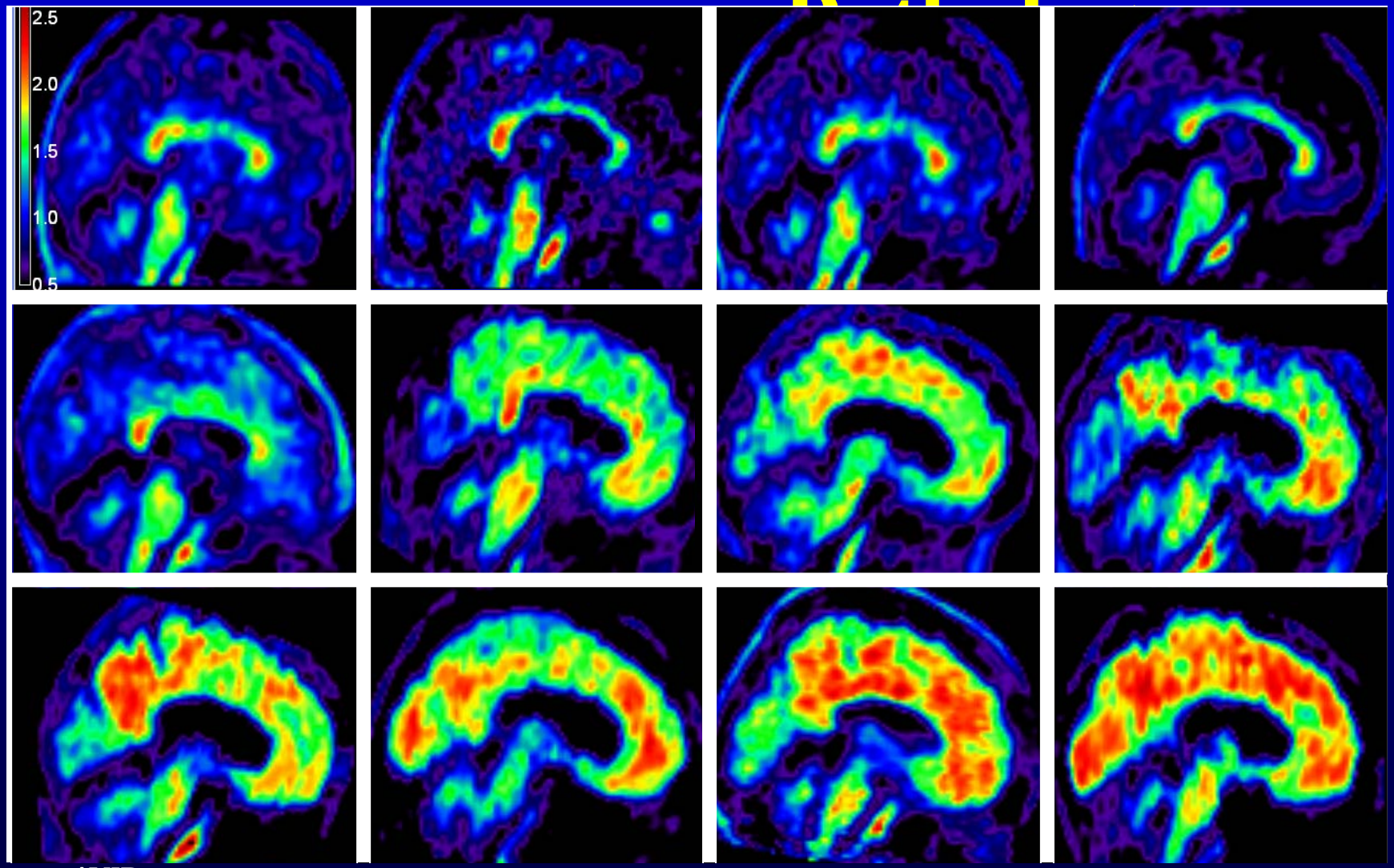
Mild small vessel disease (arteriolosclerosis and cerebral amyloid angiopathy) was a feature of all cases but none had infarcts.

SCOPE OF ADNI2

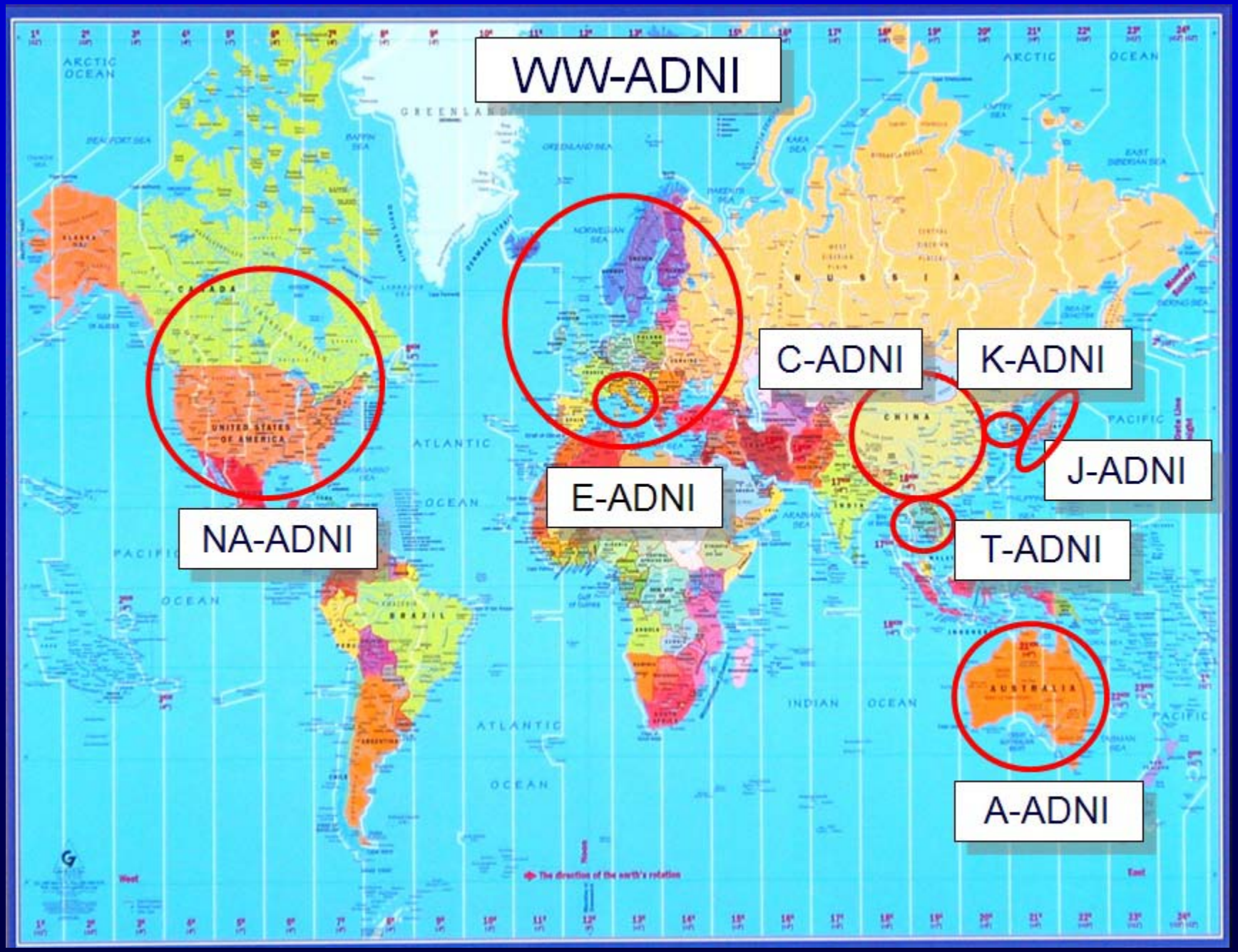
- If renewed ($69 million), ADNI2 will:
- Continue to follow more than 400 controls and MCI from ADNI1 for 5 more years
- Enroll:
  - 100 additional EMCI (supplements 200 from GO
  - 150 new controls, LMCI, and AD
- MRI at 3,6, months and annually
- F18 amyloid (AV-45)/FDG baseline and Yr2
- LP on 100% of subjects at enrollment
- Genetics

F-AV-45 Scans Spectrum of

18F-AV-45



AVID


WW-ADNI
C-ADNI
K-ADNI
J-ADNI
E-ADNI
NA-ADNI
T-ADNI
A-ADNI

ADNI Industry Scientific Advisory Board

FOUNDATION FOR THE National Institutes of Health

New members Abbott, Genentech, Roche, Bayer

Abbott — A Promise for Life
AstraZeneca — UNITED KINGDOM
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Eisai
élan
GE
Genentech — IN BUSINESS FOR LIFE
gsk GlaxoSmithKline
INNOGENETICS
Johnson & Johnson
Lilly
MERCK
NOVARTIS
Pfizer
Roche
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SYNARC — Start here, finish first.
Wyeth
alzheimer's association
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PIB/PET Supplement : *Alzheimer's Association and GE Healthcare*

Cerebrospinal Fluid Extension: *Alzheimer's Association, AstraZeneca, Cure Alzheimer's Fund, Merck, Pfizer and an anonymous foundation*

Genome-Wide Genotyping :*Gene Network Sciences, Merck, Pfizer and an anonymous foundation*

Genome-Wide Genotyping Genetic Analysis: *NIBIB, Merck, Pfizer and an anonymous foundation*

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