



# Alzheimer's Disease Neuroimaging Initiative Neuropathology Core

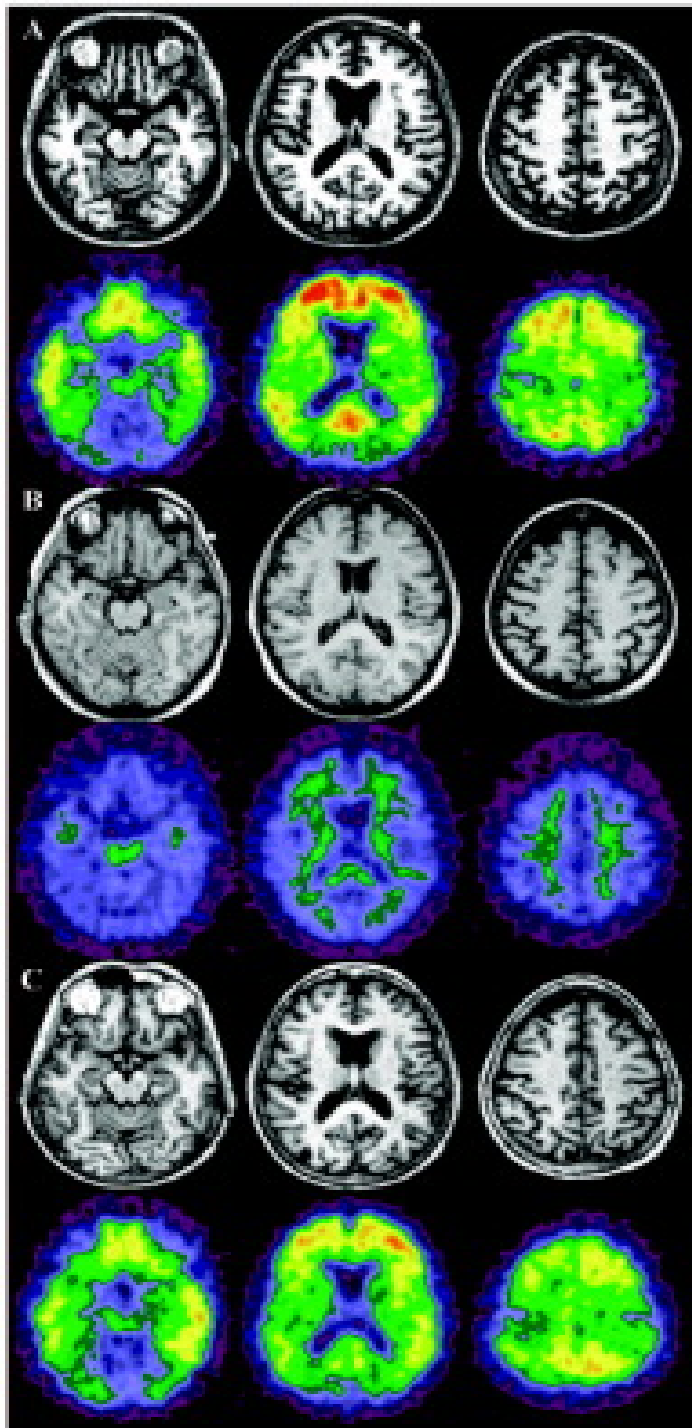
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Director

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Co-Director

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ADNI-NPC Co-ordinator  
Support: NIA/NIH U01-AG24904

MRI

PET



Distribution of Pittsburgh Compound-B (PiB) in three subjects as viewed by positron emission tomography (PET) and magnetic resonance (MR) images.

*(Fagan AM, et al. Ann Neurol 2006;59:512-9)*

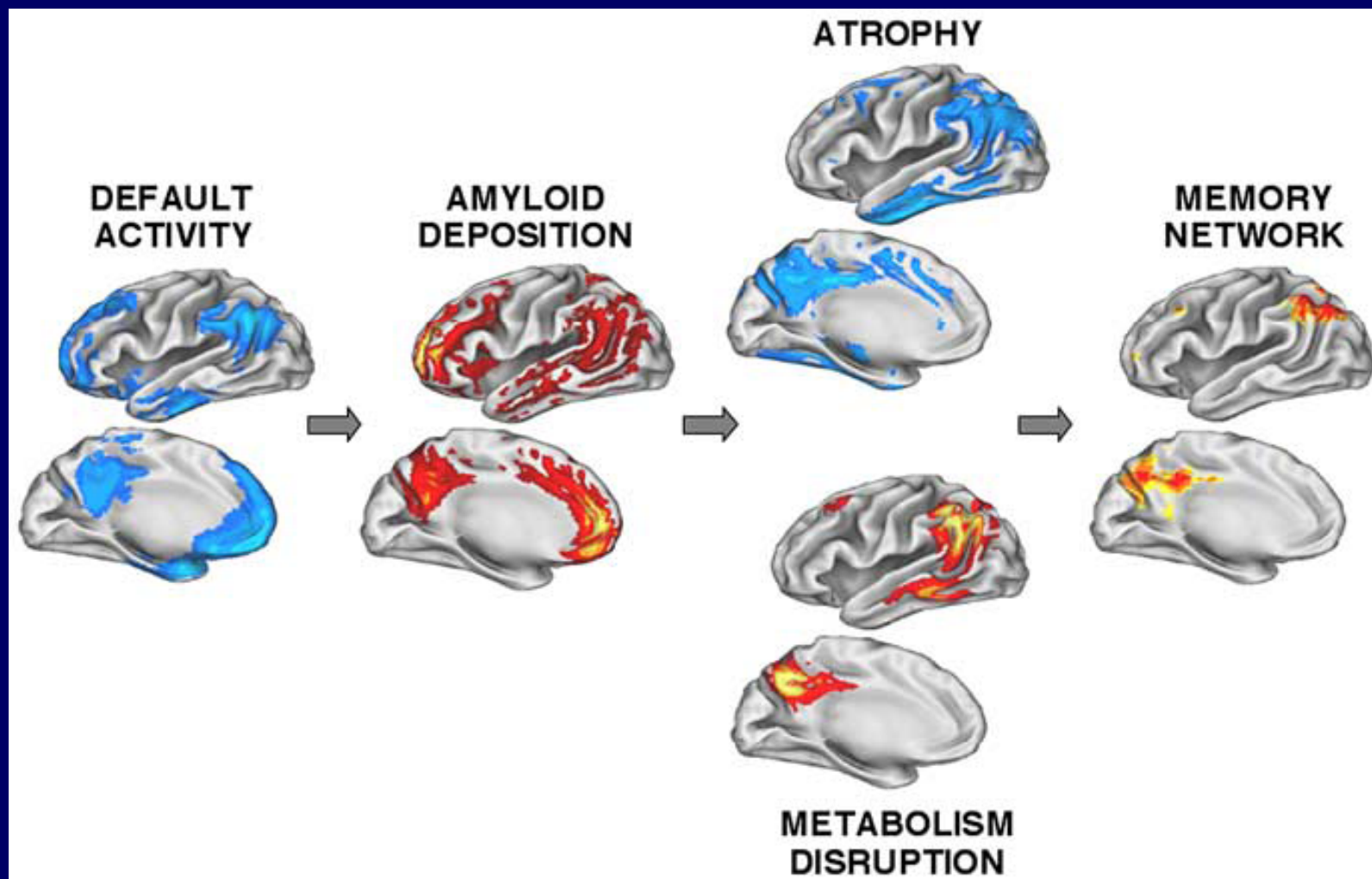
PiB  
Score

High  
DAT

Low  
CDR 0

High  
CDR 0

# Convergence and hypothetical relationships across molecular, structural, and functional measures



(Buckner RL, et al. *J Neurosci* 2005;25:7709-17)

# ADNI Neuropathology Core

## Rationale:

- Neuropathological examination is essential to validate the clinical diagnoses in the ADNI study groups (normal=200; MCI=400; mild AD=200).
- Variability in methods and interpretation of lesions among individual neuropathologists require a central laboratory, using state-of-the-art methods and current criteria, to establish uniform and standard neuropathological diagnoses.
- Clinical-neuroimaging-neuropathological correlations in any ADNI participant who comes to autopsy will be of exceptional value.
- The archiving of fixed and frozen brain tissue will facilitate biomarker studies of the earliest stages of AD.

## Predicted Minimum Number of Deaths and Autopsies During ADNI-NPC Study Period

Clinical Staging	Normal CDR = 0	MCI/ CDR = 0.5	DAT/ CDR = 1	Total
No. participants	200	400	200	800
Conservative annual death rate (%)	1%	1%	5%	-
Predicted deaths in 5 years	10	20	50	80
Predicted autopsies in 5 years	5	10	25	40

CDR, Clinical Dementia Rating; MCI, Mild Cognitive Impairment; DAT, dementia of Alzheimer type

# Administrative Structure

## ADNI Executive Committee

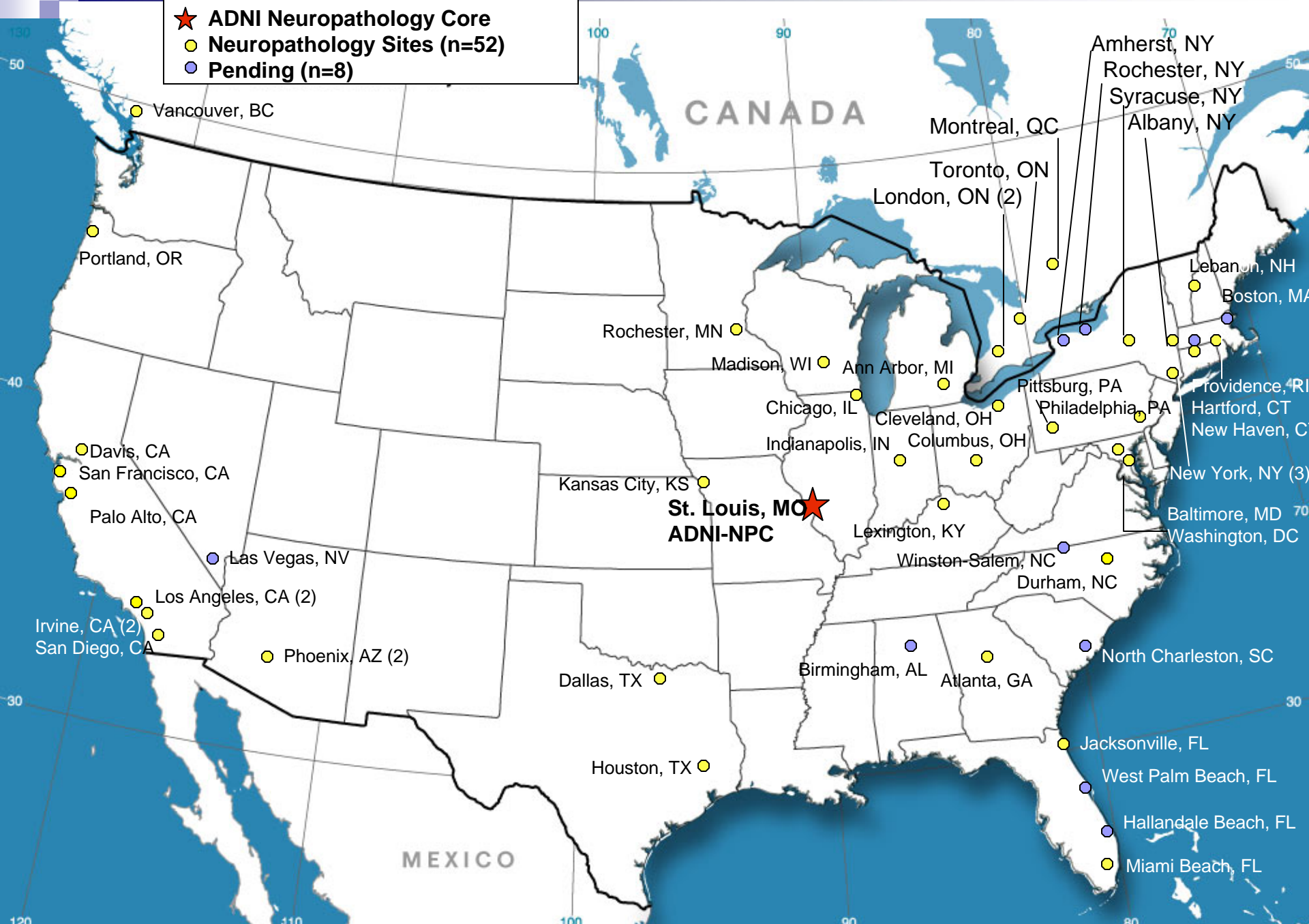
- Michael Weiner, UC San Francisco
- Arthur Toga, UC Los Angeles
- Laurel Beckett, UC Davis
- William Jagust, UC Berkeley
- John Trojanowski, Univ. of Pennsylvania
- Ron Thomas, UC San Diego
- Clifford Jack, Mayo Clinic
- Peter Snyder, Industry (Pfizer)
- Ron Petersen, Mayo Clinic

## ADNI Neuropathology Core Tissue Committee

- John Morris, Washington University
- Nigel Cairns, Washington University
- Eileen Bigio, Northwestern University
- Dennis Dickson, Mayo Clinic
- John Trojanowski, Univ. of Pennsylvania

# ADNI Sites

- ★ ADNI Neuropathology Core
- Neuropathology Sites (n=52)
- Pending (n=8)



# Specific Aims

1. Provide and implement training materials and protocols to assist clinicians at ADNI sites in obtaining voluntary consent for brain autopsy in ADNI participants.
2. Establish a central laboratory to provide uniform neuropathological assessments in all autopsied ADNI participants and promote clinical-neuroimaging-neuropathological correlations.
3. Maintain state-of-the-art resource for fixed and frozen brain tissue obtained from autopsied ADNI participants to support biomarker studies.
4. Interact with ADNI's data Co-ordinating Center to assure appropriate entry of ADNI-NPC data into ADNI database, promote data sharing and collaborative research, and integrate ADNI-NPC with all ADNI components to support administration and operations.

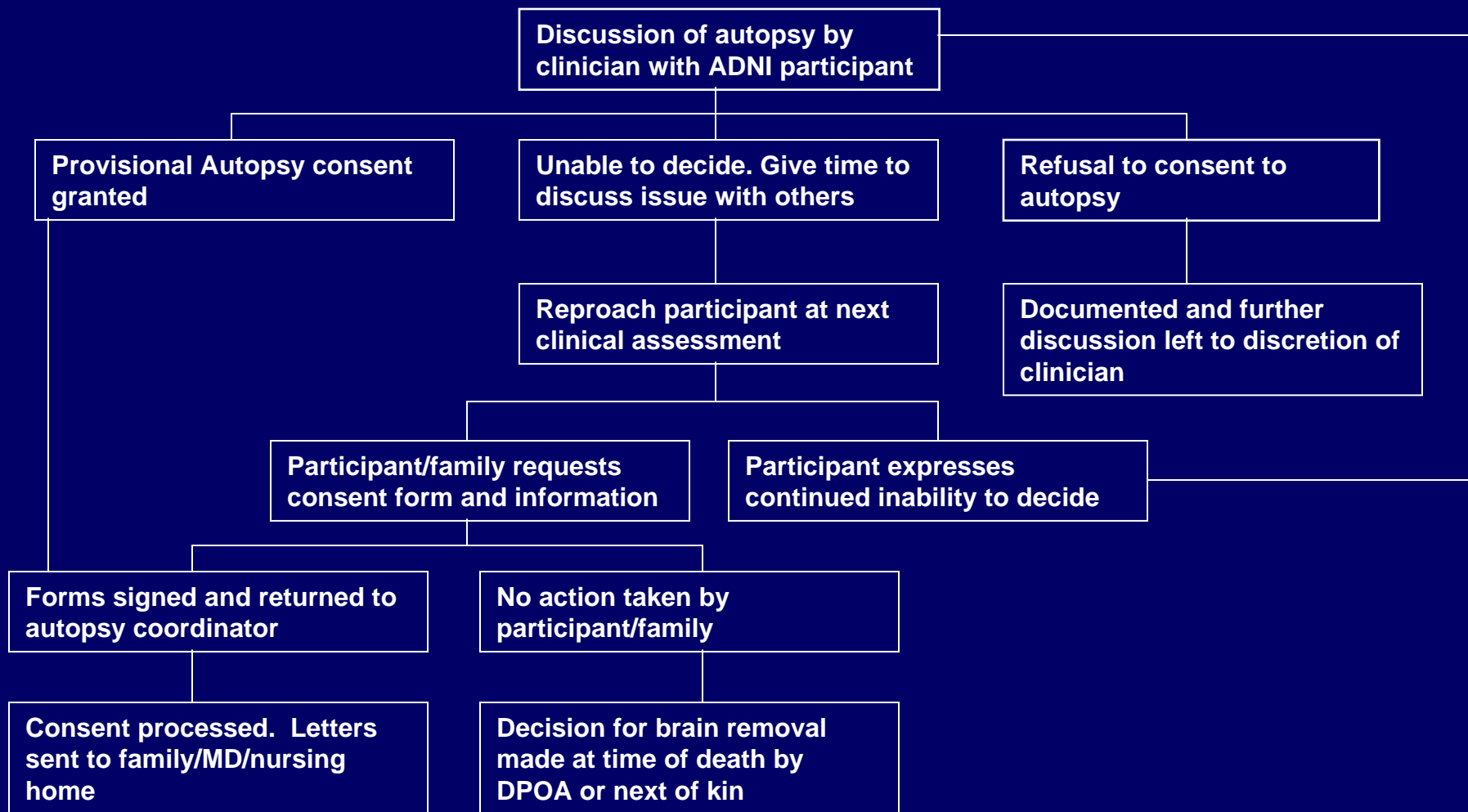


# Specific Aim #1

Provide and implement training documents and protocols in obtaining voluntary consent for brain autopsy in ADNI participants

- Use documents and protocols developed at Washington University ADRC
- Clinician-led discussion at initial assessment
  - Convey importance/value of autopsy
  - Consideration of participant's wishes
  - Address questions, misconceptions or concerns
- Support materials available at <https://adni.ucsd.edu>

# Obtaining Autopsy Consent



# Specific Aim #1

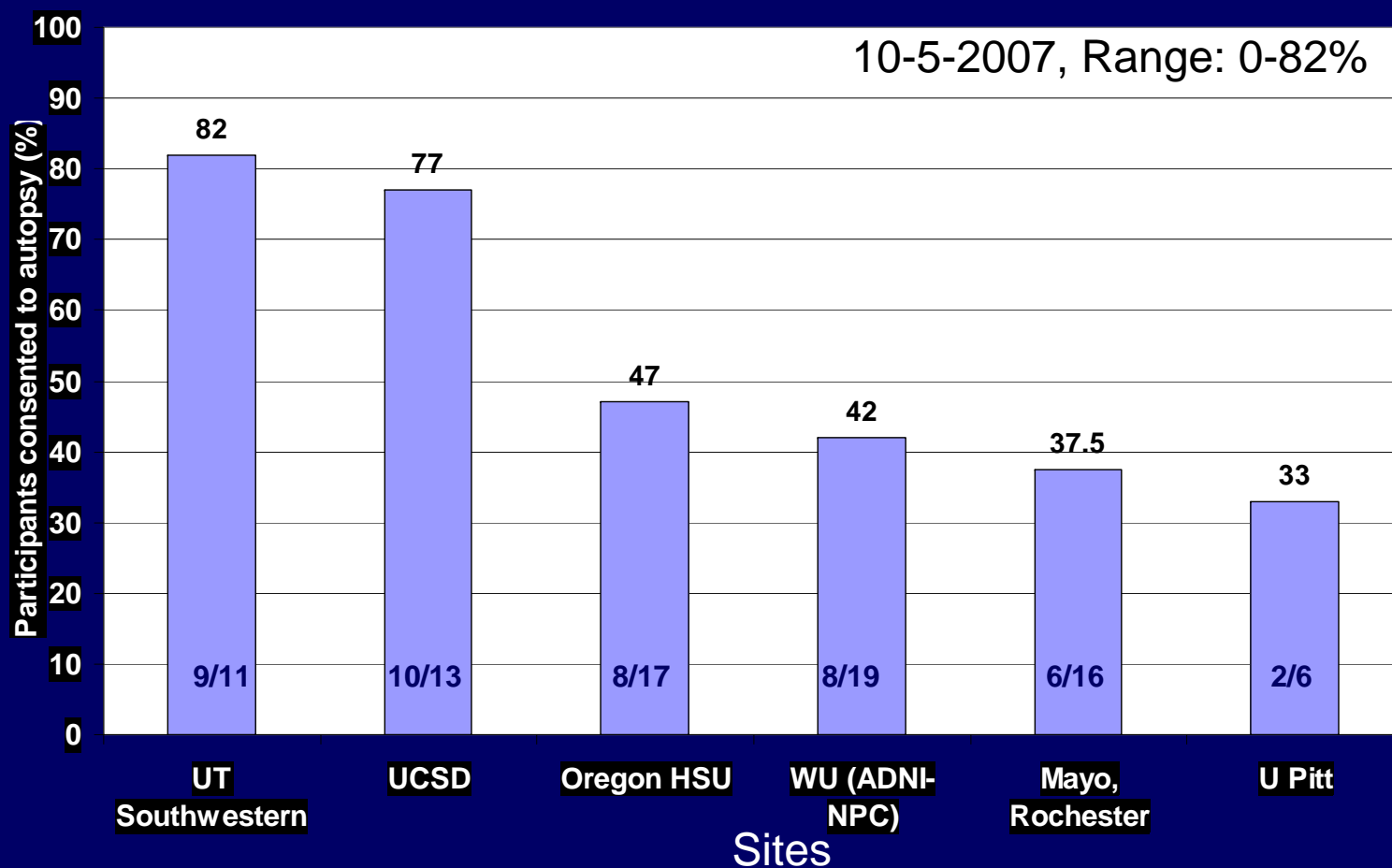
## ADNI Sites

- Identify/establish autopsy co-ordinator;
- Process consent;
- Develop/implement autopsy procedures;
- Notify ADNI-NPC of death;
- Send required tissue samples to ADNI-NPC.

## ADNI-NPC

- Provide training to sites;
- Offset costs of body transportation, autopsy procedure, and shipment of materials;
- Available via radiopager 24/7.

# ADNI Site Autopsy Consent Rates



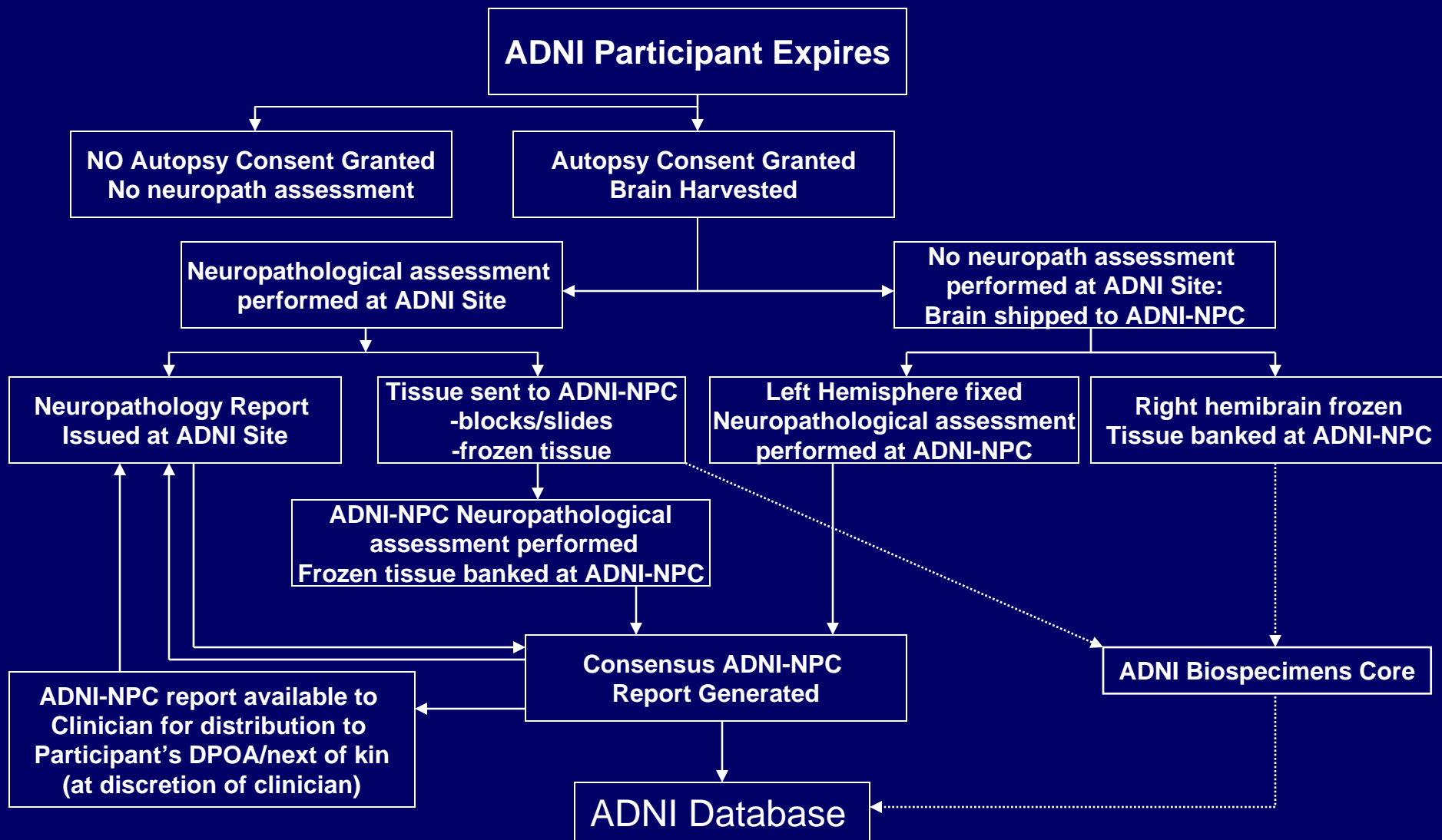
# Specific Aim #2

**To provide central, uniform neuropathologic diagnoses to validate clinical assessments**

**Why necessary?**

CERAD and BrainNet Europe both found significant inter-center variation in methods of tissue preservation, processing, staining, antigen retrieval, and different antibodies to demonstrate molecular neuropathology.

# ADNI-NPC Workflow



# Specific Aim #2

## Tissue for Quality Control and Research

### Frozen tissue :

#### Coronal slices/blocks

- Frontal lobe to include striatum
- Frontal and temporal lobe at the level of the mamillary body
- Temporal and parietal lobes at the level of the lateral geniculate nucleus
- Occipital lobe to include calcarine sulcus

### 16 Standard Paraffin Wax Blocks/Sections

- Middle frontal gyrus
- Superior and middle temporal gyri
- Inferior parietal lobe
- Occipital lobe
- Anterior cingulate gyrus
- Posterior cingulate gyrus and precuneus
- Amygdala and entorhinal cortex
- Hippocampus (LGN)
- Striatum (NBM)
- Pallidum
- Thalamus and subthalamic n.
- Midbrain
- Pons
- Medulla oblongata
- Cerebellum with dentate n.
- Spinal cord

# Specific Aim #2

## Histology

- HE, Modified Bielschowsky

## IHC

- Ubiquitin (Dako), tau (PHF1),  $\beta$ -amyloid (10D5),  $\alpha$ -synuclein (LB509).

Other: TDP-43 (ProteinTech),  $\alpha$ -Internexin, neurofilament (SMI31), prion (3F4).

## Histology Review (NACC NP Protocol)

### Neuropathologic Assessment and Diagnostic Criteria

- Khachaturian
- CERAD
- NIA-Reagan Institute
- DLB
- FTLD



# Specific Aim #3

## **Maintain a state-of-the-art brain tissue resource**

- Forward samples to ADNI Biospecimens Core
- Centralize tissues to be used in collaborative studies
- Generate sufficient number of samples to undertake clinico-pathologic and biochemical studies

# Specific Aim #4

**Interact with ADNI's Data Co-ordinating Center to ensure data entry, data sharing and collaborative research**

- Neuropathology, clinical, biological and imaging data accessible online at <https://adni.ucsd.edu>
- Online tissue request available at <http://alzheimer.wustl.edu/Research/ResourceRequest.htm>
- Tissue requests processed through WU ADRC Tissue committee and receive final approval from ADNI-NPC Tissue Committee

# Frequently Asked Questions

- **What materials do you want us to send? A. See online protocol.**
- **Do you want our blocks or separate blocks for yourselves? A. Send separate blocks or slides.**
- **Do you want our slides? A. No.**
- **Many of our subjects are harvested between 6-12 hours- a time too long for biochemistry? Please advise as to extent of acceptable post-mortem interval. A. Ideally <24h.**
- **Are funds available to pay for removal and processing of the brain according to the protocol? A. Yes, if requested.**
- **Is there an ADNI-specific Consent Form that we can use to submit to our IRB? A. No.**
- **Is there an award statement we need?  
A. Quote NIA/NIH Grant # U01-AG24904 (PI Weiner, MW; Subcontract WU).**

# Acknowledgements

- **ADRC Neuropathology Core**
- **ADNI-NPC**

- Nigel Cairns

- Lisa Taylor-Reinwald  
(ADNI-NPC Core Co-ordinator)

- Deborah Carter

- Michael Gitcho

- Katherine Paulsmeyer\*

- Jeffrey Strider

- Angela Felton

- \*former member

