

Development of ^{18}F -AV-45 for Imaging of Alzheimer's Disease Pathology in Humans

SPEAKERS

Daniel M. Skovronsky M.D., Ph.D

Neuropathologist

CEO, Avid

Adjunct Faculty

Dept of Radiology, U Penn

Chris Clark M.D.

Neurologist

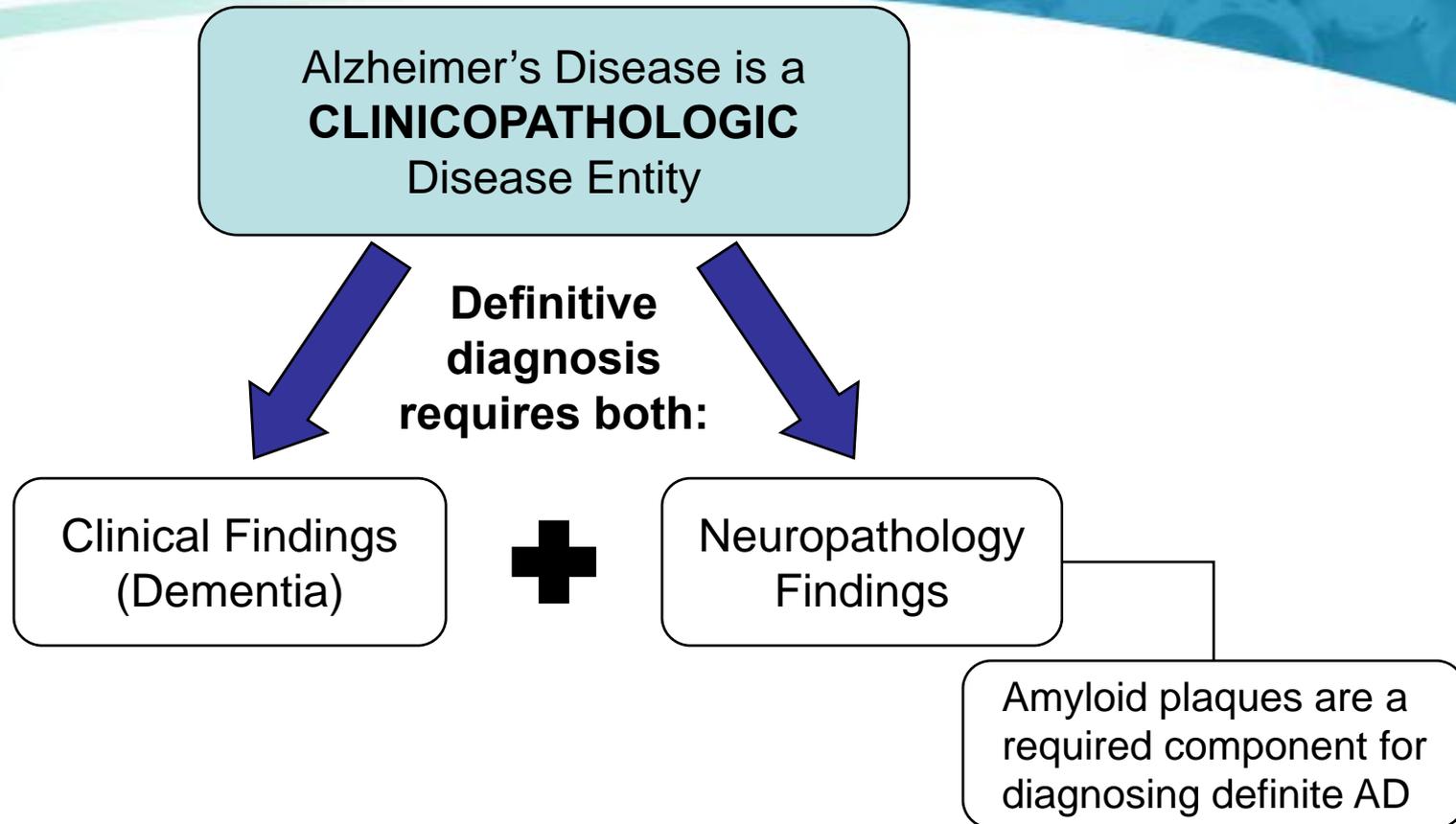
Medical Director, Avid

Director of the Center of Excellence for
Research on Neurodegenerative Disease
Dept of Neurology, U Penn

Development of ^{18}F -AV-45 for Imaging of Alzheimer's Disease Pathology in Humans

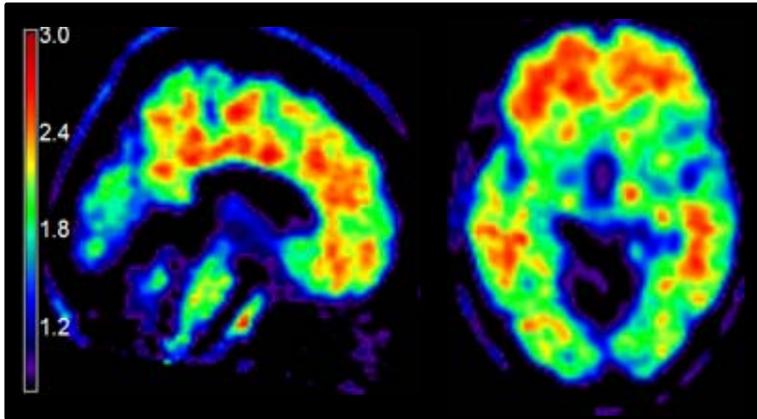
AGENDA

- | | | |
|-------------------------|--|----------------------|
| 10:00 - 10:10 am | Introduction & ^{18}F -AV-45 Data | D Skovronsky, MD PhD |
| 10:10 - 10:20 am | Clinical Utility & Reference Standard | C Clark, MD |
| 10:20 - 10:30 am | Avid development proposal | D Skovronsky, MD PhD |

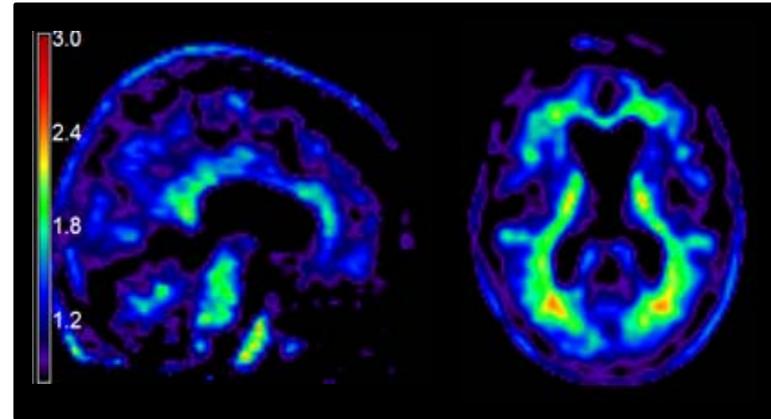


Highest level of diagnostic certainty ante-mortem is "Probable AD"

Definitive diagnosis only possible post-mortem



“Probable AD” Patient

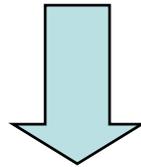


Cognitively Normal Elderly

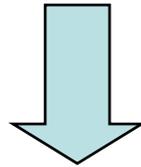
A 10 minute ^{18}F -AV-45 PET scan shows abundant cortical amyloid deposition in the AD patient (red = SUVr >2.5) but not in the elderly control (blue = SUVr ~ 1.0).

^{18}F -AV-45 PET imaging provides information about the presence or absence of amyloid pathology.

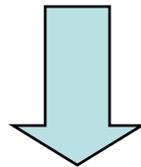
Target = Amyloid plaque pathology



Indication = Imaging amyloid pathology



Clinical Utility = No significant amyloid excludes AD



Reference Standard = Amyloid plaque histopathology

Proposed Indication:

^{18}F -AV-45 is indicated for imaging brain amyloid plaque pathology to aid in the evaluation of patients with signs or symptoms of cognitive impairment.

Clinical Utility:

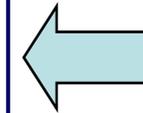
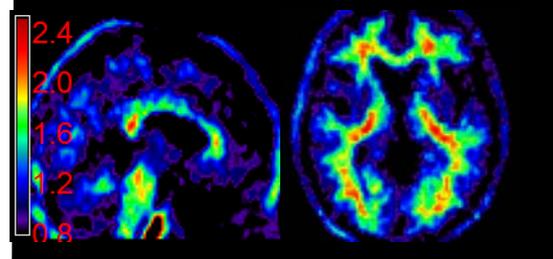
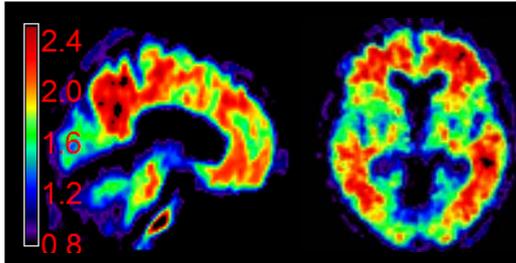
NDA: Patients with no significant brain amyloid do not have AD.
Biomarker for anti-amyloid therapy trials.

To be demonstrated: Patients positive for brain amyloid have increased likelihood of having AD or developing AD.

Probable AD

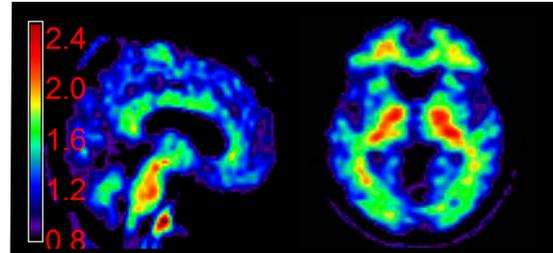
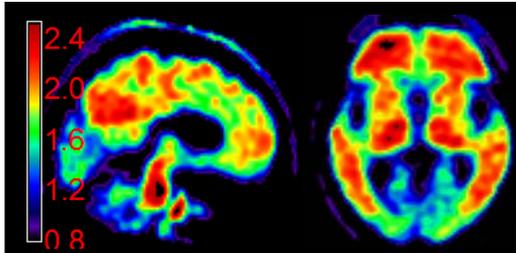
Cognitively Normal Control

AV-45

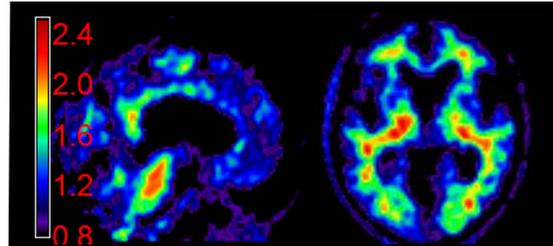
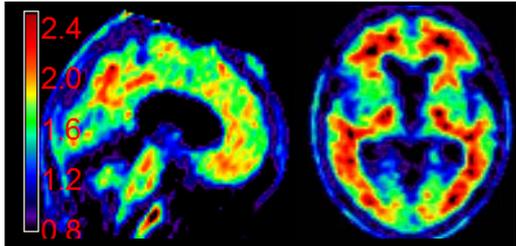


Best tracer
selected for full
development

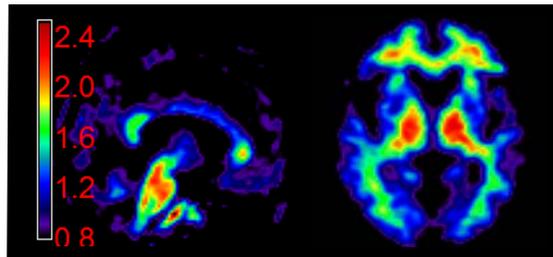
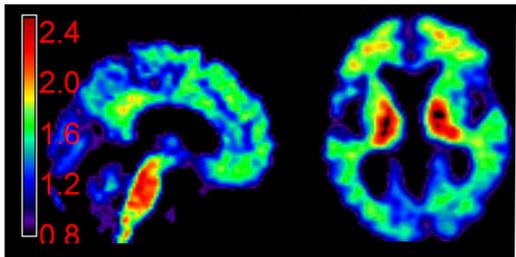
AV-138



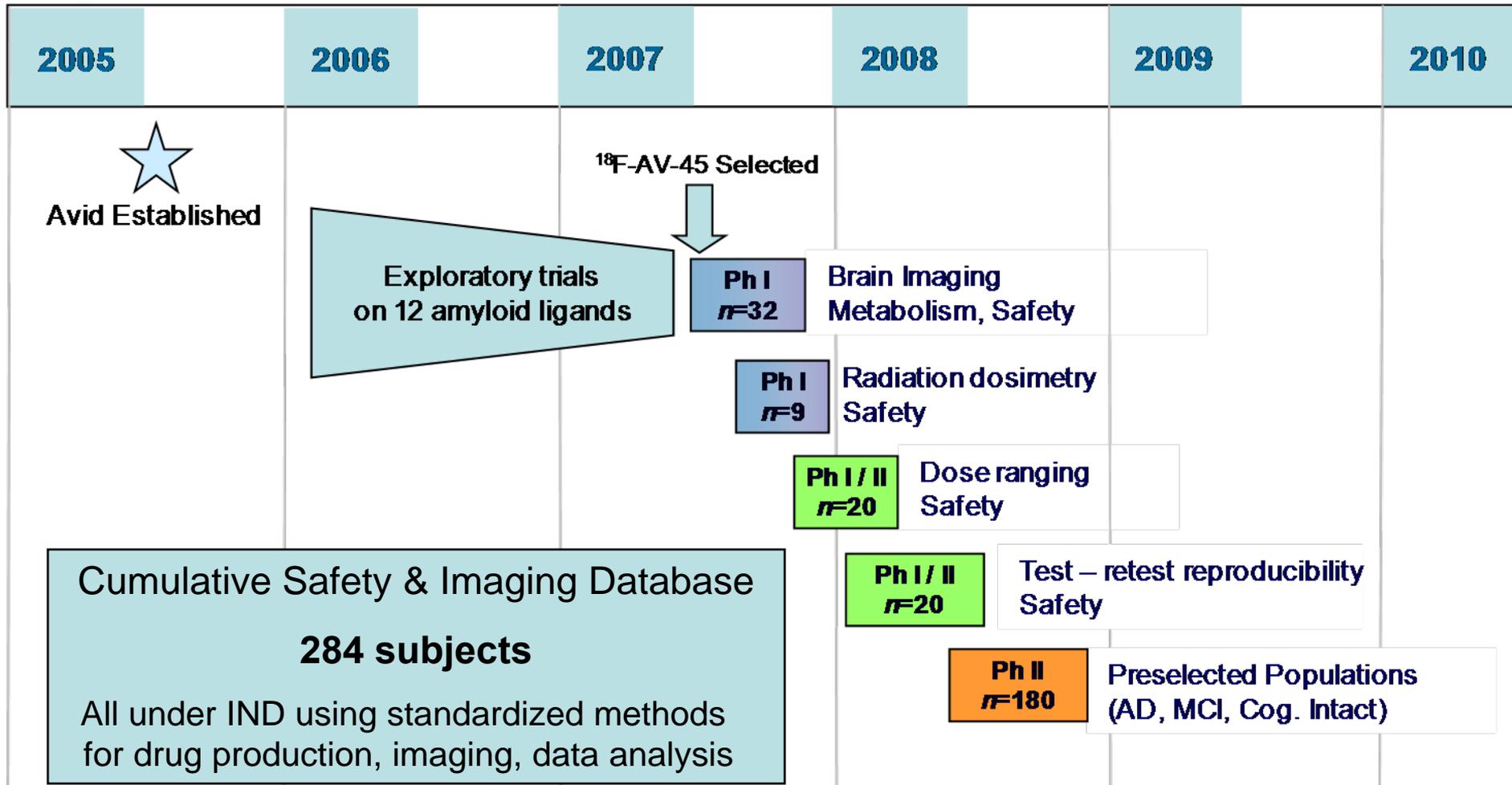
AV-144

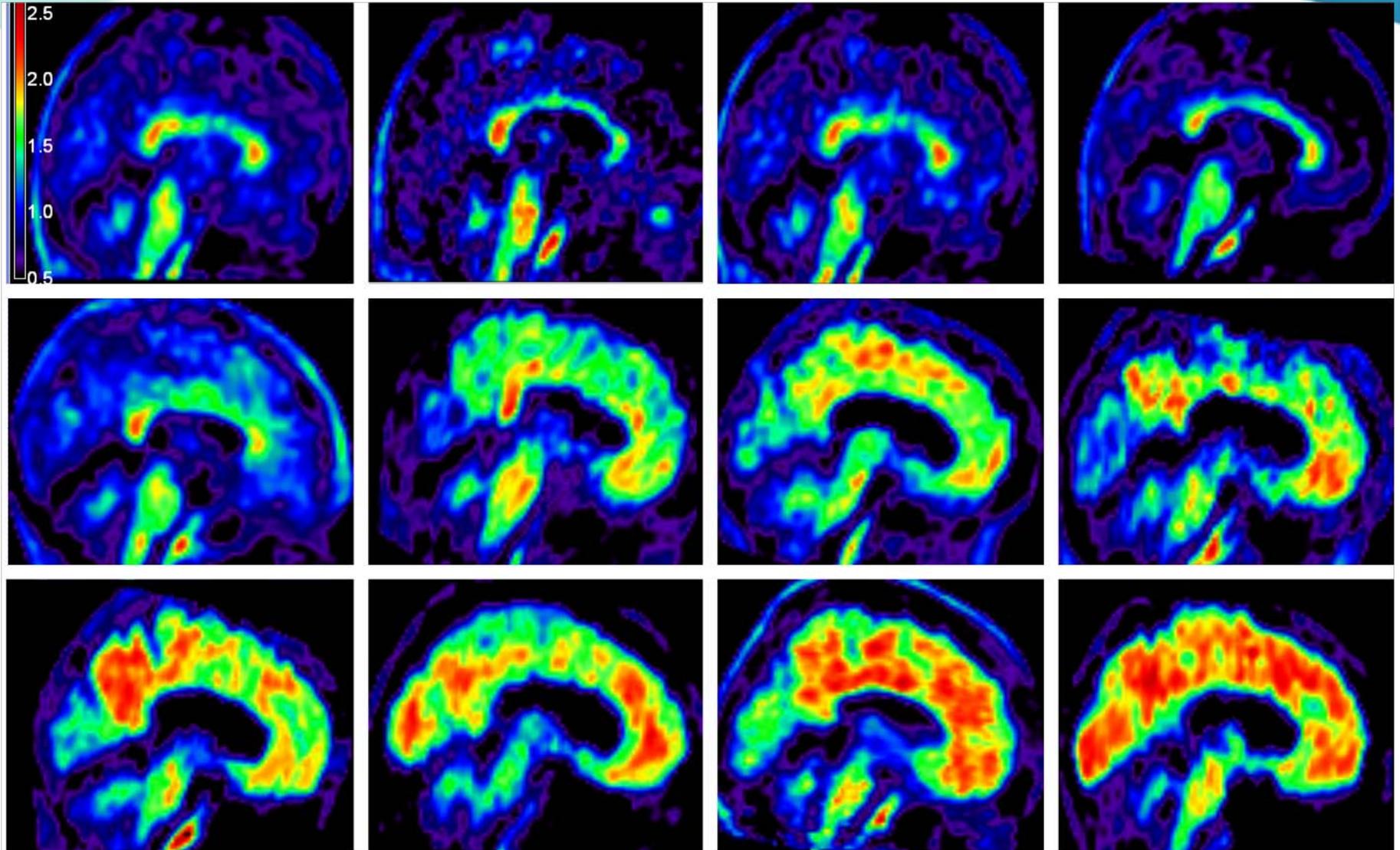


AV-19



12 potential amyloid
imaging ligands were
tested in exploratory
FDA IND trials

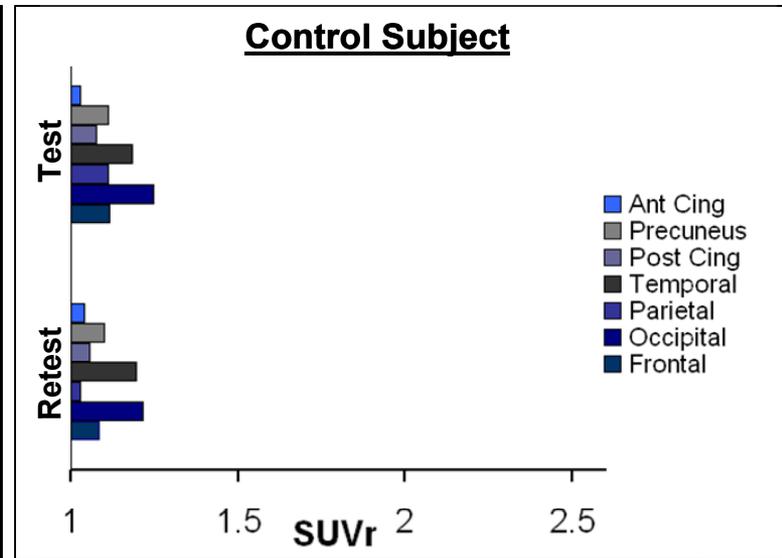
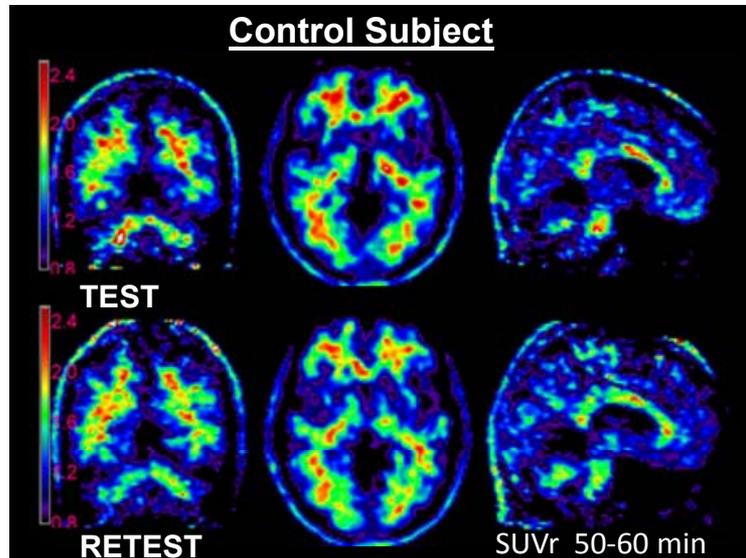
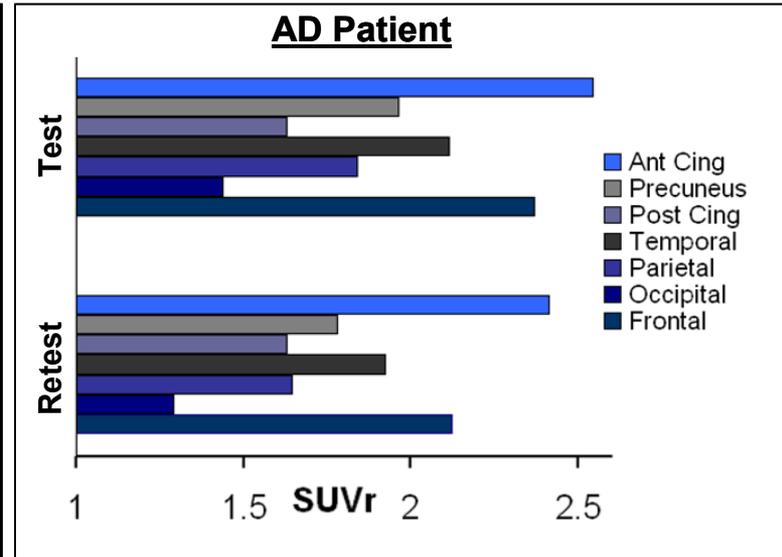
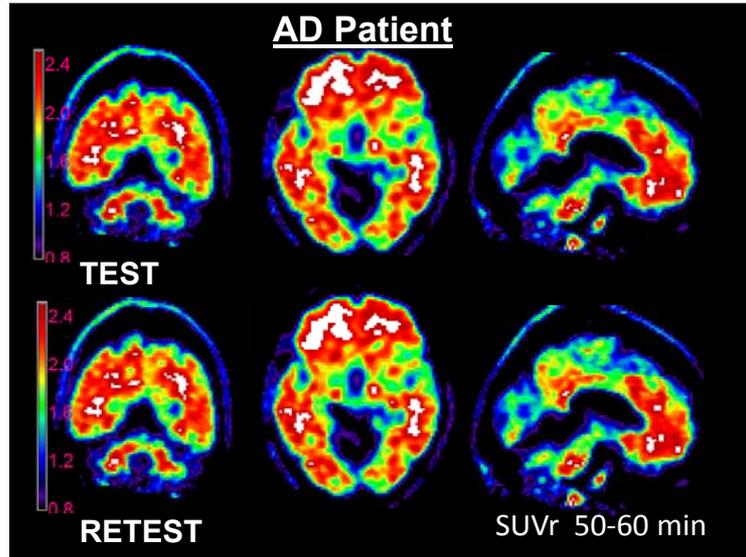


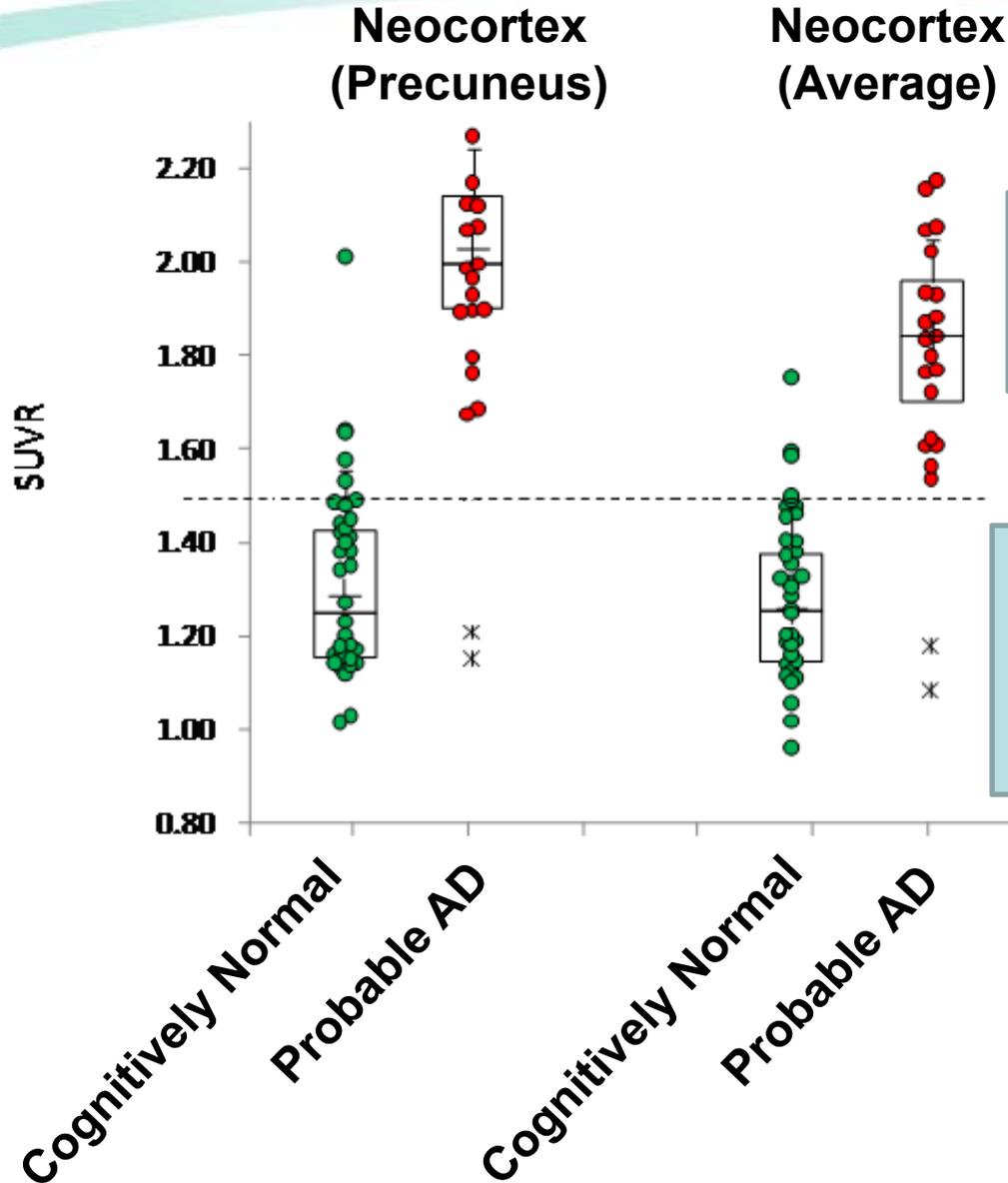


^{18}F -AV-45 Reproducibility (n=20)

Test – retest variability 3 - 5%

Test – retest correlation 0.98 - 0.99





180 subject Phase IIb Trial Imaging vs clinical diagnosis in preselected populations (analysis ongoing)

Current clinical database contains:

- 125 Cognitively Normal Elderly Controls
- 99 AD Patients
- 60 MCI Patients

60 subjects (22 AD, 38 HCs)
15 sites

Development of ^{18}F -AV-45 for Imaging of Alzheimer's Disease Pathology

AVID AGENDA

- | | | |
|----------------------|--|----------------------|
| 10:00 - 10:10 | Introduction & ^{18}F -AV-45 Data | D Skovronsky, MD PhD |
| 10:10 - 10:20 | Clinical Utility & Reference Standard | C Clark, MD |
| 10:20 - 10:30 | Avid development proposal | D Skovronsky, MD PhD |

- Patient care best when the diagnosis is correct
- Better to identify disease early
- Diagnosis most reliable when based on pathology
- Correct diagnosis improves:
 - Clinical management
 - Treatment decisions
 - Prognostic information to patient & family

Accurate AD diagnosis is important :

The evidence is that the medical community spends significant time and money diagnosing Alzheimer's today.

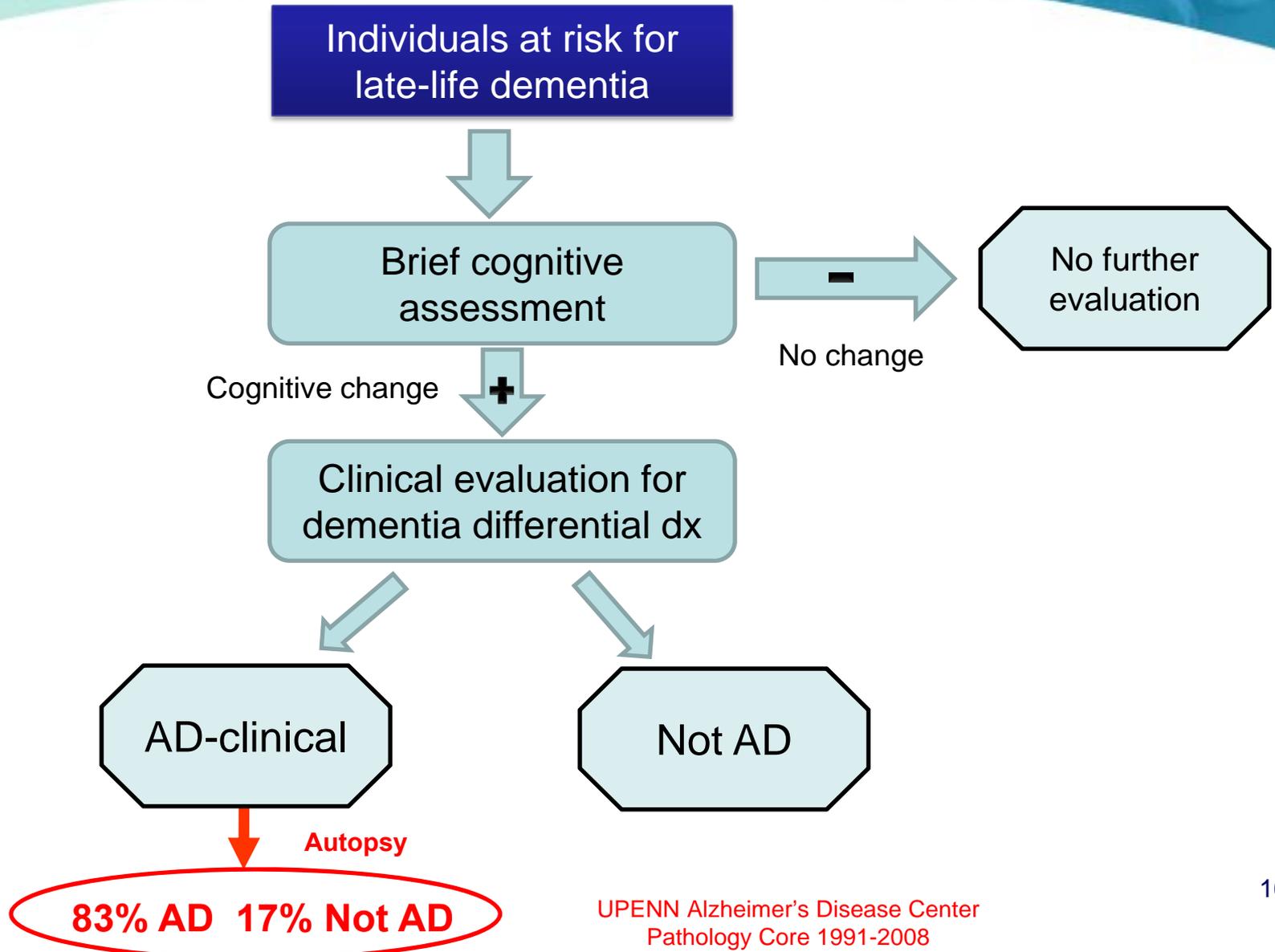
Prevalence of non-AD pathologic diagnosis: 25%

	N	AD AD + other ¹	Non-AD diagnoses
Jellinger et al., 1990	675	77%	23%
Victoroff et al., 1995	196	76%	24%
Brunnstrom et al, 2008	524	64%	36%
Univ Penn ADC, 2008	226	76%	24%

¹ includes patients with a diagnosis of mixed dementia, e.g. AD + Vascular dementia or AD + dementia with Lewy bodies.

Expert Clinician Diagnostic Accuracy²

- 78% overall **accuracy** for a clinical diagnosis of AD
- 17% **false positive rate** for a clinical diagnosis of AD (range 10 – 35%)



Amyloid imaging leads to better patient management

Negative ^{18}F -AV-45 PET

- No significant amyloid pathology (not AD)

Positive ^{18}F -AV-45 PET

- Amyloid pathology likely

Amyloid imaging can help rule-out AD in those patients who have cognitive impairment and diagnostic uncertainty.

Utility for clinical trials developing new therapies

- Improve patient selection for disease modifying therapies in trials (~30 such trials ongoing)
 - Exclude amyloid negative individuals
 - Identify amyloid positive individuals
 - First horizon AD
 - Second horizon MCI
 - Third horizon primary prevention
- Potential outcome measure?

Generally Accepted Truths

Reference Standards should:

- Provide **DIRECT** information about the target of interest
- Be well **STANDARDIZED** - based on well controlled trials
- Be **VALIDATED** vs. truth standard
- Be **INDEPENDENT** of the test agent
- Be **GENERALLY AVAILABLE** to the drug development community
- Be **FDA APPROVED** or **FDA VALIDATED** as a measure of truth

Candidate Reference Standards

Strengths

Weaknesses

	Strengths	Weaknesses
Clinical diagnosis	Widely available	Limited diagnostic accuracy
MRI	Good definition of regional atrophy	Overlap with non-AD dementias Not validated against amyloid histopathology
¹⁸F-FDG PET	Spatial information on hypometabolism	Does not image amyloid pathology Not validated against amyloid histopathology
¹¹C-PiB PET	Research data available	Data not obtained under standard IND Not validated against amyloid histopathology
CSF biomarkers	Extensive data available Linked to pathology	Overlap between diagnostic groups Not validated against amyloid histopathology
Histopathology	Defines disease pathology Spatial correlation with imaging	Requires autopsy study

Candidate Reference Standards

Strengths

Weaknesses

	Strengths	Weaknesses
Clinical diagnosis	Widely available	Limited diagnostic accuracy
MRI	Good definition of regional atrophy	Overlap with non-AD dementias Not validated against amyloid histopathology
¹⁸F-FDG PET	Spatial information on hypometabolism	Does not image amyloid pathology Not validated against amyloid histopathology
¹¹C-PiB PET	Research data available	Data not obtained under standard IND Not validated against amyloid histopathology
CSF biomarkers	Extensive data available Linked to pathology	Overlap between diagnostic groups Not validated against amyloid histopathology
Histopathology	Defines disease pathology Spatial correlation with imaging	Requires autopsy study

Candidate Reference Standards

Strengths

Weaknesses

	Strengths	Weaknesses
Clinical diagnosis	Widely available	Limited diagnostic accuracy
MRI	Good definition of regional atrophy	Overlap with non-AD dementias Not validated against amyloid histopathology
¹⁸F-FDG PET	Spatial information on hypometabolism	Does not image amyloid pathology Not validated against amyloid histopathology
¹¹C-PiB PET	Research data available	Data not obtained under standard IND Not validated against amyloid histopathology
CSF biomarkers	Extensive data available Linked to pathology	Overlap between diagnostic groups Not validated against amyloid histopathology
Histopathology	Defines disease pathology Spatial correlation with imaging	Requires autopsy study

Strengths

Weaknesses

	Strengths	Weaknesses
Clinical diagnosis	Widely available	Limited diagnostic accuracy
MRI	Good definition of regional atrophy	Overlap with non-AD dementias Not validated against amyloid histopathology
¹⁸F-FDG PET	Spatial information on hypometabolism	Does not image amyloid pathology Not validated against amyloid histopathology
¹¹C-PiB PET	Research data available	Data not obtained under standard IND Not validated against amyloid histopathology
CSF biomarkers	Extensive data available Linked to pathology	Overlap between diagnostic groups Not validated against amyloid histopathology
Histopathology	Defines disease pathology Spatial correlation with imaging	Requires autopsy study

Candidate Reference Standards

Strengths

Weaknesses

	Strengths	Weaknesses
Clinical diagnosis	Widely available	Limited diagnostic accuracy
MRI	Good definition of regional atrophy	Overlap with non-AD dementias Not validated against amyloid histopathology
¹⁸F-FDG PET	Spatial information on hypometabolism	Does not image amyloid pathology Not validated against amyloid histopathology
¹¹C-PiB PET	Research data available	Data not obtained under standard IND Not validated against amyloid histopathology
CSF biomarkers	Extensive data available Linked to pathology	Overlap between diagnostic groups Not validated against amyloid histopathology
Histopathology	Defines disease pathology Spatial correlation with imaging	Requires autopsy study

Candidate Reference Standards

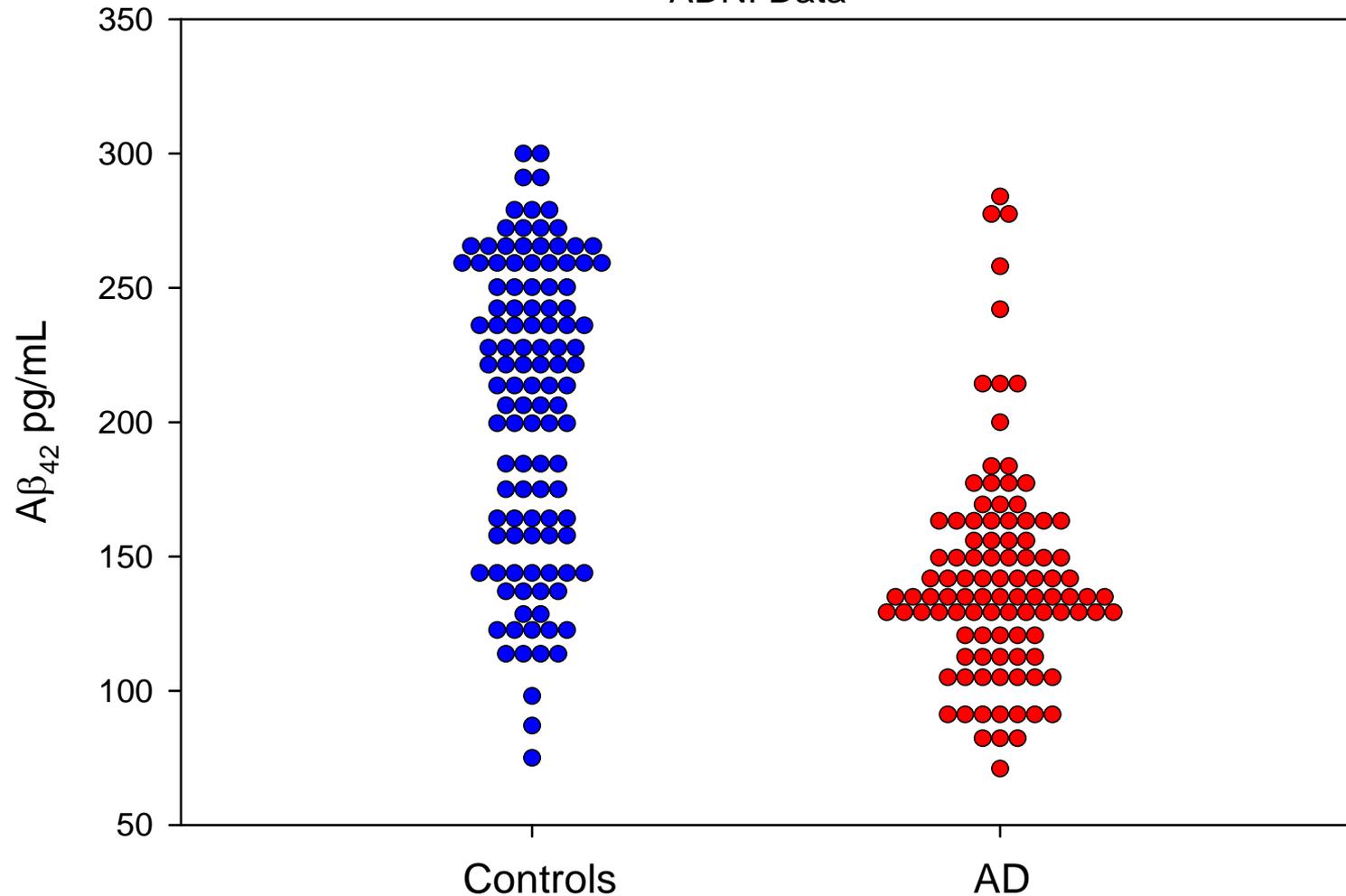
Strengths

Weaknesses

	Strengths	Weaknesses
Clinical diagnosis	Widely available	Limited diagnostic accuracy
MRI	Good definition of regional atrophy	Overlap with non-AD dementias Not validated against amyloid histopathology
¹⁸F-FDG PET	Spatial information on hypometabolism	Does not image amyloid pathology Not validated against amyloid histopathology
¹¹C-PiB PET	Research data available	Data not obtained under standard IND Not validated against amyloid histopathology
CSF biomarkers	Extensive data available Linked to pathology	Overlap between diagnostic groups Not validated against amyloid histopathology
Histopathology	Defines disease pathology Spatial correlation with imaging	Requires autopsy study

CSF $A\beta_{42}$ baseline values

ADNI Data



Candidate Reference Standards

Strengths

Weaknesses

	Strengths	Weaknesses
Clinical diagnosis	Widely available	Limited diagnostic accuracy
MRI	Good definition of regional atrophy	Overlap with non-AD dementias Not validated against amyloid histopathology
¹⁸F-FDG PET	Spatial information on hypometabolism	Does not image amyloid pathology Not validated against amyloid histopathology
¹¹C-PiB PET	Research data available	Data not obtained under standard IND Not validated against amyloid histopathology
CSF biomarkers	Extensive data available Linked to pathology	Overlap between diagnostic groups Not validated against amyloid histopathology
Histopathology	Defines disease pathology Spatial correlation with imaging	Requires autopsy study

Pathology correlation studies have been used to validate imaging for other targets

Silverman et al., 2001	138 subjects ¹⁸ F-FDG PET	Mean interval to pathology = 2.9 yrs
Walker et al., 2007	20 subjects ¹²³ I-FP-CIT SPECT	Mean interval to pathology = 2.8 yrs
Jagust et al., 2008	93 subjects MRI for vascular pathology	Mean interval to pathology = 2.7 yrs

Previous limitation = delay between scan and autopsy

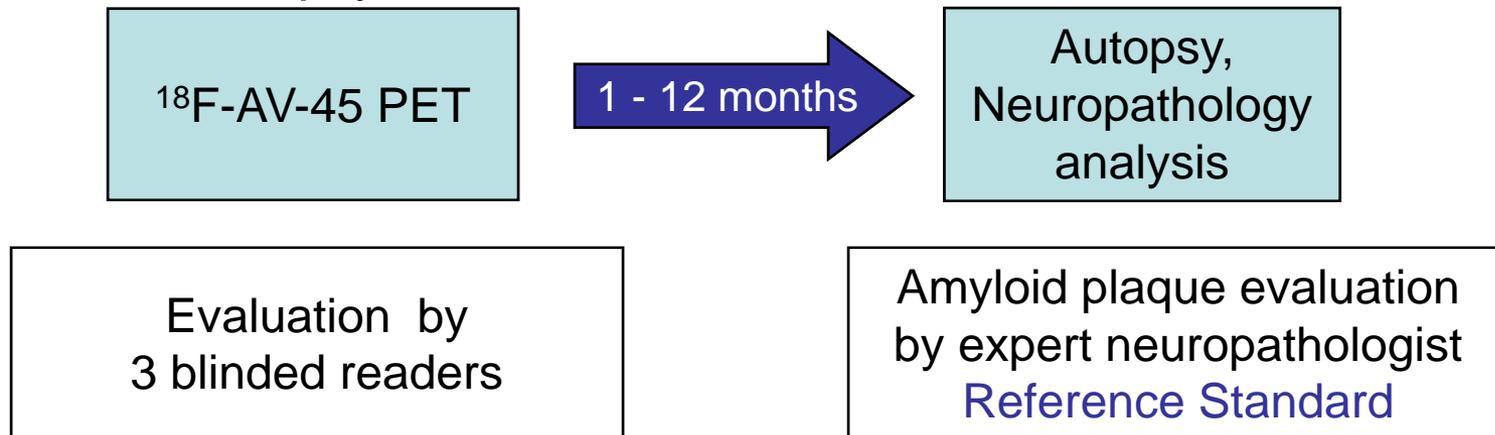
Development of ^{18}F -AV-45 for Imaging of Alzheimer's Disease Pathology in Humans

AVID AGENDA

10:00 - 10:10 am	Introduction & ^{18}F-AV-45 Data	D Skovronsky, MD PhD
10:10 - 10:20 am	Clinical Utility & Reference Standard	C Clark, MD
10:20 - 10:30 am	Avid development proposal	D Skovronsky, MD PhD

Phase III Study

Image elderly individuals (with varying degrees of cognitive impairment) who have consented to brain donation studies and follow to autopsy.



Study population will include subjects who are clinically cognitively normal, mildly impaired and have probable AD.

Goal is to have an autopsy population that includes a wide range of levels of amyloid deposition (from negative to abundant plaques).

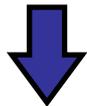
Image Evaluation

Qualitative read:

- Amyloid negative / amyloid positive
- Blinded readers

Quantitative evaluation:

- SUV ratio to cerebellum (SUVR)
- Pre-established thresholds for + / -



Neuropathology

Qualitative read (CERAD rating)

- None or sparse / moderate or frequent
- Blinded reader

Quantitative evaluation:

- Plaque count per high power field

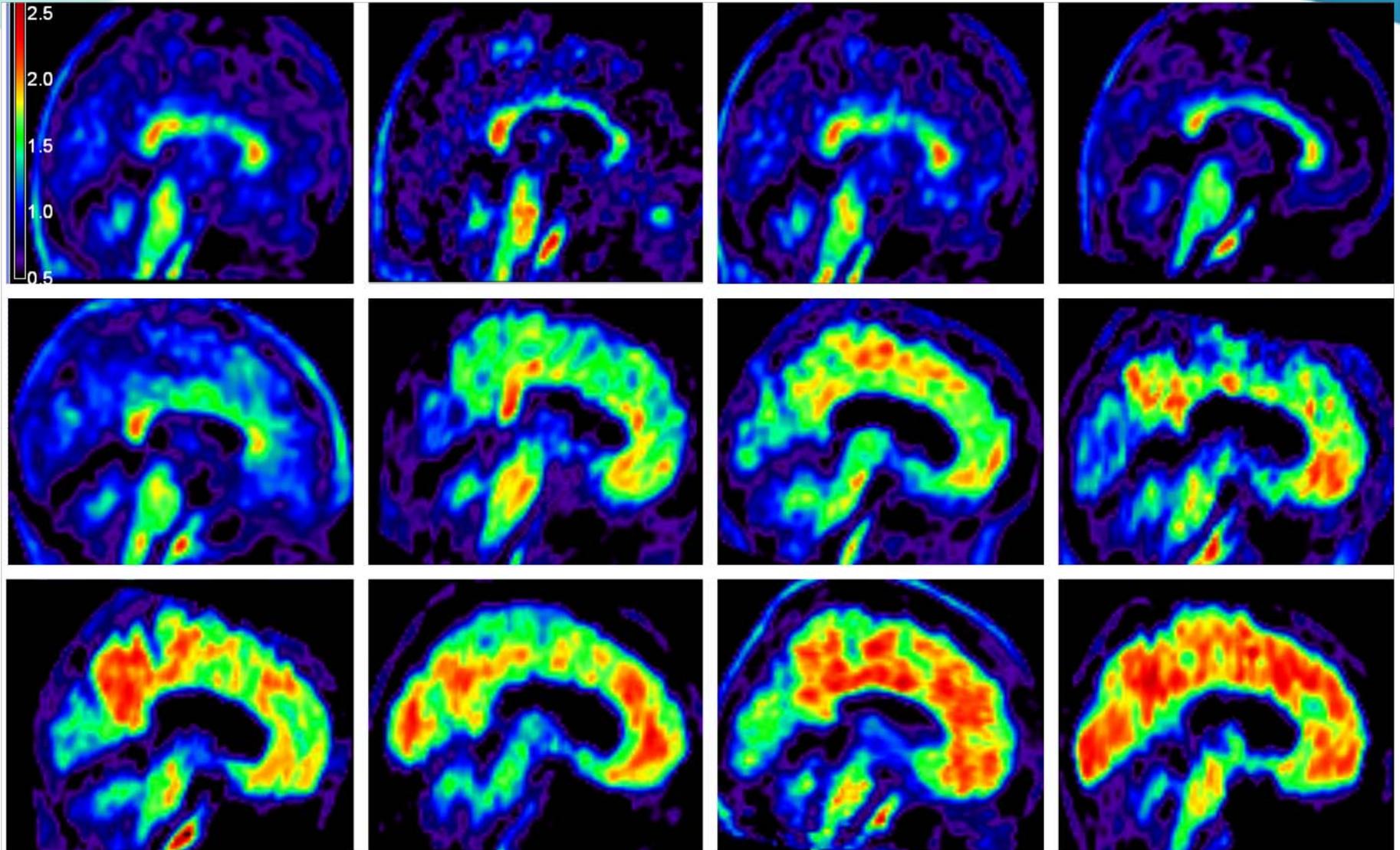


Key Outcome Variables

Negative Predictive Value (primary)

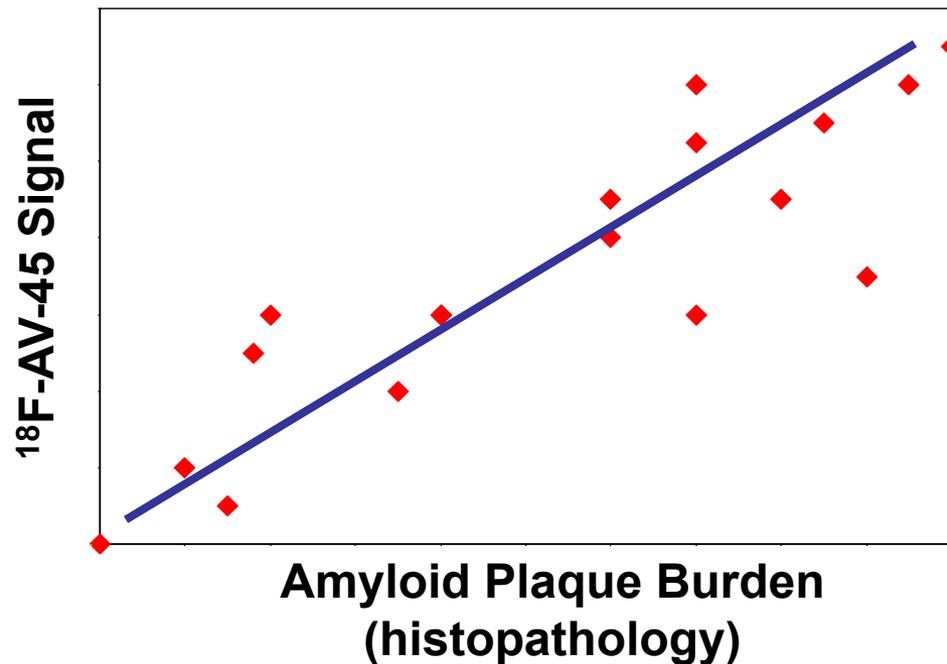
- Percentage of negative PET scans that are none/sparse for amyloid pathology at autopsy

Correlation of SUVR to plaque counts (secondary)



Anticipated prospective quantitative analysis
in 30 - 50 subjects to validate ^{18}F -AV-45

Correlation of Imaging Quantitation to Truth Standard



- FDA guidance suggests pathology detection as one potential indication for imaging agents
 - Guidance for Industry: Developing Medical Imaging Drug and Biological Products Part 2: Clinical Indications, June 2004
- Imaging results may be compared to histopathology as a truth standard
 - Guidance for Industry: Developing Medical Imaging Drug and Biological Products Part 3: Design, Analysis, and Interpretation of Clinical Studies, June 2004

→ *Avid proposal follows FDA guidance*

Well-controlled trials in cognitively impaired populations

Study	Population	<i>n</i>	Long Term Follow-Up
A05	AD MCI Normal Elderly	180	All Subjects
A06	Presenting for evaluation of cognitive impairment	~ 100	Selected Cases
A10	AD FTD Normal Elderly	~ 50	Selected Cases
Treatment Trials	AD (prior to initiation of novel therapy)	300 - 500	All Subjects (Placebo vs. Rx)

INITIAL APPROVAL

Clinical Trials:

Phase III autopsy study

Immediate Benefits:

1. **Clinically useful to exclude AD** in differential diagnosis
2. **Standardized biomarker** to facilitate development of disease modifying therapeutics

POST-APPROVAL

Clinical Trials:

Long term outcome trials

Future Benefits:

1. **Clinically useful to indicate positive likelihood of AD** in differential diagnosis
2. Establish **prognostic utility** of scans in patients with mild impairments or preclinical subjects to enable prevention trials

