CSF tau

Is it an informative biomarker of AD pathology

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Disclosures

T-tau and p-tau 181 ELISA kits

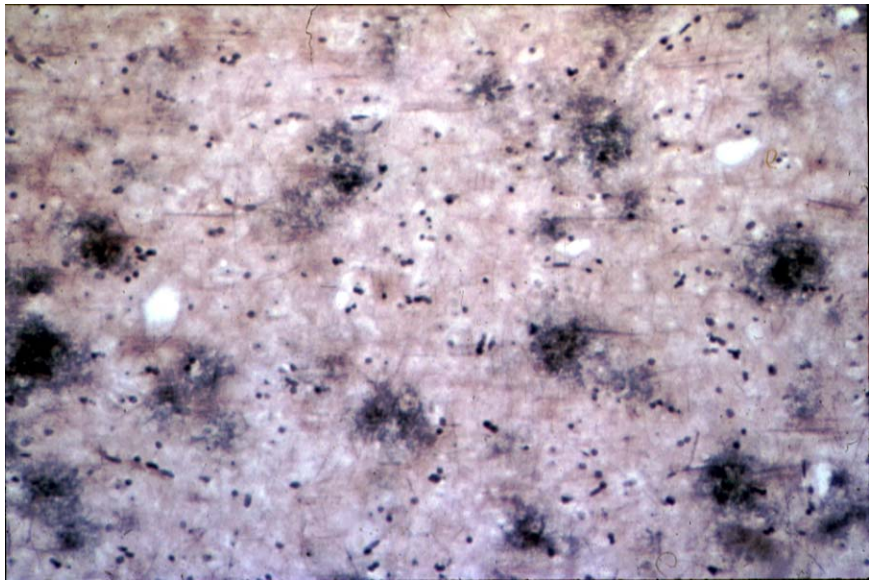
Provided by Innogenetics

CSF tau

- Increased tau predicts AD pathology at autopsy
- tau increased when symptoms are very mild
- Increased tau not present in all patients with AD

Hypothesis

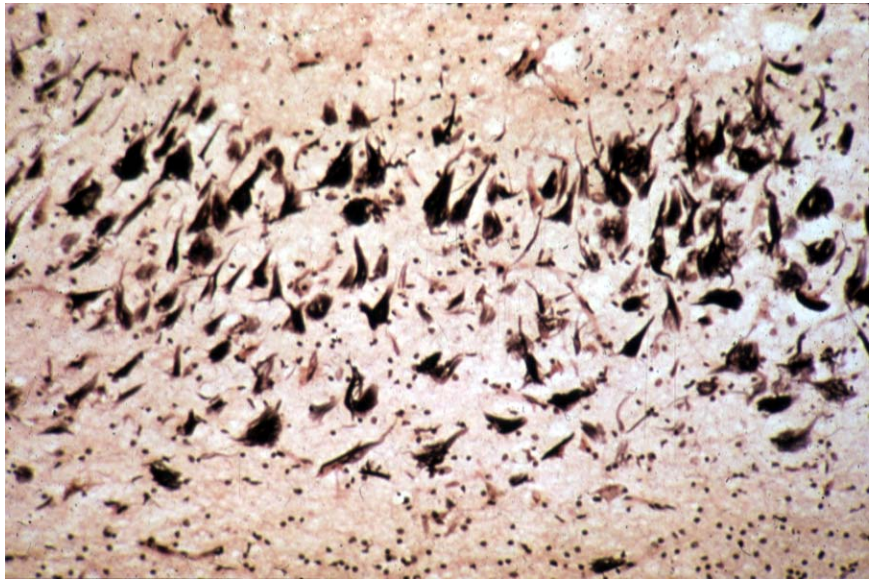
- Effective & efficient strategy for:
  - Diagnosis at earliest stage
  - Evaluation of pathologically targeted treatment
  - Monitoring treatment benefit in the community
- Will be enhanced by:
  - Detection & monitoring of biochemical markers of AD pathology

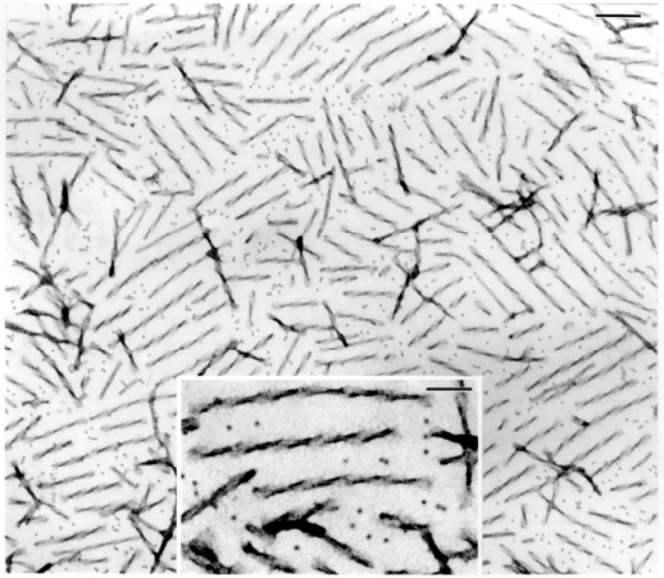


Pathology

Amyloid Plaque

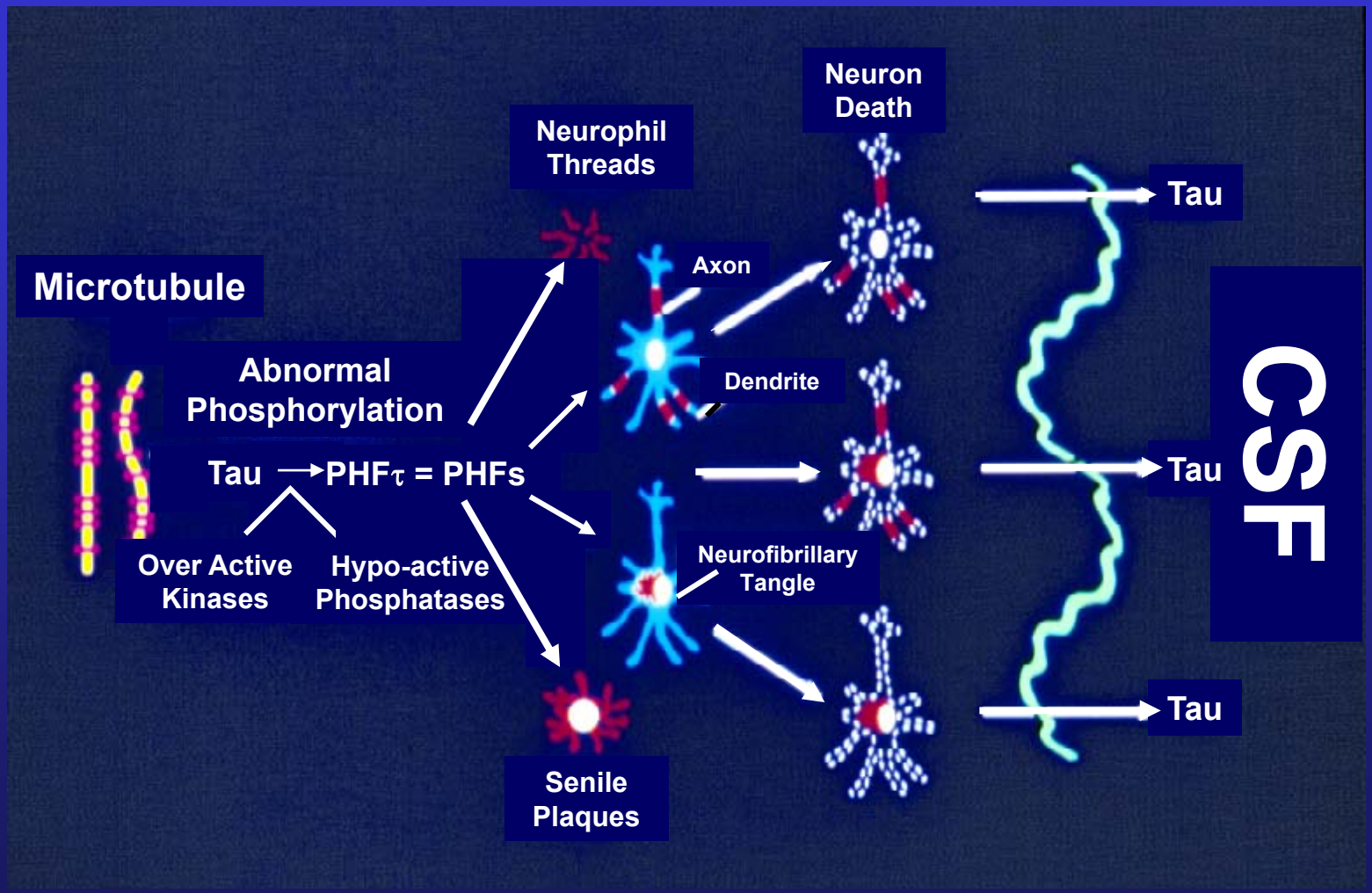
Neurofibrillary Tangle





From Lee et al. Science (1991) 251, 675-8

Pathogenesis of PHF-Tau

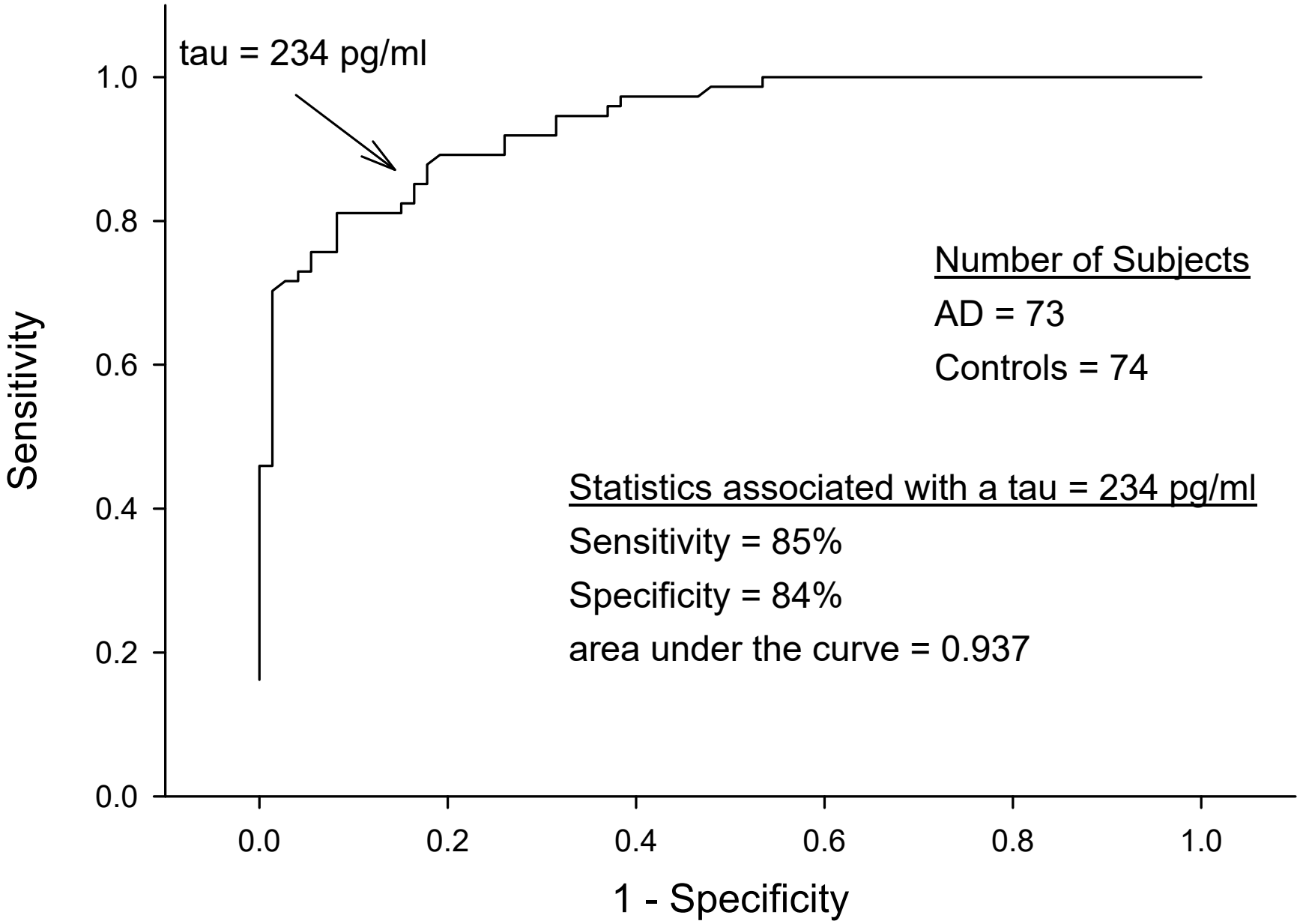


CSF tau

- Increased tau predicts AD pathology at autopsy
- tau increased when symptoms are very mild
- Increased tau not present in all patients with AD

CSF t-tau

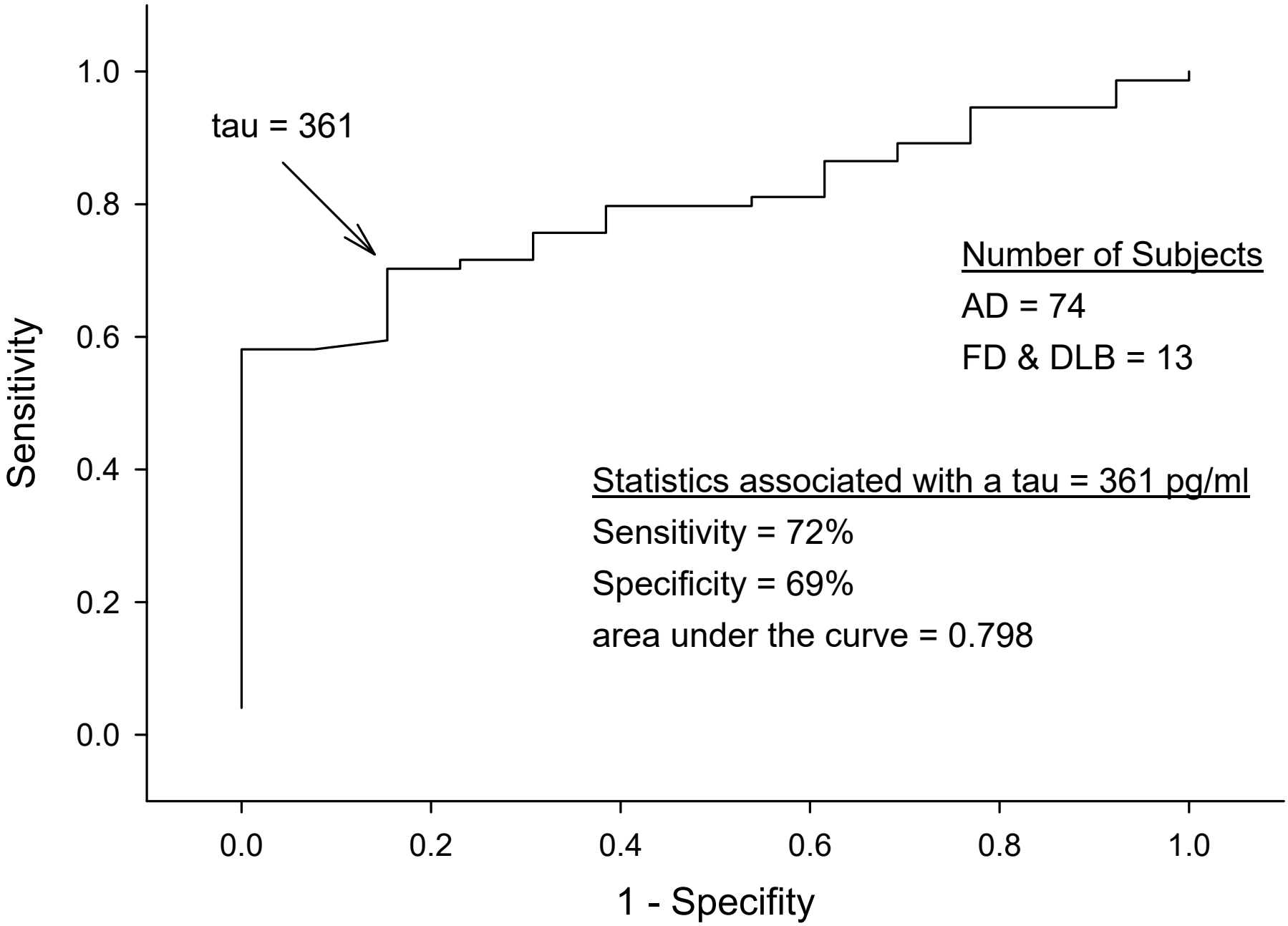
Diagnosis	N	Mean tau pg/ml	SD	Range
AD	74	612	430	89-2206
Controls	73	140	97	60-500
FTD	10	272	120	93-427
DLB	3	282	22	257-300

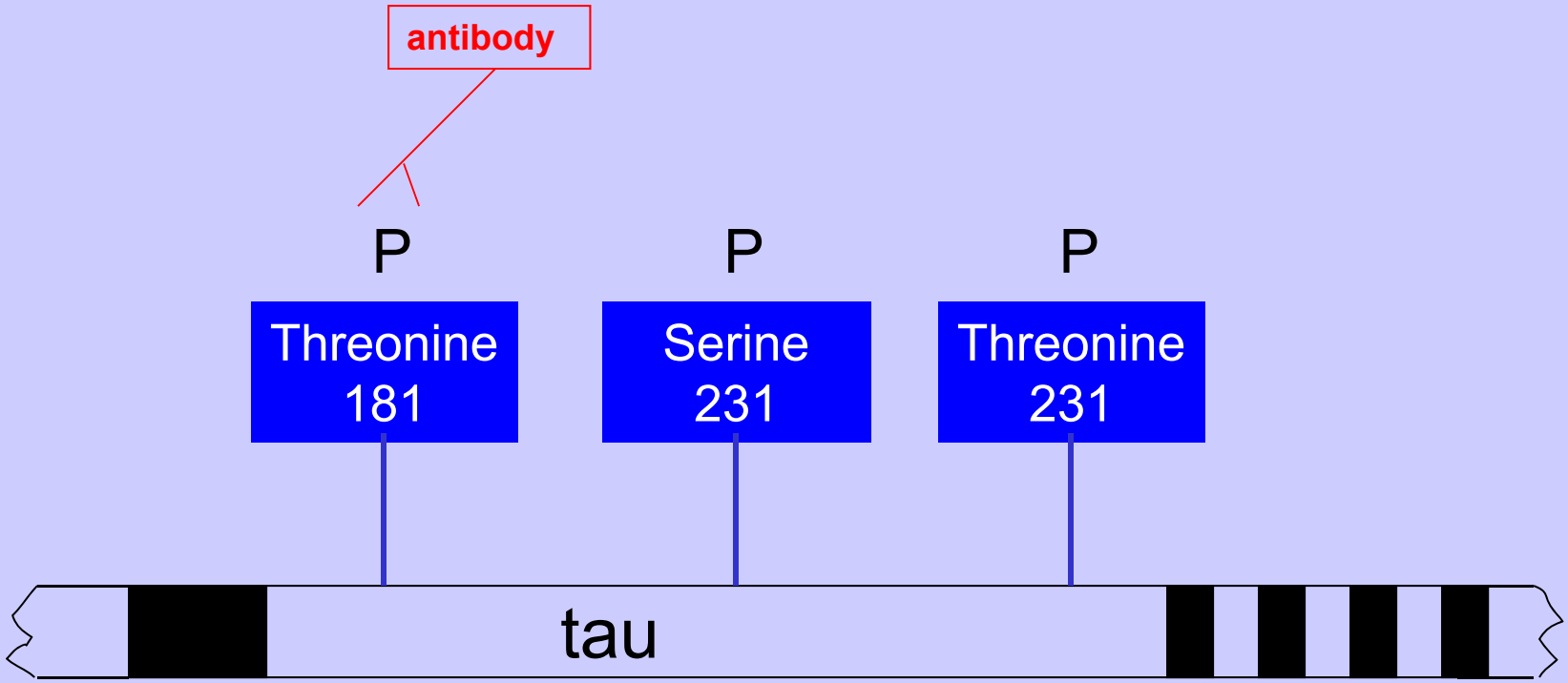

tau = 234 pg/ml
Number of Subjects
AD = 73
Controls = 74
Statistics associated with a tau = 234 pg/ml
Sensitivity = 85%
Specificity = 84%
area under the curve = 0.937
Sensitivity
1 - Specificity
0.0
0.2
0.4
0.6
0.8
1.0

AD vs Controls

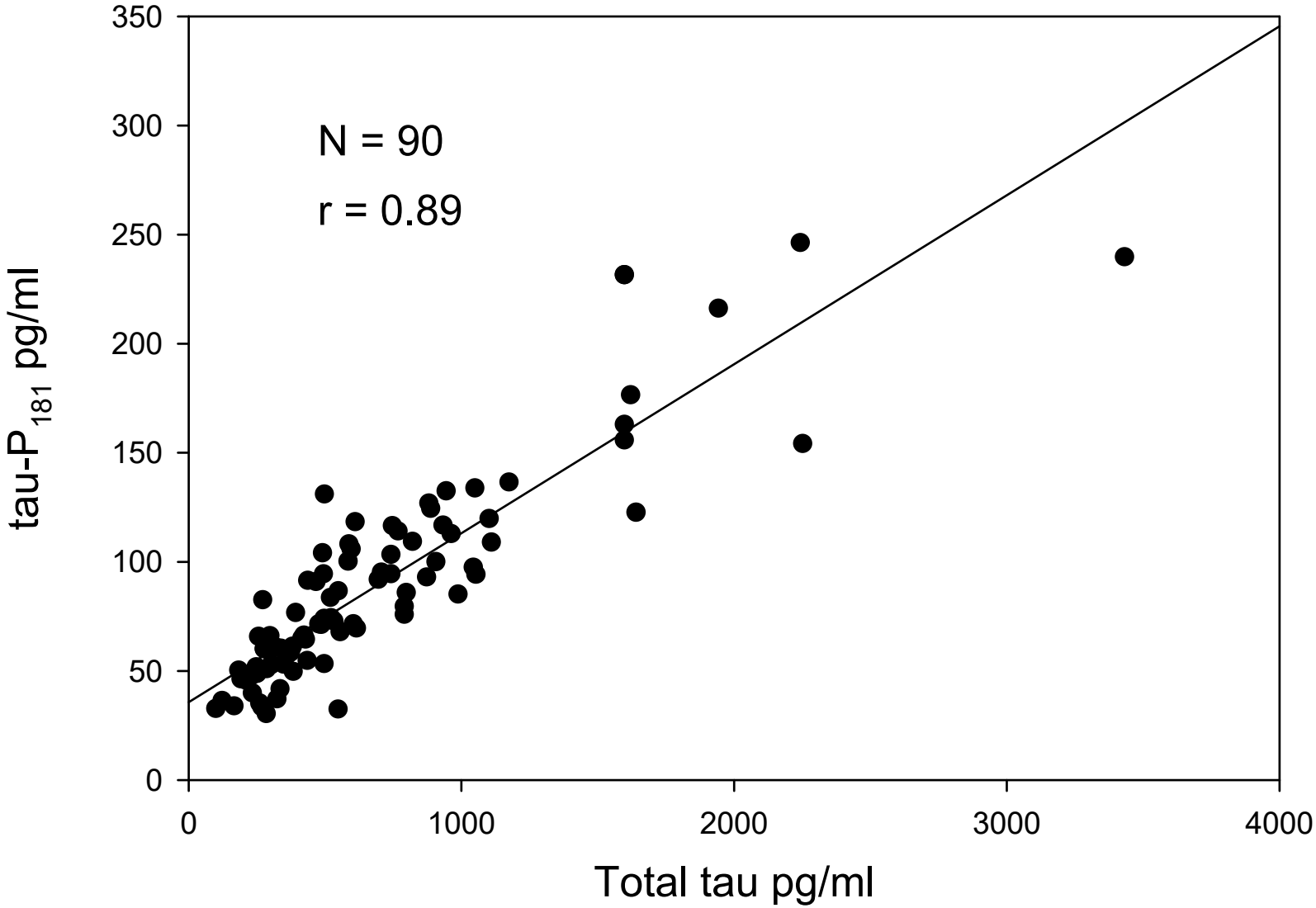
CSF tau = 234

Sensitivity	85%
Specificity	83%
PPV	87%
NPV	82%
PLR	4.7


1.0
0.8
0.6
0.4
0.2
0.0
Sensitivity
tau = 361
Number of Subjects
AD = 74
FD & DLB = 13
Statistics associated with a tau = 361 pg/ml
Sensitivity = 72%
Specificity = 69%
area under the curve = 0.798
0.0
0.2
0.4
0.6
0.8
1.0
1 - Specifity


antibody
P
P
P
Threonine 181
Serine 231
Threonine 231
tau

Correlation of total tau with P_{181} tau in CSF of patients with Alzheimer's disease



Correlation

t-tau and p-tau 181

	Number Subjects	Correlation
All subjects	232	0.75
Alzheimer's	109	0.83

CSF tau in MCI

Is CSF tau elevated early (before the onset of dementia symptoms) in the pathology of Alzheimer's disease?

CSF t-tau
mildly impaired individuals
(MMS >24)

Diagnosis	N	t-tau	MMS
AD	73	621	27
MCI	43	444	27

CSF tau in individuals with Mild Cognitive Impairment who progress to dementia

Diagnosis	N	Duration months	Tau (SD)
Alzheimer's	25	14.7	839 (425)
Frontal Dementia	4	8.0	337 (155)

Is More better than Less?

Are two biomarkers better than one?

- CSF tau and β-amyloid
- CSF tau and F2 isoprostane
- Some other combination

AD vs Controls

F2 isoprostane >42 pg/ml

AD – 19

Control - 31

Sensitivity	84%
Specificity	84%
PPV	87%
NPV	81%
PLR	5.2

AUC = 0.88

Diagnostic Statistics

AD (diagnosis confirmed) N = 19
Controls (clinical) N = 31

	Sens	Spec	PPV	NPV	PLR
t-tau >361	63%	84%	70	79%	3.9
F2 IP >42	84%	84%	87	81%	5.2
Either	89%	87%	81	93%	6.8

Biomarker Correlations

Alzheimer's disease – pathological diagnosis

N = 21

t-tau – p-tau 181	0.98
t-tau - %β-amyloid 1-42	0.58
t-tau – F2 isoprostane	0.26

CSF tau as a biochemical Marker of Alzheimer's Disease?

The Gold Standard

- ✓ Ability to detect a fundamental feature of AD neuropathology
- ✓ Validated in neuropathologically confirmed AD cases
- ✓ Ability to detect AD early in its course
- ➢ Ability to distinguish AD from other dementias
- ➢ Reliable

  Non-invasive, simple and inexpensive

Biomarkers of AD

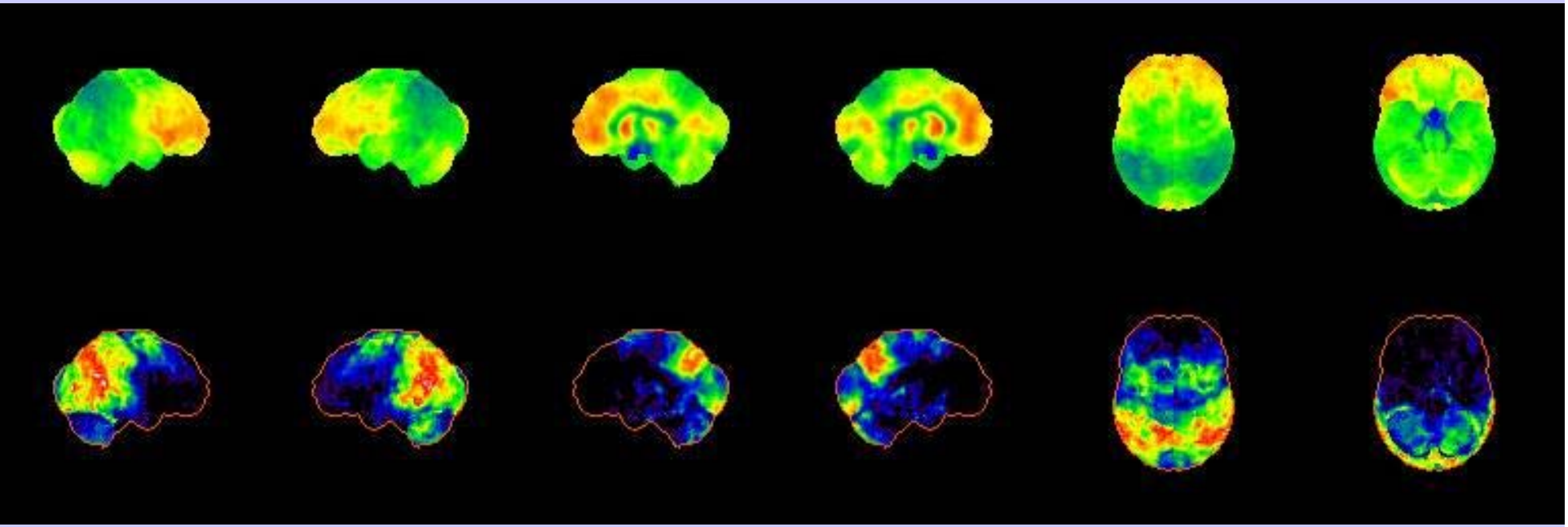
PET

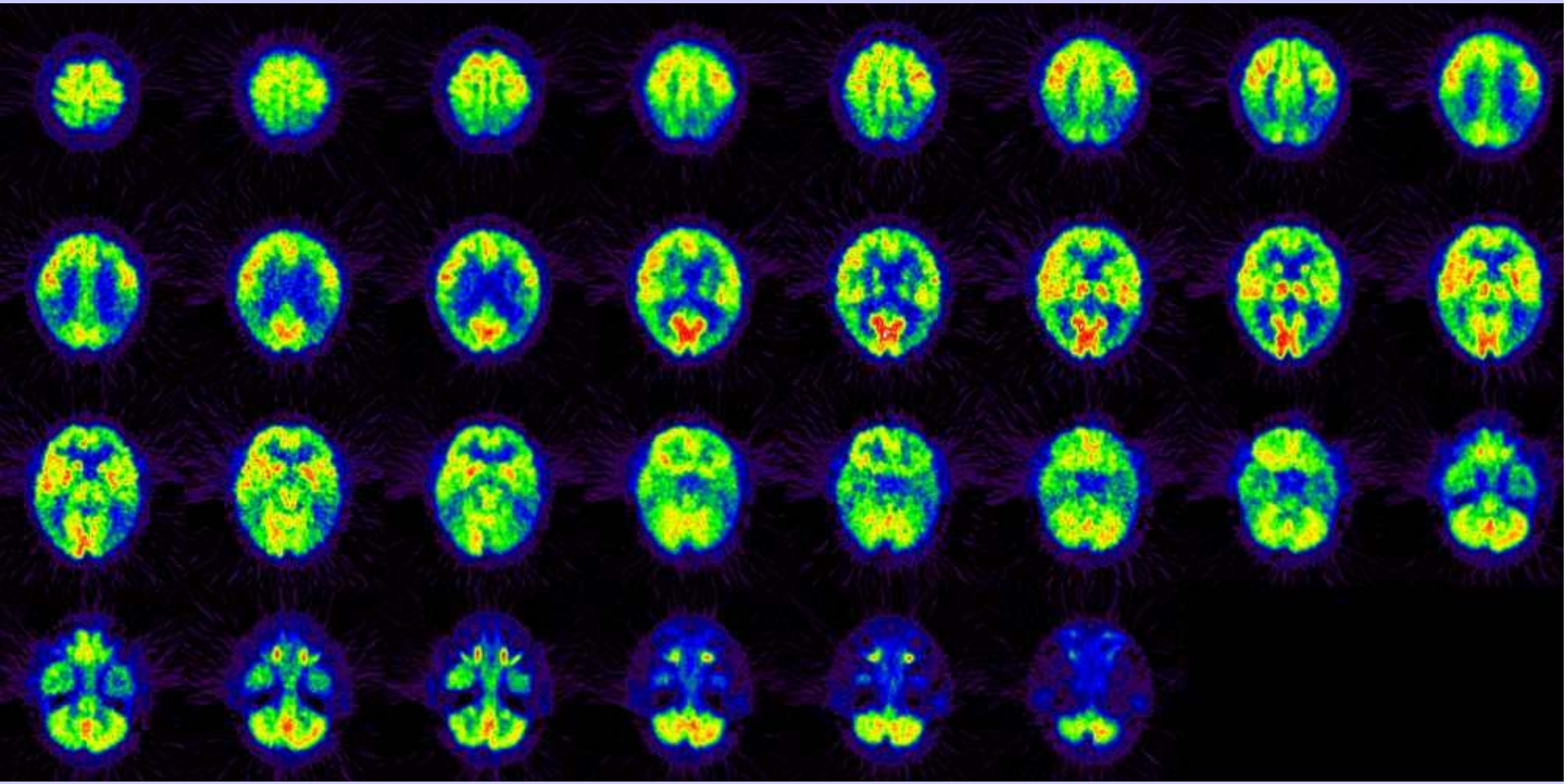
Regional metabolic impairment

- Standard format
- Stereotaxtic Surface Projection

Pathology specific imaging

- Amyloid ligand imaging





CSF t-tau
mildly impaired individuals
(MMS >24)

Diagnosis	N	t-tau	MMS
AD	73	621	27
MCI	43	444	27
FD	20	329	27

Annual CSF-MRI Study- 3Time points

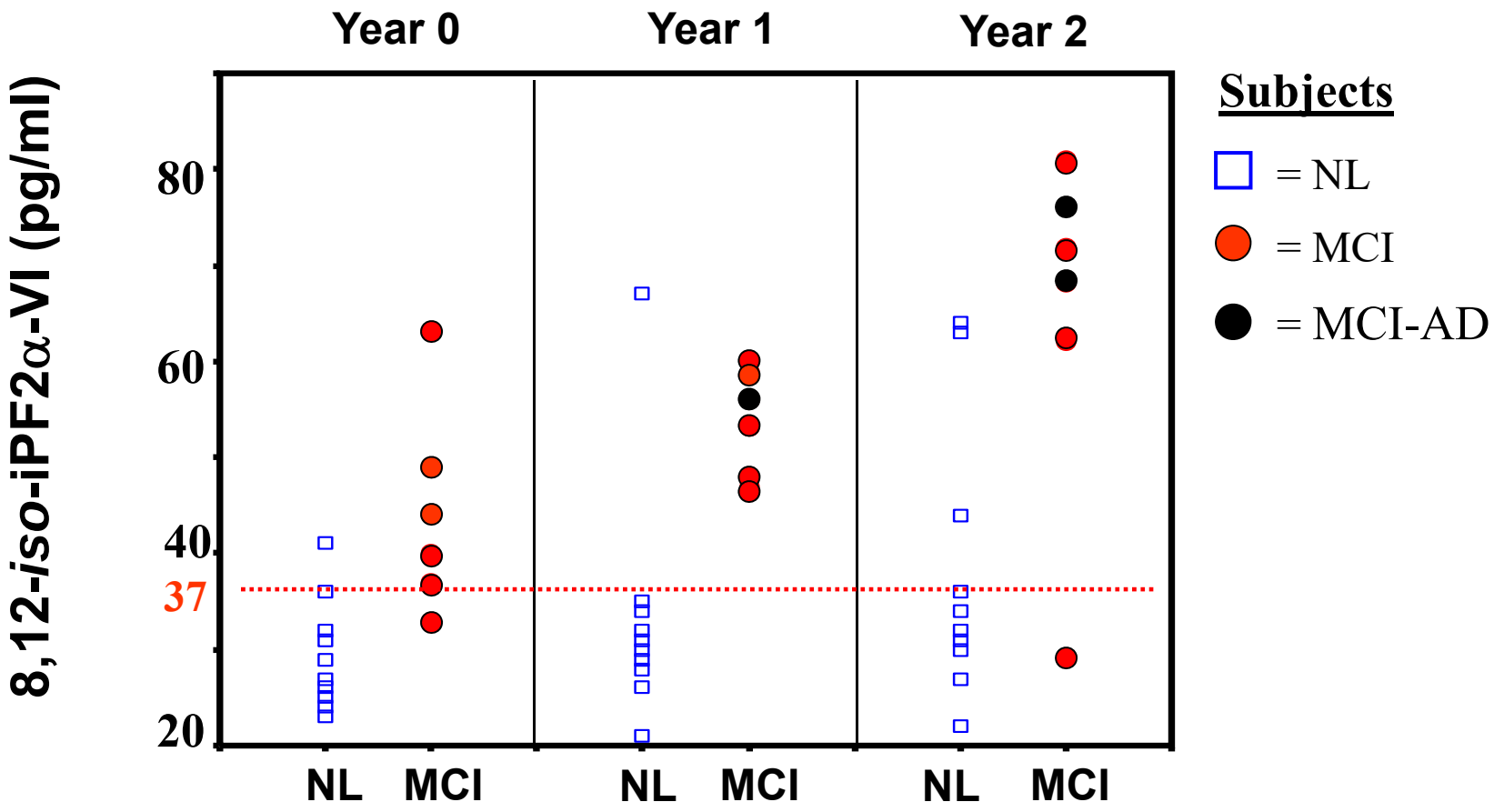
Outcome Groups

	NL	MCI
Sample size	10	6
% Female	50	33
# Convert to AD	0	2
ApoE E4 +	1	2
Age	63	70
MMSE-baseline	30	28
Education	17	14

NYU 2003

Annual Group Isoprostane Differences

NL n=10, MCI n=6



Sensitivity	83	100	83
Specificity	90	90	70
Overall	***88****	***94****	***75****

NYU & U of P
2003

*p<.05

Classifications from Longitudinal Isoprostane Changes

NL(10) MCI(6)

Classification Accuracy with Sensitivity = 83%

Interval	Specificity	Overall
Year 0 ~ 1	90	88 *
Year 1 ~ 2	80	81 *

*p<.05

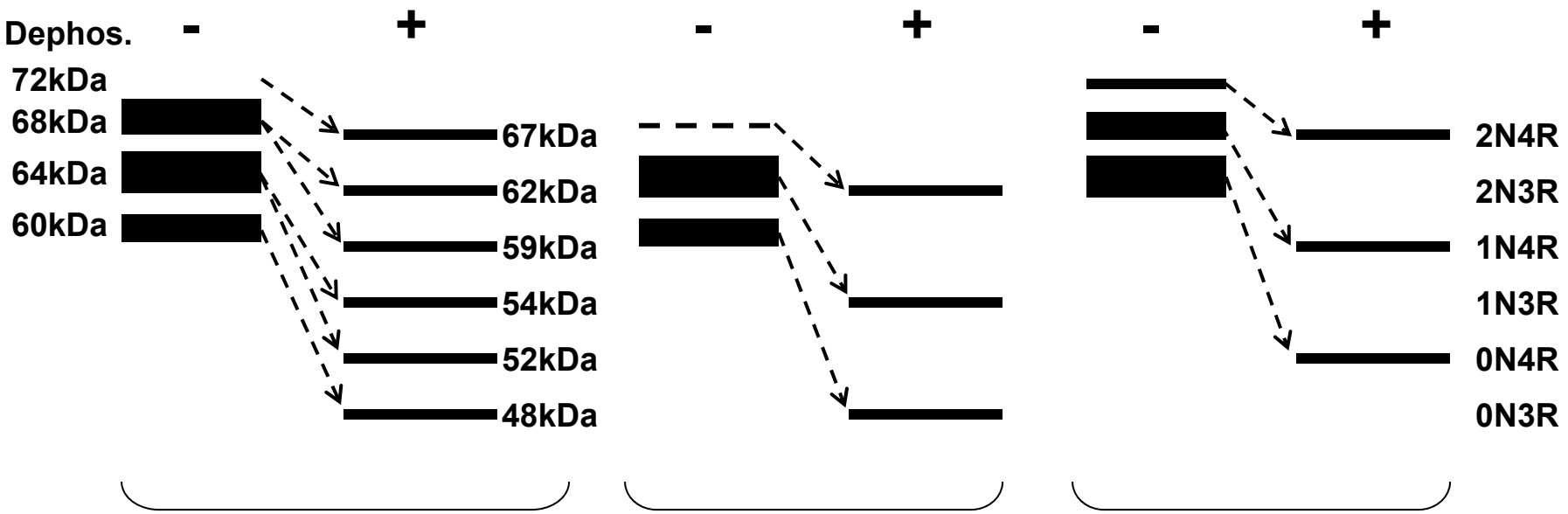
NYU & U of P 2003

Diagnostic Frequency

Univ Penn Memory Disorder Clinic

Diagnosis	Clinic (N=607)	Autopsy (N=113)
Alzheimer's	68%	66%
MCI	12%	
Frontal dementia	7%	15%
Lewy body dementia	2%	3%
Vascular dementia	2%	3%
Other	9%	10%

Sarkosyl-insoluble Tau Bands Before and After Dephosphorylation



- AD
- ALS/PDC
- Down's syndrome
- FTDP-17 (G272V, V337M,etc.)
- GSS
- Nieman-Pick disease type C

- FTDP-17 (ΔK280)
- Pick's disease

- CBD
- FTDP-17 (mutations in I10, L284L, etc.)
- PSP