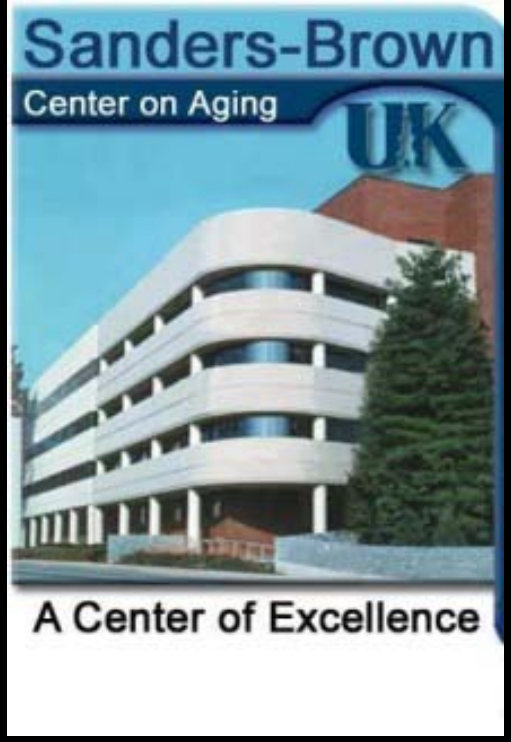
NACC for Data Mining:

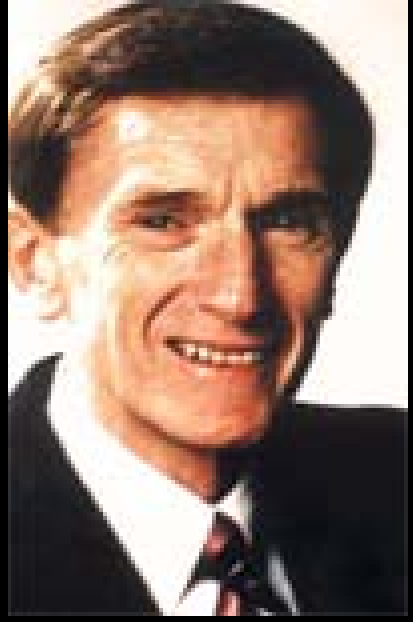
Clinical-pathological correlations in dementia with Lewy bodies (DLB)

Pete Nelson



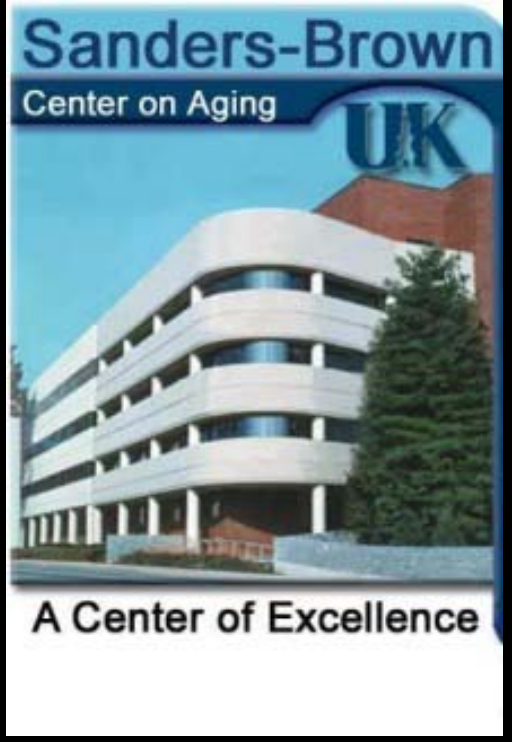
UK ADC:

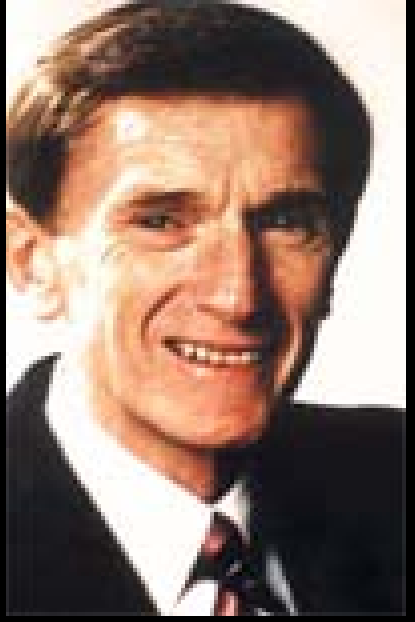
Long-term longitudinal autopsy series with emphases on data quality, continuity, nondemented controls, and Alzheimer's Disease.



Dr. William Markesbery

UK ADC Database





Dr. William Markesbery

- Independent/outside validation
- Remove some "local biases"
- More varied demographics
- More statistical power

UK ADC Database

NACC Registry data

Clinical-pathological correlations are extremely relevant as we enter an age of tailored neurotherapeutics

Goals:
Help Researchers
Help Clinicians

Clinical-pathological correlations in DLB

Clinical-pathological correlations in DLB

Challenges:

What is the gold standard ?
(clinical? pathological? biomarkers?)

What to do with AD + DLB cases?

What about Parkinson's disease dementia?

Clinical-pathological correlations in DLB

Challenges:

- What is the gold standard?
  - NEUROPATHOLOGY IS THE GOLD STANDARD
- What to do with AD + DLB cases?
  - TREAT AD, DLB, AND AD+DLB AS DIFFERENT CATEGORIES
- What about Parkinson's disease dementia?
  - FOR THE TIME BEING, EXCLUDE/IGNORE IT

NACC data:

For DLB clinical-pathological correlations, N~3000

Questions:

1. How do clinical (antemortem) diagnoses of AD, DLB, and AD+DLB match up with pathological results?

2. How is DLB pathology associated with global cognitive decline or severity?

3. Are there risk factors for DLB pathology among NACC Registry cases?

Question #1:

How do antemortem clinical diagnoses of AD, DLB, and AD+DLB match up with pathological results?

Dementia with Lewy bodies

Ian McKeith, Jacobo Mintzer, Dag Aarsland, David Burn, Helen Chiu, Jiska Cohen-Mansfield, Dennis Dickson, Bruno Dubois, John E Duda, Howard Feldman, Serge Gauthier, Glenda Halliday, Brian Lawlor, Carol Lippa, Oscar L Lopez, João Carlos Machado, John O'Brien, Jeremy Playfer, and Wayne Reid on behalf of the International Psychogeriatric Association Expert Meeting on DLB

Lancet Neurol. 2004 Jan;3(1):19-28.

Validity and reliability of consensus criteria for DLB[26]

Reference	Number of cases DLB	Other	Diagnostic criteria	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	κ	Comments and recommendations
Mega et al[19]	4	24 AD	Probable	75	79	100	93	F=0·25, H=0·59 P=0·46	Retrospective; suggests 4/6 of H, C, R, B, N, Fl
Litvan et al[20]	14	105 PD, PSP, MSA, CBD, AD	None applied; retrospective clinical diagnosis	18	99	75	89	0·19–0·38	Retrospective; no formal criteria for DLB used; comparison mainly with movement disorder
Holmes et al[21]	9	80 AD, VaD	Probable	22	100	100	91	NA	Retrospective; no specific recommendations; cases with mixed pathology were hardest to diagnose
Luis et al[17]	35	56 AD	Probable	57	90	91	56	F=0·30, H=0·91, P=0·61	Retrospective; suggests H, P, Fl, and rapid progression
Verghese et al[22]	18	94 AD	Probable	61	84	48	90	F=0·57, H=0·87	Retrospective; suggests 3/6 of P, Fl, H, N, D, and F
			Possible	89	28	23	91	P=0·90	
Lopez et al[23]	8	40	..	0	100	0	80		Retrospective; probable DLB not diagnosed once by a team of four raters; no specific recommendations
Hohl et al[24]	5	10 AD	Probable	100	8	83	100	NA	Consensus criteria applied retrospectively; clinician diagnosis without consensus criteria had PPV of 50
			Possible	100	0	NA	NA	NA	
McKeith et al[16]	29	50 AD, VaD	Probable	83	95	96	80	NA	Prospective; false-negative cases associated with comorbid pathology
Lopez et al[25]	13	26 AD	Probable	23	100	100	43		Prospective; met NINCDS–ADRDA criteria for AD, only four met DLB criteria

PPV=positive predictive values; NPV=negative predictive values; AD=Alzheimer's disease; F=falls; H=hallucinations; C=cogwheeling; P=parkinsonism; R=rigidity; B=bradykinesia; N=neuroleptic sensitivity; Fl=fluctuation; NA=not available; PD=Parkinson's disease; PSP=progressive supranuclear palsy; MSA=multiple system atrophy; CBD=corticobasal degeneration; VaD=vascular dementia. *Movement Disorders*

9 studies

Sensitivity	Specificity	PPV
58%	84%	77%

Dementia with Lewy bodies

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9 studies

Sensitivity	Specificity	PPV
58%	84%	77%
0-100%	0-100%	0-100%
Range		

Clinical-pathological correlation in DLB: NO "perfect" way to perform this study!

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9 studies

Total N=135

Tests of Agreement Between Clinical Diagnoses and Pathological Diagnoses
(NACC Registry MDS data, yr 2000-)

ADCs -- state-of-the-art diagnostics

(N = 162 cases of Pure DLB)

(J. NEUROLOGY, In Press)

Tests of Agreement Between Clinical Diagnoses and Pathological Diagnoses

(NACC Registry MDS data, yr 2000-)

Event	Sensitivity (%)	Specificity (%)	PPV (%)	kappa (95% C.I.)
AD versus others (control or AD+DLB or DLB)	85.0	51.1	64	0.36 (0.33, 0.39)
AD+DLB versus others (pure AD, pure DLB, control)	12.1	96.0	22	0.10 (0.05, 0.15)
DLB versus others (control, AD+DLB, pure AD)	**32.1**	**98.3**	**53**	**0.37 (0.29, 0.45)**

(N=162 cases of Pure DLB)

(J. NEUROLOGY, In Press)

POINT 1:

We may have a ways to go before clinical cues and biomarkers predict DLB pathology accurately

Question #2:

How does DLB pathology, by itself or in combination with other brain disease(s), correlate with cognitive impairment severity?

POINT 2:

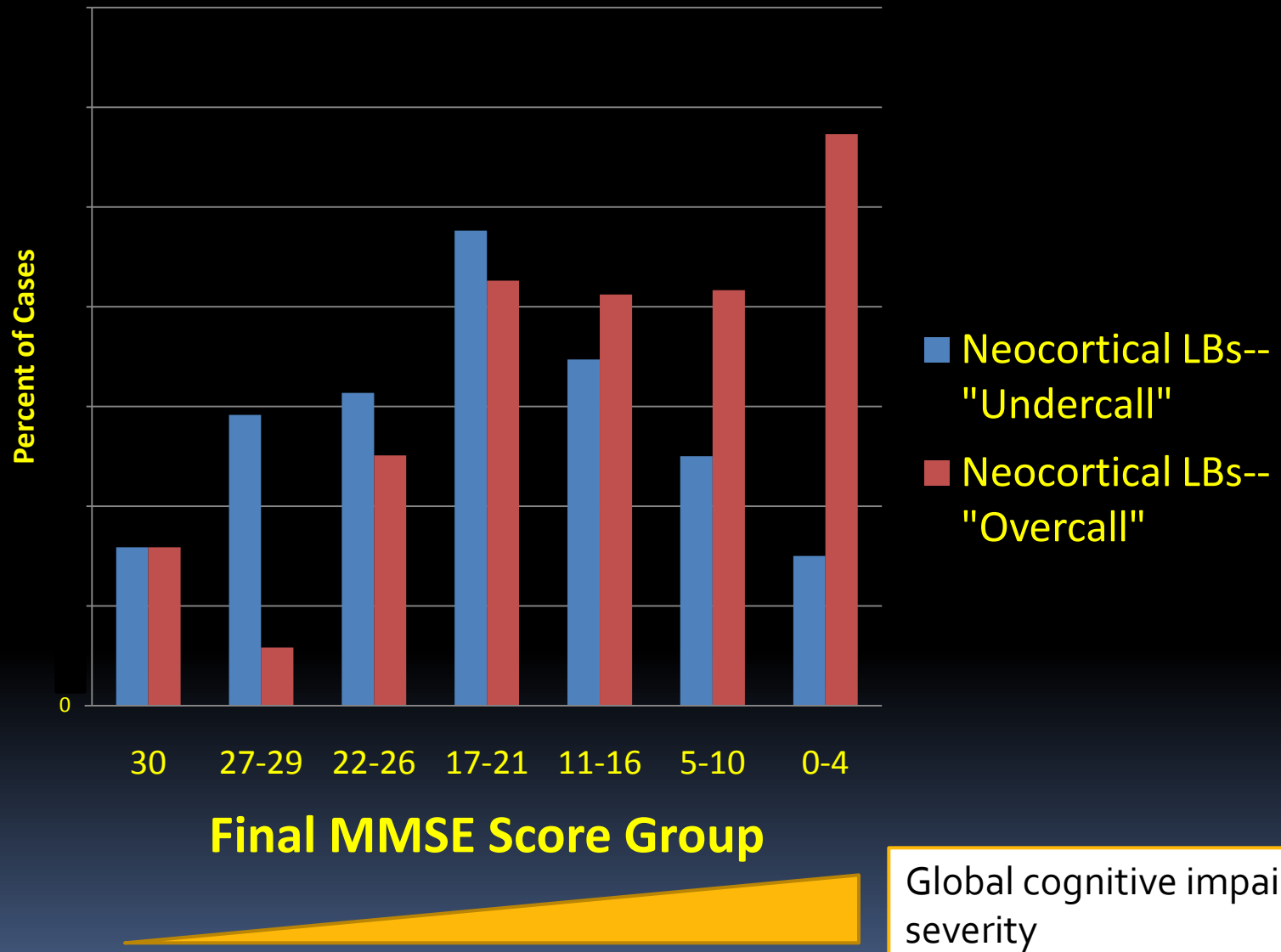
"Pure" DLB pathology correlates with a relatively modest loss in final MMSE score whether or not one corrects for obvious confounders.

Neocortical DLB pathology by itself is NOT generally a pathological substrate associated with "end-stage" global dementia although it may be otherwise a debilitating disease.

These results can provide practical guidance to clinicians and help to decrease antemortem diagnostic mistakes:

- “Undercall” (false-negative) clinical diagnosis of DLB
- “Overcall” (false-positive) clinical diagnosis of DLB

"Overcalls" and "Undercalls" of neocortical LBs by Final MMSE Score



(J. NEUROLOGY, In Press)

We may have a ways to go before clinical cues and biomarkers predict DLB pathology accurately

However:

- Clinical ‘false positives’ are relatively frequently seen in very impaired patients
- Clinical ‘false negatives’ are relatively frequently seen in the context of moderate global cognitive impairment

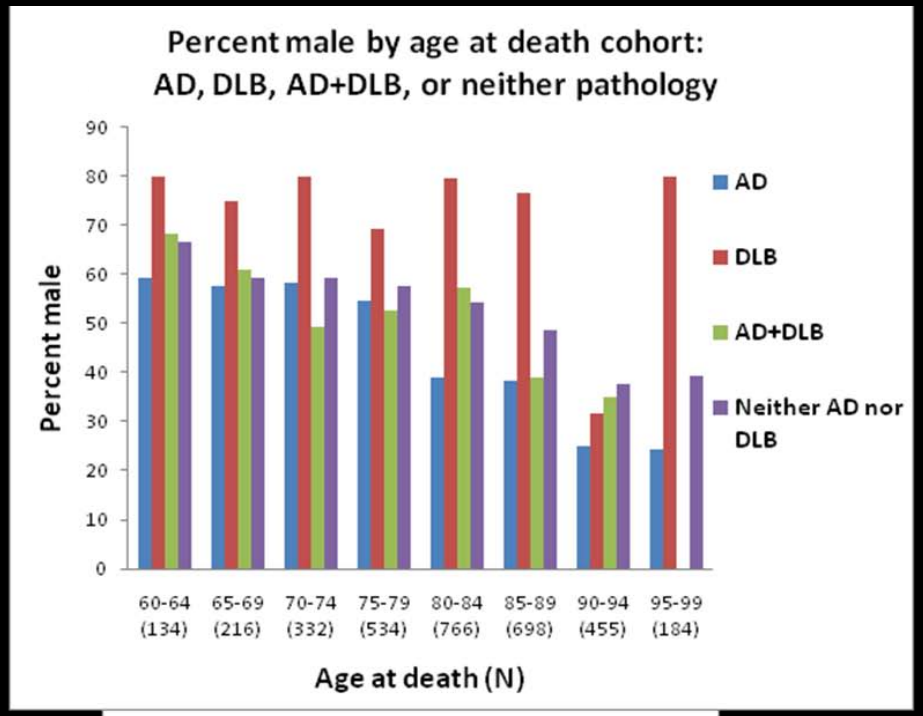
Question #3:
Are there risk factors for DLB pathology?

Pathology

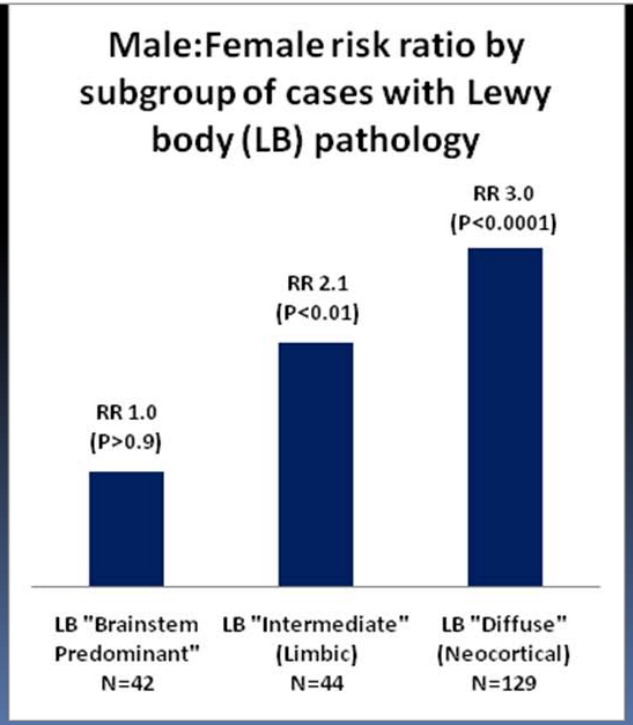
		AD only	DLB Only	AD+DLB	Neither AD nor DLB	Total
NACC	Male	734	109	240	451	1534
	Female	883	42	230	483	1638
* Excluding UK ADC	Total	1617	151	470	934	3172
	Relative risk (M:F)	0.89	2.77	1.11	1.00	
	95% CI	0.83-0.95	1.95-3.93	0.94-1.32	0.90-1.11	
UK ADC	Male	77	22	35	141	275
	Female	147	11	61	164	383
	Total	224	33	96	305	658
	Relative risk (M:F)	0.73	2.79	0.80	1.20	
	95% CI	0.58-0.92	1.37-5.65	0.52-1.17	1.02-1.40	

Persons dying with “Pure” DLB pathology are much more likely to be male than female

Arch. Neurol., *Submitted*



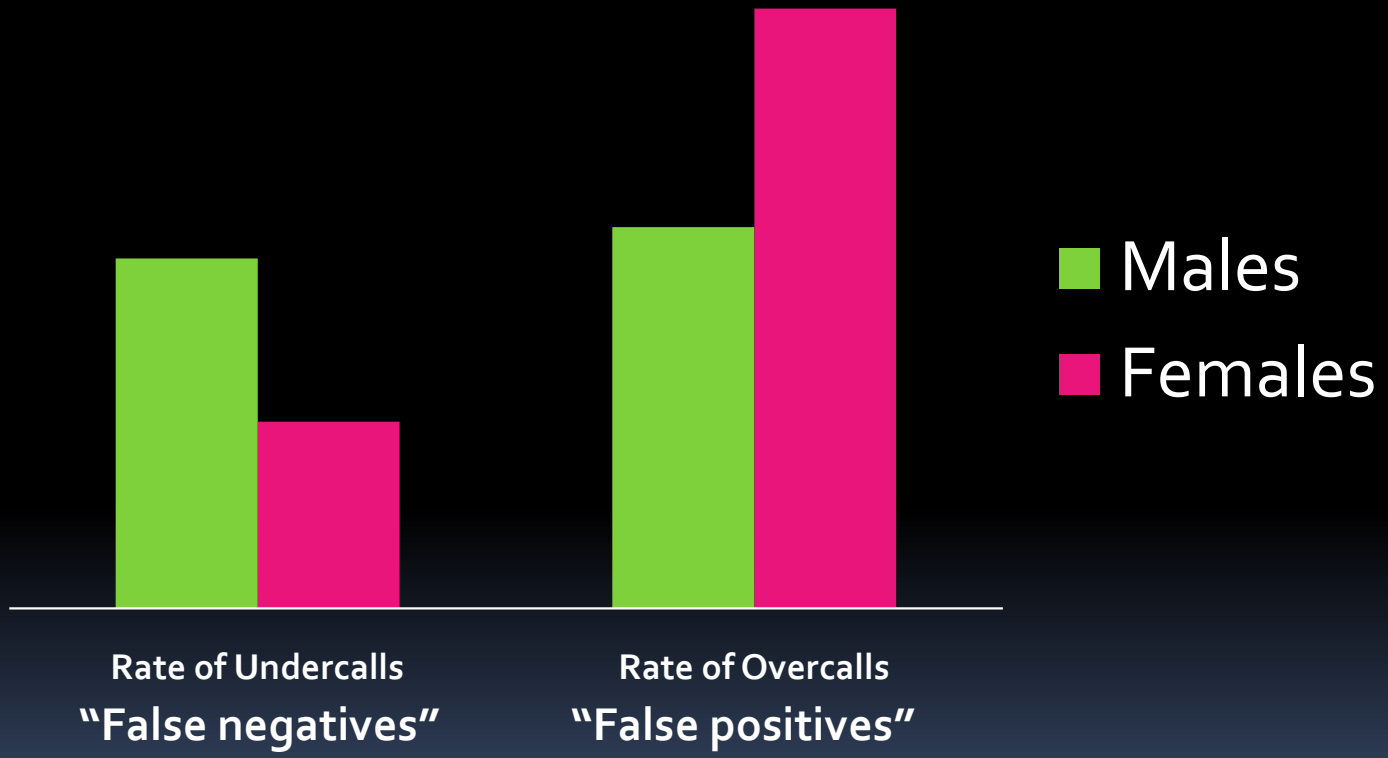
Higher risk for males dying with DLB pathology holds true across different age-at-death cohorts



Highest M:F risk ratio *is seen in persons dying with "diffuse" (neocortical) DLB path subtype*

Arch. Neurol., *Submitted*

Clinical diagnostic mistakes in DLB: Males versus Females (NACC Registry, N=2862)



POINT 3:

The likelihood of dying with neocortical DLB pathology is much higher in males than females

Females tend to be “overcalled” for DLB

Males tend to be “undercalled” for DLB

Relationship between female gender and risk of dying with AD pathology is more dependent on age of death

NACC data: personal experience–

Fantastic for retrospective case:control clinical-pathological correlation

--VERY rich clinical and pathological repertoire

--Can help harmonize clinical and pathological parameters

--Can help evaluate clinical and environmental risk factors

(How many other such datasets in the world?)

Administration has been professional, helpful, and efficient

Thanks

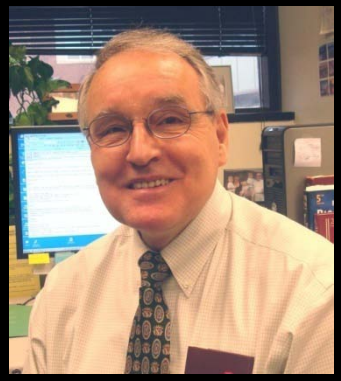
Dr. William Markesbery

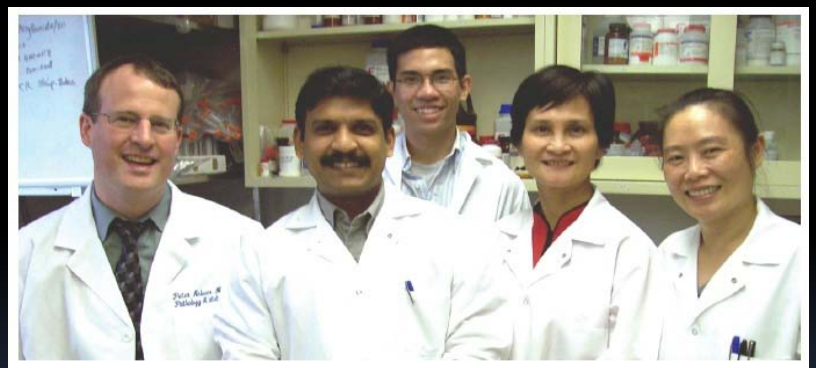
NIH/NIA	Pilot Grant
NIH/NINDS	K08 Grant
NIH/NINDS	R01 Grant
Alz Association	NIRG Grant

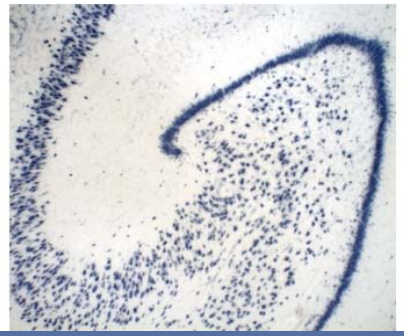
NACC grant U01 AG016976

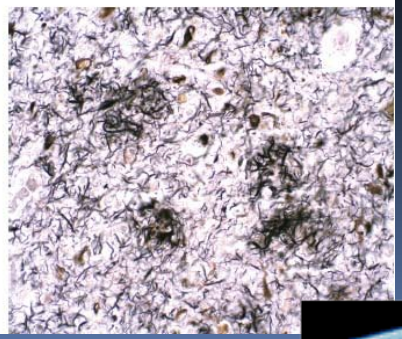
Erin Abner, MPH

Dick Kryscio, PhD









Greg Jicha
MD, PhD

Fred Schmitt, PhD

Areas where NACC Registry data is currently of limited utility:

- Longitudinal (“disease course”) questions
- Sensitive cognitive testing questions
- True population epidemiology questions
- Quantitative neuropathology
- Areas such as cerebrovascular disease where the basic rubrics for clinical-pathological correlation are lacking

NACC data: Started with ~11,000 cases

Initial exclusions: Yr<1998
(~4000 excluded)

FTD, CBD, PSP, Pick's, prion disease
triplet repeat disorders
(~3,000 excluded)

Additional exclusions due to missing
clinical and/or pathological data: ~1000