Mild Cognitive Impairment: The Current Status

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Updates on Dementia
Stanford University
June 4, 2008

Disclosures

- Elan Pharmaceuticals: Chair SMC
- GE Healthcare: Consultant

MILD COGNITIVE IMPAIRMENT

- Conceptual framework
- Epidemiology
- Clinical features
- Outcome
- Predictors
- Neuropathology
- Unresolved issues
- Clinical trials

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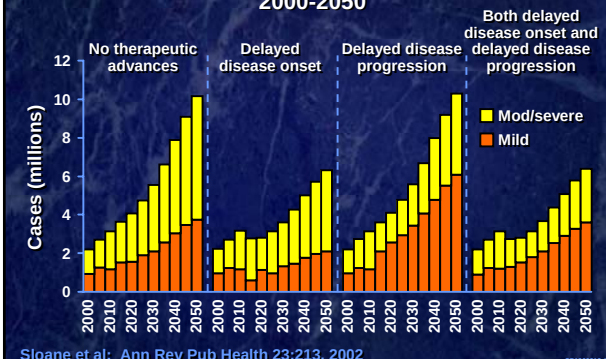
Prevalence of Mild, Moderate/Severe and Total Cases of Alzheimer's Disease in the United States 2000-2050



Sloane et al: Ann Rev Pub Health 23:213, 2002

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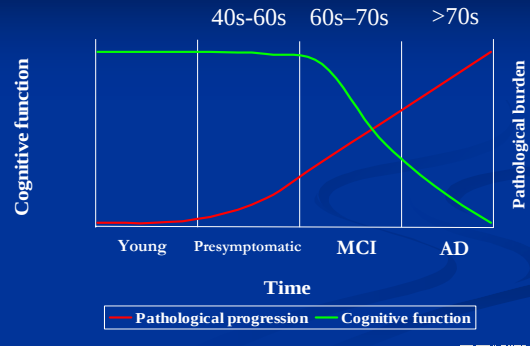
Time Course: AD Pathology (in situ) & Clinical Expression



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Cognitive Continuum

Normal

Mild Cognitive Impairment

Alzheimer's Disease

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Clinical Features

MILD COGNITIVE IMPAIRMENT
Original Criteria

- Memory complaint
- Memory impaired for age
- Normal general cognitive function
- Normal activities of daily living
- Not demented

Case

83 y/o Retired Priest

- Word finding difficulties
- Mild memory concerns
- ADL's preserved

83 Y/O PRIEST

- NEUROPSYCHOLOGY PROFILE
  - VIQ 140
  - PIQ 110
  - FSIQ 129
  - WORKING MEMORY 128
  - VeMI 92
  - ViMI 111

83 Y/O PRIEST

- LEARNING EFFIC 104
- DELAYED RECALL 71
- TRAILS A & B 50% ile
- BOSTON NAMING TEST 59/60
- FLUENCY 80% ile

34 months later

MILD COGNITIVE IMPAIRMENT
Original Criteria

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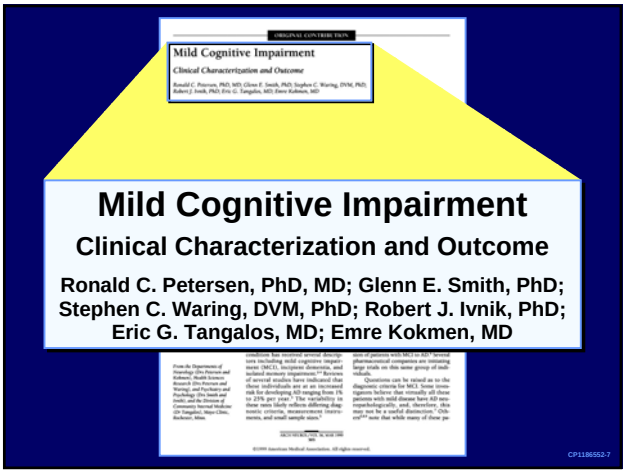
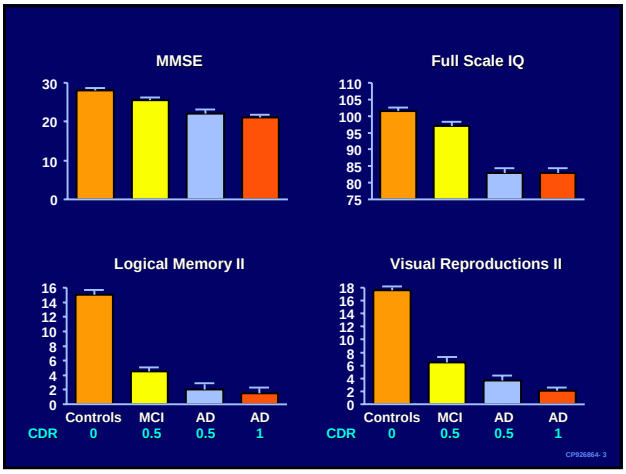
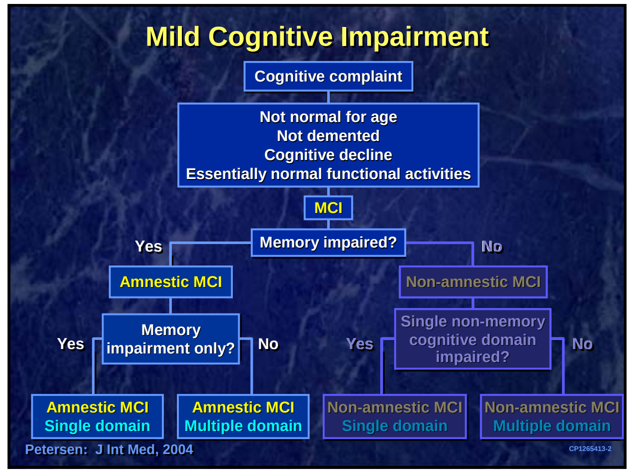
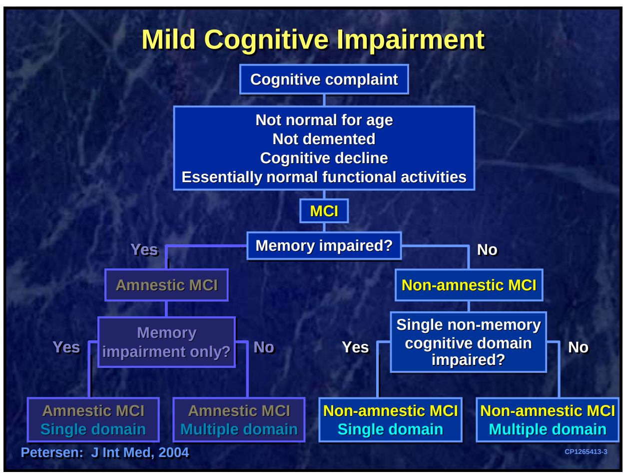
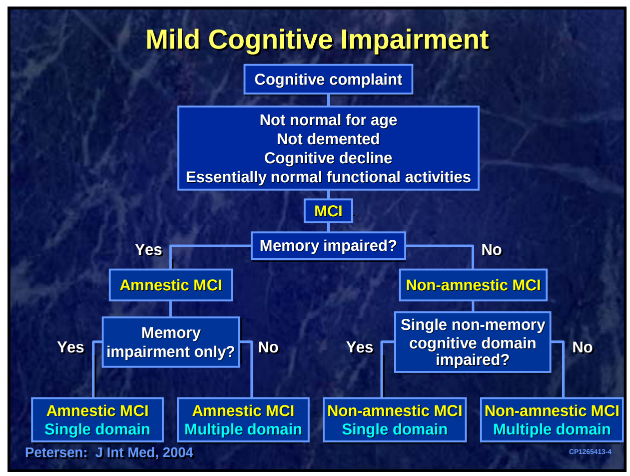




Current Classification Scheme for MCI







MCI Outcomes

Etiology

Clinical classification		Degen-erative	Vascular	Psychiatric	Med Cond
Amnestic MCI	Single domain	AD		Depr	
	Multiple domain	AD	VCI	Depr	
Non-amnestic MCI	Single domain	FTD			
	Multiple domain	DLB	VCI		

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MCI Outcomes

Etiology

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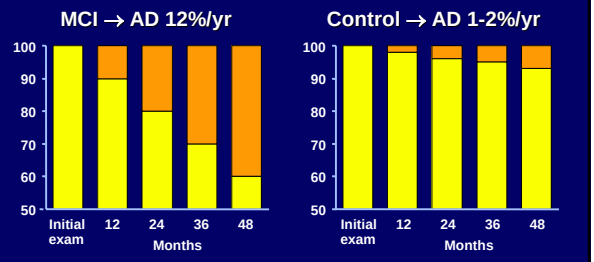
Mild Cognitive Impairment



Petersen RC et al: Arch Neurol 56:303-308, 1999

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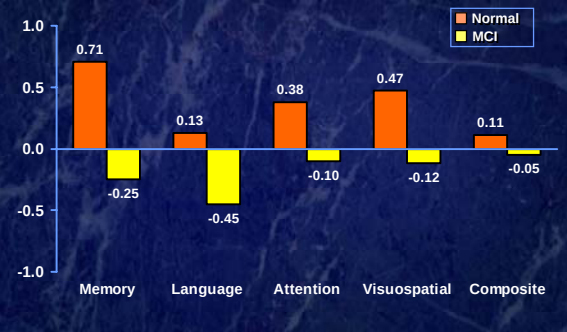
MOANS Change Scores



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MCI Studies

Study	Number of Subjects	Age	MCI Prevalence	Progression Rate
Leipzig	980	75+	19.3%	8.7%
Italy	2830	65-84	16.1%	13.6%
India	960	67	15.0%	--
Vienna	581	75-76	24.0%	19.5%/10.7%
Cache County	206	65+	--	18.3%
Mayo	1969	70-89	16.3%	(10%)

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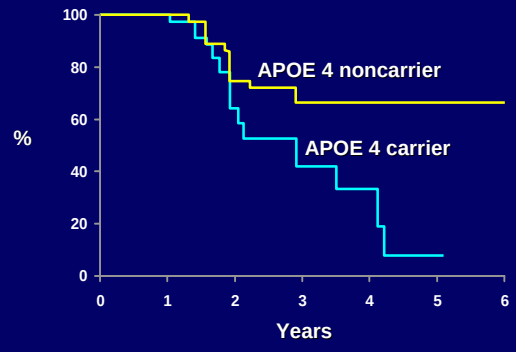
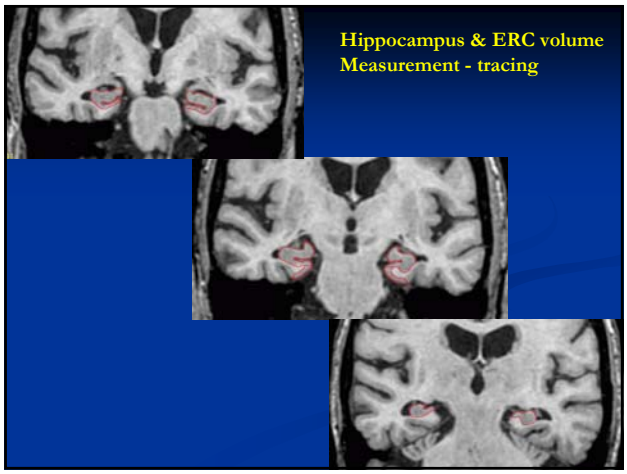
MILD COGNITIVE IMPAIRMENT
Predictors of Outcome

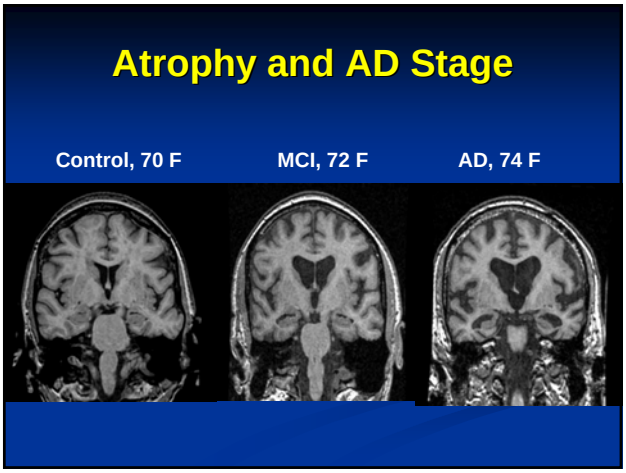
- Apo-E Status
  +E4
- Clinical severity
- Hippocampal volumes
- ? FDG-PET
- ? CSF Biomarkers
- ? Amyloid imaging

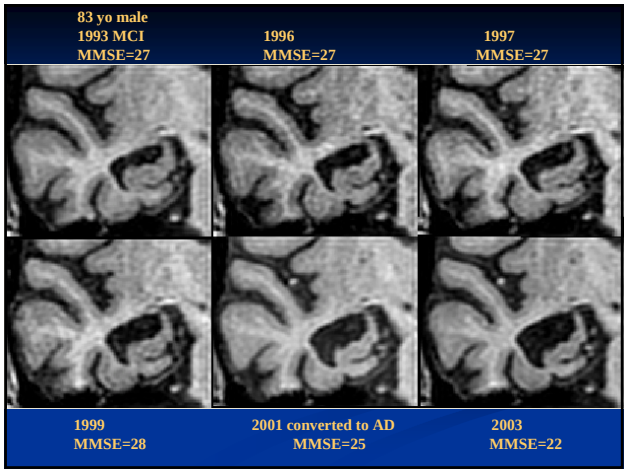
MCI: Conversion to Dementia

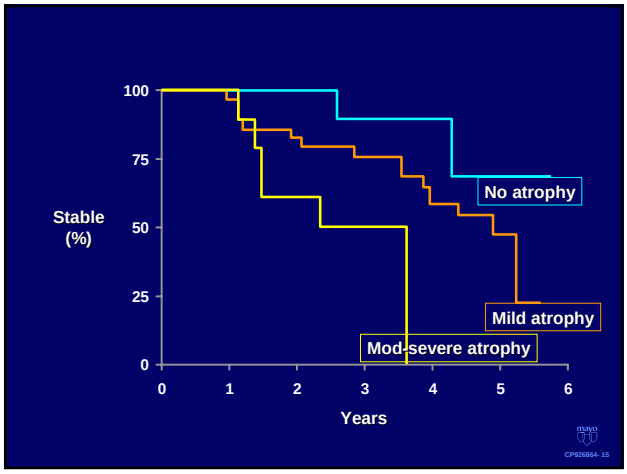




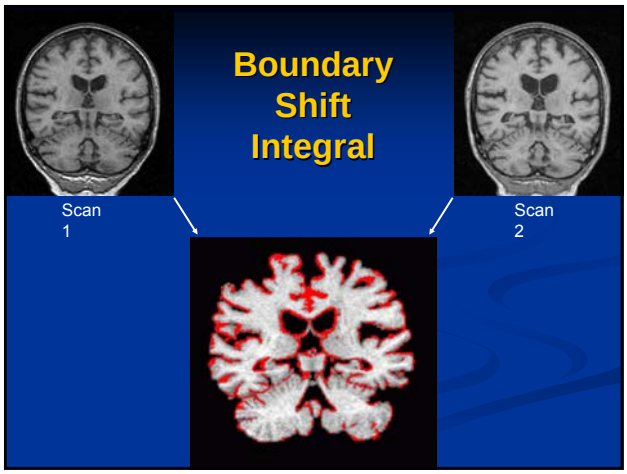
Atrophy and AD Stage





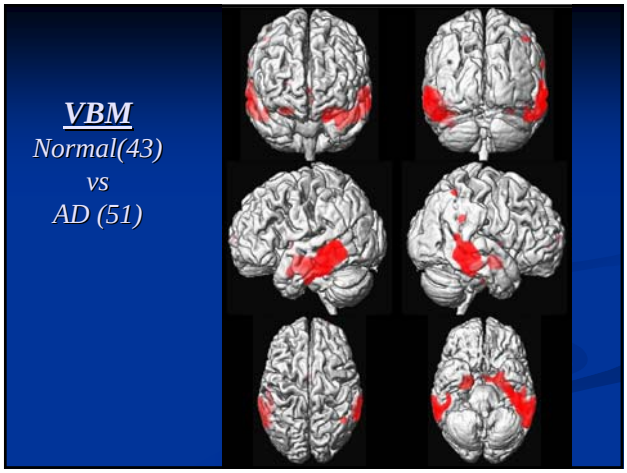


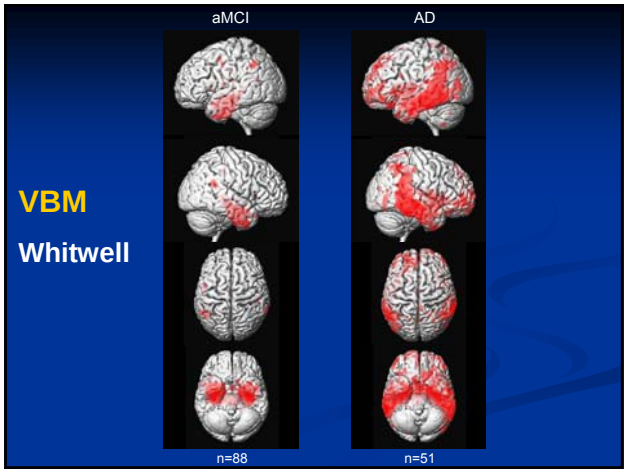
Boundary Shift Integral

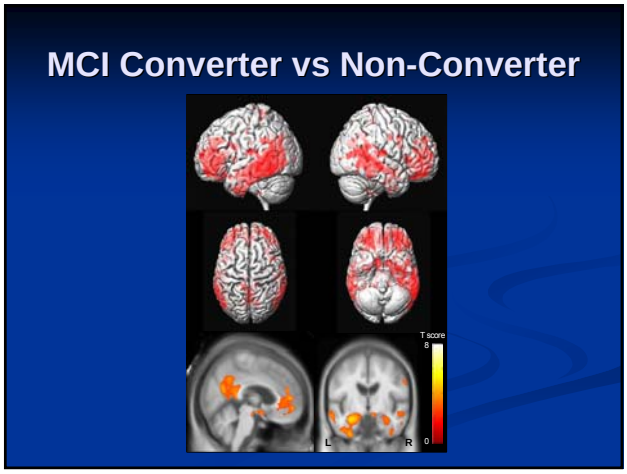


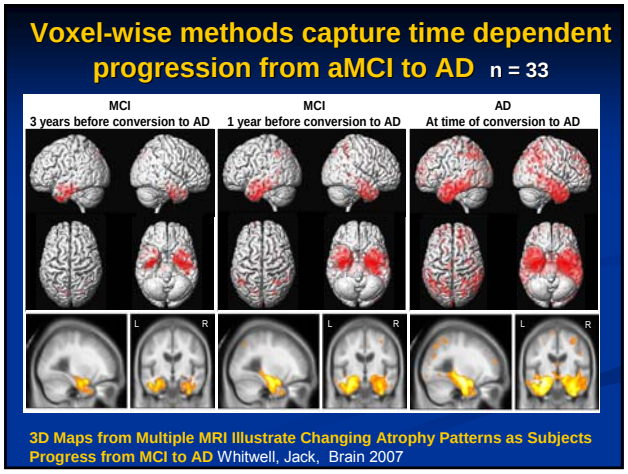
New Neuroimaging Research

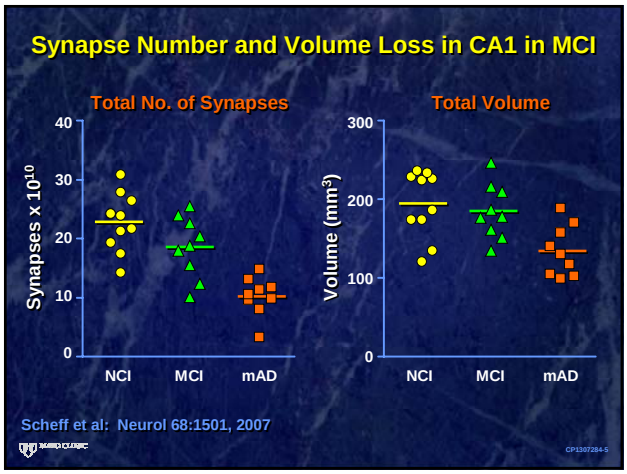
Voxel-based Morphometry



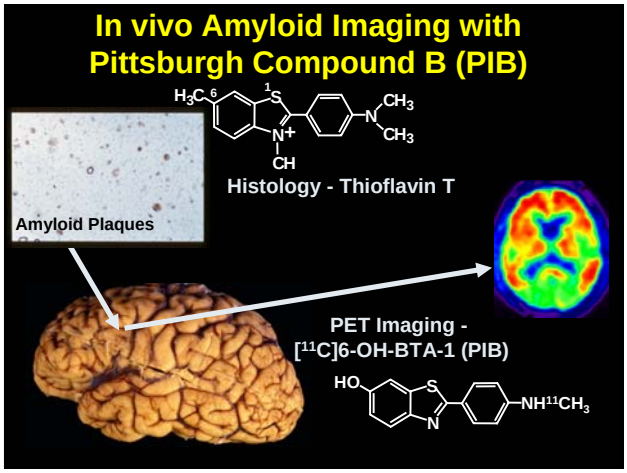


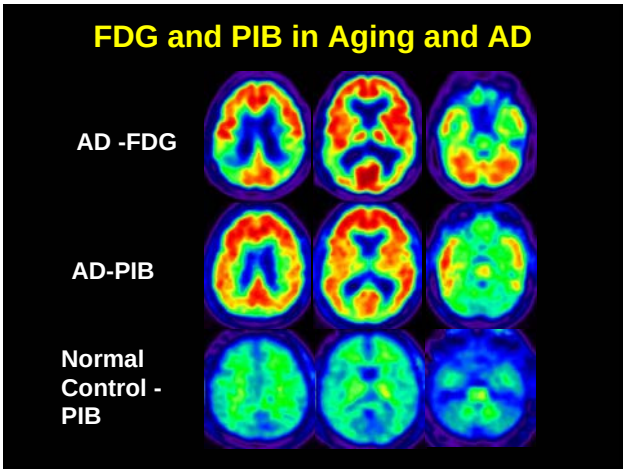


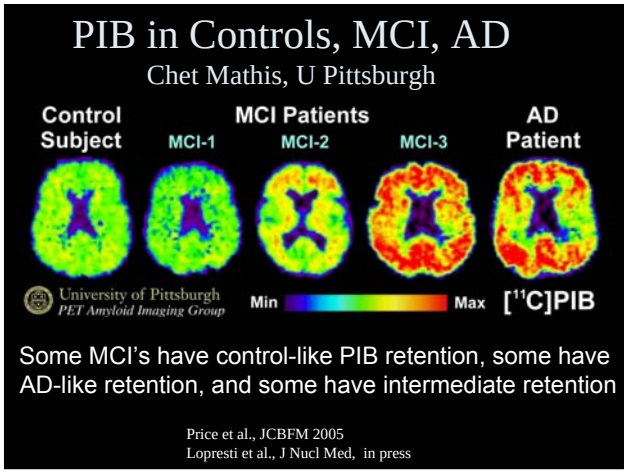


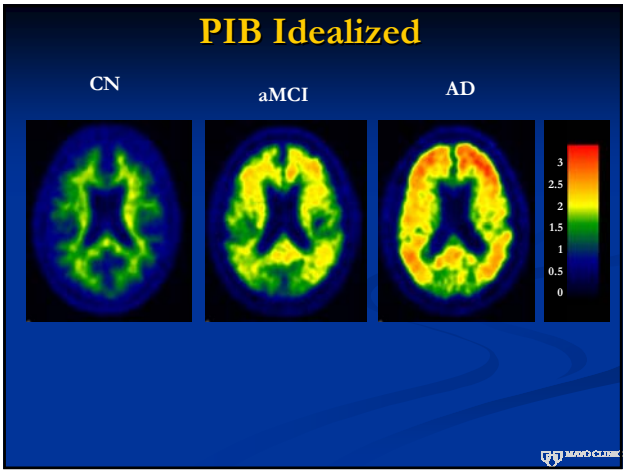


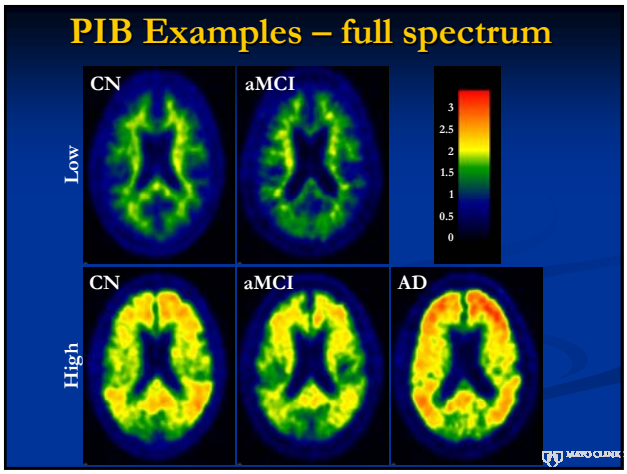
Molecular Neuroimaging



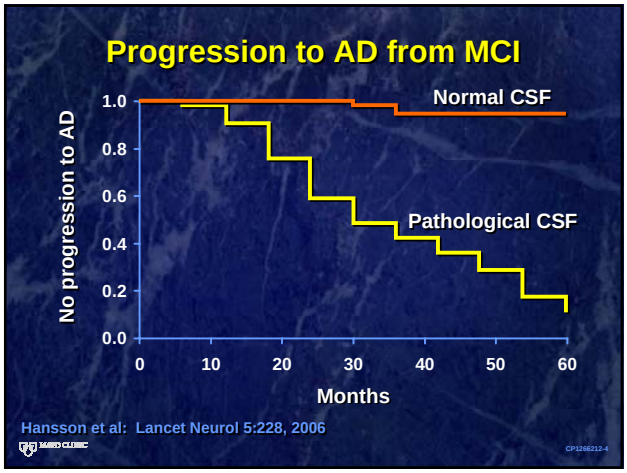


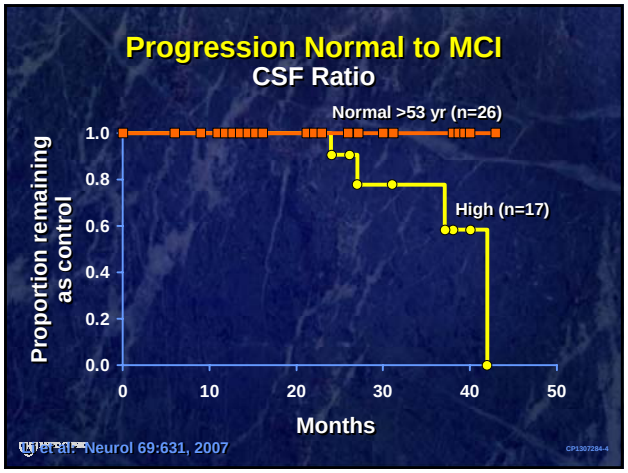


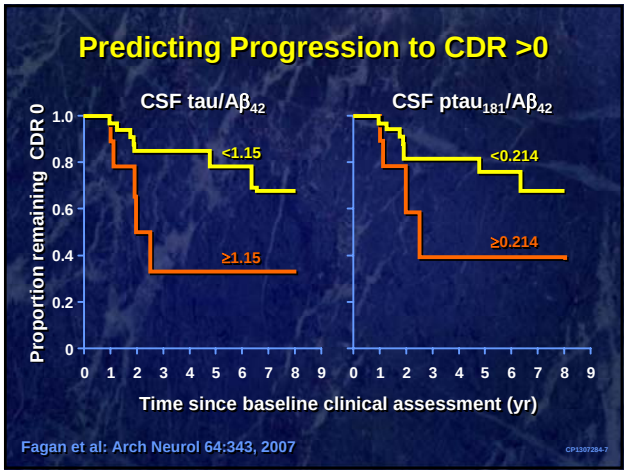




Cerebrospinal Fluid







Alzheimer's Disease Neuroimaging Initiative ADNI

ADNI

- Observational study of imaging and biomarkers
- Normals = 200
- MCI = 400
- AD = 200
- MRI, FDG PET, PiB, CSF, biomarkers
- 3 years

ADNI Demographics

	Normal controls (n=229)	MCI (n=398)	AD (n=192)	P
Age, mean (SD)	76.4 (5.0)	75.3 (7.5)	75.8 (7.4)	0.15
Female (%)	48.0	35.4	47.4	0.002
Years of education, mean (SD)	15.6 (3.1)	16.0 (2.9)	14.7 (3.1)	<0.001
Apolipoprotein E e4: Positive (%)	26.6	53.5	65.6	<0.001

CP1307278-1

ADNI Cognitive Function

	Normal (n=229)	MCI (n=398)	AD (n=192)
Estimated premorbid verbal IQ	119.8 (9.0)	116.2 (9.7)	113.6 (9.9)
Memory			
Auditory verbal learning			
Trials 1-5 correct	43.3 (9.09)	30.7 (9.03)	23.2 (7.70)
Delayed recall (%)	65.8 (27.6)	32.1 (31.4)	11.3 (21.9)
Language			
Boston Naming	27.9 (2.3)	25.5 (4.1)	22.3 (6.2)
Category fluency total	34.6 (8.1)	26.7 (7.5)	20.3 (7.5)
Executive function			
Trail A time	36.5 (13.2)	44.8 (22.8)	68.2 (36.8)
Trail B time	89.2 (44.3)	130.5 (73.5)	199.6 (86.8)
Digit symbol correct	45.7 (10.2)	36.9 (11.1)	26.7 (12.9)
Visuospatial ability			
Clock draw: Copy	4.86 (0.43)	4.65 (0.68)	4.31 (1.00)
Attention			
Digit span: Forward	8.78 (1.99)	8.22 (2.01)	7.54 (1.94)
Digit span: Backward	7.21 (2.16)	6.17 (2.2)	4.96 (1.83)

CP1307278-2

ADNI Cognitive Function

	Normal (n=229)	MCI (n=398)	AD (n=192)
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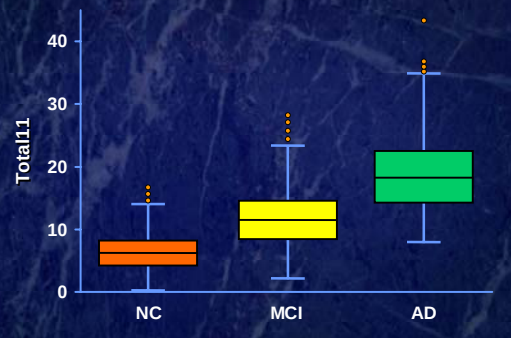
ADAS-Cog Baseline



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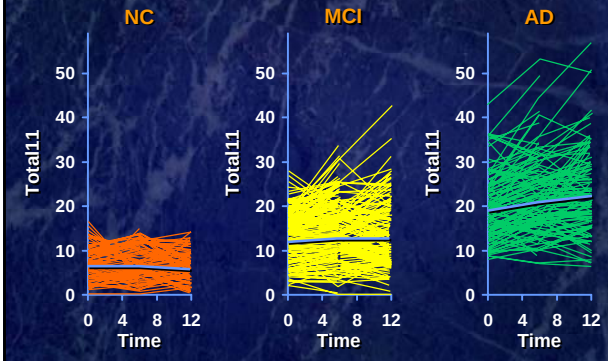
ADAS-Cog



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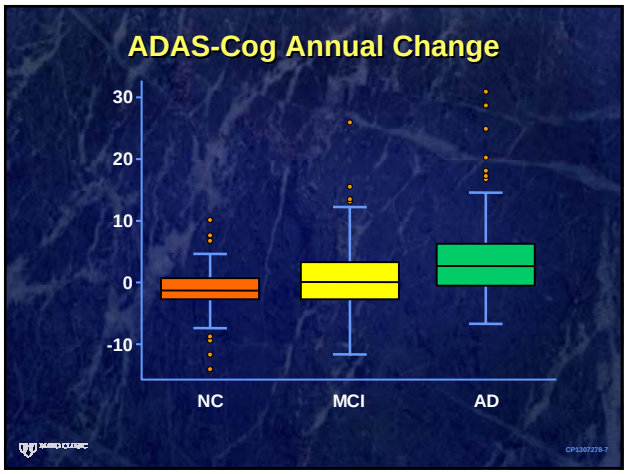
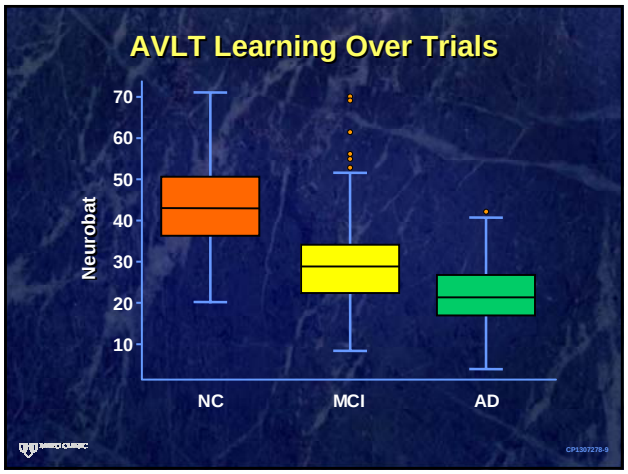
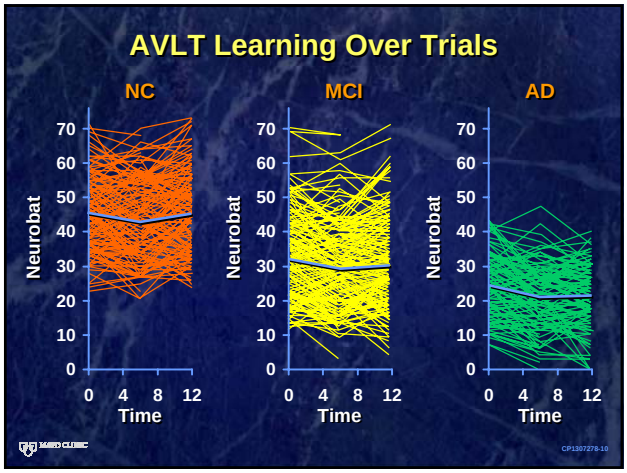
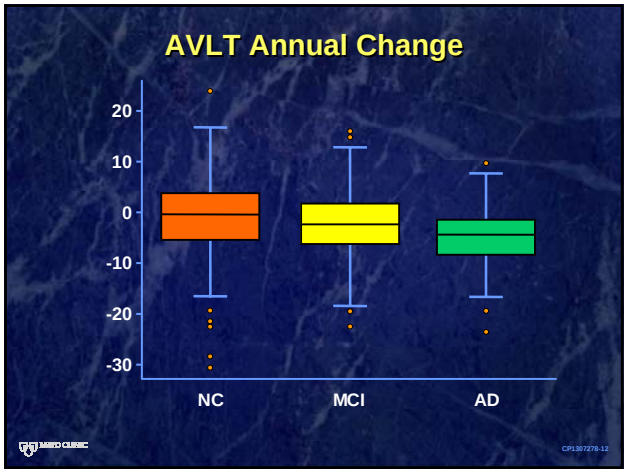
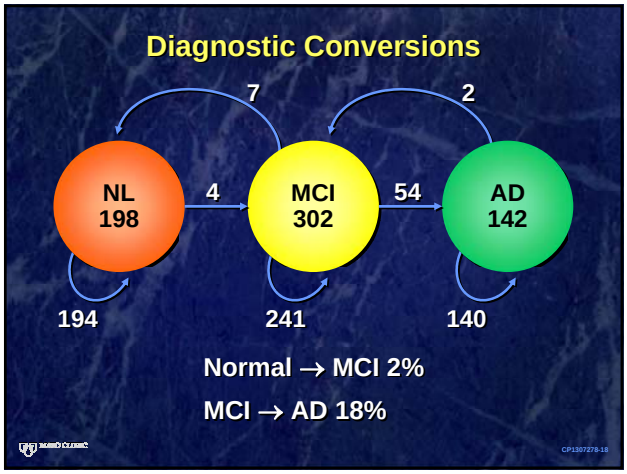










Amnestic MCI
Baseline Data

	ADCS	ADNI	UDS	MCSA
No.	259	398	2,128	241
Age	72.9 (7.6)	75.3 (7.5)	76.1 (9.6)	82.0 (5.2)
Educ	14.7 (3.1)	16.0 (2.9)	14.5 (3.5)	13.1 (3.5)
MMSE	27.3 (1.8)	27.0 (1.8)	26.9 (2.7)	25.4 (2.5)
CDR, SoB	1.9 (0.8)	1.6 (0.9)	1.4 (1.2)	0.9 (1.0)
ADAS-Cog	11.0 (4.2)	11.5 (4.4)	–	–

Amnestic MCI
First 12-Month Change

	ADCS	ADNI	UDS	MCSA
MMSE	-0.8 (2.3)	-1.0 (2.0)	-0.6 (2.8)	-0.1 (3.1)
CDR, SoB	+0.4 (1.3)	+0.7 (1.3)	+0.5 (1.4)	+0.4 (1.1)
ADA-Cog	+0.6 (4.1)	+1.0 (4.5)	–	–

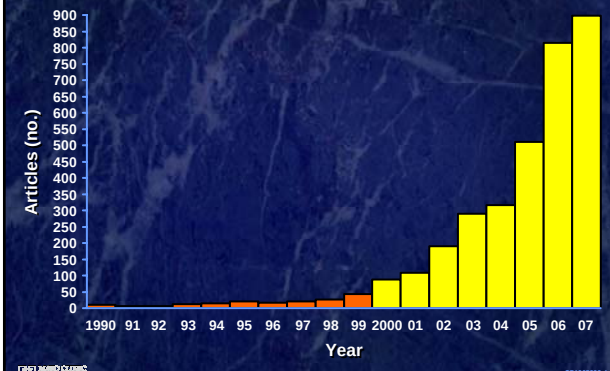
Breadth of MCI Research

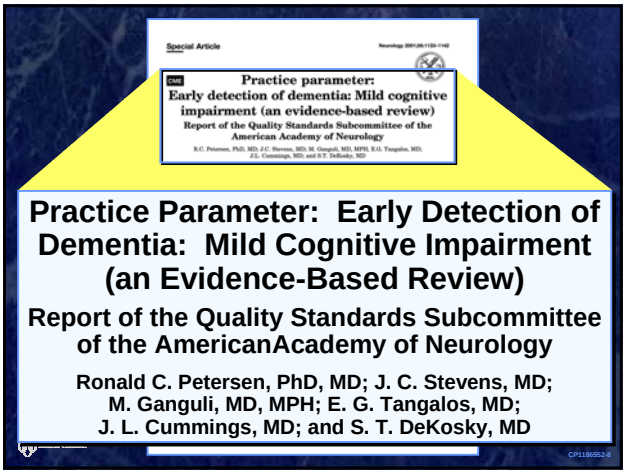
- Epidemiology
- Clinical
- Imaging
- Biomarkers
- Mechanism of disease
- Neuropathology
- Clinical trials

AAN PRACTICE PARAMETER DETECTION SUMMARY RECOMMENDATIONS

- GUIDELINE
  - PATIENTS WITH A MILD COGNITIVE IMPAIRMENT SHOULD BE RECOGNIZED AND MONITORED FOR A COGNITIVE AND FUNCTIONAL DECLINE DUE TO THEIR INCREASED RISK FOR SUBSEQUENT DEMENTIA

Publications on MCI





Mild Cognitive Impairment Should Be Considered for *DSM-V*

Ronald C. Petersen, PhD, MD, and John O'Brien, DM

ABSTRACT

Mild cognitive impairment is a topic of great activity from both clinical and research perspectives. It represents a transitional state between the cognitive changes of aging and the earliest clinical manifestations of dementia. We present a case for its inclusion in the *Diagnostic and Statistical Manual of Mental Disorders* (5th ed; *DSM-V*) based on clinical, outcome, epidemiological, neuroimaging, and pathophysiological data. The strongest case for inclusion can be made for the amnestic subtype, which is likely a clinical precursor of Alzheimer's disease. Arguments are presented as to why mild cognitive impairment can be considered as an entity distinct from normal aging and from clinically probable Alzheimer's disease and why it deserves consideration as a separate construct. In many respects, mild cognitive impairment fulfills criteria for inclusion more adequately than many other conditions currently codified in *DSM-IV*. Future research directions to help clarify some of the remaining uncertainties are proposed. (*J Geriatr Psychiatry Neurol* 2006;19:147-154)

Keywords: mild cognitive impairment; Alzheimer's disease; dementia; *DSM-V*

Petersen and O'Brien: J Geriat Psych and Neurol 19:147, 2006

CP1266212-9

So, is MCI too late?

EDITORIAL

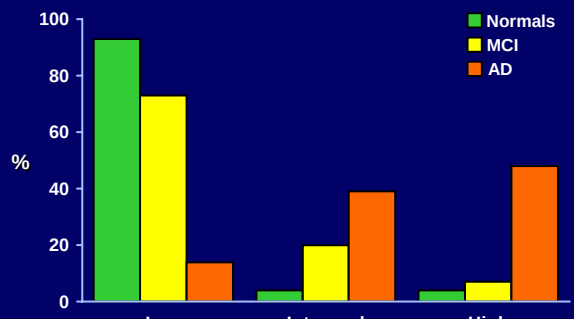
Is amnestic mild cognitive impairment always AD?

William Jagust, MD

Jagust: Neurol 70:502, 2008

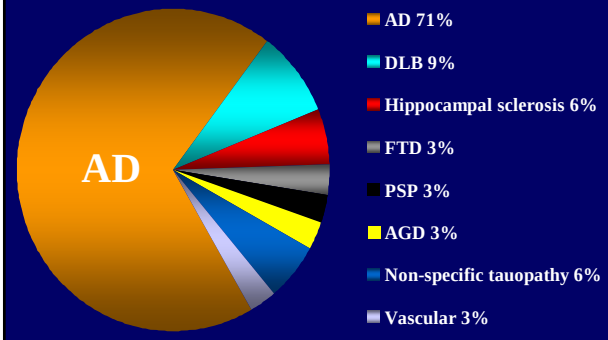
CP1307284-1

NIA-REAGAN



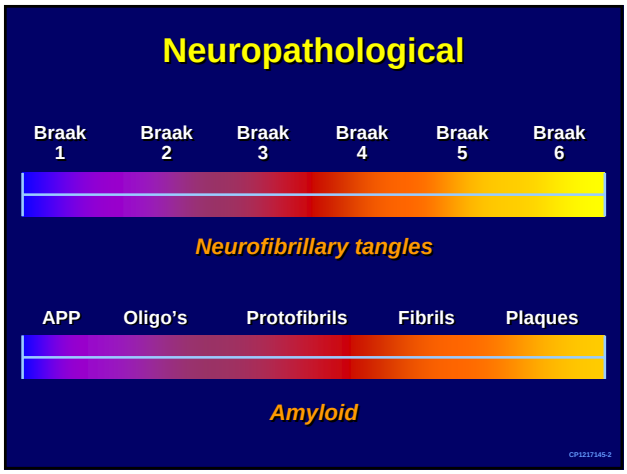
CP1183543-12

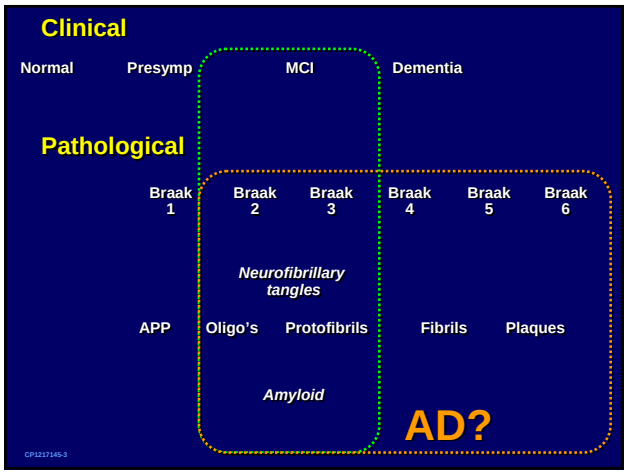
Pathological Outcome of MCI

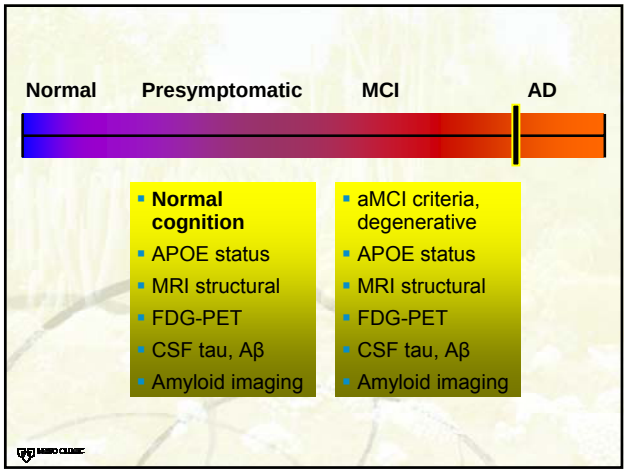


Clinical

CP1217145-1







MCI SUMMARY

- USEFUL CONCEPT
- CRITERIA AVAILABLE
  - CLINICIAN INVOLVED
  - ALOGORITHM
- OUTCOME DEPENDENT
- NEUROPATH TRANSITIONAL
- CLINICAL TRIALS FEASIBLE

MAYO ALZHEIMER'S DISEASE RESEARCH CENTER

- **Rochester**
  - Brad Boeve
  - David Knopman
  - Eric Tangalos
  - Joe Parisi
  - Cliff Jack
  - Walter Rocca
  - Bob Ivnik
  - Glenn Smith
  - Rosebud Roberts
  - Shane Pankratz
  - Yonas Geda
- **Jacksonville**
  - Steve Younkin
  - Dennis Dickson
  - Neill Graff-Radford
  - Shu-Hui Yen
  - Todd Golde
  - Mike Hutton
  - John Lucas
  - Tanis Ferman
  - Floyd Willis

mayo