Overview of Alzheimer's Disease and Related Dementias

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NAPA Advisory Council
Washington
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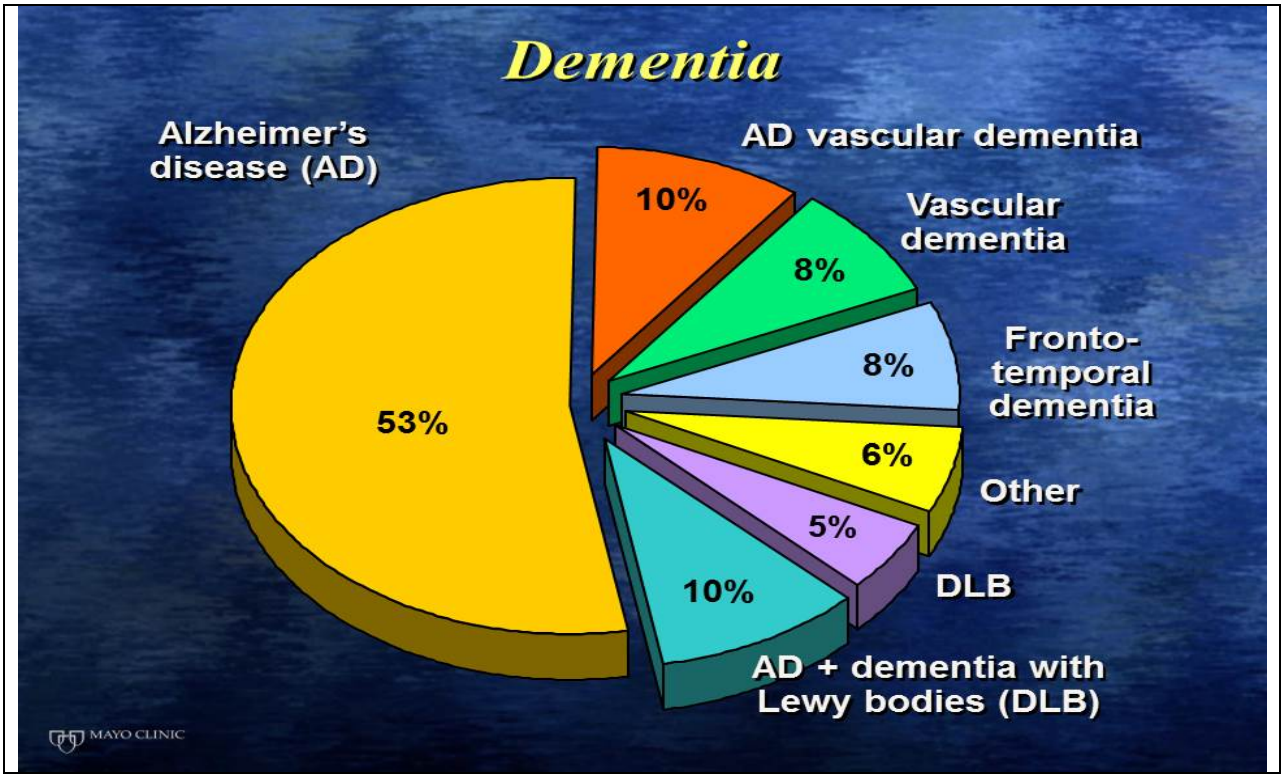

AD Related Dementias

- Frontotemporal lobar degeneration
- Dementia with Lewy bodies
- Vascular cognitive impairment-dementia

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ALZHEIMER'S DISEASE

- Degenerative etiology
- Gradual progression
- Basic neurological exam normal early
- Clinical-pathology correlation 80-90%

Criteria for AD

National Institute on Aging

Alzheimer's Association

Alzheimers and Dementia, May, 2011

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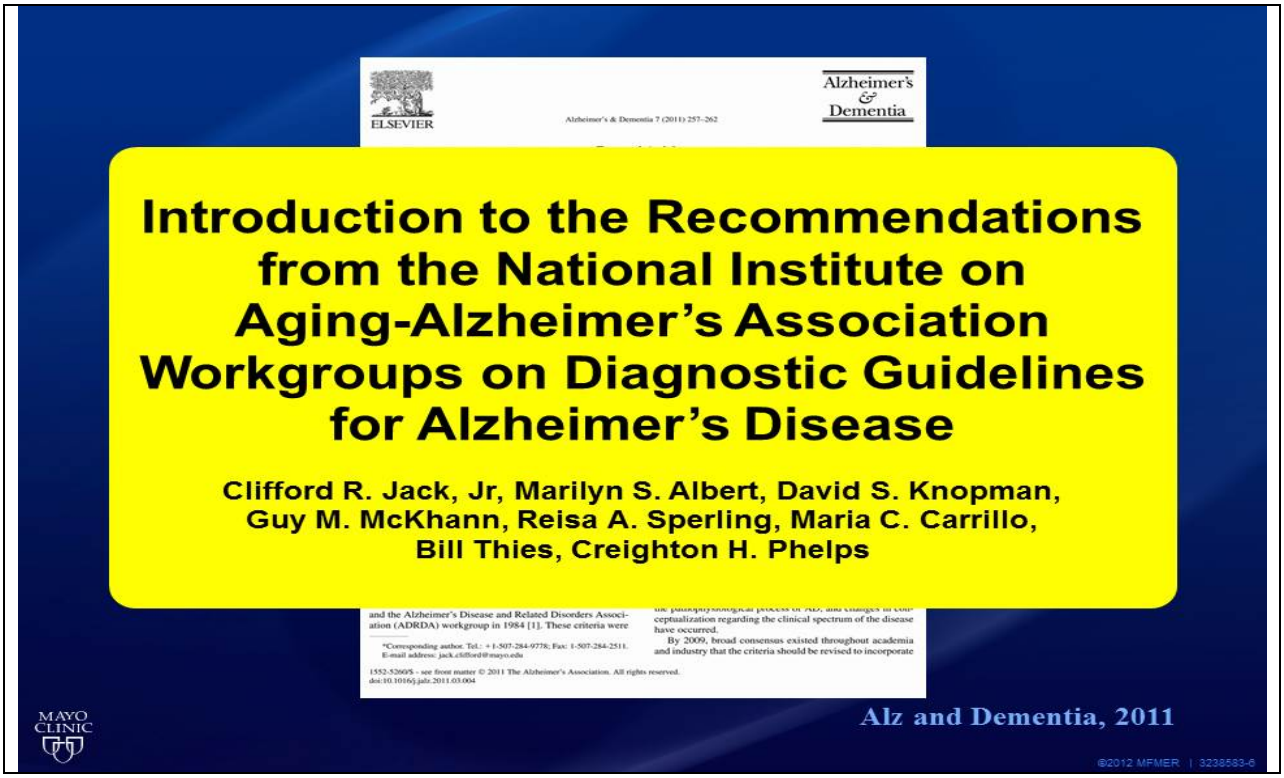

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Alz and Dementia, 2011

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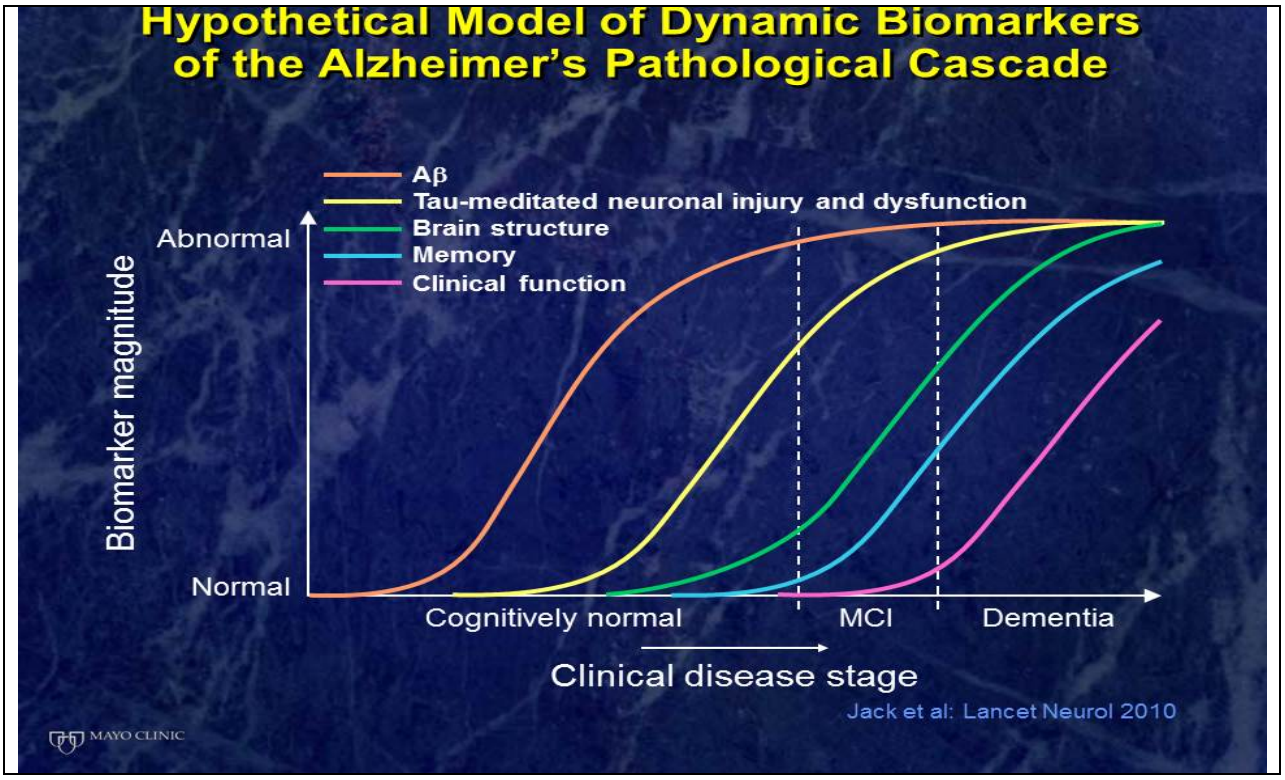
Hypothetical Model of Dynamic Biomarkers of the Alzheimer's Pathological Cascade
Aβ
Tau-meditated neuronal injury and dysfunction
Brain structure
Memory
Clinical function
Abnormal
Normal
Biomarker magnitude
Cognitively normal
MCI
Dementia
Clinical disease stage
Jack et al: Lancet Neurol 2010
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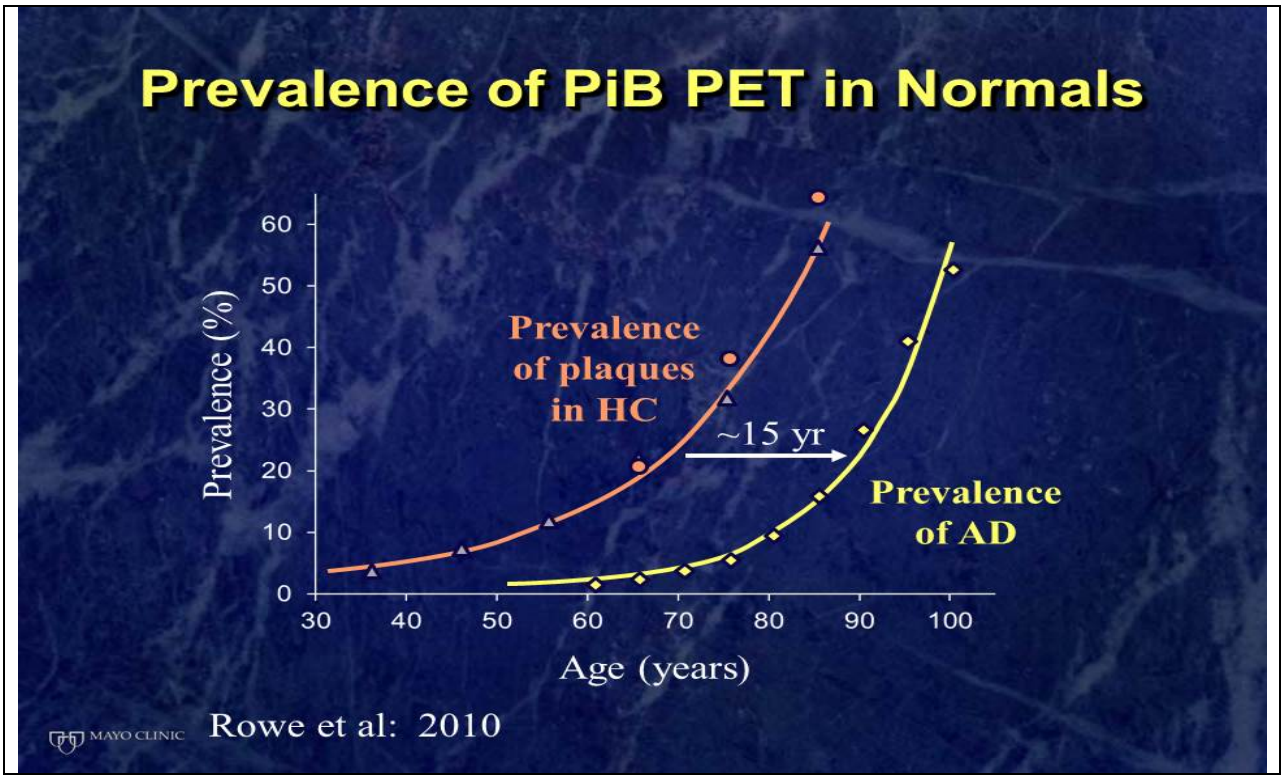
Prevalence of PiB PET in Normals
Prevalence (%)
60
50
40
30
20
10
0
30
40
50
60
70
80
90
100
Age (years)
Prevalence of plaques in HC
~15 yr
Prevalence of AD
Rowe et al: 2010
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Biomarkers for AD

- Early biomarkers
  - Amyloid deposition
    - PET imaging
    - CSF amyloid
- Later biomarkers
  - Neurodegeneration
    - Structural MRI
    - FDG PET
    - Tau PET
    - CSF tau

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Neuroimaging in AD

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Neuroimaging in AD

- Structural MRI
- Functional imaging
  FDG PET
- Molecular imaging
  Amyloid PET imaging

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Structural Imaging in AD

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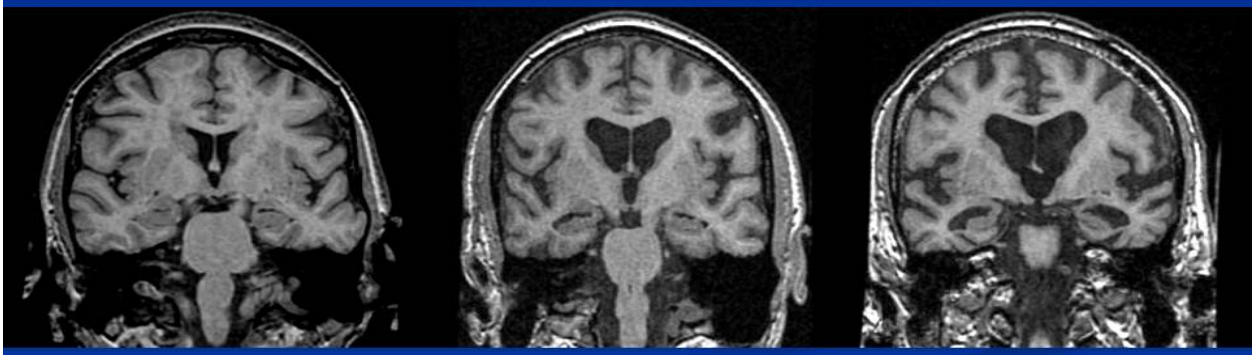
Structural MRI: Atrophy and AD Stage

Control, 70, F | MCI, 72, F | AD, 74, F



Functional Imaging in AD

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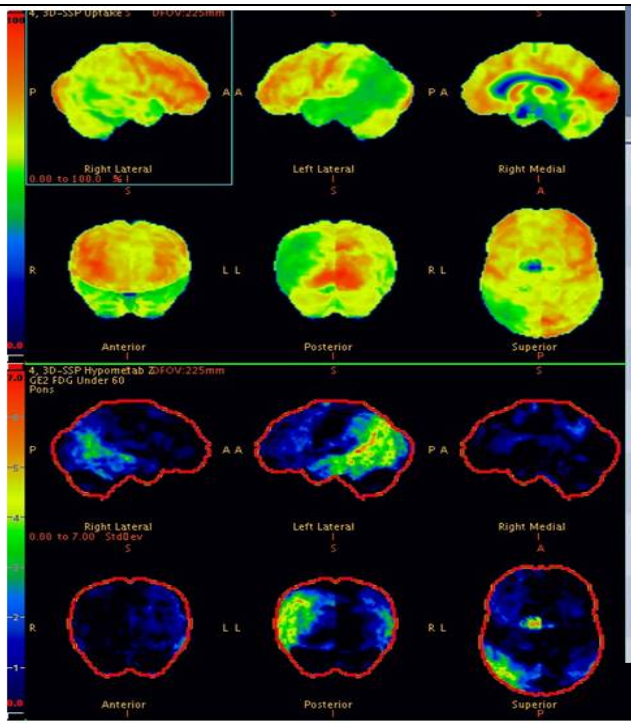
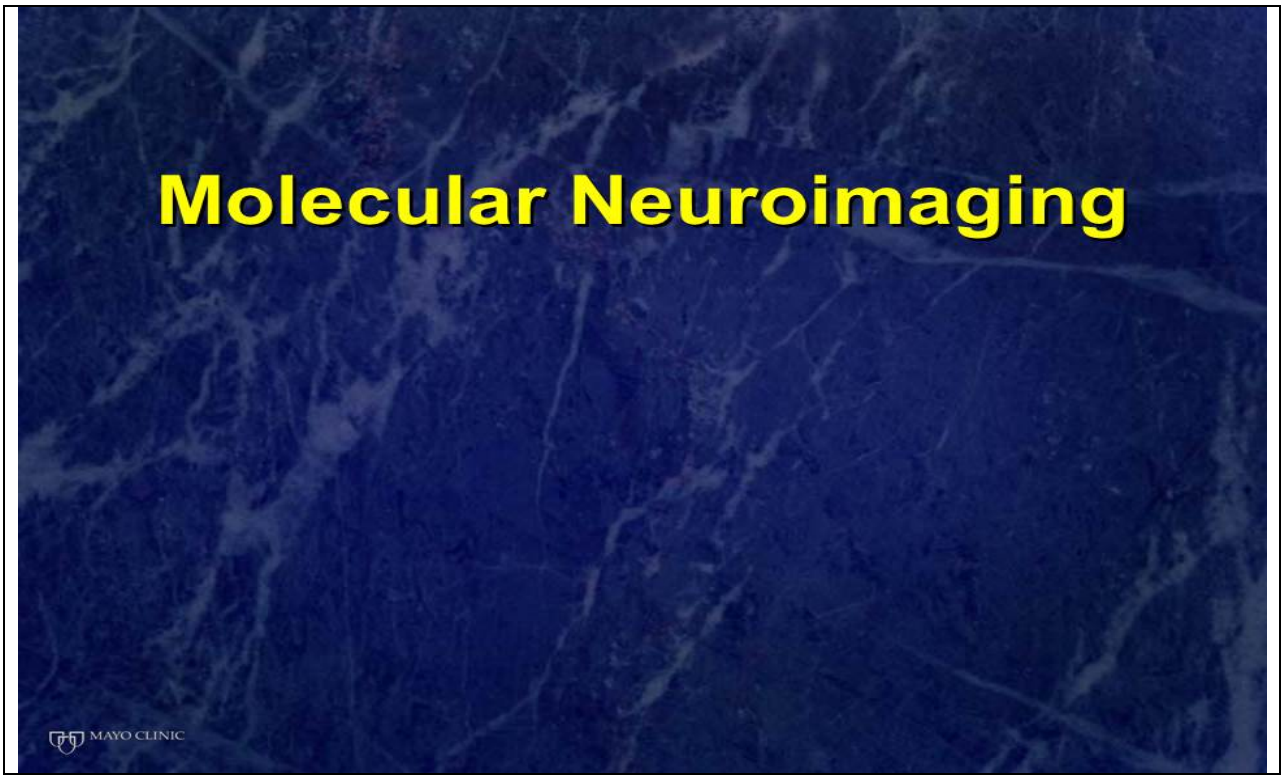


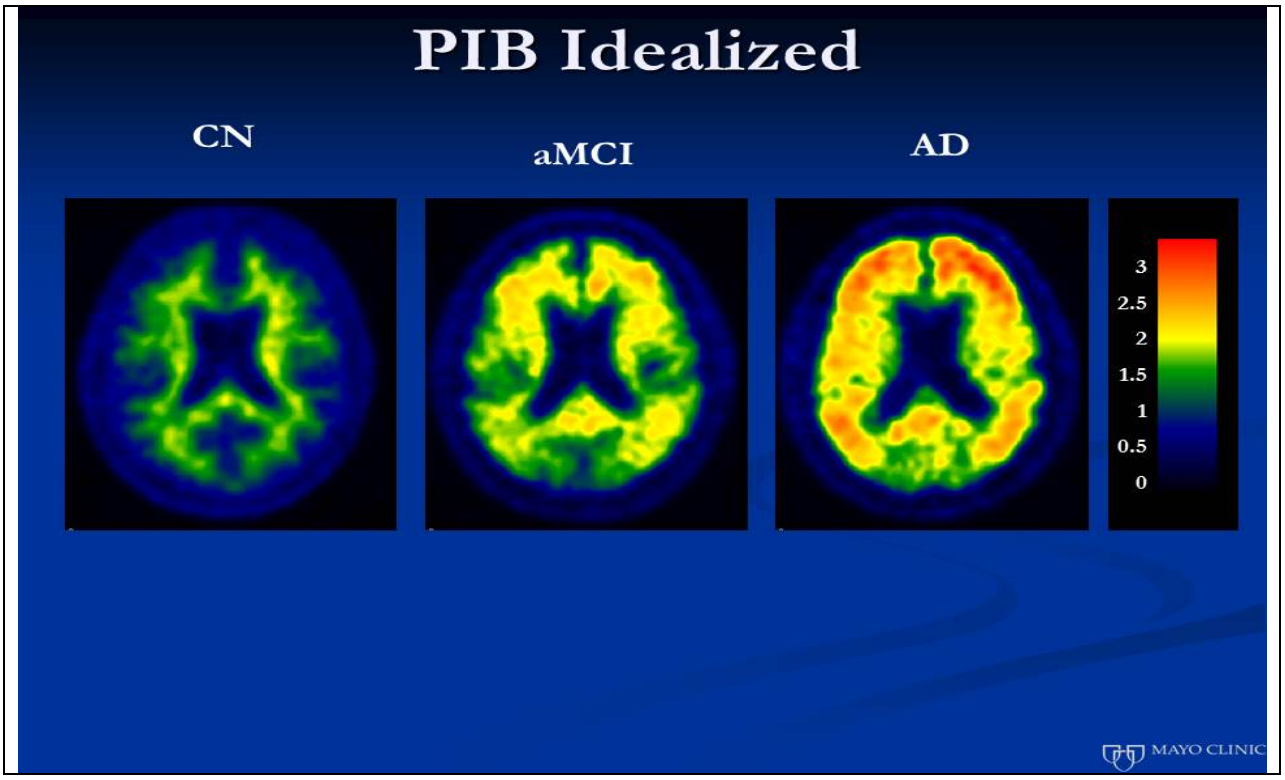
(Z-Score)

Normals File: GE2 FDG Under 60

Normalized By: Pons

Cortical Regions	R/L	Mean
Parietal Association	R	0.91
	L	2.84
Temporal Association	R	1.41
	L	2.72
Frontal Association	R	-0.19
	L	0.75
Occipital Association	R	0.72
	L	2.55
Posterior Cingulate	R	0.09
	L	0.38
Anterior Cingulate	R	0.05
	L	0.10
Medial Frontal	R	-0.17
	L	0.57
Medial Parietal	R	0.17
	L	1.35
Sensorimotor	R	-0.45




PIB Idealized
CN
aMCI
AD
3
2.5
2
1.5
1
0.5
0
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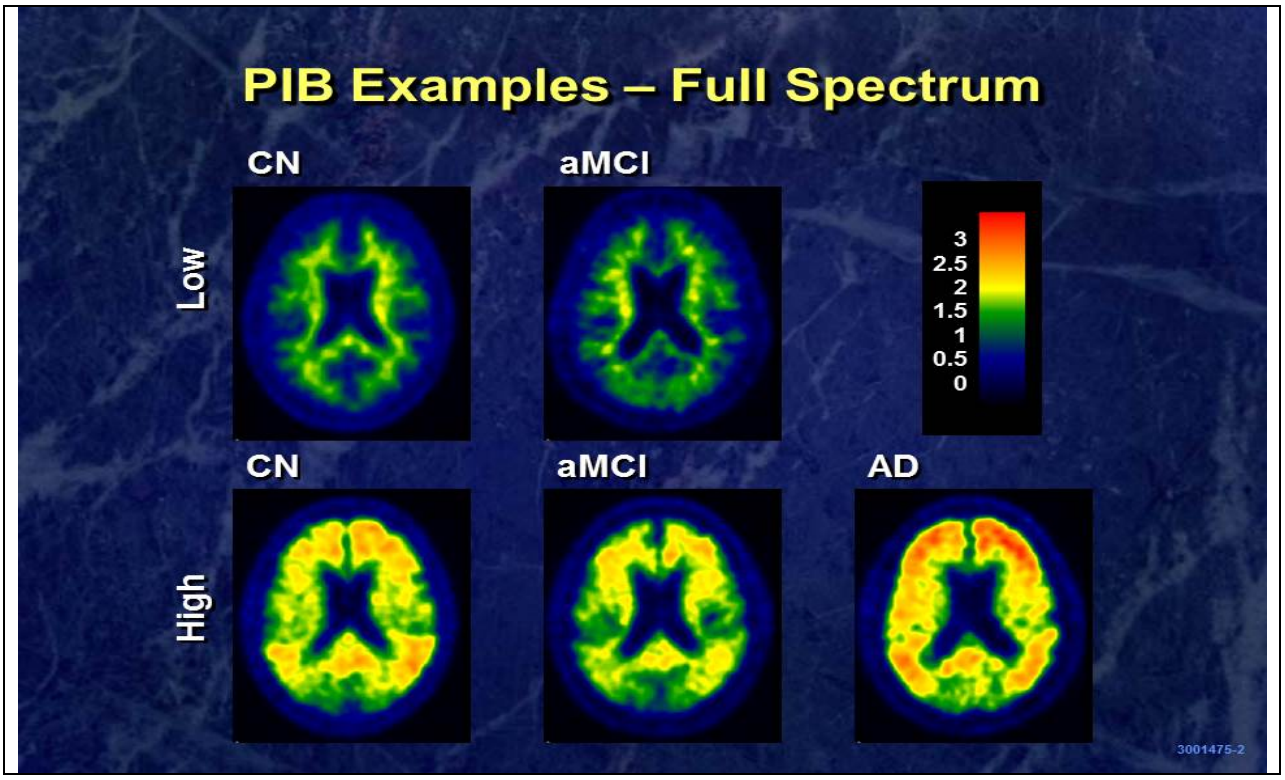
PIB Examples – Full Spectrum
CN
aMCI
Low
3
2.5
2
1.5
1
0.5
0
CN
aMCI
AD
High
3001475-2

Tau PET Imaging

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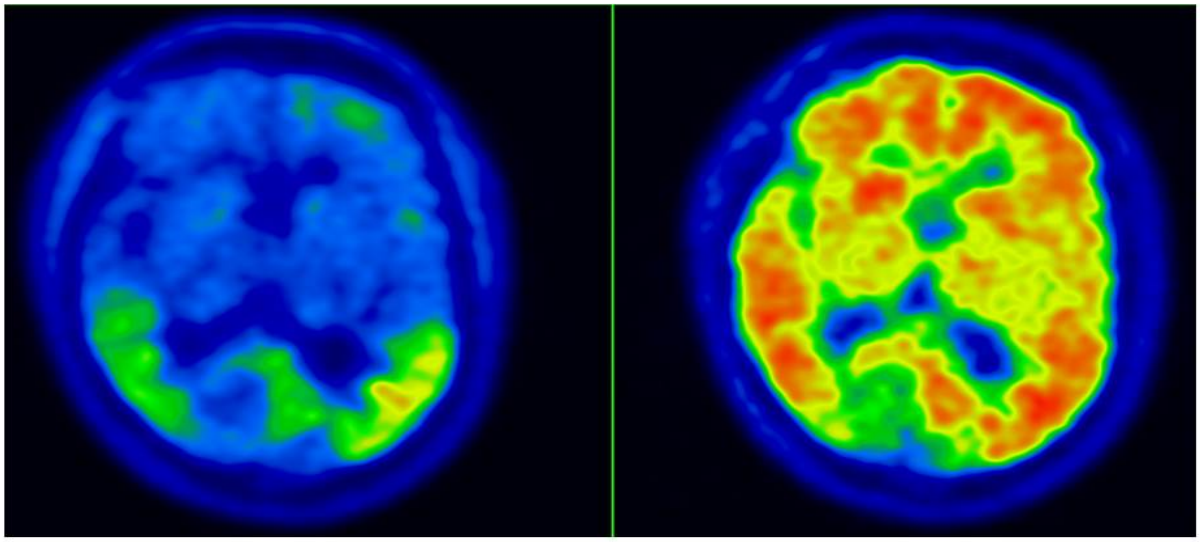

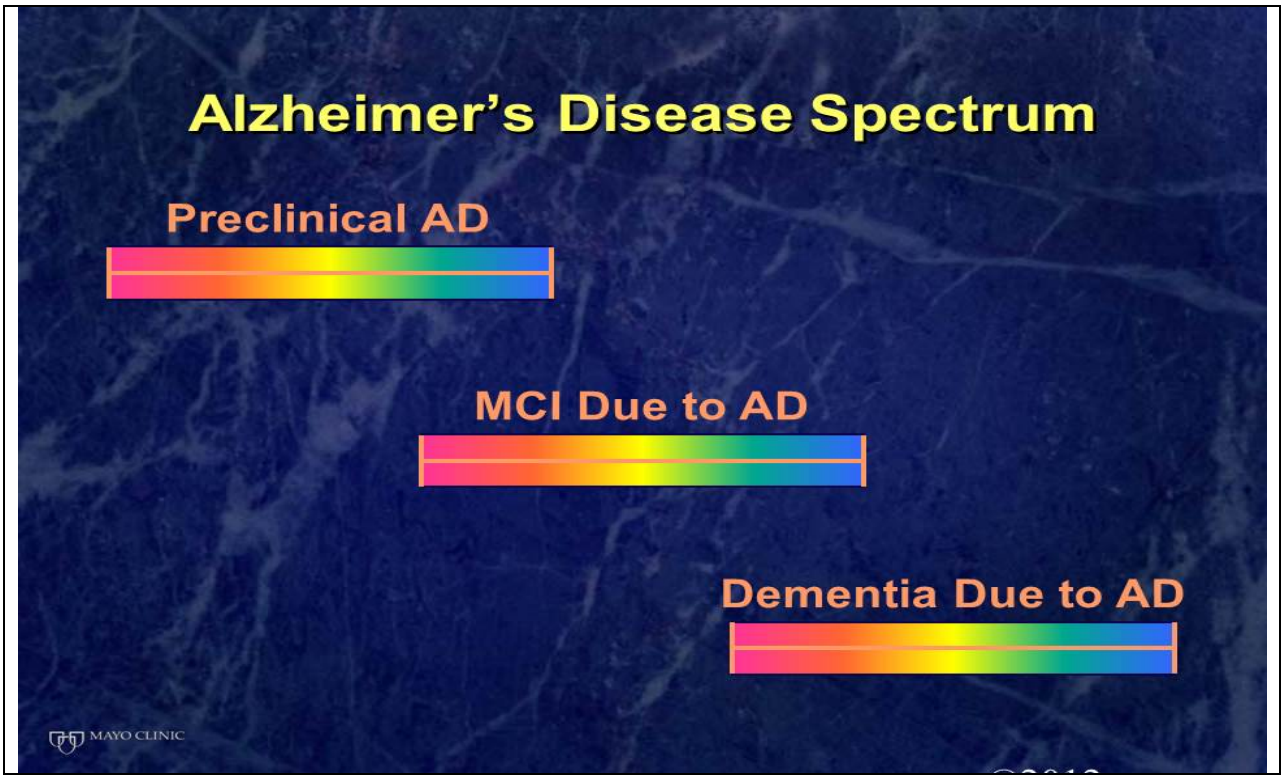
Alzheimer's Disease Spectrum
Preclinical AD
MCI Due to AD
Dementia Due to AD
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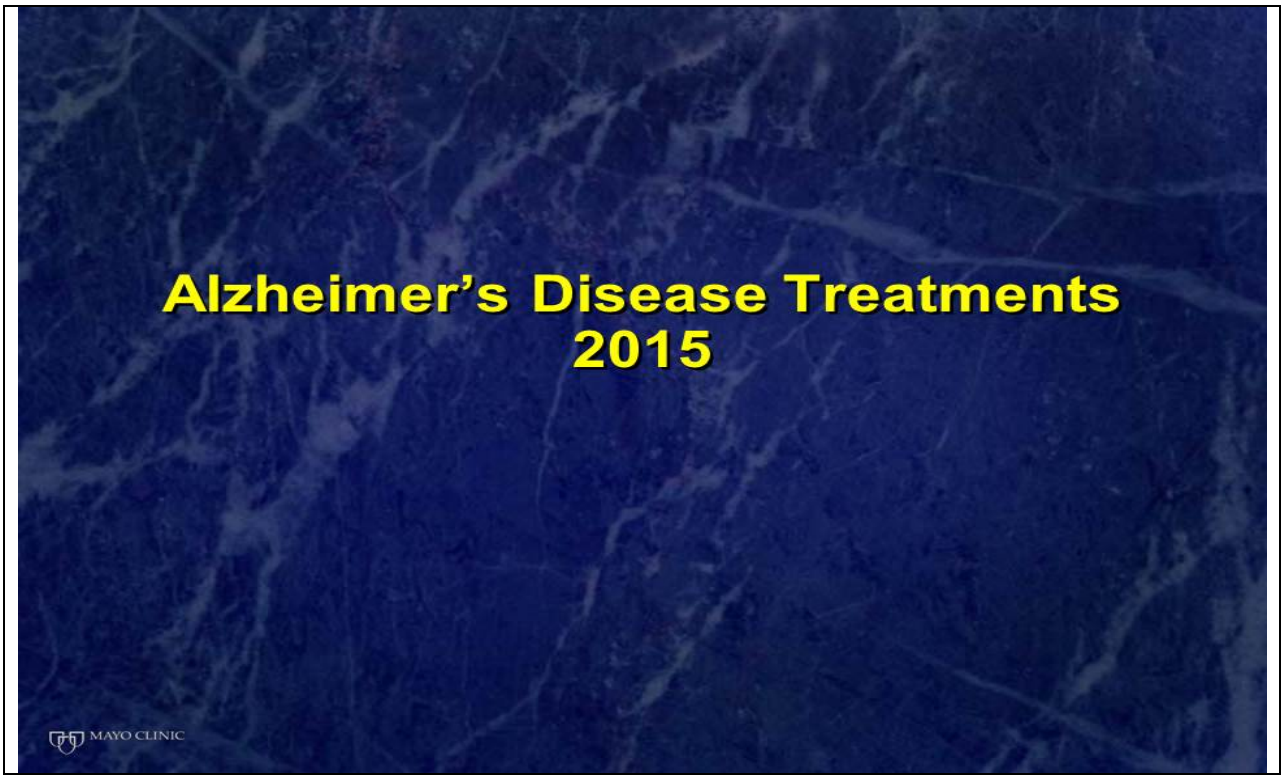
Alzheimer's Disease Treatments
2015
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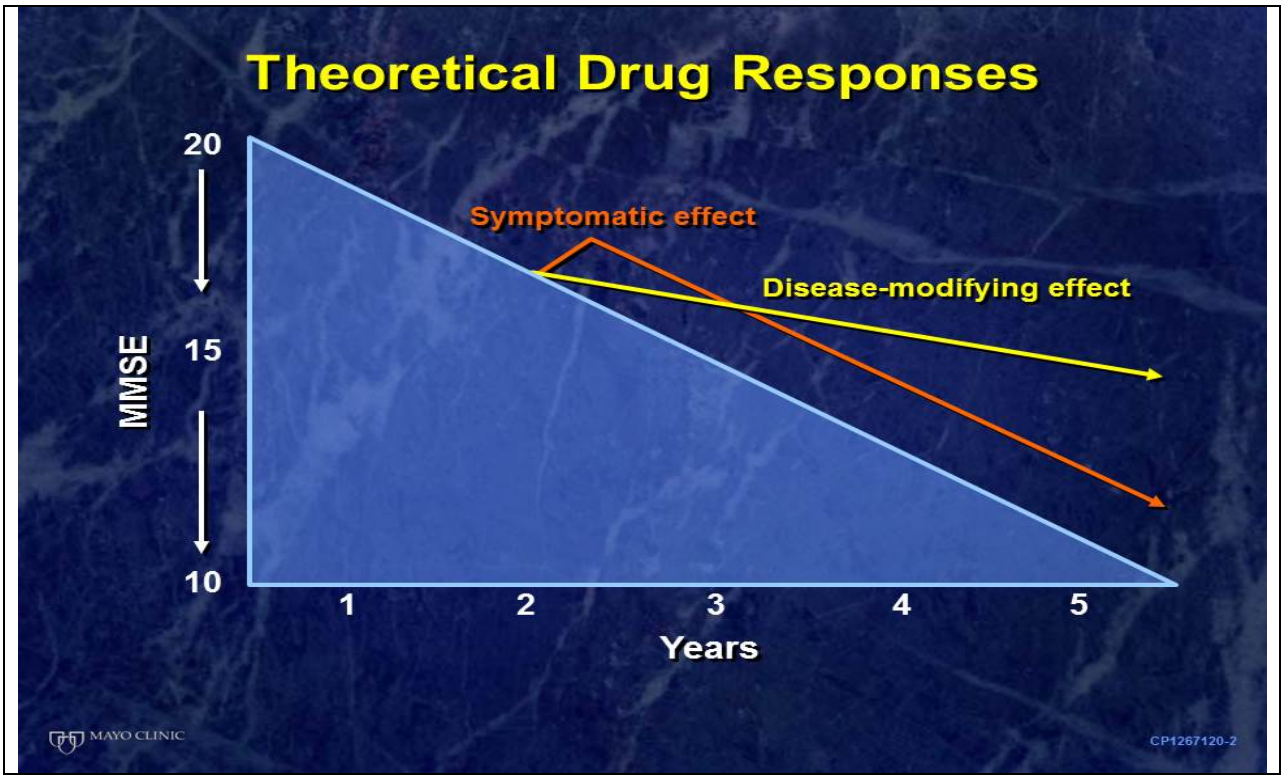
Theoretical Drug Responses
20
15
10
MMSE
Symptomatic effect
Disease-modifying effect
1
2
3
4
5
Years
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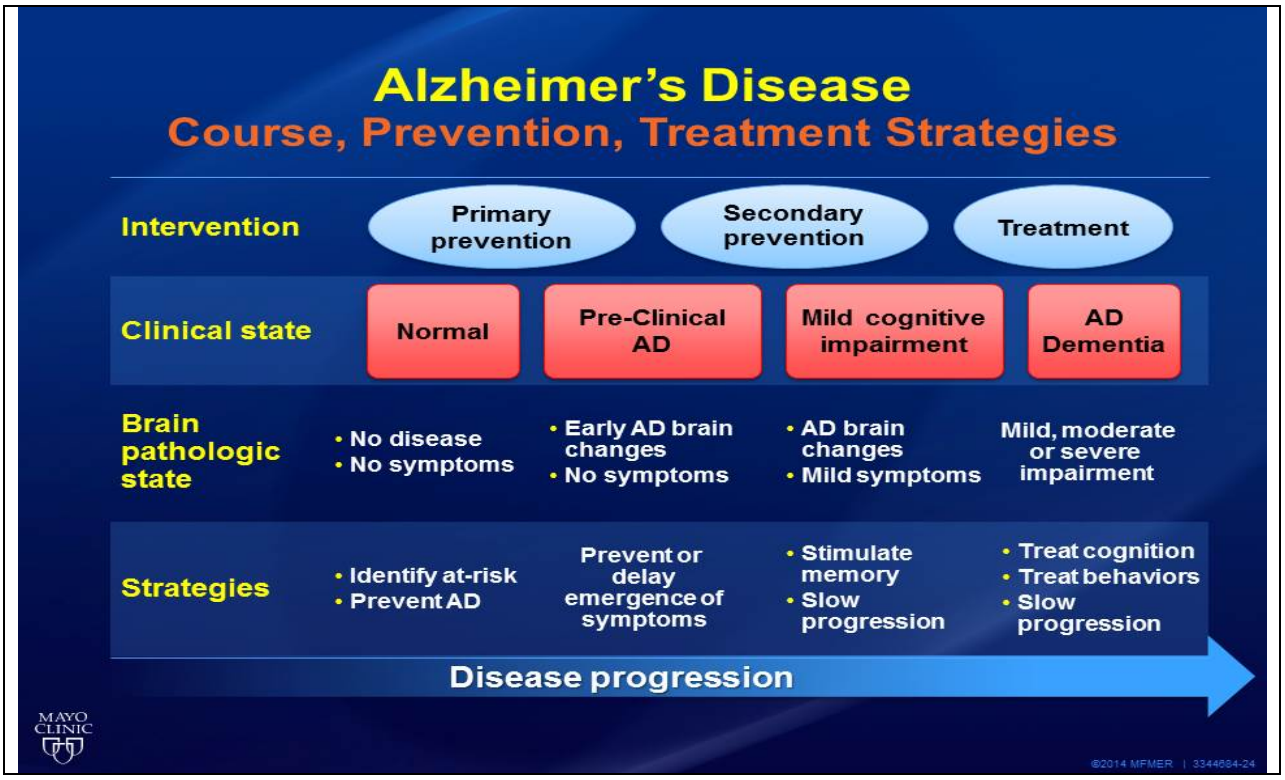
Alzheimer's Disease
Course, Prevention, Treatment Strategies
Intervention
Primary prevention
Secondary prevention
Treatment
Clinical state
Normal
Pre-Clinical AD
Mild cognitive impairment
AD Dementia
Brain pathologic state
• No disease
• No symptoms
• Early AD brain changes
• No symptoms
• AD brain changes
• Mild symptoms
Mild, moderate or severe impairment
Strategies
• Identify at-risk
• Prevent AD
Prevent or delay emergence of symptoms
• Stimulate memory
• Slow progression
• Treat cognition
• Treat behaviors
• Slow progression
Disease progression
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SYMPTOM MODIFYING AGENTS

AD TREATMENTS

- CHOLINESTERASE DRUGS
  - DONEPEZIL (ARICEPT)
  - RIVASTIGMINE (EXELON)
  - GALANTAMINE (RAZADYNE)
- NMDA ANTAGONIST
  - MEMANTINE (NAMENDA)

Immunotherapy

- Passive immunization
  - Polyclonal antibodies
    - IVIG
  - Monoclonal antibodies
    - bapineuzumab
    - solanezumab
    - crenezumab
    - gantenerumab
    - aducanumab

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Secretase Inhibition

- Beta secretase inhibitors
  - Promising
- Gamma secretase inhibitors
  - Challenges

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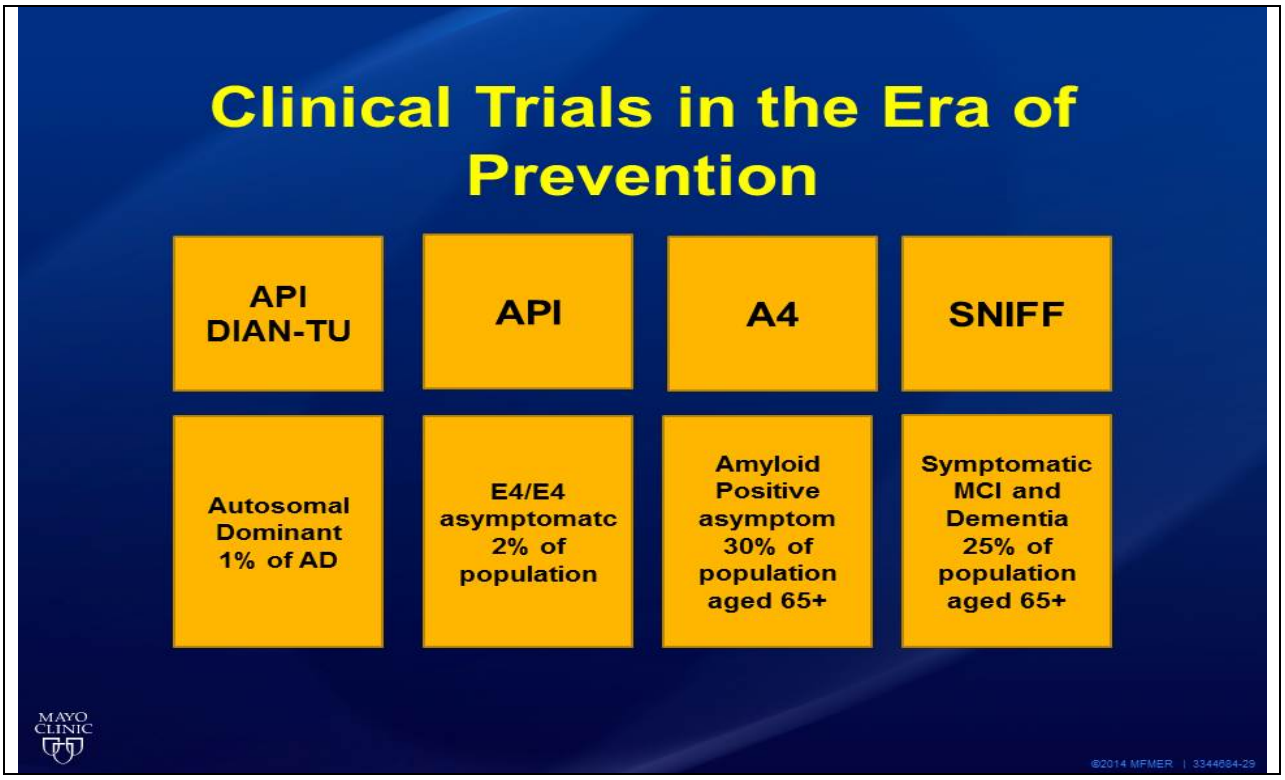
Clinical Trials in the Era of Prevention
API DIAN-TU
API
A4
SNIFF
Autosomal Dominant 1% of AD
E4/E4 asymptomatc 2% of population
Amyloid Positive asymptom 30% of population aged 65+
Symptomatic MCI and Dementia 25% of population aged 65+
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Lifestyle Modifications
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Effect of Physical Activity on Cognitive Function

JAMA®

Online article and related content current as of September 2, 2008.

Effect of Physical Activity on Cognitive Function in Older Adults at Risk for Alzheimer Disease: A Randomized Trial

Nicola T. Lautenschlager; Kay L. Cox; Leon Flicker; et al.

JAMA. 2008;300(9):1027-1037 (doi:10.1001/jama.300.9.1027)

Conclusions

- Moderate exercise (150 minutes/wk) resulted in improved cognitive function at 6 months
- Some benefits maintained at 18 mos

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So, where are we?

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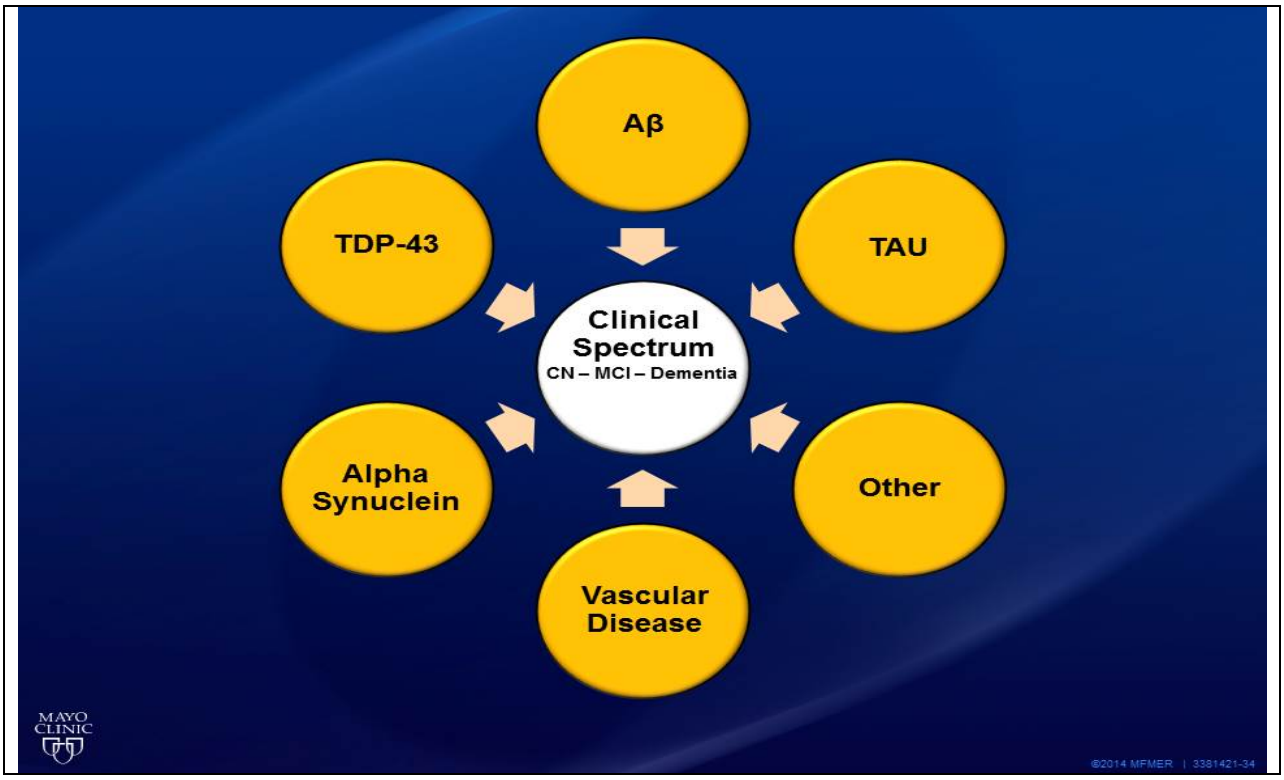

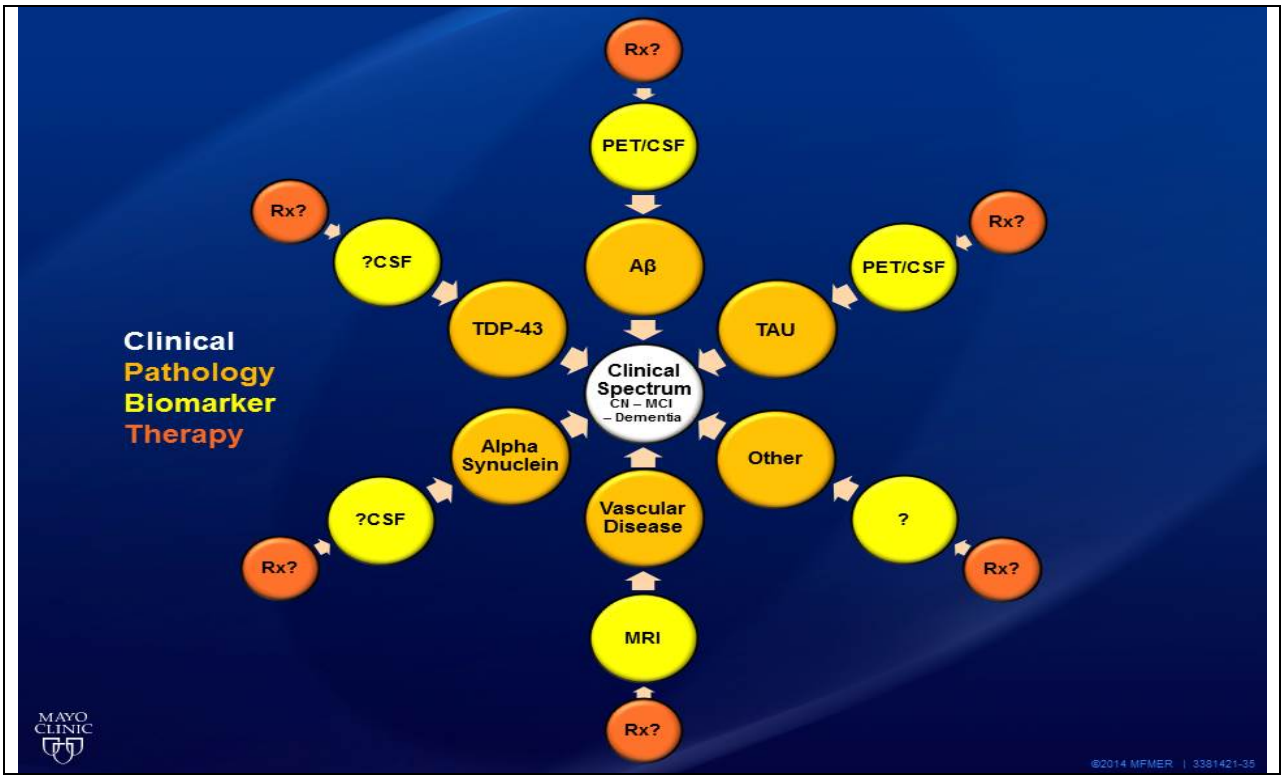
Rx?
PET/CSF
Rx?
?CSF
Aβ
PET/CSF
Rx?
TDP-43
TAU
Clinical
Pathology
Biomarker
Therapy
Clinical Spectrum
CN – MCI – Dementia
Alpha Synuclein
Other
?CSF
Vascular Disease
?
Rx?
Rx?
MRI
Rx?
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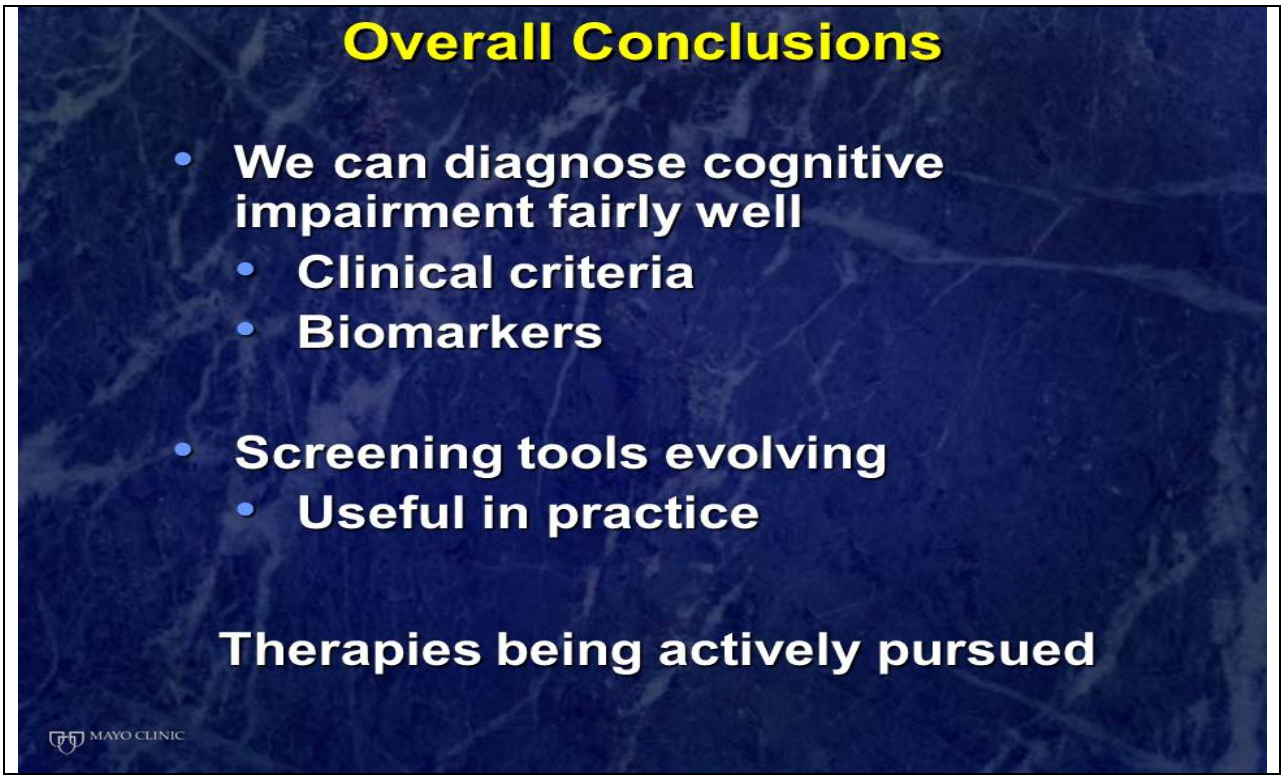
Overall Conclusions
We can diagnose cognitive impairment fairly well
Clinical criteria
Biomarkers
Screening tools evolving
Useful in practice
Therapies being actively pursued
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Thank You
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