Mild Cognitive Impairment
A Construct in Evolution

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  - U01 AG024904
  - U24 AG057437
  - R01 AG011378
  - UF1 NS125417
  - Alzheimer's Association
  - GHR Foundation
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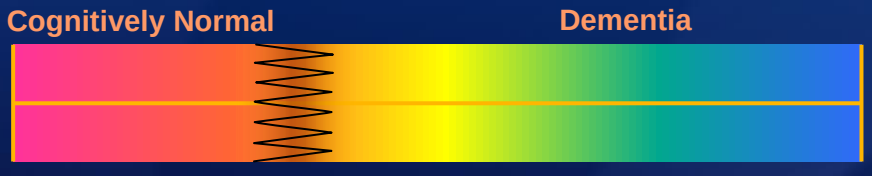
Old Conception of Alzheimer's Disease



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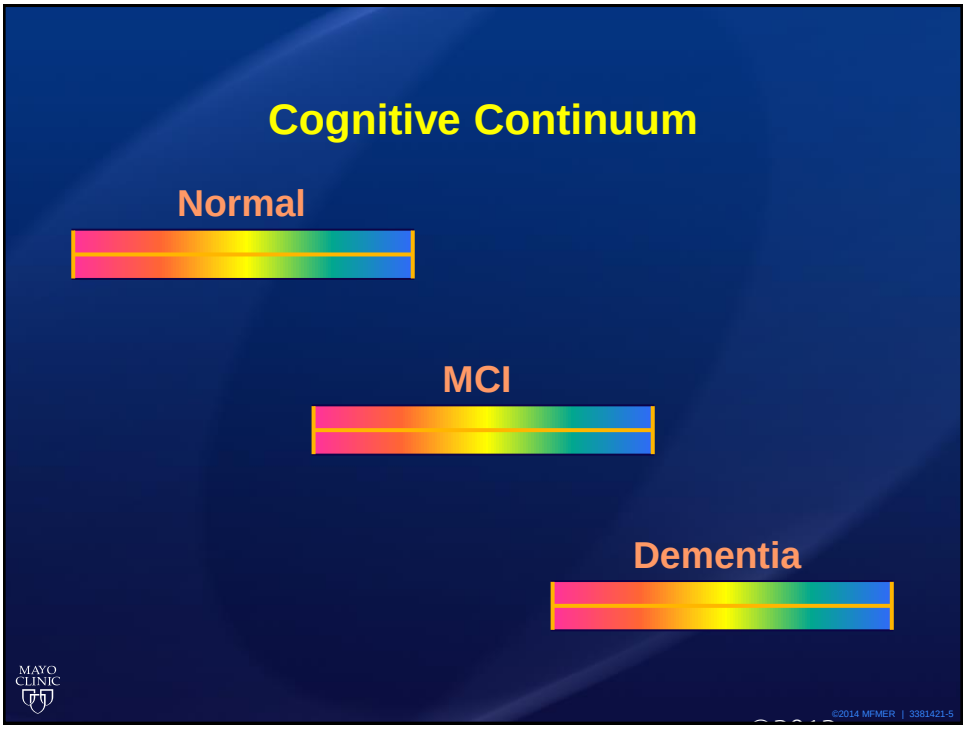
Cognitive Continuum
Normal
MCI
Dementia
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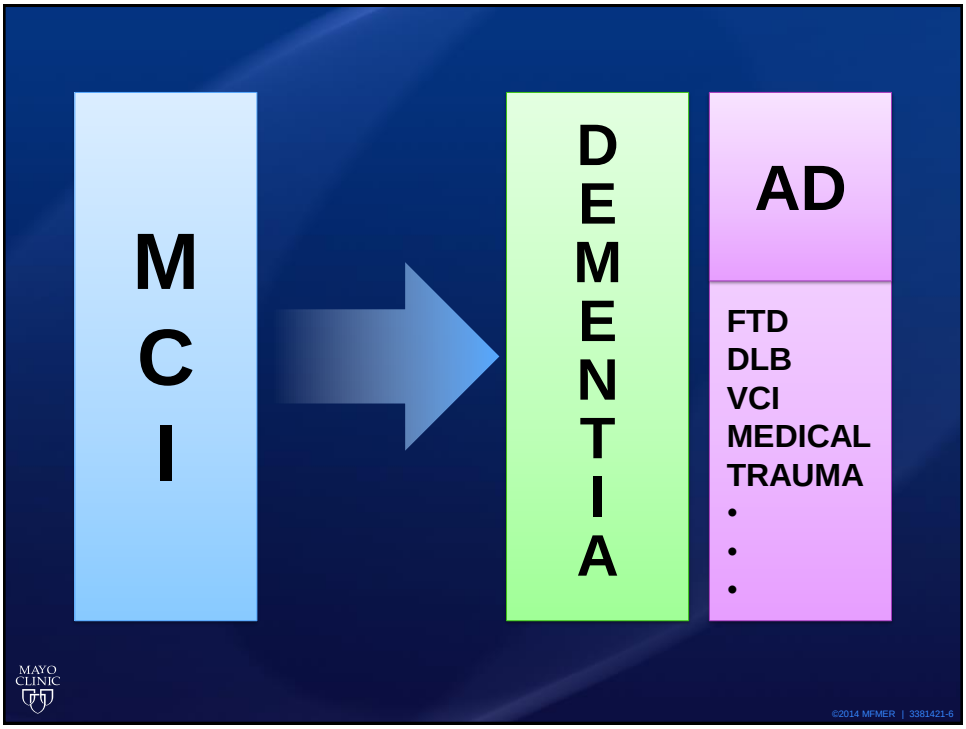
MCI
DEMENTIA
AD
FTD
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Mild Cognitive Impairment

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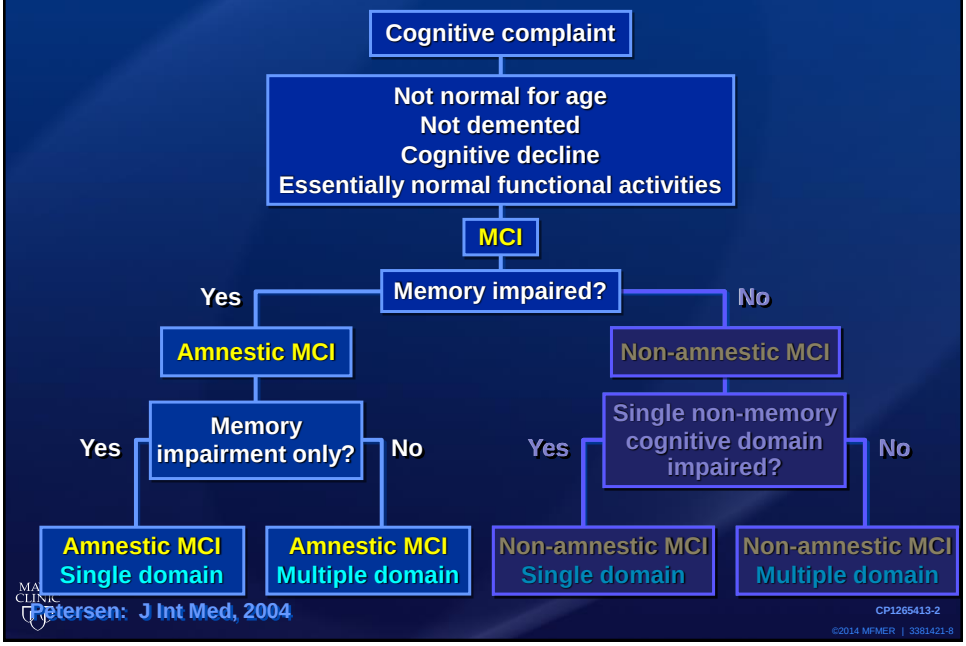
Mild Cognitive Impairment



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Petersen: J Int Med, 2004

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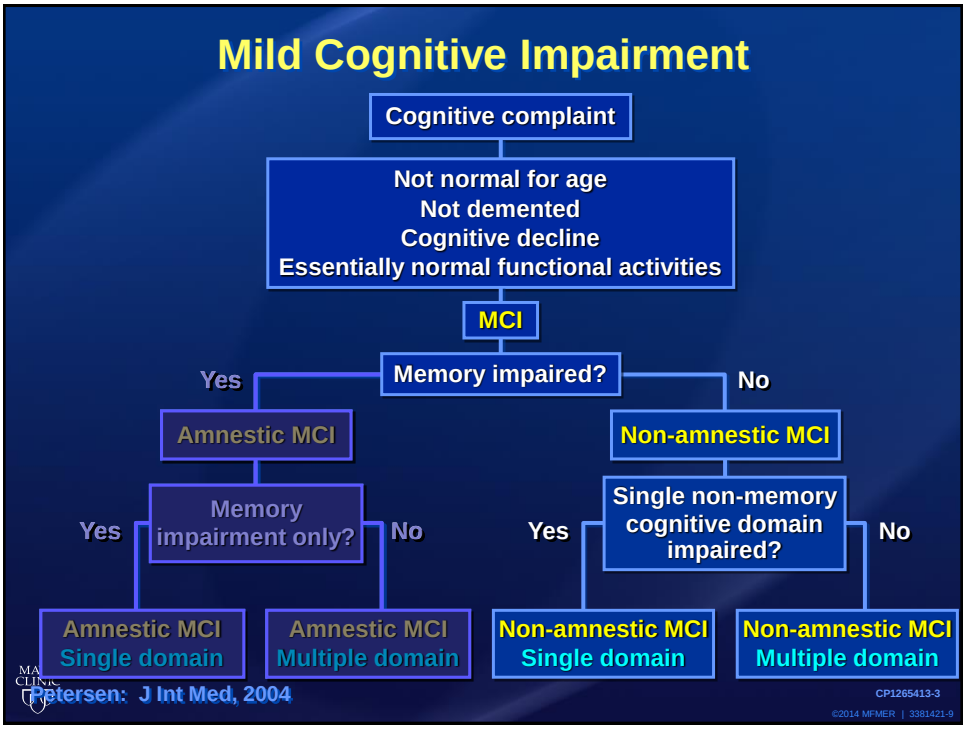
Mild Cognitive Impairment
Cognitive complaint
Not normal for age
Not demented
Cognitive decline
Essentially normal functional activities
MCI
Memory impaired?
Yes
No
Amnestic MCI
Non-amnestic MCI
Memory impairment only?
Yes
No
Single non-memory cognitive domain impaired?
Yes
No
Amnestic MCI Single domain
Amnestic MCI Multiple domain
Non-amnestic MCI Single domain
Non-amnestic MCI Multiple domain
Petersen: J Int Med, 2004
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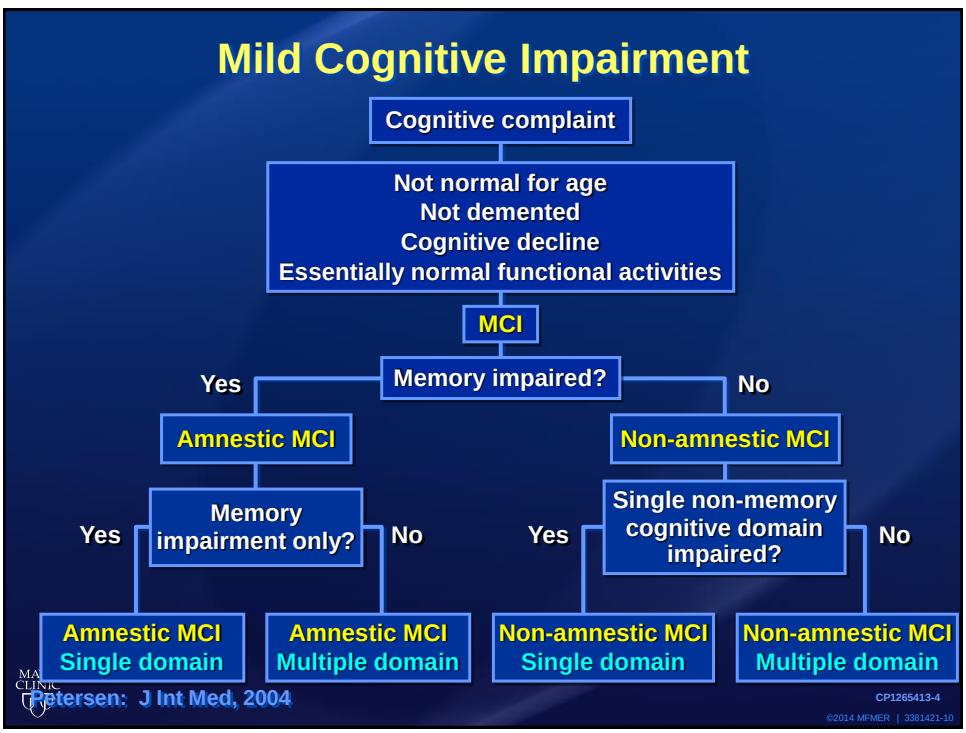
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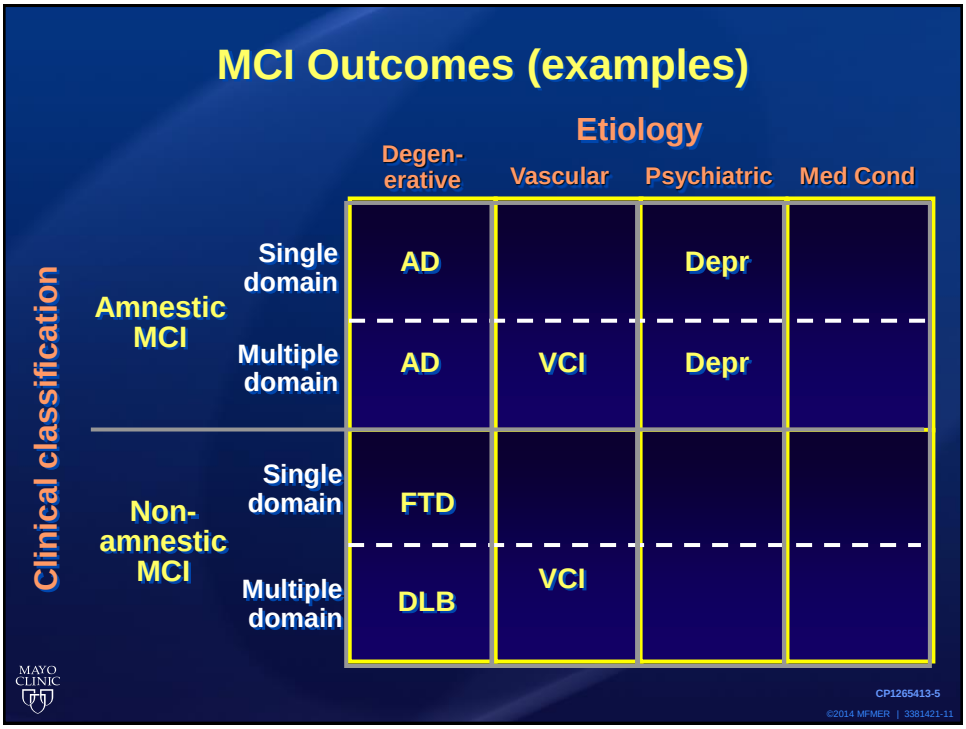
MCI Outcomes (examples)
Etiology
Degen-erative
Vascular
Psychiatric
Med Cond
Clinical classification
Amnestic MCI
Non-amnestic MCI
Single domain
Multiple domain
Single domain
Multiple domain
AD
Depr
AD
VCI
Depr
FTD
VCI
DLB
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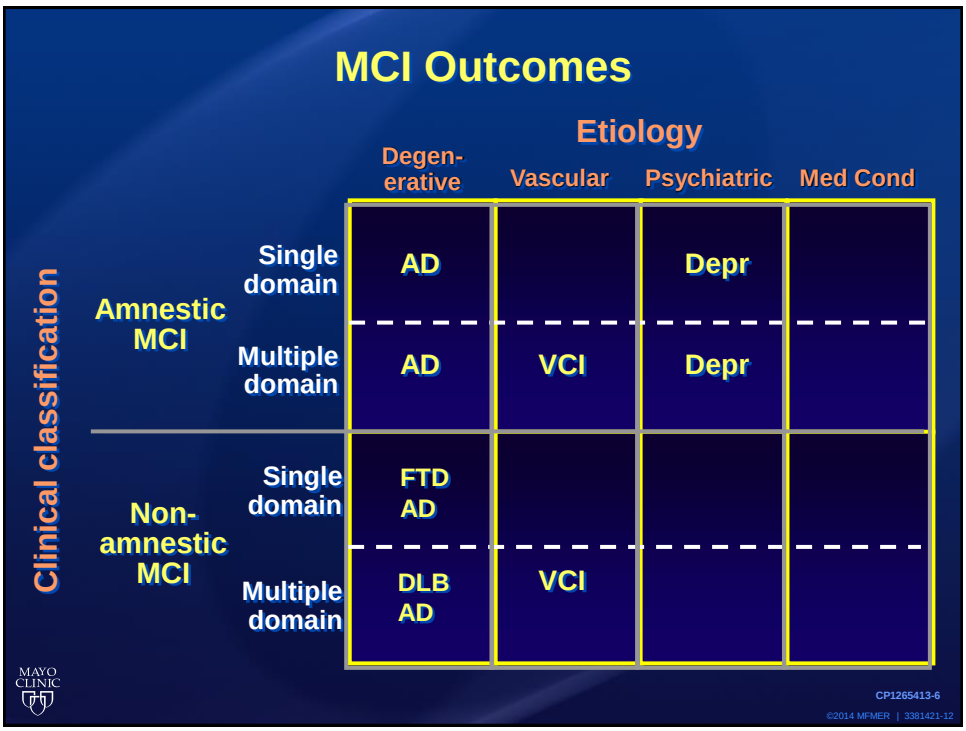
MCI Outcomes
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AD
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VCI
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FTD AD
VCI
DLB AD
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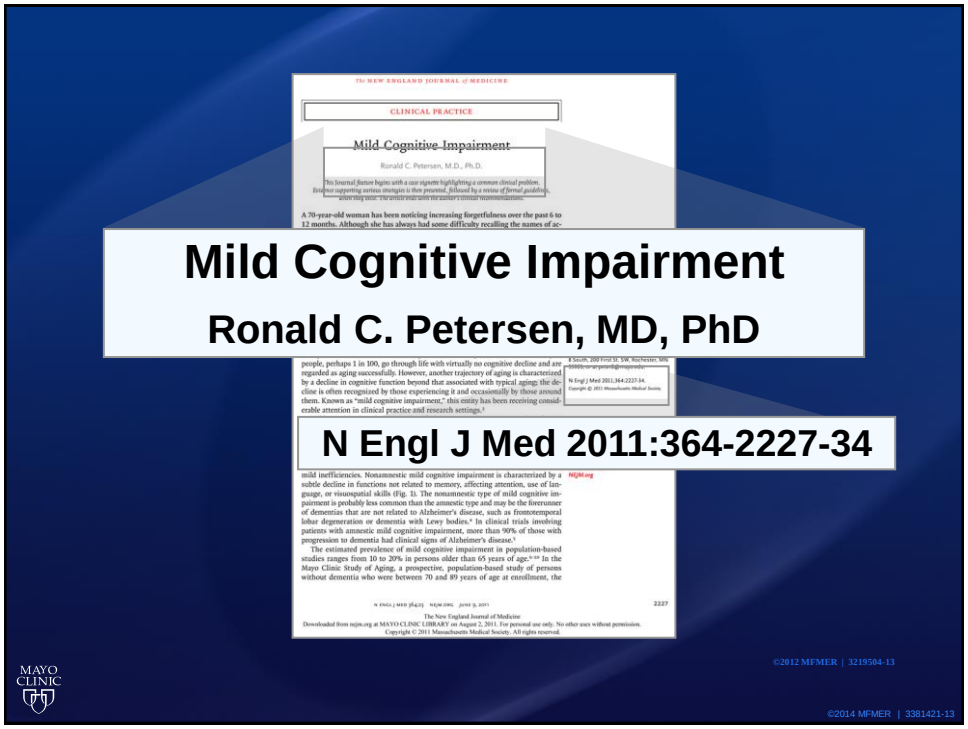

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Alzheimer's Disease as we know it may be changing…

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NINCDS-ADRDA Criteria 1984

views & reviews

Article abstract—Clinical criteria for the diagnosis of Alzheimer's disease include insidious onset and progressive impairment of memory and other cognitive functions. There are no motor, sensory, or coordination deficits early in the disease. The diagnosis cannot be determined by laboratory tests. These tests are important primarily in identifying other possible causes of dementia that must be excluded before the diagnosis of Alzheimer's disease may be made with confidence. Neuropsychological tests provide confirmatory evidence of the diagnosis of dementia and help to assess the course and response to therapy. The criteria proposed are intended to serve as a guide for the diagnosis of probable, possible, and definite Alzheimer's disease; these criteria will be revised as more definitive information becomes available.

Clinical diagnosis of Alzheimer's disease:

Report of the NINCDS-ADRDA Work Group* under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease

Guy McKhann, MD; David Drachman, MD; Marshall Folstein, MD; Robert Katzman, MD; Donald Price, MD; and Emanuel M. Stadlan, MD

Alzheimer's disease is a brain disorder characterized by a progressive dementia that occurs in middle or late life. The pathologic characteristics are degeneration of specific nerve cells, presence of neuritic plaques, and neurofibrillary tangles. Alterations in transmitter-specific markers include forebrain cholinergic systems, and, in some cases, noradrenergic and somatostatinergic systems that innervate the telencephalon.

A Work Group on the Diagnosis of Alzheimer's Disease was established by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA). The group intended to establish and to describe clinical criteria for the diagnosis of Alzheimer's disease of particular importance for research protocols and to describe approaches that would be useful for assessing the natural history of the disease. The need to refine clinical diagnostic criteria has been emphasized because 20% or more of cases with the clinical diagnosis of Alzheimer's disease are found at autopsy to have other conditions and not Alzheimer's disease. Moreover, therapeutic trials can be meaningfully compared only if uniform criteria are used for diagnosis and response to treatment.

The need for this report was suggested by the National Advisory Council of the NINCDS. The report has been reviewed by workshop participants, representatives of the National Advisory Neurological and Communicative Disorders and Stroke Council, representatives of the ADRDA, and designated reviewers representing professional societies concerned with the diagnosis of Alzheimer's disease. (For list of professional societies and designated reviewers, see page 943.)

The report was developed by subgroups that addressed medical history, clinical examination, neuropsychological testing, and laboratory assessments; the report was then discussed in plenary session. Based on a consensus of the participants, criteria were developed to serve as a clinical basis for diagnosis. These criteria should be useful also for comparative studies of patients in different kinds of investigations, including case control studies, therapeutic trials, evaluation of new diagnostic laboratory tests, and clinicopathologic correlations.

The criteria are not yet fully operational because of insufficient knowledge about the disease. The criteria are compatible with definitions in the current Diagnostic and Statistical Manual of Mental Disorders (DSM III) and in the International Classification of Diseases. These criteria must be regarded as tentative and subject to change. Additional longitudinal studies, confirmed by autopsy, are necessary to establish the validity of these criteria in com-

*For Work Group Participants and Affiliations, see page 943.

Accepted for publication March 20, 1984.

Address correspondence and reprint requests to Dr. Stadlan, 7550 Wisconsin Avenue, Federal Building, Room 700, Bethesda, MD 20205.

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Alzheimer's Disease as a Clinical – Pathological Entity

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Alzheimer's & Dementia

Alzheimer's & Dementia 14 (2018) 535-562

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

Contributors: Cerise Elliott, Eliezer Masliah, Laurie Ryan, and Nina Silverberg

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[b]Department of Neurological Sciences, Rush University, Chicago, IL, USA
[c]Department of Psychiatry and Neurochemistry, University of Gothenburg, Gothenburg, Sweden
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[e]Office of Drug Evaluation, FDA, Silver Spring, MD, USA
[f]Biogen, Cambridge, MA, USA
[g]Department of Neurology, Washington University, St. Louis, MO, USA
[h]Department of Public Health and Neuroscience, University of California Berkeley, Berkeley, CA, USA
[i]Department of Psychiatry, University of Cologne, Medical Faculty, Cologne, Germany
[j]Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[k]Prothena Biosciences, Inc., San Francisco, CA, USA
[l]Barcelonaßeta Brain Research Center, Pasqual Maragall Foundation and Hospital Clínic-IDIBAPS, Barcelona, Spain
[m]Department of Pathology, Stanford University, Stanford, CA, USA
[n]Formerly at National Institute on Aging, Bethesda, MD, USA
[o]Department of Neurology, University of California San Francisco, San Francisco, CA, USA
[p]Department of Molecular Imaging, Austin Health, University of Melbourne, Melbourne, Australia
[q]Department of Neurology, VU University Medical Center, Amsterdam, Netherlands
[r]Formerly at Eli Lilly and Company, Indianapolis, IN, USA
[s]Department of Neurology, Brigham and Women's Hospital, Boston, MA, USA

Abstract In 2011, the National Institute on Aging and Alzheimer's Association created separate diagnostic recommendations for the preclinical, mild cognitive impairment, and dementia stages of Alzheimer's disease. Scientific progress in the interim led to an initiative by the National Institute on Aging and Alzheimer's Association to update and unify the 2011 guidelines. This unifying update is labeled a "research framework" because its intended use is for observational and interventional research, not routine clinical care. In the National Institute on Aging and Alzheimer's Association Research Framework, Alzheimer's disease (AD) is defined by its underlying pathologic processes that can be documented by postmortem examination or *in vivo* by biomarkers. The diagnosis is not based on the clinical consequences of the disease (i.e., symptoms/signs) in this research framework, which shifts the definition of AD in living people from a syndromal to a biological construct. The research framework focuses on the diagnosis of AD with biomarkers in living persons. Biomarkers are grouped into those of β amyloid deposition, pathologic tau, and neurodegeneration [AT(N)]. This

The authors' conflict of interest statements can be viewed online at https://doi.org/10.1016/j.jalz.2018.02.018.

The [nia] National Institute on Aging program staff are acknowledged for their key contributions in leadership and scientific guidance on this project.

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E-mail address: jack.clifford@mayo.edu

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Alzheimer's Disease

1984
NINCDS-ADRDA Criteria
Clinical-Pathological definition

↓

2011
NIA-AA Criteria
Clinical syndrome with biomarkers for amyloid and neurodegeneration

↓

2018
NIA-AA Framework
Alzheimer's disease as a biological entity
defined by positive biomarkers for amyloid and tau
Clinical Spectra Independent

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2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

Clifford R. Jack, Jr.,[a,*], David A. Bennett[b], Kaj Blennow[c], Maria C. Carrillo[d], Billy Dunn[e], Samantha Budd Haeberlein[f], David M. Holtzman[g], William Jagust[h], Frank Jessen[i], Jason Karlawish[j], Enchi Liu[k], Jose Luis Molinuevo[l], Thomas Montine[m], Creighton Phelps[n], Katherine P. Rankin[o], Christopher C. Rowe[p], Philip Scheltens[q], Eric Siemers[r], Heather M. Snyder[d], Reisa Sperling[s]

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Jack et al: Alzheimer's & Dementia 14(2018)535-562.

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What is the definition of AD?

- Term AD refers to **pathologic change** – not specific syndrome
- AD is identified at **post mortem** by pathologic changes and/or in vivo by **biomarkers**
  - Symptoms are part of the disease continuum not its definition
- **Major shift in thinking**

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New AD Framework
Clinical Considerations

Typical clinical syndromes

(Cognitively unimpaired, MCI, dementia)

New clinical staging system

(For amyloid positive persons on Alzheimer's spectrum)

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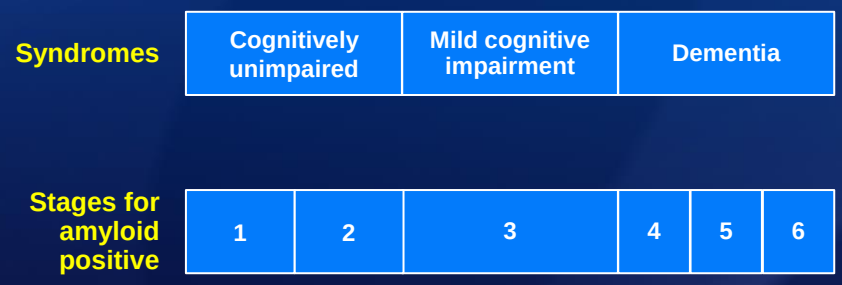
Clinical Spectra for AD
(Alzheimer's Clinical Syndrome)



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Clinical Stages

- Stage 1
  - Performance in expected range
  - No report of decline
  - No change by partner or longitudinal test
- Stage 2
  - Performance in expected range
  - Transitional cognitive decline
    - Subjective cognitive decline or
    - Documented evidence of decline or
    - Subjective plus objective decline
    - Neurobehavioral symptoms

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Clinical Stages

- Stage 3
  - Performance in impaired range
  - Decline from baseline
    - Individual report or
    - Observer's report or
    - Longitudinal change
  - Any domain
  - ADL's independent but may be less efficient

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Clinical Stages

- **Stage 4**
  - **Mild dementia**
- **Stage 5**
  - **Moderate dementia**
- **Stage 6**
  - **Severe dementia**

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MCI and Biomarkers

- **Combination quite predictive of outcome**
- **Imaging or fluid, CSF, plasma predicts clinical outcome on AD spectrum**

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Plasma in MCI

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Individualized prognosis of cognitive decline and dementia in mild cognitive impairment based on plasma biomarker combinations

Nicholas C. Cullen[1,11], Antoine Leuzy[1,11], Sebastian Palmqvist [1,2], Shorena Janelidze[1], Erik Stomrud[1,2], Pedro Pesini[3], Leticia Sarasa[3], José Antonio Allué[3], Nicholas K. Proctor [4], Henrik Zetterberg [5,6,7,8], Jeffrey L. Dage[4], Kaj Blennow [5,6], Niklas Mattsson-Carlgren[1,9,10,12] ✉ and Oskar Hansson [1,2,12] ✉

Cullen et al., Nature Aging, 2020

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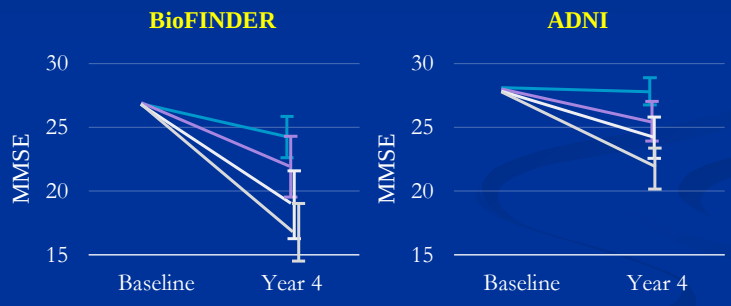
Modeling cognitive decline using plasma P-tau181 and NfL



Redrawn from: Cullen et al: Nature Aging; VOL 1; January 2021; 114-123

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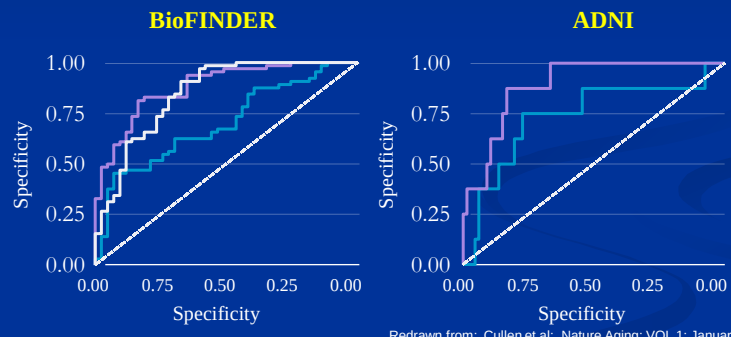
ROC curves for clinical conversion across cohorts



Redrawn from: Cullen et al: Nature Aging; VOL 1; January 2021; 114-123

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Not All MCI is Early AD

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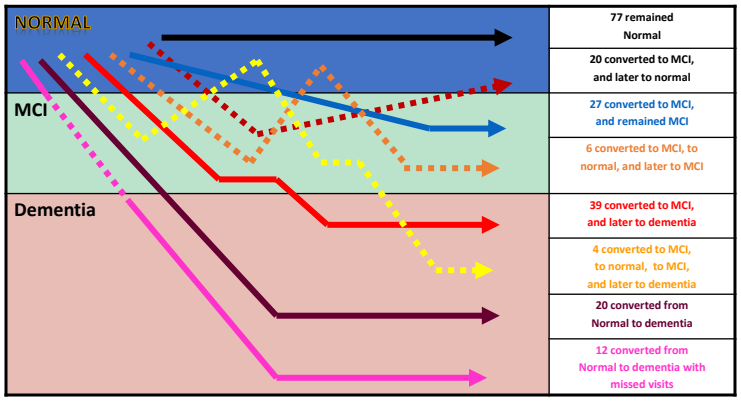
The progression from normal to MCI to Dementia: Patterns of change in cognitive classification in 205 *Cardiovascular Health Study* normal participants during a 14-year follow up.



Lopez OL, et al., Neurology 2012

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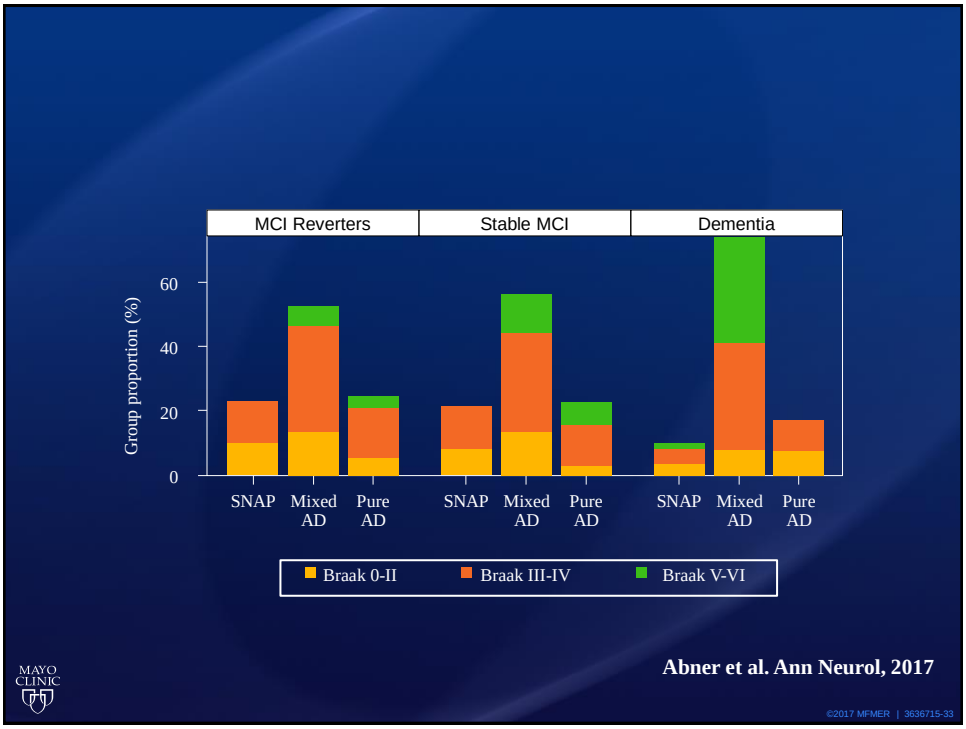

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Common causes of MCI in the adult

Neurodegenerative	Non-neurodegenerative: CNS	Non-neurodegenerative: systemic
• Alzheimer's disease	• Clinical CVA/TIA	• Thyroid disease
• Parkinson's disease	• Silent vascular infarcts	• Cardiovascular disease
• Lewy body disease	• Non-specific arteritis	• Hypertension
• Frontotemporal lobar degeneration	• CAA	• Diabetes mellitus
• PSP	• Neoplasms	• Sleep apnea
• MSA	• Infections	• Chronic liver disease
• Spinocerebellar degeneration	• TBI	• Chronic kidney disease
	• Depression	• Infections
	• Other psychiatric disorders	• Medications

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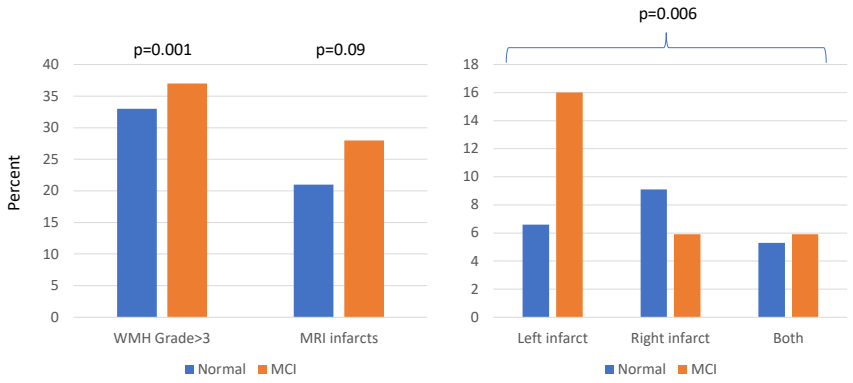
Baseline cerebrovascular and neuroimaging characteristics in CHS



Lopez OL, 2022

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Table 1 Research criteria for the clinical diagnosis of probable and possible MCI-LB

Essential for a diagnosis of MCI-LB is MCI defined by the presence of each of the following:
Concern by the patient, informant, or clinician regarding cognitive decline.
Objective evidence of impairment in 1 or more cognitive domains. The cognitive impairment may include any domain, but is more likely to be associated with attention-executive and/or visual processing deficits.
Preserved or minimally affected performance of previously attained independence in functional abilities, which do not meet the criteria for dementia.
Core clinical features
Fluctuating cognition with variations in attention and alertness.
Recurrent visual hallucinations.
RBD.
One or more spontaneous cardinal features of parkinsonism: these are bradykinesia (defined as slowness of movement and decrement in amplitude or speed), rest tremor, or rigidity.
Proposed biomarkers
Reduced dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET.
Polysomnographic confirmation of REM sleep without atonia.
Reduced meta-iodobenzylguanidine (MIBG) uptake on myocardial scintigraphy.
Probable MCI-LB can be diagnosed if:
Two or more core clinical features of DLB are present, with or without the presence of a proposed biomarker, or
Only 1 core clinical feature is present, but with 1 or more proposed biomarkers.
Probable MCI-LB should not be diagnosed based on biomarkers alone.
Possible MCI-LB can be diagnosed if:
Only 1 core clinical feature of DLB is present, with no proposed biomarkers, or
One or more of the proposed biomarkers is present, but there are no core clinical features.
Supportive clinical features
Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; prolonged or recurrent delirium; autonomic dysfunction, e.g., constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities including passage, and sense of presence phenomena; systematized delusions; apathy, anxiety, and depression.
Potential biomarkers of MCI-LB
Quantitative EEG showing slowing and dominant frequency variability.
Relative preservation of medial temporal lobe structures on structural imaging.
Insular thinning and gray matter volume loss on MRI.
Low occipital uptake on perfusion/metabolism scan.
MCI plus supportive clinical features or potential biomarkers are insufficient to diagnose MCI-LB but may raise suspicion of it and prompt biomarker investigation and may add weight to an existing MCI-LB diagnosis.
MCI-LB is less likely in the presence of any other physical illness or brain disease including cerebrovascular disease, sufficient to account in part or in total for the clinical picture, although these do not exclude an MCI-LB diagnosis and may serve to indicate mixed or multiple pathologies contributing to the clinical presentation.
Abbreviations: DLB = dementia with Lewy bodies; MCI = mild cognitive impairment; MCI-LB = MCI with Lewy bodies. These should be used in conjunction with the corresponding article text, which gives further information about core and supportive clinical features and the use of biomarkers as they apply to MCI-LB.

Lewy Body - MCI

Probable and Possible MCI-LB	
Cognitive impairment is present	Attention-executive function deficits and/or visual processing deficits
Instrumental activities of daily living	Preserved or minimally affected
Core clinical features	Fluctuating cognition
	Visual hallucinations
	REM behavioral disorder
	Parkinsonism: bradykinesia, tremors, rigidity
Probable MCI-LB	Two or more core clinical features are present
Possible MCI-LB	One core clinical feature is present
	One core clinical feature is present + biomarker

McKeith I, et al. 2020; 94: 743-755

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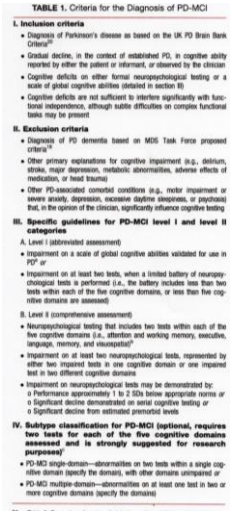

TABLE 1. Criteria for the Diagnosis of PD-MCI

I. Inclusion criteria

- Diagnosis of Parkinson's disease as based on the UK PD Brain Bank Criteria[20]
- Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, or observed by the clinician
- Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities (detailed in section II)
- Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present

II. Exclusion criteria

- Diagnosis of PD dementia based on MDS Task Force proposed criteria[18]
- Other primary explanations for cognitive impairment (e.g., delirium, stroke, major depression, metabolic abnormalities, adverse effects of medication, or head trauma)
- Other PD-associated comorbid conditions (e.g., motor impairment or severe anxiety, depression, excessive daytime sleepiness, or psychosis) that, in the opinion of the clinician, significantly influence cognitive testing

III. Specific guidelines for PD-MCI level I and level II categories

A. Level I (abbreviated assessment)

- Impairment on a scale of global cognitive abilities validated for use in PD[6] or
- Impairment on at least two tests, when a limited battery of neuropsychological tests is performed (i.e., the battery includes less than two tests within each of the five cognitive domains, or less than five cognitive domains are assessed)

B. Level II (comprehensive assessment)

- Neuropsychological testing that includes two tests within each of the five cognitive domains (i.e., attention and working memory, executive, language, memory, and visuospatial)[6]
- Impairment on at least two neuropsychological tests, represented by either two impaired tests in one cognitive domain or one impaired test in two different cognitive domains
- Impairment on neuropsychological tests may be demonstrated by:
  - o Performance approximately 1 to 2 SDs below appropriate norms or
  - o Significant decline demonstrated on serial cognitive testing or
  - o Significant decline from estimated premorbid levels

IV. Subtype classification for PD-MCI (optional, requires two tests for each of the five cognitive domains assessed and is strongly suggested for research purposes)[7]

- PD-MCI single-domain—abnormalities on two tests within a single cognitive domain (specify the domain), with other domains unimpaired or
- PD-MCI multiple-domain—abnormalities on at least one test in two or more cognitive domains (specify the domains)

Litvan I, et al. Mov Disorders 2012;27: 349-356

Parkinson's disease - MCI

Most frequent MCI type
Multiple cognitive domain: Memory, executive, and visuospatial deficits.

Frequency: 42% – 60%
High prevalence of depression
Low Aβ-42 and Aβ-40 in CSF
Less amyloid deposition than in AD patients
Cognitive measures correlate with PET tau and amyloid tracers
Mixed pathology at autopsy: Predominant LB, AD, CAA

High conversion rates to PDD
42% converted to PPD at 6-year follow-up
and 91% and 16-year follow up.

Yarnall AJ, et al. Neurology 2014; 82: 308-316.
1055
Galtier I, et al. J Clin Exp Neuropsychol 2016; 38: 40-50.
Marras C, et al. Mov Disorders. 2013; 28: 626-633.
Hobson & Meara. Int J Geriat Psychiatry 2015; 30(10): 1048-
Gomperts SN, et al. JAMA Neurology 2016; 73: 1334-1341.
Knox MG, et al. Mov Disorders 2020; 35: 845-856

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Practical Stuff

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Coding for MCI

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Coding for MCI

- Nervous System (Medical) Codes

- (ICD 9)331.83
- (ICD 10) G31.84 Mild cognitive impairment

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DSM 5

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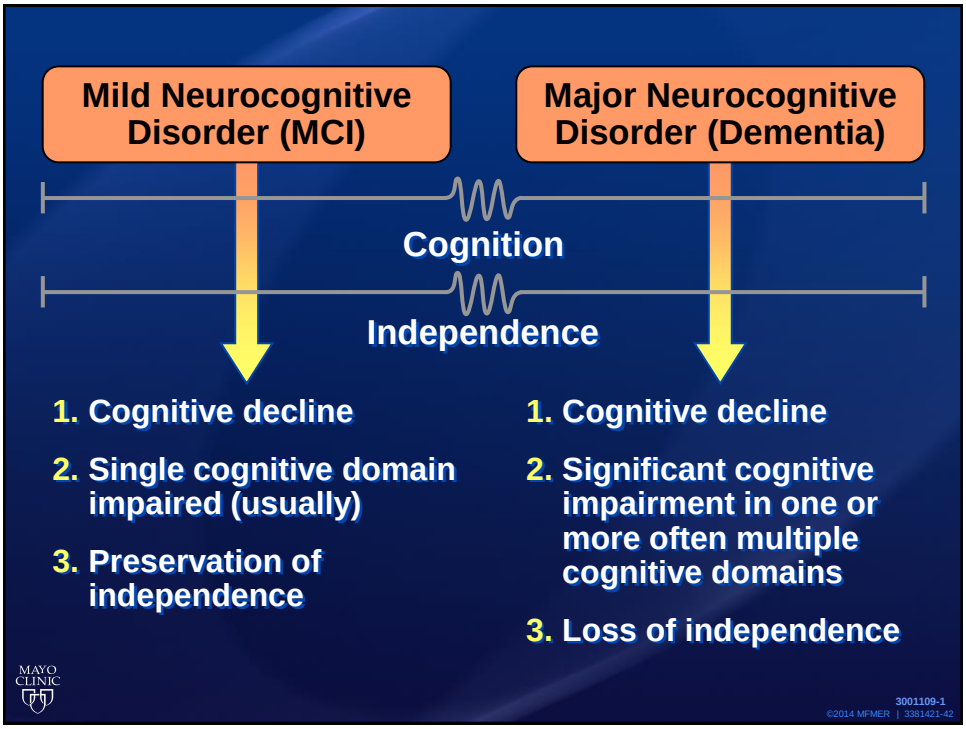

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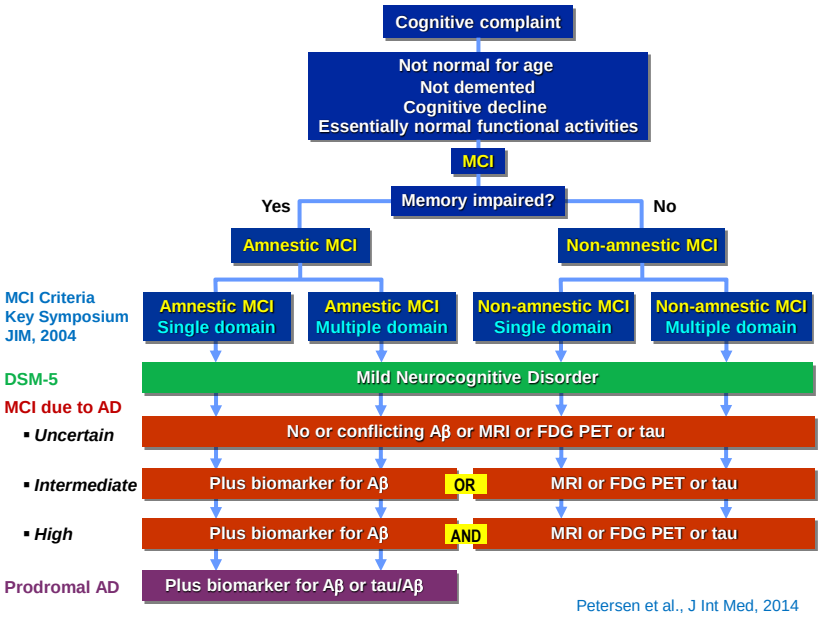
Mild Cognitive Impairment



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Petersen et al., J Int Med, 2014

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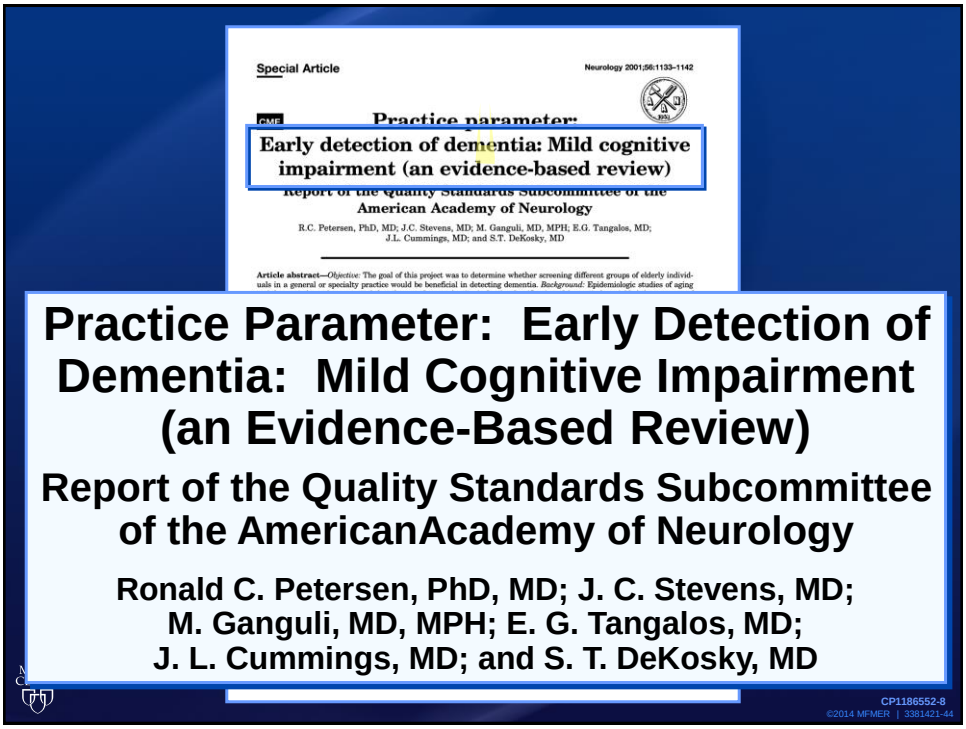

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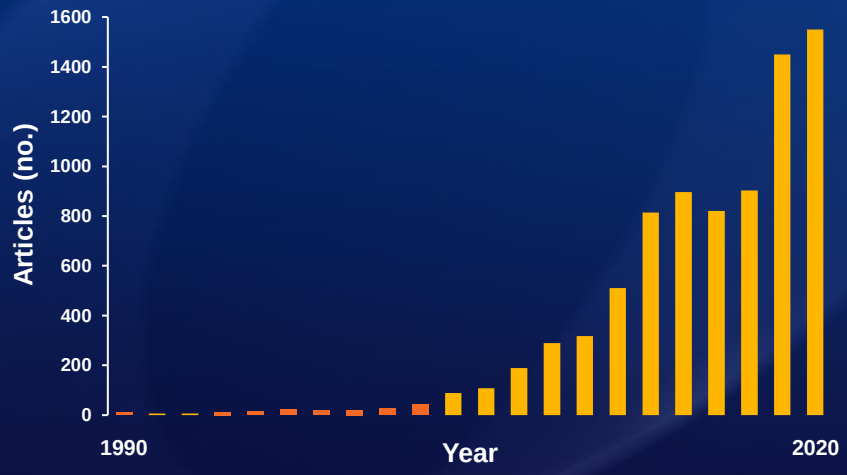
Publications on MCI



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AAN Practice Parameter on MCI 2018

Practice guideline update summary: Mild cognitive impairment

Petersen et al., Neurology, 90:126-135, 2018

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AAN Practice Parameter on MCI

- Evidence-based medicine review of the literature
  - 11,500+ studies evaluated
  - 326 full review
- 3 primary questions
  - What is the prevalence of MCI?
  - What is the outcome of MCI?
  - Are there any treatments for MCI?
    - Pharmacologic
    - Non-pharmacologic

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AAN Practice Parameter on MCI

Conclusions

1. Prevalence

   20 Class I studies

   Prevalence age-related but overall

   15-20% in age 65 and up

2. Outcome

   9 Class I studies

   Rates of progression to dementia

   age related: 5-20%/year (10-15%)

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AAN Practice Parameter on MCI Conclusions

3. Treatments
   - Pharmacological
   - 10 Class II studies, 1 Class I
   - No FDA approved drugs (2018)

   - Non-pharmacological
   - 4 Class II studies
     - exercise
     - intellectual activities

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Alzheimer's Disease Treatments 2022

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Pharmacological Therapies for MCI

- Currently one drug approved for MCI by the FDA (accelerated approval)
- Lifestyle
  - Physical exercise
  - Cognitive training
  - Blood pressure control

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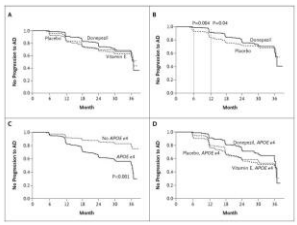
Do cholinesterase inhibitors prevent Clinical AD?

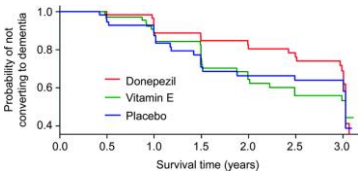
Category	Gal-INT-18 [33]: Galantamine	Gal-INT-11 [32]: Galantamine	InDDEX [31]: Rivastigmine	Salloway [36]: Donepezil	Petersen [37]: Donepezil	Koontz [34]: Galantamine
Duration of the study	2 y	2 y	3–4 y	24 wk	3 y	16 wk
Subjects completing the study (ChEI; placebo)	—	—	51%; 63%	68%; 83%	64%; 74%	50%; 36%
Conversion rate (ChEI; placebo)	17%; 21%	13%; 18%	17%; 21%	—	25%; 28%	—
Jadad quality score (0–5)	2	2	3	3	3	3

Raschetti, et. al. PLoS. 2007



Petersen, et. al. NEJM. 2005

Amnestic MCI with depressive symptoms



Lu, et. al. Neurology. 2009

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Amyloid Lowering Therapies in MCI

- Aducanumab
- Donanemab
- Lecanemab
- Gantenerumab

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Phase III study results

	Status	Number enrolled	Population	Doses studied	Level of evidence	Results summary
Engage	Terminated 8/2019	1647	MCI due to AD or mild AD 50-85 years of age MMSE ≥ 24 Positive Amyloid PET On stable AD medications Reliable informant or caregiver	Low dose: 3 or 6 mg/kg after titration High dose: 10 mg/kg after titration	Class II	1. Aducanumab does not significantly affect mean change in CDR-SB versus placebo. 2. Aducanumab decreases amyloid PET SUVR versus placebo
Emerge	Terminated 8/2019	1638	MCI due to AD or mild AD 50-85 years of age MMSE ≥ 24 Positive Amyloid PET On stable AD medications Reliable informant or caregiver	Low dose: 3 or 6 mg/kg after titration High dose: 10 mg/kg after titration	Class II	1. Aducanumab 10 mg/kg results in less worsening on the CDR-SB versus placebo but to a less than clinically significant degree 2. Aducanumab 3-10 mg/kg decreases amyloid PET SUVR versus placebo

Data from Day, et. al. Neurology. 2022

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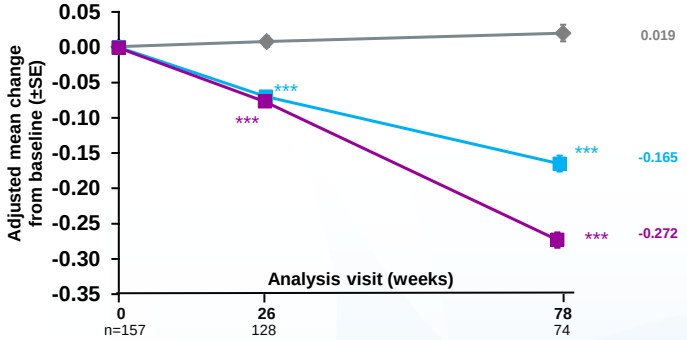
EMERGE: Longitudinal change from baseline in amyloid PET SUVR



	0	26	78
Placebo	n=157	128	74
Low dose aducanumab	n=157	125	79
High dose aducanumab	n=171	136	87

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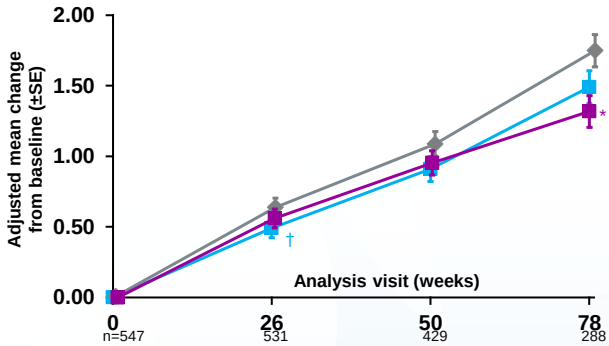
EMERGE: Longitudinal change from baseline in CDR-SB



	0	26	50	78
Placebo	n=547	531	429	288
Low dose aducanumab	n=543	512	420	289
High dose aducanumab	n=547	513	431	299

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CLARITY AD
lecanemab

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Clarity AD Study Design

Clarity AD is a global, placebo-controlled, double-blind, parallel-group, randomized study

Patient Population

- 1,795 patients with Early AD
- MCI due to AD or mild Alzheimer's dementia
- Amyloid pathology confirmed
- MMSE score between 22 and 30 at screening and baseline
- WMS-IV LMSII ≥1 SD below age-adjusted mean at screening

Randomization Phase (18 months)

R 1:1

- **Lecanemab** 10 mg/kg biweekly (IV infusion)
- **Placebo** Biweekly (IV infusion)

Extension Phase (open-label)

- **Lecanemab** 10 mg/kg biweekly (IV infusion)

Randomization Phase Primary Outcome Measure:

Change from Baseline in the CDR-SB (Time Frame: 18 months)

Extension Phase Primary Outcome Measures

Number of Participants with TEAEs (Time Frame: up to Month 45)

Change from Core Study Baseline in CDR-SB (Time Frame: up to Month 45)

Randomization will be stratified according to

- Clinical subgroup (MCI due to AD or mild AD dementia)
- Presence or absence of ongoing approved AD treatment (eg, acetylcholinesterase inhibitors, memantine, or both)
- ApoE4 status (ie, carriers or non-carriers)
- Geographical region

3 optional longitudinal sub-studies

- Amyloid burden (amyloid PET)
- Brain tau pathology (tau PET)
- CSF biomarkers of neurodegeneration

58 AD, Alzheimer's disease; ApoE4, apolipoprotein E4; CDR-SB, Clinical Dementia Rating-sum of boxes; CSF, cerebrospinal fluid; IV, intravenous; MCI, mild cognitive impairment; MMSE, Mini-Mental State Exam; PET, positron emission tomography; SD, standard deviation; TEAEs, treatment emergent adverse events; WMS-IV LMSII, Wechsler Memory Scale IV-Logical Memory (subscale) II.

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Study Population - Clarity-AD

	Clarity AD Total N=1795
Patient Characteristic	
Age, median (range), years	72 (50, 90)
Age ≥65, %	80
Female, %	52
Caucasian, %	77
MCI due to AD, %	62
ApoE4 carriers,* %	69
Clinical Endpoints	
CDR-SB, mean (SD)	3.2 (1.3)
ADCOMS, mean (SD)	0.4 (0.1)
ADAS-Cog, mean (SD)	25.3 (7.3)
MMSE, mean (SD)	25.6 (2.2)
Global CDR, mean (SD)	0.6 (0.2)

Data from Eisai/Biogen presentation at the ADPD 2022 conference

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Efficacy – Clarity-AD (Phase 3)

- Primary outcome: CDR-SB at 18 mo
  - 27% slowing of cognitive worsening (p=0.00005)
  - Treatment difference -0.45
  - Treatment benefit was seen as early as 6 mo after starting therapy
- Secondary outcomes (pre-planned hierarchical analysis)
  - Amyloid PET SUVR p<0.01
  - ADAScog-14 p<0.01
  - ADCOMS p<0.01
  - ADCS-ADL p<0.01

Data from Eisai/Biogen Press Release from Sep 28, 2022

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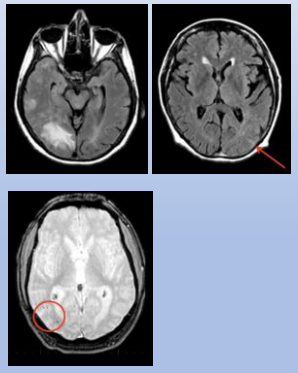
ARIA frequencies in Clarity-AD (Phase 3)

- **ARIA-E**
  - 1.7% placebo vs. 12.5% treatment group
- *Symptomatic ARIA-E*
  - 0% placebo vs. 2.8% treatment group
- **ARIA-H**
  - 8.7% placebo vs. 17% treatment group
- *Symptomatic ARIA-H*
  - 0.2% placebo vs. 0.7% treatment group



Images from Sperling R, et al. Lancet Neurol 2012; 11: 241-249

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Clarity AD

- Topline results
- N = 1795
- MCI and mild dementia due to AD
- 18 month study
- 27% slowing
- CDR-SB change of -0.45 SB relative to placebo
- Secondary measures: PET, ADAS-Cog 14, ADCOMS, ADCS-ADL significant
- ARIA E: 12.5% (2.8%) vs 1.7% (0.0%)
- ARIA H: 17% (0.7%) vs 8.7% (0.2%)

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CLINICAL EXPECTATIONS AND MEANINGFULNESS

- Temporal evolution of pathophysiology
- Length of RCT
- Measurement of change
  - Symptomatic vs Disease Modifying
  - Points on a scale
  - Time
- Cumulative benefit over time
- Multiple pathologies active

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Clinical Dementia Rating

Clinical dementia rating (CDR)	1	0.5	1	2	3

	Impairment				
	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully orientated except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented to place of examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to placed	Orientated to person only
Judgement & Problem Solving	Solves everyday problems and handles business and financial affairs well; judgement good in relation to past performance	Slight impairment in solving problems, similarities and differences	Moderate difficulty in handling problems, similarities and differences; social judgement usually maintained	Severely impaired in handling problems, similarities and differences; social judgement usually impaired	Unable to make judgements or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activity	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretence of independent function outside home Appears well enough to be taken to functions outside the family home independent function	Appears to ill to be taken to functions outside the family home
Home & Hobbies	Life at home, hobbies and intellectual interests well maintained	Life at home, hobbies and intellectual interest slightly impaired	Mild but definite impairment of function at home more difficult tasks abandoned; more complicated hobbies and interests abandoned	Only simple tasks preserved; very restricted interests, poorly maintained	No significant function in home
Personal Care	Full capable of self-care		Needs prompting	Requires assistance in dressing, hygiene, keeping of personal effects	Required much help with personal care; frequent incontinence

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Clinical Dementia Rating

Clinical dementia rating (CDR)	1	0.5	1	2	3

	None 0	Questionable 0.5	Mild 1	Moderate 2	Severe 3
Memory	No memory loss or slight inconsistent forgetfulness	Consistent slight forgetfulness; partial recollection of events; "benign" forgetfulness	Moderate memory loss; more marked for recent events; defect interferes with everyday activities	Severe memory loss; only highly learned; new material rapidly lost	Severe memory loss; only fragments remain
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activity	Unable to function independently at these activities although may still be engaged in some; appears normal to casual inspection	No pretence of independent function outside home Appears well enough to be taken to functions outside the family home independent function	Appears to ill to be taken to functions outside the family home

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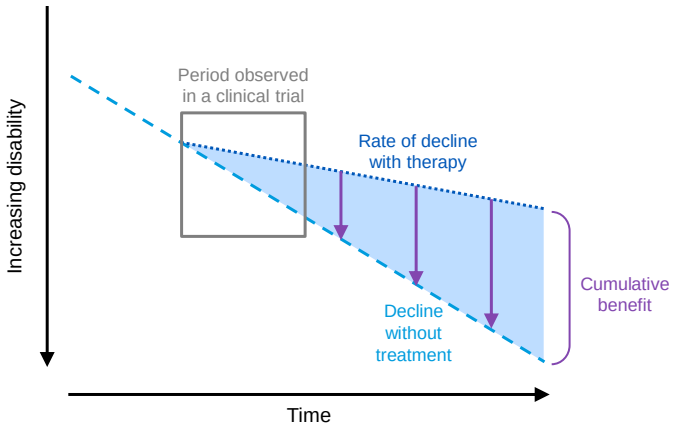
Cumulative Benefit Over Time from a DMT



Petersen et al: Under review adapted from Asuuncao et al. 2022

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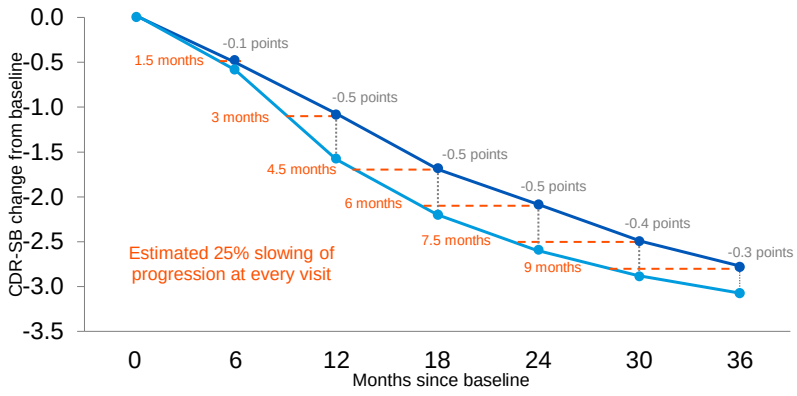
Potential Savings from a DMT



Petersen et al: Under review adapted from Raket (2022)

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But, at the end of the day…

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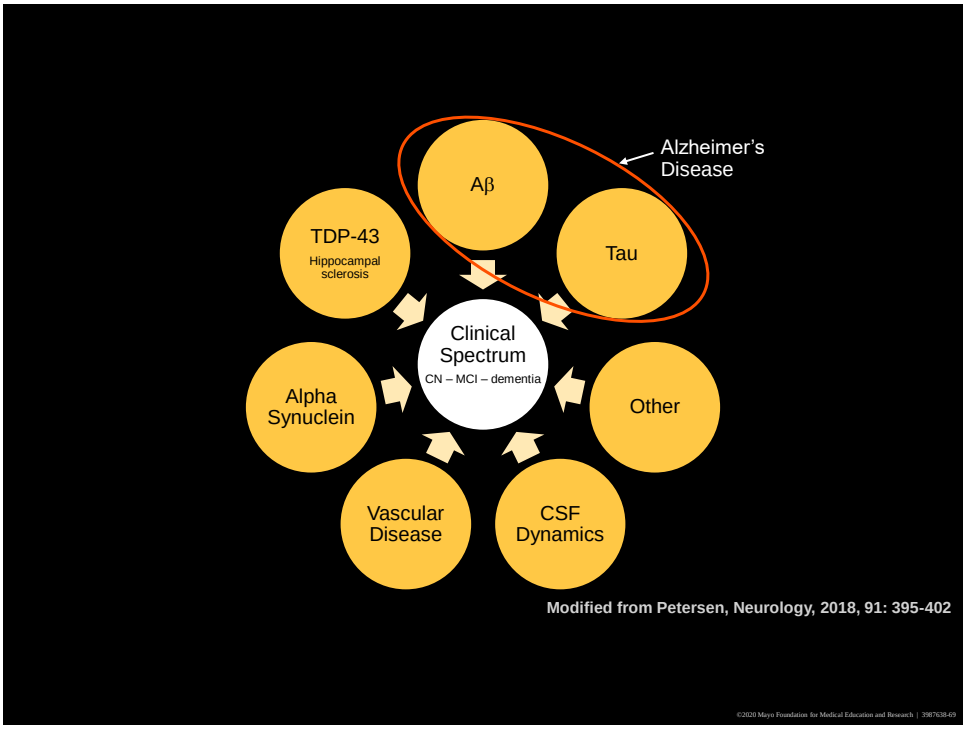
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Tau
TDP-43
Hippocampal sclerosis
Clinical Spectrum
CN – MCI – dementia
Alpha Synuclein
Other
Vascular Disease
CSF Dynamics
Modified from Petersen, Neurology, 2018, 91: 395-402
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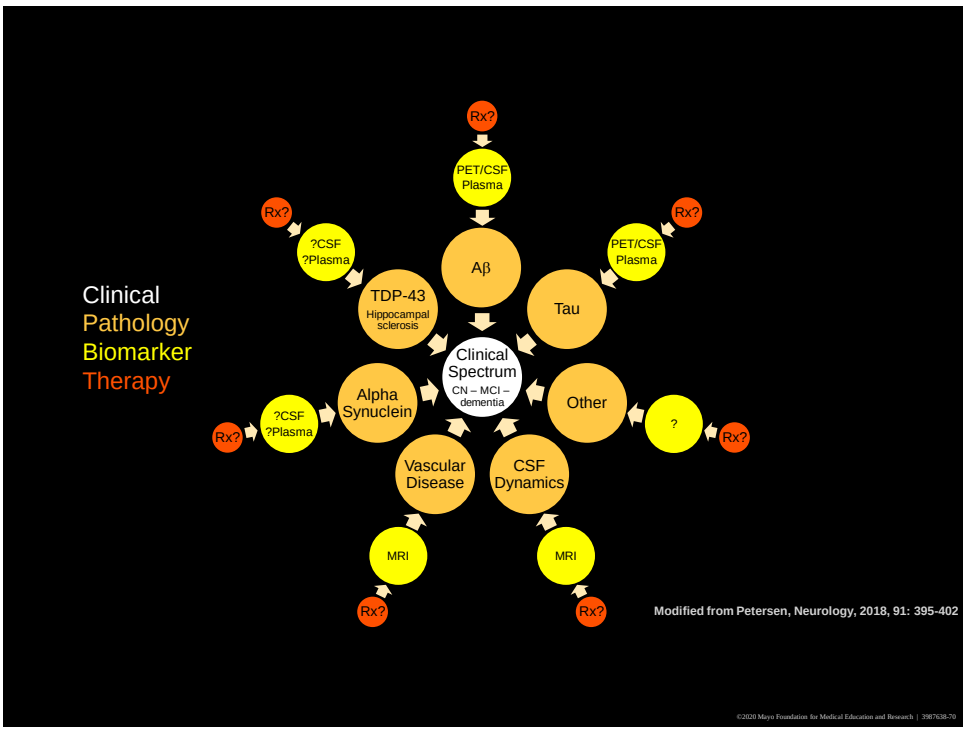
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Aβ
Tau
TDP-43
Hippocampal sclerosis
Clinical Spectrum
CN – MCI – dementia
Alpha Synuclein
Other
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Thank You

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