Mild Cognitive Impairment
A Construct in Evolution

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Disclosures

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- NIH:
  - U01 AG006786
  - P30 AG062677
  - U01 AG024904
  - U24 AG057437
  - R01 AG011378
  - UF1 NS125417
  - Alzheimer's Association
  - GHR Foundation
  - Mayo Foundation for Education and Research

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Old Conception of Alzheimer's Disease

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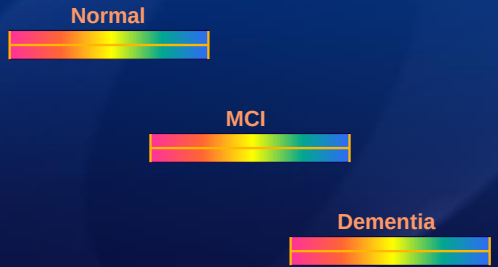
Cognitive Continuum



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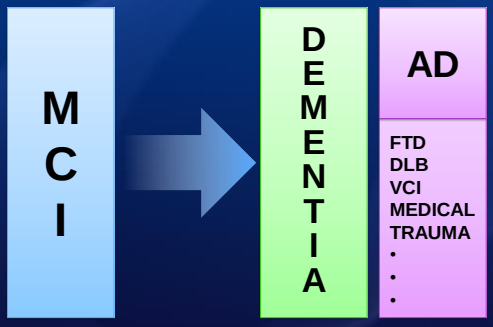

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Mild Cognitive Impairment

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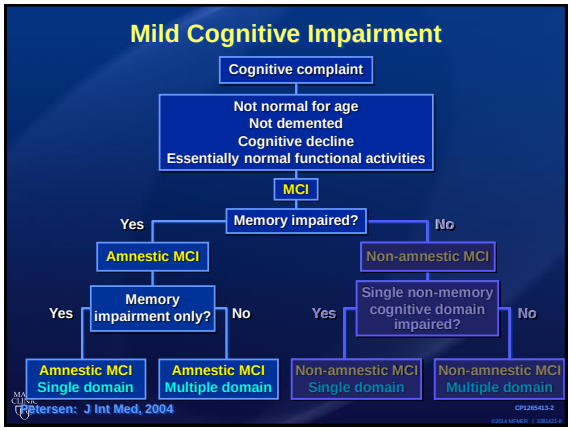
Mild Cognitive Impairment



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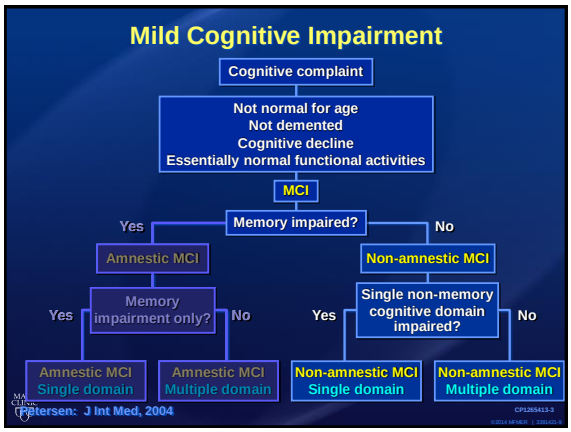

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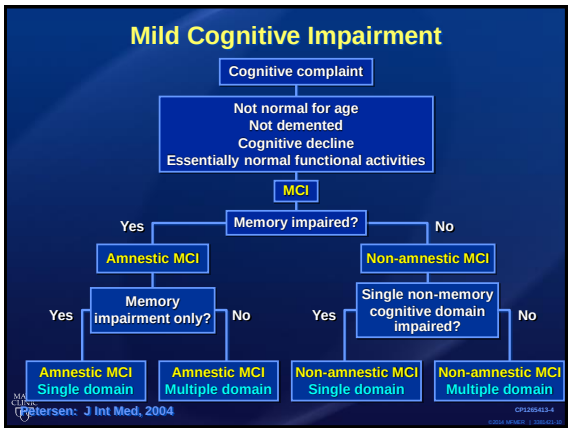
Mild Cognitive Impairment



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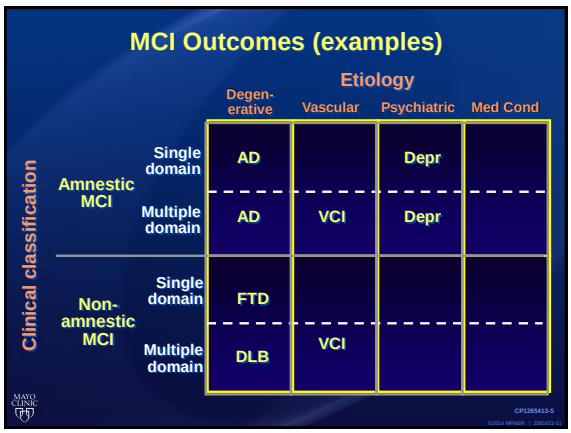
MCI Outcomes (examples)



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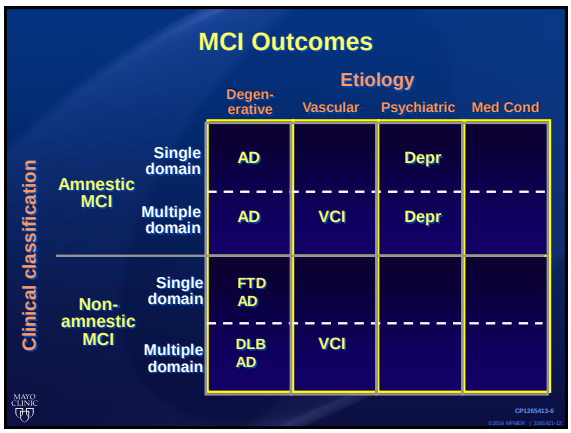
MCI Outcomes



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Mild Cognitive Impairment

Ronald C. Petersen, MD, PhD


Mild Cognitive Impairment

N Engl J Med 2011:364-2227-34

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

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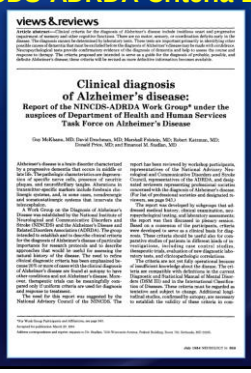
NINCDS-ADRDA Criteria 1984


views & reviews

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

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Alzheimer's Disease as a Clinical – Pathological Entity

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Alzheimer's & Dementia

2011 National Institute on Aging–Alzheimer's Association (NIA-AA) Research Framework

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

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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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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)

Syndromes	Cognitively unimpaired	Mild cognitive impairment	Dementia

Stages for amyloid positive	1	2	3	4	5	6

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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[1,9], Antoine Leuzy[1,9], 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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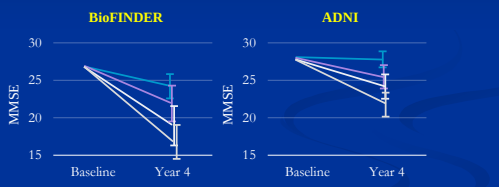
Modeling cognitive decline using plasma P-tau181 and NfL



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

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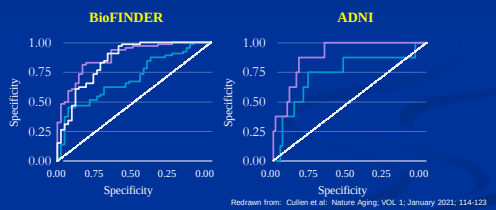
ROC curves for clinical conversion across cohorts



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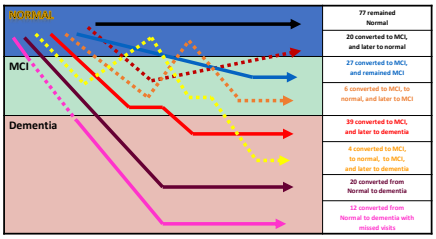
The progression from normal to MCI to Dementia: Patterns of change in cognitive classification in 205 *Cardiovascular Health Study* normal participants during a 14-year follow up.



Lopez OL, et al., Neurology 2012

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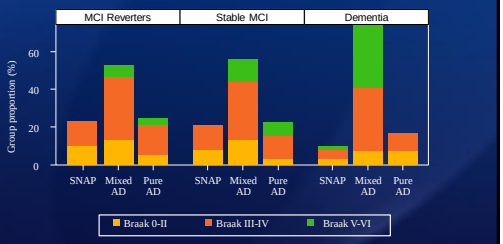

Abner et al. Ann Neurol, 2017

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Common causes of MCI in the adult

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

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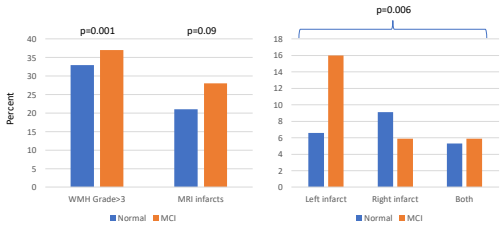
Baseline cerebrovascular and neuroimaging characteristics in CHS



Lopez OL, 2022

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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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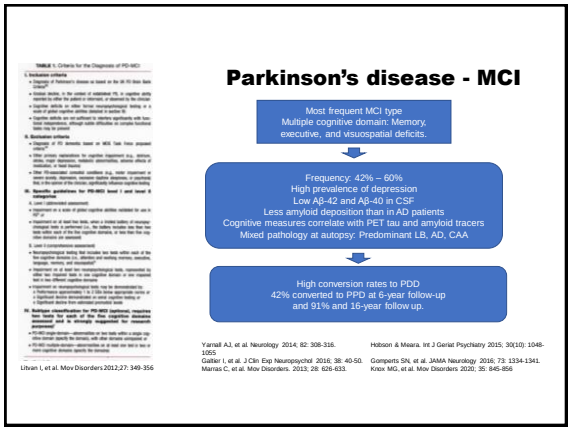

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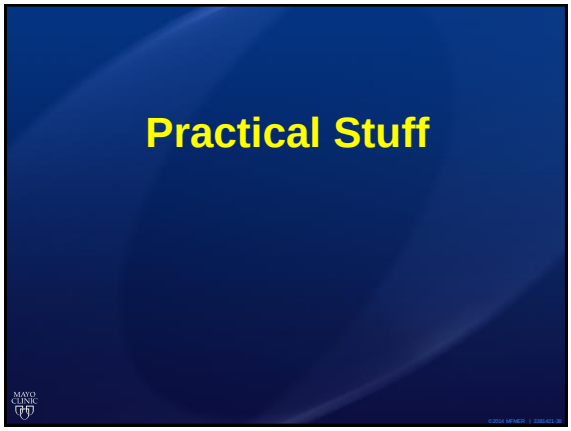

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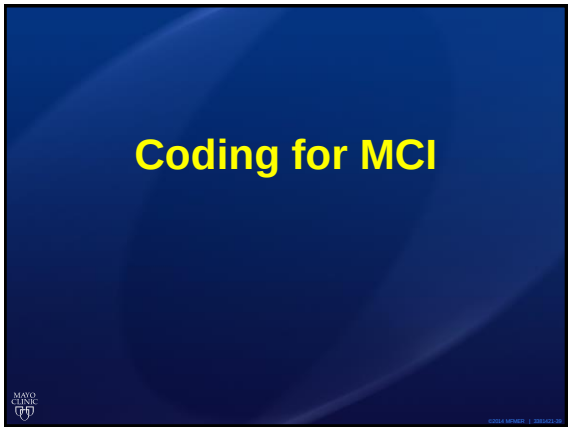

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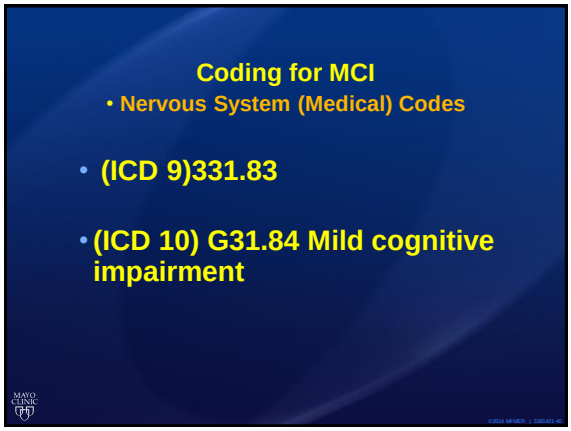

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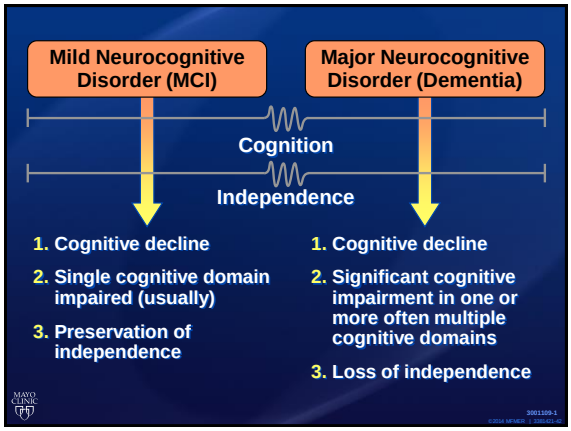

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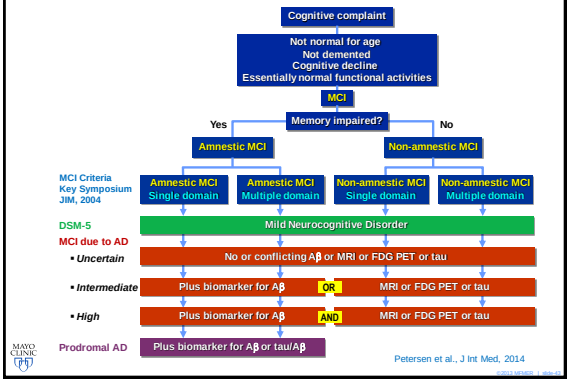
Mild Cognitive Impairment



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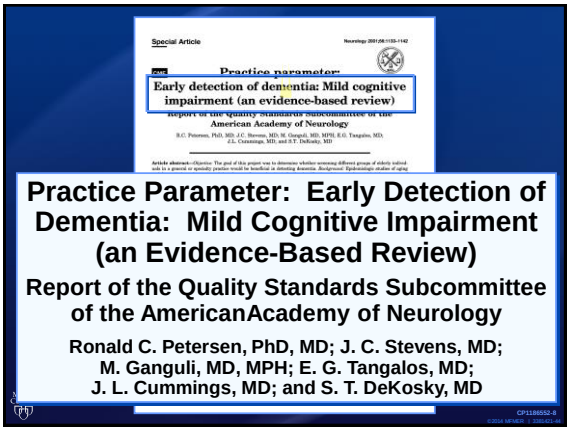

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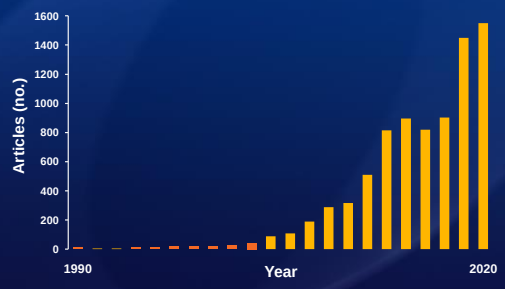
Publications on MCI



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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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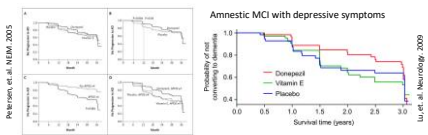
Do cholinesterase inhibitors prevent Clinical AD?

Category	Gal-INT-10 [33]: Galantamine	Gal-INT-11 [32]: Galantamine	InDDEX [31]: Rivastigmine	Salloway [36]: Donepezil	Petersen [37]: Donepezil	Kosmis [34]: Galantamine
Duration of the study	2 y	2 y	3–4 y	24 wk	3 y	16 wk
Subjects completing the study (CMI: placebo	—	—	51%; 63%	68%; 83%	64%; 74%	50%; 36%
Conversion rate (CMI: placebo)	17%; 21%	7.9%; 18%	17%; 21%	—	20%; 28%	—
Adas‖ quality score (0–5)	2	2	3	3	3	3

Raschetti, et. al. PLoS. 2007



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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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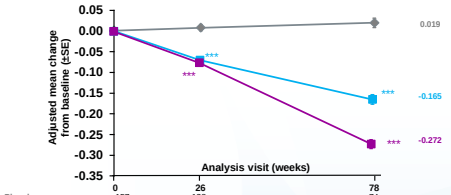
EMERGE: Longitudinal change from baseline in amyloid PET SUVR



	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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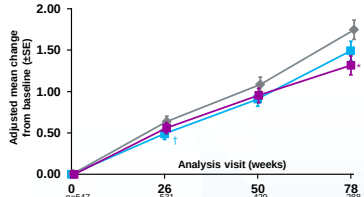
EMERGE: Longitudinal change from baseline in CDR-SB



	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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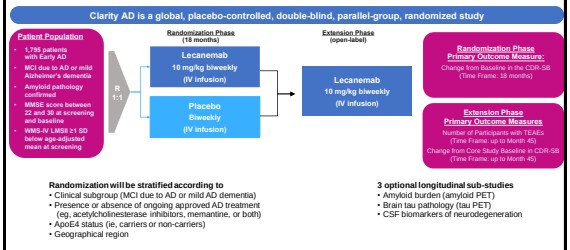
Clarity AD Study Design



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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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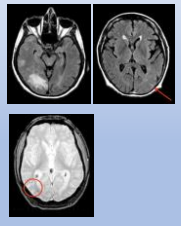
ARIA frequencies in Clarity-AD (Phase 3)

- **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 this 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
Hobbies	hobbies and intellectual interests well maintained	and intellectual interest slightly impaired	function at home more difficult tasks abandoned; more complicated hobbies and interests abandoned	very restricted interests, poorly maintained	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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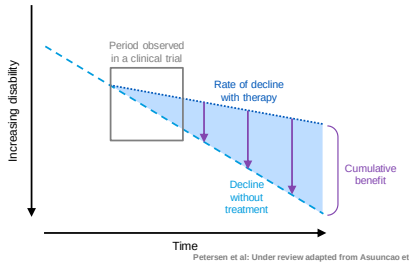
Cumulative Benefit Over Time from a DMT



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

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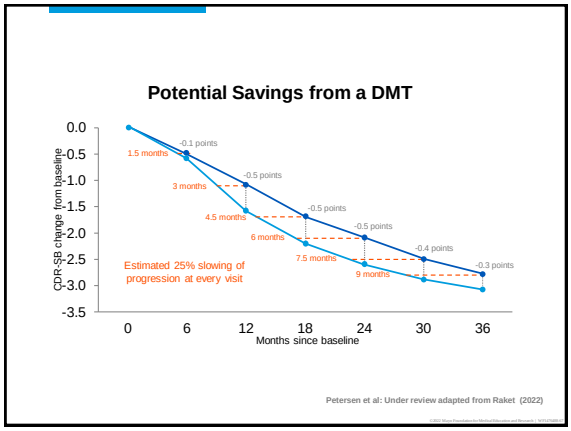

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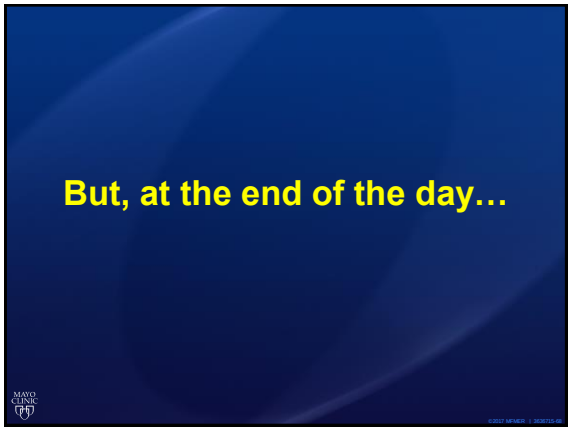

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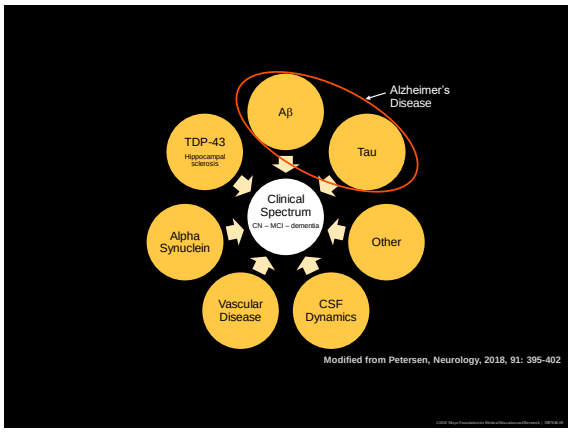

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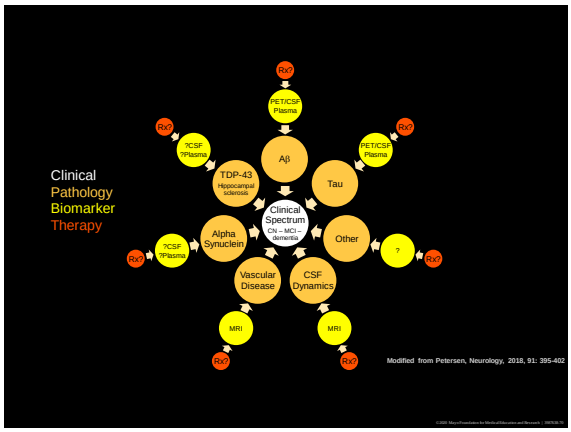

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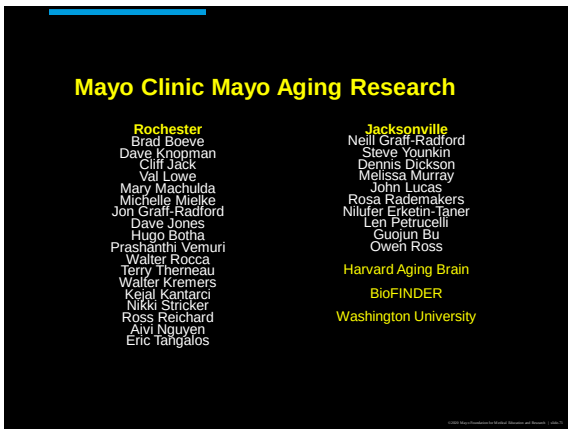

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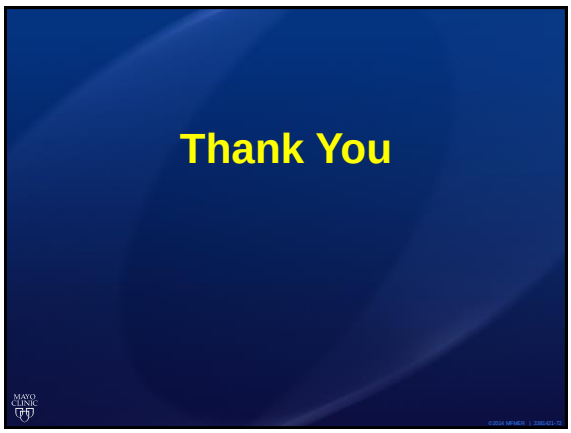

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