The DETECT Initiative in Early Alzheimer's Disease:
OPTIMIZING COLLABORATION AND MULTIDISCIPLINARY CARE TO FACILITATE TIMELY DIAGNOSIS

Welcome to the pre-program component of ***The DETECT Initiative in Early Alzheimer's Disease: Optimizing Collaboration and Multidisciplinary Care to Facilitate Timely Diagnosis.*** In this brief activity, you will be presented with **Points to Ponder** and view 2 whiteboard animations: one on distinguishing mild cognitive impairment (MCI) in Alzheimer's disease (AD) and the other on pathophysiological changes that can serve as pharmacologic targets in the treatment of AD. Additionally, completing the provided clinical primer on foundational elements of AD will prepare you for a dynamic, interactive clinical workshop experience.

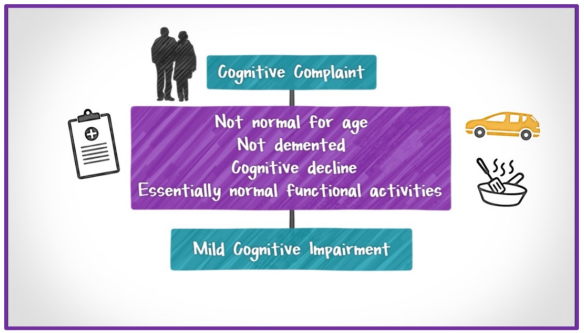
POINTS TO PONDER

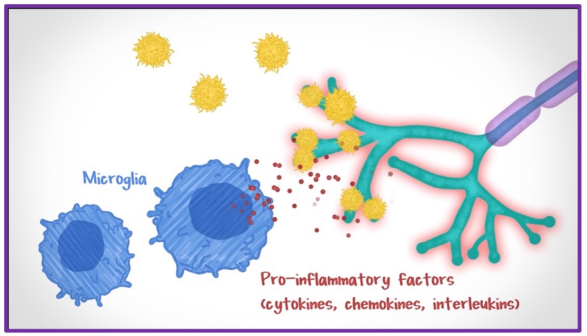
1. Why is early diagnosis of Alzheimer's disease important?
2. Describe how you provide multidisciplinary care to your patients with mild cognitive impairment (MCI) or AD.
3. What percentage of the patients with AD that you see were diagnosed in the early stages of the disease (ie, MCI)?
4. When should you consider intervention with symptomatic treatment and disease-modifying therapy?
5. What is the greatest challenge to convincing patients (or their caregivers) to enter a clinical trial?

ANIMATIONS

Click on each image to view

Establishing a Diagnosis of MCI in AD





Pathophysiologic Changes as Pharmacologic Targets in AD

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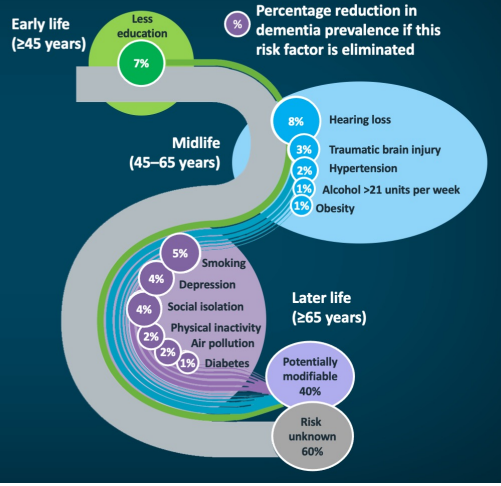
Key Facts About AD and ADRD

- **Alzheimer's disease (AD) and AD-related dementias (ADRD):**
  - Are highly prevalent, often co-occur in late life; are costly and incurable neurodegenerative diseases
  - Caused by protein misfolding and toxicity ⇒ neuroinflammation and cellular disruption, injury, and death
  - Are marked by complex, dynamic processes that occur over decades of presymptomatic phases
  - Can result in heterogeneous presentations (syndromes) in symptomatic "clinical" phases
  - Amyloid/tau/neurodegeneration biological framework of AD separates pathobiological disease stages from clinical illness and syndromic stages
- Prevalence and burden of AD/ADRD are significantly increasing as populations age worldwide
- **Many clinicians confound "common-but-impaired" with "normal" cognitive changes, often delaying diagnosis for several years in patients with concerns or symptoms; many patients never receive a diagnosis**
- With biomarkers found in cerebrospinal fluid and on PET imaging, as well as emerging blood-based biomarkers, AD can now be accurately diagnosed during life, enabling development and use of therapies that target underlying biology of AD

Alzheimers Disease International. World Alzheimer Report 2019: Attitudes to dementia (www.alzint.org/u/WorldAlzheimerReport2019.pdf). Accessed 1/28/2023. Atri A. *Med Clin North Am*. 2019;103:263-293. Knopman DS, et al. *Nat Rev Dis Primers*. 2021;7:33. Hansson O. *Nat Med*. 2021;27:954-963.

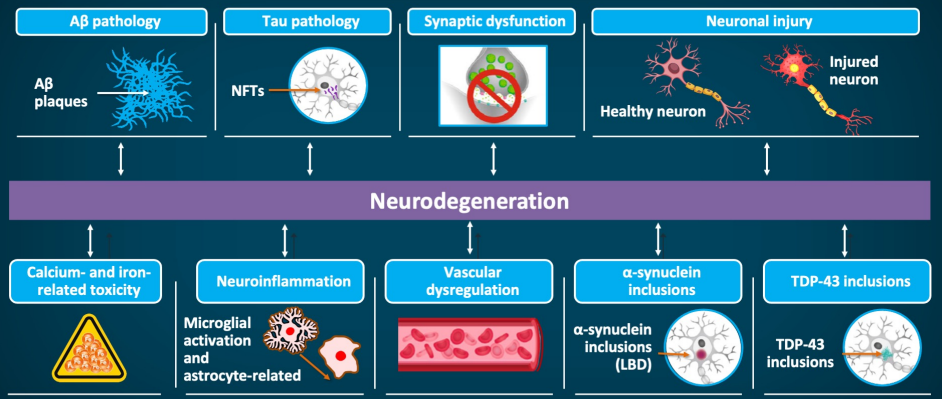
Prevalence of AD and Potential Modifiable Risk Factors

- It is theorized that modifying these 12 risk factors may prevent or delay up to *40% of worldwide dementias*
- **Early**-life (≤45 years) risks affect cognitive reserve (ie, less education)
- **Mid-** and **later**-life (≥45 years) risk factors influence reserve and triggering of neuropathological developments



Livingston G, et al. *Lancet*. 2020;396:413-446.

Multiple Mechanisms Implicated in AD and ADRD



Aβ = amyloid beta; NFT = neurofibrillary tangle; LBD = Lewy body dementia; TDP-43 = transactive response DNA-binding protein 43; DNA = deoxyribonucleic acid.

Modified from Molinuevo JL, et al. *Acta Neuropathol*. 2018.136:821-853. Hampel H, et al. *Nat Rev Drug Discov*. 2010;9:560-574.

Clinicopathologic Spectrum of Potential Contributors to Cognitive Impairment or Dementia

Genes	• *PRNP*	• *APP* • *PSEN1* • *PSEN2* • *(APOE)* • *(ABCA7)* • *(TOMM4D)*	• *MAPT*	• *C9orf72* • *GRN* • *VCP* • *TARDBP* • *TBK1* • *DCTN1*	• *FUS*	• *PARK2* • *LRRK2* • *SNCA* • *SLARB2* • *DJ1* • *PINK1* • *(GBA)*
Normal proteins	PrP^C	$A\beta_{42}$ and $A\beta_{40}$	Tau (3R or 4R)	TDP-43	FUS	α-synuclein
Misfolded and/or aggregated proteins	PrP^{Sc}	Aβ	Hyperphosphorylated tau	TDP-43	FUS	Lewy bodies
	Extracellular		Intracellular			
	Aggregation in venerable CNS areas					
Pathology	Prion disease	AD	AD		Lewy body	
Syndromes	Prion-related dementia • CJD and variant CJD • Fatal familial insomnia • Gerstmann-Sträussler-Scheinker syndrome	AD dementia • "Amnestic" late-onset AD • Behavioral dysexecutive AD • Logopenic variant PPA • Posterior cortical atrophy	FTD • Behavioral variant FTD • Nonfluent/agrammatic variant PPA • Semantic variant PPA • FTD-MND • Corticobasal syndrome • Progressive supranuclear palsy syndrome		LBD dementia • Dementia with Lewy bodies • Parkinson disease dementia	

Cerebrovascular: vascular-ischemic brain injury

Toxins/drugs (alcohol)
Metabolic
Trauma
Infectious
Inflammatory
Autoimmune
Neoplastic
Anoxic
Sleep disorders
Normal-pressure hydrocephalous
Severe psychiatric conditions
Other neurologic contributors

PrP = cellular prion protein; TDP = TAR DNA-binding protein; FUS = fused in sarcoma; CNS = central nervous system; CJD = Creutzfeldt-Jakob disease; PPA = primary progressive aphasia; FTD = frontotemporal dementia; FTD/MND = FTD with motor neuron disease.

Elahi FM, Miller BL. *Nat Rev Neurol*. 2017;13:457-476. Atri A. *Med Clin North Am*. 2019;103:263-293.

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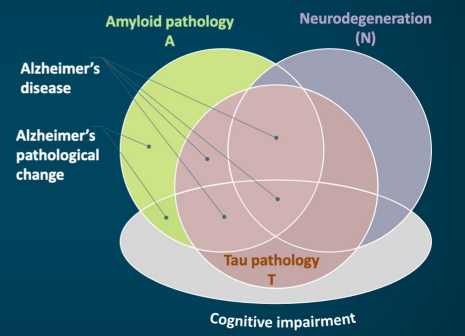
NIA-AA Research Framework: *Defining AD Biologically*

- **A = aggregated Aβ or associated pathologic state**
  - CSF $A\beta_{42}$ or $A\beta_{42}/A\beta_{40}$ ratio
  - Amyloid PET
- **T = aggregated tau (neurofibrillary tangles) or associated pathologic state**
  - CSF phosphorylated tau
  - Tau PET
- **(N) = neurodegeneration or neuronal injury**
  - Anatomic MRI
  - FDG PET
  - CSF total tau

Venn diagram of AT(N) biomarkers



NIA = National Institute on Aging; AA = Alzheimer's Association; Aβ40 = 40-amino acid form of Aβ; Aβ42 = 42-amino acid form of Aβ; CSF = cerebrospinal fluid; FDG = fluorodeoxyglucose; MRI = magnetic resonance imaging; PET = positron emission tomography.

Modified from Jack CR, Jr, et al. *Alzheimers Dement*. 2018;14:535-562.

Symptomatic Stages of AD

National Institute on Aging and Alzheimer's Association Research Framework

Stage 1	Stage 2	Stage 3 (MCI)	Stage 4	Stage 5	Stage 6
No objective or subjective evidence for cognitive decline or impairment and no behavioral symptoms	Subjective or subtle objective cognitive decline (or both), and criteria for impairment not met; mild, recent-onset behavioral symptoms could co-occur or could be the predominant symptom	Objective cognitive decline to the level of impairment, and mild functional impairment possible, but independence preserved	Mild dementia	Moderate dementia	Severe dementia

No objective cognitive impairment → Severe objective cognitive impairment

The stages apply only to individuals who are in the Alzheimer's disease continuum, which is defined by biomarker evidence of amyloid pathology with or without tau pathology and is irrespective of neurodegeneration status

Color scheme indicates continuous progression of cognitive impairment in an individual, from no objective cognitive impairment (blue) to severe objective cognitive impairment (red).

MCI = mild cognitive impairment.

Jessen F, et al. *Lancet Neurol*. 2020;19:271-278. Jack CR, Jr, et al. *Alzheimers Dement*. 2018;14:535-562.

Three Fundamental Steps in Assessment

Step 1: Is something potentially abnormal?

- Detection of potential impairment
  - delineate the cognitive functional status
- At what likely level:
  - Cognitively unimpaired (CU)
  - Subjective cognitive decline (SCD)
  - Mild cognitive impairment (MCI)
  - Mild dementia

Step 2: Identify pattern of what is abnormal

What are the characteristics of what is wrong?

- Define cognitive-behavioral syndrome
  - ie, amnestic syndrome, primary progressive aphasia, post-cortical atrophy
- Delineating domains of impairment
  - ie, single domain vs multidomain, non-amnestic, behavioral, and language dementia in mild stages

Step 3: Step 3: What is causing it?

What are potential causes, etiologies, and contributing factors?

- AD
- Lewy body disease
- Primary tauopathies
- TDP43 proteinopathy
- Vascular ischemic brain injury
- Obstructive sleep apnea
- Alcohol misuse
- Polypharmacy
- Anxiety/mood disorder

TDP43 = TAR DNA protein 43.

Atri A. *Med Clin North Am*. 2019;103:263-293.

MMSE vs MoCA

Mini-Mental Status Exam (MMSE)[1,2]

- Widely used **screening test for cognitive impairment (CI)**
- Scores range from 0 to 30
- Scores should be considered in alignment to patient background (education, culture, social factors)
- A score of 26 may provide concern for MCI (put in clinical context for individuals)

Montreal Cognitive Assessment (MoCA)[2-4]

- Designed as a **screening instrument for the detection of MCI**
- Scores range from 0 to 30
- Measures executive functions and multiple cognitive domains
- Use MoCA to assess for impairment with MMSE scores that are unimpaired
- Although a total score of ≥26 is considered normal, this can still be consistent with impairment

1. Liss JL, et al. *J Intern Med*. 2021;290:310-334. 2. Shaughnessy L, et al. *J Clin Psychiatry*. 2019;80:MS18002BR2C. 3.Nasreddine ZS, et al. *J Am Geriatr Soc*. 2005;53:695-699. 4. MoCA Cognition. FAQ (https://mocacognition.com/faq/). MoCA. About us (https://mocacognition.com/about/). URLs accessed 1/28/23.

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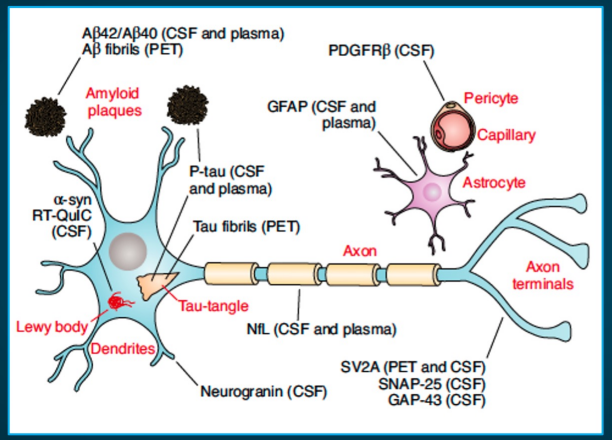
CLINICAL PRIMER

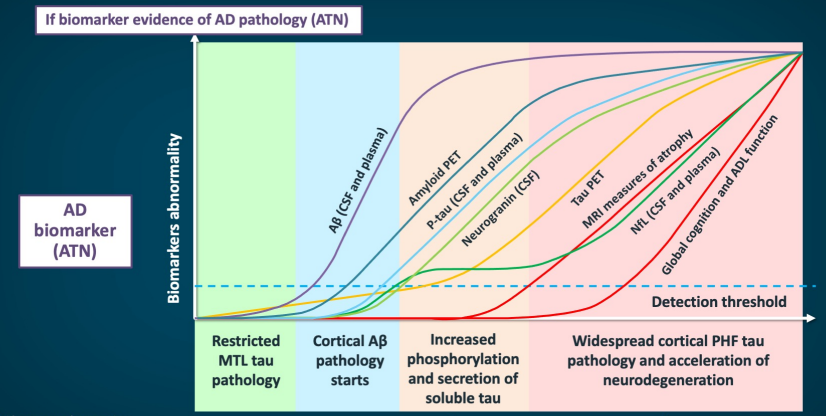
Biomarkers in Neurodegenerative Diseases: A Neuronal View



PDGFRβ = platelet-derived growth factor receptor beta; GFAP = glial fibrillary acidic protein; P-tau = phosphorylated tau; α-syn = alpha-synuclein; RT-QuIC = real-time quaking-induced conversion; NfL = neurofilament light; SV2A = synaptic vesicle glycoprotein 2A; SNAP-25 = synaptosomal-associated protein 25; GAP-43 = growth-associated protein 43.

Hansson O. *Nat Med*. 2021;27:954-963.

Trajectory of Biomarkers in the AD Continuum: ATN



ATN = amyloid, tau, neurodegeneration; MTL = medial temporal lobe; ADL = activities of daily living; PHF = paired helical filaments.

Modified from Hansson O. *Nat Med*. 2021;27:954-963.

Biomarkers for Alzheimer's Disease

	Biomarker changes consistent with Alzheimer's disease	
	Biomarker measurement	**Biomarker changes**
A	$A\beta_{42}$ accumulation[1,2]	$A\beta_{42}$ levels ↓ in CSF $A\beta_{42}$ plaques can be seen on amyloid PET scan
T	Tau_{HP} accumulation[3]	Tau_{HP} levels ↑ in CSF Hyperphosphorylated tau can be seen on tau PET scan
	Synaptic dysfunction[4]	Temporoparietal hypometabolism on FDG-PET (also hypoperfusion on SPECT); probably associated with AD pathology but non-specific
N	Loss of brain volume[5]	Atrophy can be seen on MRI and can be measured with MRI volumetrics (hippocampus and MTL, temporoparietal atrophy; non-specific)
	Neurogranin[6]	Ng levels ↑ in CSF in AD, but not other neurodegenerative disorders
	NfL[6]	CSF or plasma; concentration ↑ in AD, particularly rapid disease progression May reflect subcortical/white matter damage across range of disorders

A = amyloid; T = tau; N = neurodegeneration; HP = hyperphosphorylated; SPECT = single-photon emission computed tomography; Ng = neurogranin.

1. Morris JC, et al. *Arch Neurol*. 2009;66:1469-1475. 2. Sperling RA, et al. *Neuron*. 2009;63:178-188. 3. Fagan AM, et al. *Arch Neurol*. 2007;64:343-349. 4. de Leon MJ, et al. *AJNR Am J Neuroradiol*. 1983;4:568-571. 5. Atiya M, et al. *Alzheimer Dis Assoc Disord*. 2003;17:177-195. 6. Liss JL, et al. *J Intern Med*. 2021;290:310-334.

Brain Changes on FDG-PET in Normal Aging, MCI, AD, and FTD

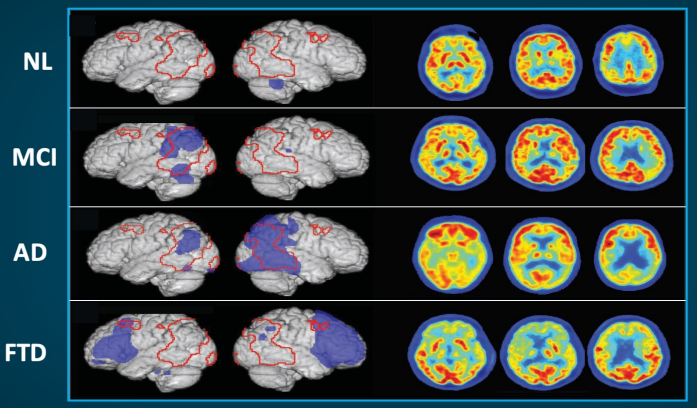


Image courtesy of Bradford Dickerson, MD.

NL = normal; FTD = frontotemporal dementia.

Reiman EM, et al. *N Engl J Med*. 1996;334:752-758. Reiman EM, et al. *Proc Natl Acad Sci USA*. 2001;98:3334-3339. Reiman EM, et al. *Proc Natl Acad Sci USA*. 2004;101:284-289. Reiman EM, et al. *Proc Natl Acad Sci USA*. 2005;102:8299-8302. Bonifacio G, Zamboni G. *Postgrad Med J*. 2016;92:333-340.

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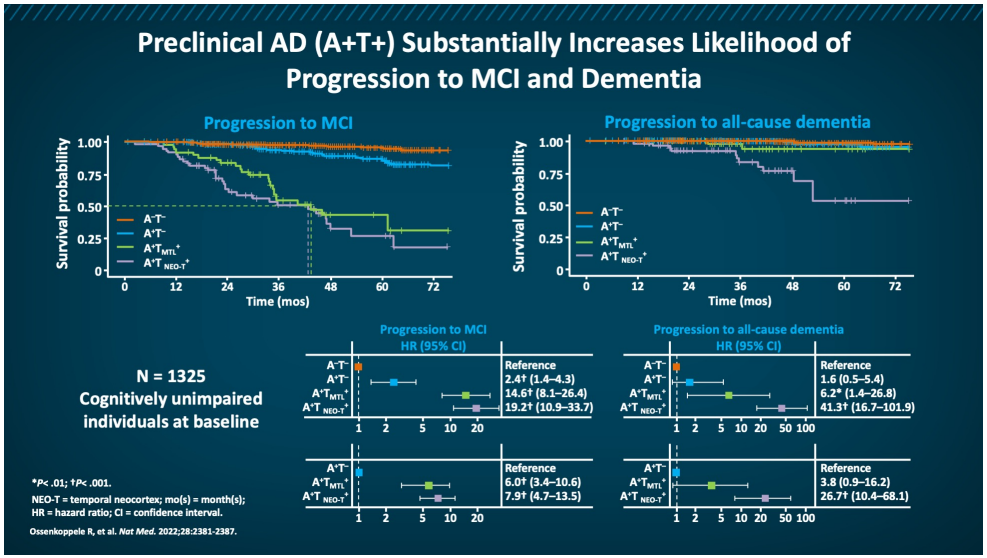

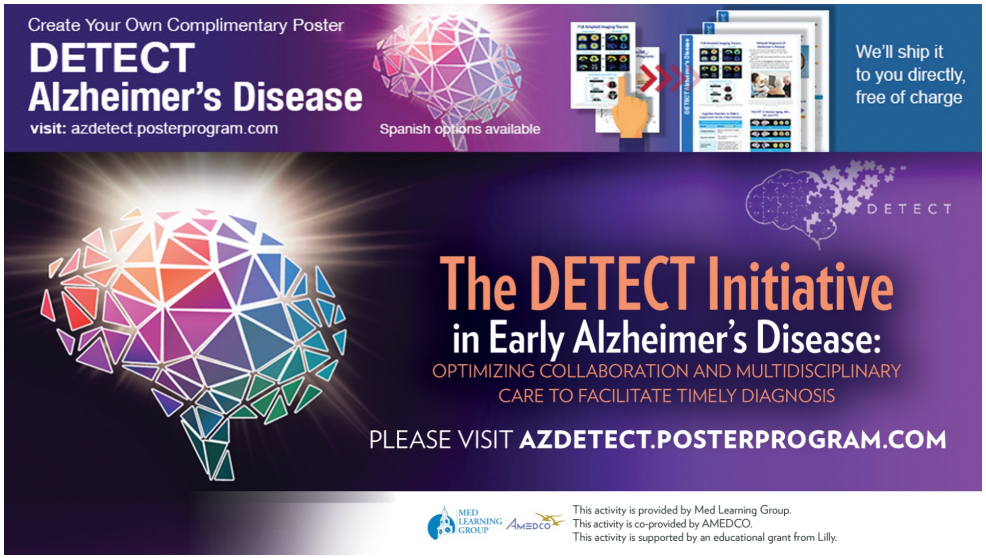

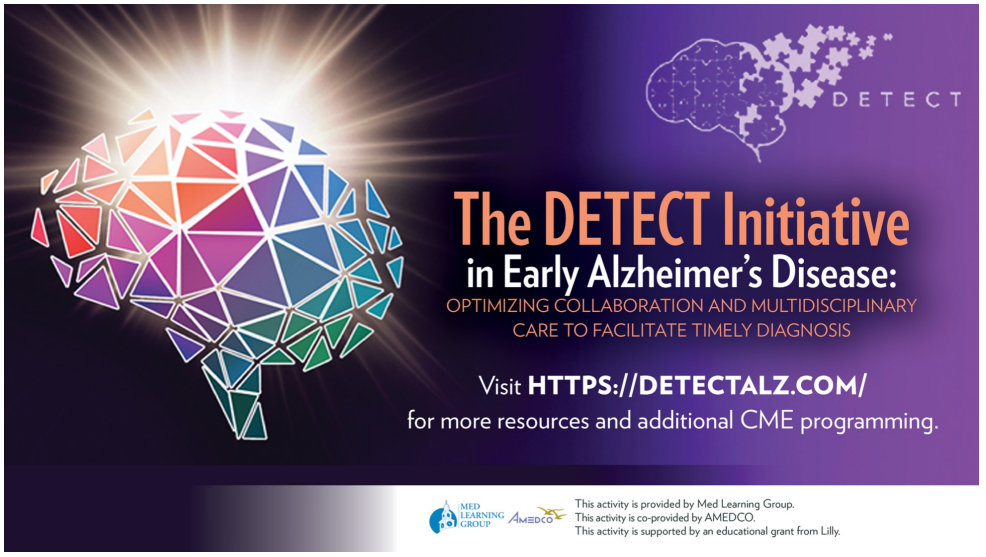

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