BRIDGING COMMUNITY:

Collaborative Efforts in Early Detection and Intervention for Alzheimer's Disease

This activity is supported by an educational grant from Lilly.

Faculty

Ariel Cole, MD, CMD, FAAFP
Director, AdventHealth Geriatric Medicine Fellowship
Geriatrics Clerkship Director, Orlando Campus
Florida State University College of Medicine
Winter Park, FL, USA

Alireza Atri, MD, PhD
Chief Medical Officer
Banner Research
Director, Banner Sun Health Research Institute
Sun City, AZ, USA

Anton P. Porsteinsson, MD
William B. and Sheila Konar Professor of Psychiatry, Neurology, Neuroscience, and Medicine
Director, Alzheimer's Disease Care, Research and Education Program (AD-CARE)
University of Rochester School of Medicine
Rochester, NY, USA

Elizabeth Poynor, MD, PhD
Chair, Women's Health and Gynecology Atria Institute
Clinical Professor Obstetrics and Gynecology, NYU Langone
New York, NY, USA

Activity Overview

Target Audience

This activity is intended for primary care practitioners (including ob/gyns and NPs/PAs), general neurologists, psychiatrists, and other members of the multidisciplinary, interprofessional healthcare team in the U.S. who are uniquely positioned to manage patients at risk of cognitive impairment and Alzheimer's Disease (AD).

Educational Objectives

After completing this activity, the participant should be better able to:

- Integrate strategies into care plans that optimize brain health for patients with factors that increase the risk of cognitive decline and AD
- Describe the latest evidence supporting the need for the early detection of mild cognitive impairment in the AD continuum
- Develop patient-centered communication strategies to address brain health and cognitive concerns with patients and their caregivers

Agenda

- Introduction and pre-assessment
- Integrating Evidence-Based Strategies for Improving Brain Health: Managing Modifiable Risk Factors in Cognitive Decline and AD
    - Advanced epidemiology and pathophysiology of cognitive decline and AD
- Recognizing the Critical Role of Early Detection in the AD Continuum to Improve Outcomes: Leveraging Assessment, Advanced Diagnostics, and Treatment Strategies
    - Transformative impact of early detection in AD: Detailed exploration of AD as a continuum and the importance of preclinical detection
    - Benefits of Early Recognition of Cognitive Impairment
    - Taking Advantage of the Medicare Annual Wellness Visit
    - The Diagnostic Process
    - The Role of Biomarkers in Identifying Patients Early in the Disease Course and Informing Treatment
    - Medical Management of Early AD
- Designing Patient-Centered Communication Plans for Discussing Brain Health and Cognitive Concerns
    - Effective communication strategies
    - Empathetic and clear communication techniques
    - Addressing emotional and practical concerns
- Conclusion, Post-Assessment/Post-Test, & Evaluation

Accreditation Information

In support of improving patient care, Medical Learning Institute Inc is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Participation information will be shared through the ACCME's Program and Activity Reporting System (PARS).

AAFP CME Credit

The AAFP has reviewed Bridging Community: Collaborative Efforts in Early Detection and Intervention for Alzheimer's Disease and deemed it acceptable for up to 1.0 Enduring Materials, Self-Study AAFP Prescribed credit(s). Term of Approval is from 01/15/2025 to 01/14/2026. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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Nurse Practitioner

This education activity will be submitted to the American Association of Nurse Practitioners® for approval of up to 1.0 contact hours of accredited education. Upon AANP's approval to activity application, they will provide their approved NP credit statement and activity ID# to use.

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Ariel Cole, MD, CMD, FAAFP has no relevant financial relationships with ineligible companies to disclose for this educational activity.

Planner/Presenter
Alireza Atri, MD, PhD has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor: Eisai, Life Molecular Imaging, Novo Nordisk; *Research Support/Grant:* ACTC, ADCS, Alzheon, Athira, AZ Alzheimer's Research Consortium and AZ DHS, ATRI, GAP, Biogen, Biohaven, Eisai, Foundation for NIH (FNIH), Gates Ventures, Indiana University, Johns Hopkins, Lilly, NIA/NIH, USC, Vivoryon, Washington University St. Louis; *Other:* Royalties or licenses: Oxford University Press / Support for attending meetings and/or travel: Alzheimer's Association (US), Alzheimer's Disease International (ADI), American Academy of Neurology (AAN), Michael J Fox Foundation (MJFF)
The following relationships have ended within the last 24 months:
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Anton P. Porsteinsson, MD has a financial interest/relationship or affiliation in the form of:
Consultant/Advisor: Acadia Pharmaceuticals, Athira, Axsome, Biogen, Bristol Myers Squibb, Cognitive Research Corp, Eisai, IQVIA, Lundbeck, Novartis, ONO Pharmaceuticals, Otsuka, WCG, WebMD, and Xenon; *Research Support (grants to institution)*: Alector, Athira, Biogen, Cassava, Eisai, Eli Lilly, Genentech/Roche, Vaccinex, NIA, NIMH, and DOD

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Disclaimer

Participants have an implied responsibility to use the newly acquired information to enhance patient outcomes and their own professional development. The information presented in this CE activity is not meant to serve as a guideline for patient management. Any procedures, medications, or other courses of diagnosis or treatment discussed or suggested in this CE activity should not be used by clinicians without evaluation of their patient's conditions and possible contraindications and/or dangers in use, review of any applicable manufacturer's product information, and comparison with recommendations of other authorities.

Method of Participation

There are no fees for participating in or receiving credit for this CE activity. In order to receive credit, learners must participate in the entire CE activity, complete the activity evaluation form and your certificate of credit will be generated. A passing score of 70% or higher is needed to obtain credit. You will receive your certificate from Medical Learning Institute Inc.
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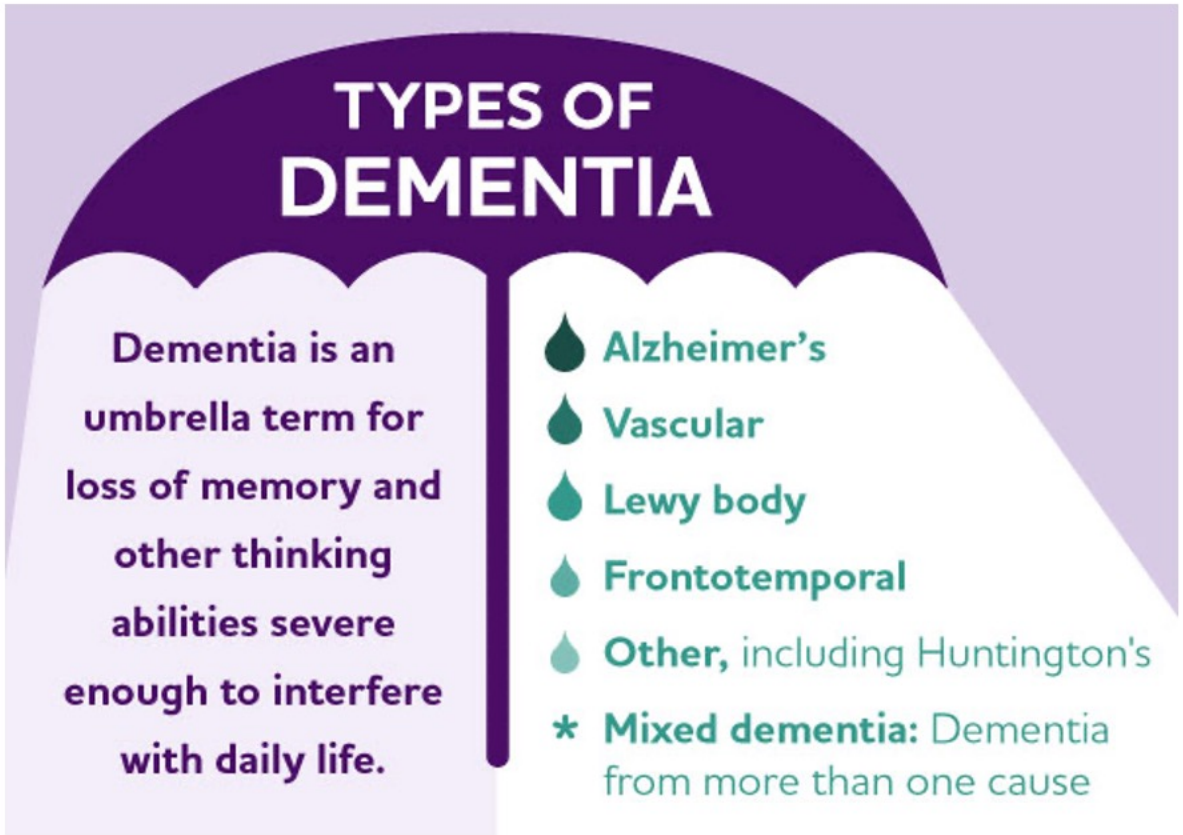
For Physician, If requesting MOC credit, the post-test and evaluation are required in their entirety as well as your ABIM ID number, DOB (MM/DD), and a score of 70% or higher is needed to obtain MOC credit.

Categories in Cognitive Disorders Spectrum



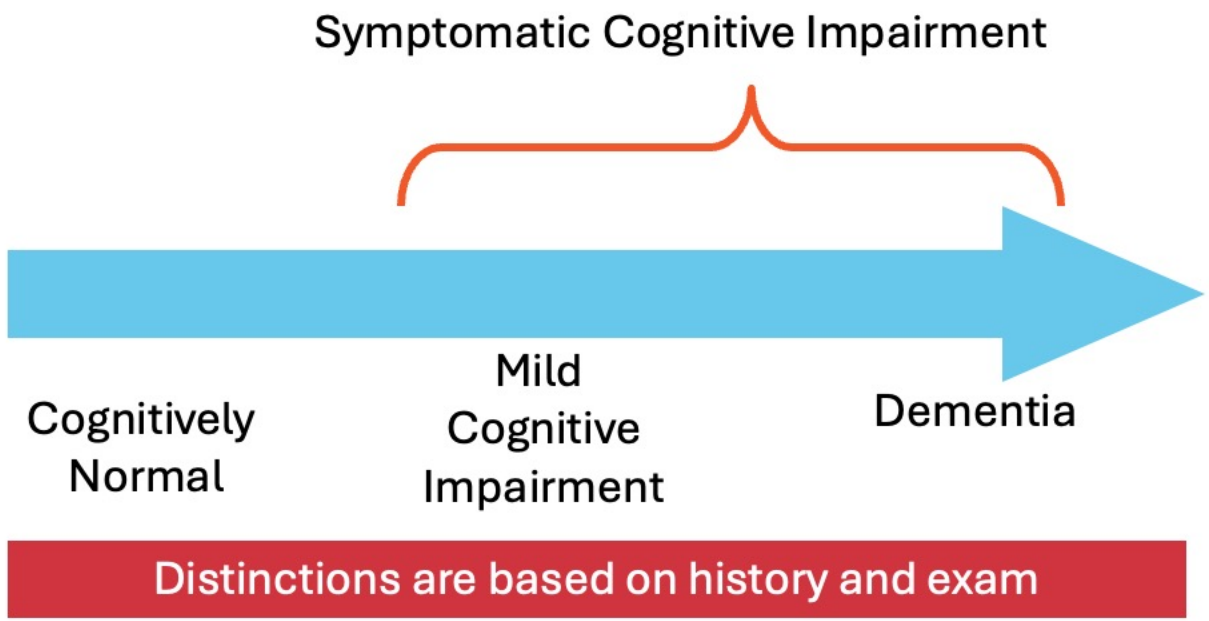
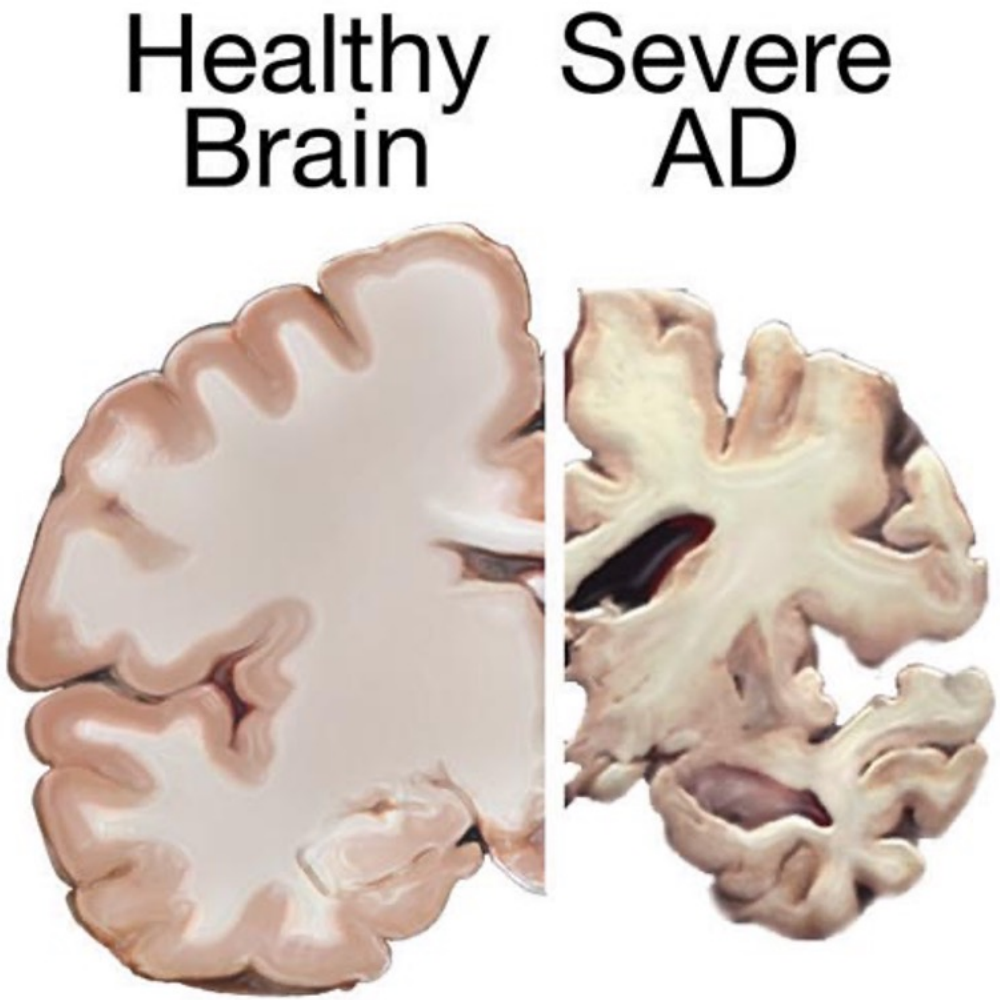


Image from: https://www.alz.org/media/HomeOffice/Inline%20Image/what-is-dementia-causes-symptoms-inlineimage.jpg.
Mayo Clinic. Mild Cognitive Impairment. October 24, 2024. https://www.mayoclinic.org/diseases-conditions/mild-cognitive-impairment/symptoms-causes/syc-20354578. Accessed December 11, 2024.

Alzheimer's Disease

- Significant cognitive impairment affecting social or occupational functioning, representing a significant decline from previous level of functioning
- Slow, progressive decline
- Long presymptomatic phase (20 years)
- Pathological hallmarks:
    1. Neuritic plaques with extracellular amyloid beta deposition
    2. Neurofibrillary tangles with intracellular hyperphosphorylated tau protein



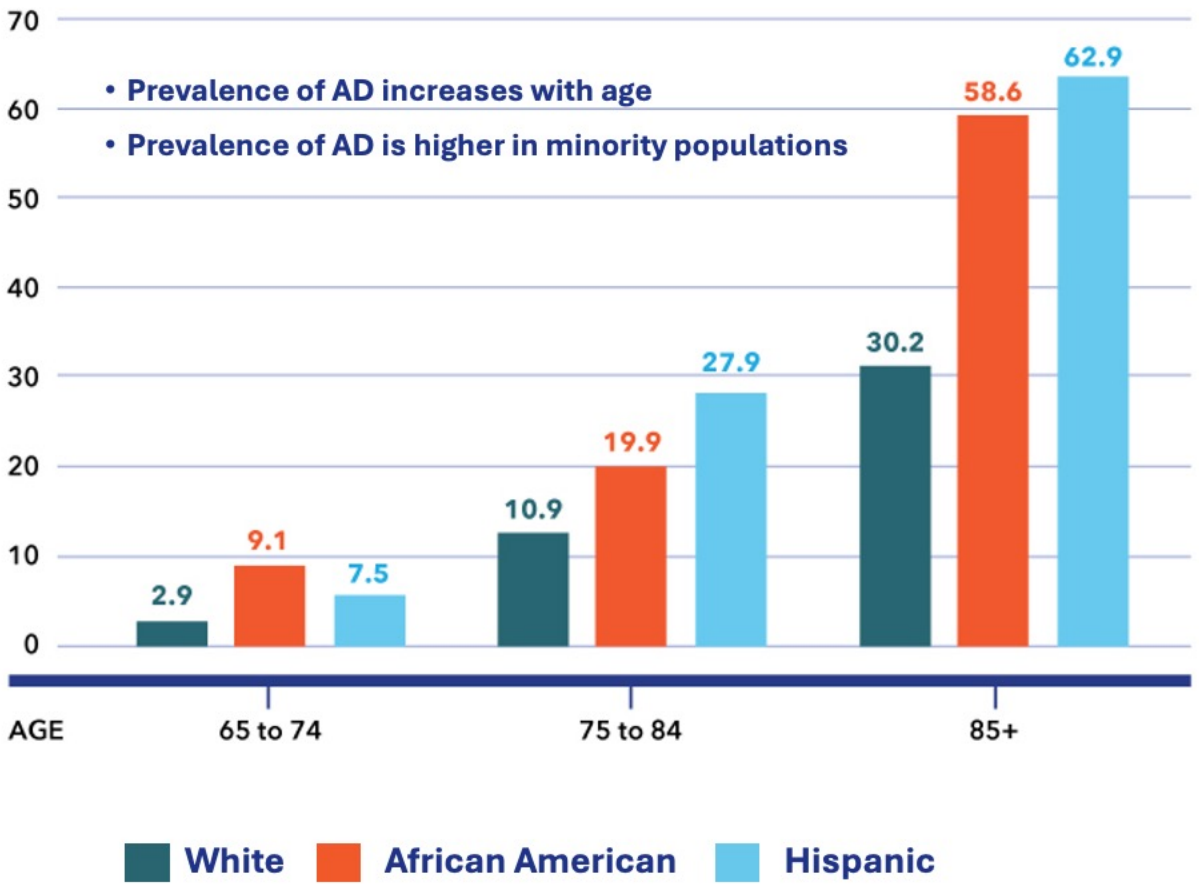
AD, Alzheimer's disease.

Image from: https://commons.wikimedia.org/wiki/Alois_Alzheimer#/media/File:Auguste_D_aus_Marktbreit.jpg.

Sheppard O, Coleman M. Alzheimer's Disease: Etiology, Neuropathology and Pathogenesis. In: Huang X, editor. *Alzheimer's Disease: Drug Discovery*. Brisbane (AU): Exon Publications; 2020. https://www.ncbi.nlm.nih.gov/books/NBK566126/ doi: 10.36255/exonpublications.alzheimersdisease.2020.ch1. Accessed December 11, 2024.

Alzheimer's Disease

- Most common cause of dementia
- 6th leading cause of death in US
- Currently, approximately **6 million** people affected in US, **32 million** worldwide
- Projected to be ~**13-16 million** by 2050 in US
- 10% > 65 y/o, 40% > 85 affected in US



Alzheimer's Association. 2024 Alzheimer's Disease Facts and Figures. *Alzheimers Dement* 2024;20(5).

Pathophysiology of AD

- Complex neuropathology with multiple mechanisms contributing to pathogenesis and progression
- Brain amyloid accumulation is clearly involved, but also clearly not the entire cause of AD
  - Anti-amyloid antibody medications have yet to improve cognitive function or even stop progression of the disease
  - Elevated brain amyloid is a common finding in brains of clinically normal persons in post-mortem studies
- Hyperphosphorylation of tau protein damages neuronal structure and function, leading to cell death
  - Correlates with brain amyloid burden
  - Inhibitors for the kinases that phosphorylate tau are currently in studies

Sheppard O, Coleman M. Alzheimer's Disease: Etiology, Neuropathology and Pathogenesis. In: Huang X, editor. *Alzheimer's Disease: Drug Discovery*. Brisbane (AU): Exon Publications; 2020. https://www.ncbi.nlm.nih.gov/books/NBK566126/ doi: 10.36255/exonpublications.alzheimersdisease.2020.ch1.

New Clinical Diagnostic Criteria on the Horizon: 2023 Update to the NIA-AA

- In 2018, NIA-AA developed a biological definition of AD
  - Criteria included Aβ, tau, and neurodegeneration (ATN)
  - Intended for use as research diagnostic criteria
- In August 2023, the NIA-AA definition was updated using the most well-validated biomarkers
  - Changed to form the updated ATNIVS scheme
    - Retained Aβ plaques and tau tangles as core criteria
    - Added neurodegeneration and inflammation as nonspecific biomarkers
    - Added biomarkers of non-AD co-pathology
  - Intended to advance prior criteria toward clinical use

Categorization of Fluid Analyte and Imaging Biomarkers

Category	Fluid (CSF or plasma)	Imaging
Core biomarkers		
Core 1		
Aβ plaques (A)	Aβ42	Aβ PET
Phosphorylated and secreted AD tau (T_1)	p-tau 217, p-tau 181, p-tau 231	
Core 2		
AD tau proteinopathy (T_2)	pT205, MTBR-243, non-phosphorylated tau fragments	Tau PET
Nonspecific biomarkers of AD pathology		
Neural injury, dysfunction, or degeneration (N)	NfL	Anatomic MRI, FDG PET
Inflammation (I)	GFAP	
Biomarkers of non-AD copathology		
Vascular injury (V)		Infarction on MRI or CT, WMH
α-synuclein (S)	αSyn-SAA (CSF)	

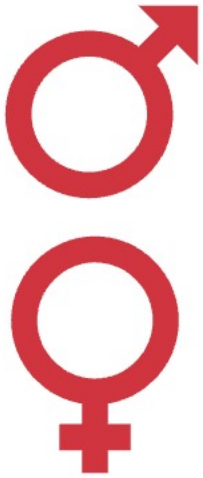
PET **or** fluid results are used to stage AD as initial-, early-, intermediate-, or advanced-stage disease (stages A-D).

ATNIVS, amyloid, tau, neurodegeneration, inflammation, vascular burden, alpha-synuclein; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; NIA-AA , National Institute on Aging and the Alzheimer's Association.

Jack CR Jr, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement*. 2024;20(8):5143-5169.

Long-Established Risk Factors for Dementia

- **Age** – aging is the strongest known risk factor
- **Sex** – women are more likely to develop dementia than men
- **Ethnicity** – people from certain ethnic communities appear to be at a higher risk (e.g., people from South Asia)
- **Genetics** – there are > 20 genes that have been linked to a risk of dementia, including *APOE*
- **Medical conditions**, particularly those that damage the heart, have been linked to an increased risk of dementia:
  - Type-2 diabetes
  - High blood pressure
  - High cholesterol
  - Obesity



APOE, apolipoprotein E.

Alzheimer's Society. Risk factors for dementia. Factsheet 450LP, 2016. https://www.alzheimers.org.uk/sites/default/files/pdf/factsheet_risk_factors_for_dementia.pdf. Accessed December 11, 2024.

Measuring Risk of Developing Dementia

Methods for dementia risk assessment

Type of approach	Target population	Technique(s)	Variables of interest
Epidemiological	Asymptomatic adults	Self-report and other measures	Demographics; health history; health behaviours
Genetic testing	Asymptomatic adults	Blood, saliva sample	Variants/mutations in selected genes
Other biomarkers	Older adults in preclinical phases	Neuroimaging; lumbar puncture	Brain structure volumes; proteome features in biological fluids
Clinical assessment	Older adults with MCI	Neuropsychological testing; neurological exam with informant history	Cognitive functioning; history of symptoms

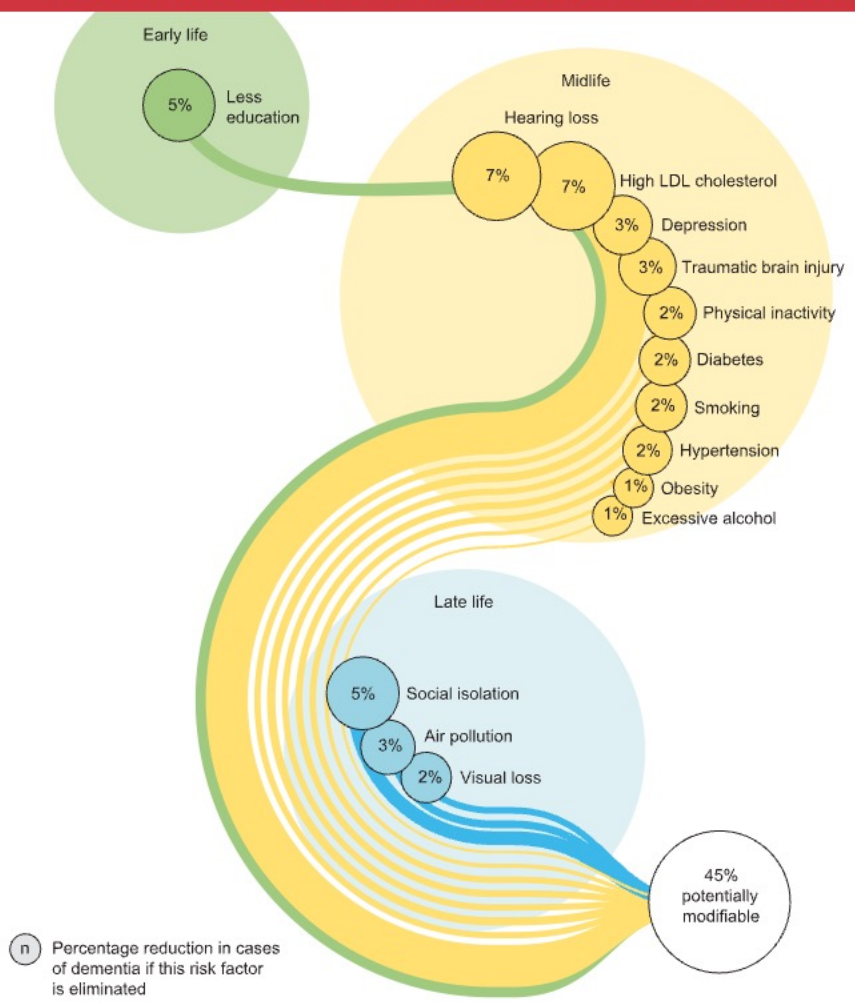
- Risk factors should be delivered in a way that patients can understand
  - Use of natural frequencies, rather than just percentages
  - Use of graphical representation for risk information
- Patients should be presented with printed, take-home material to reinforce the information they have been given
- Patients should be provided with strategies for coping with the risk information

MCI, mild cognitive impairment.
Adapted from: Roberts JS, Tersegno SM. Estimating and disclosing the risk of developing Alzheimer's disease: challenges, controversies and future directions. *Future Neurol.* 2010;5(4):501–517.

Lancet Commission Reports on the Modifiable Risk Factors for Dementia

- The 2017 Lancet commission on dementia prevention identified 9 existing risk factors in their report:
  - **Less education**
  - **Hypertension**
  - **Hearing impairment**
  - **Smoking**
  - **Obesity**
  - **Depression**
  - **Physical inactivity**
  - **Diabetes**
  - **Infrequent social contact**
- In 2020, 3 modifiable risk factors were added:
  - **Excessive alcohol consumption**
  - **Head injury**
  - **Air pollution**
- In 2024, 2 modifiable risk factors were added:
  - **Vision loss**
  - **High cholesterol**

Potentially modifiable risk factors for dementia



Livingston G, et al. Dementia prevention, intervention, and care. *Lancet*. 2017;390(10113):2673-2734; Livingston G, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413-446. Livingston G, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet*. 2024;404(10452):572-628.

Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER)

- The FINGER study targeted various modifiable vascular and lifestyle-related risk factors that have been associated with dementia risk in an **at-risk group** of elderly people from the general population

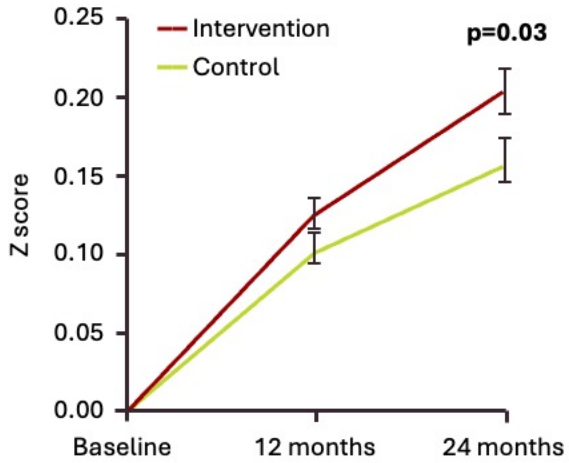
- 2654 individuals were screened
- 1260 were randomized
  - Intervention group, n=631
  - Control group, n=629

- The intervention involved:
  1. Personalized dietary guidance, including individual consultations and group sessions to support lifestyle modifications
  2. A structured physical exercise program combining muscle strength training (1–3 times per week) and aerobic activities (2–5 times per week)
  3. Cognitive training through a mix of group and individual sessions, complemented by social activities
  4. Regular monitoring of metabolic and vascular risk factors throughout the study period

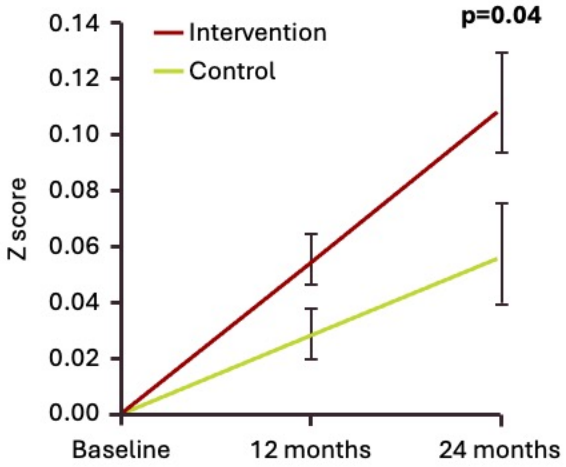
Ngandu T, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015;385(9984):2255–2263.

FINGER Study – Results

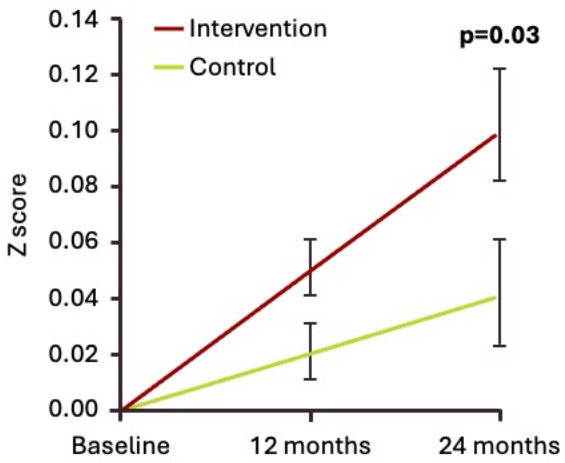
Primary: NTB total score (composite z-score)



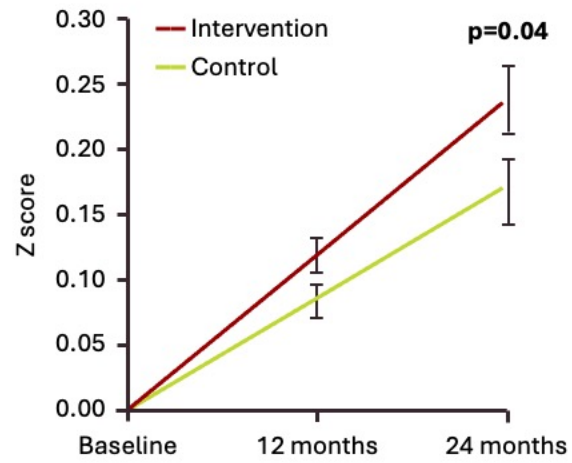
Executive functioning



Processing speed



Memory (complex tasks)



Improvement:	+25%	+83%	+150%	+40%

Outcomes of FINGER study:

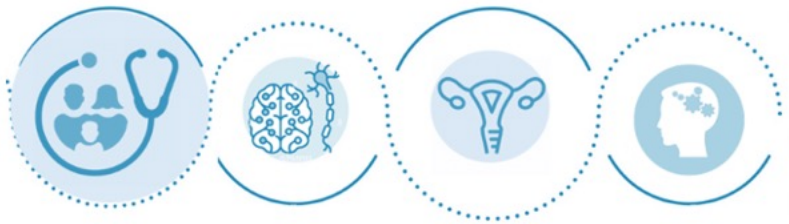
- Lower risk of cognitive decline
- Lower risk of functional decline (ADLs)
- Better health-related quality of life

ADL, activity of daily living; NTB, neuropsychological test battery.

Ngandu T, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 2015;385(9984):2255–2263; Kivipelto. Personal communication. Kulmala J, et al. The Effect of Multidomain Lifestyle Intervention on Daily Functioning in Older People. *J Am Geriatr Soc*. 2019;67(6):1138–1144; Strandberg TE, et al. Health-related quality of life in a multidomain intervention trial to prevent cognitive decline (FINGER). *Eur Geriatr Med*. 2017;8:164–167.

Multidisciplinary Clinical Perspectives

A 52-year-old overweight female with hypertension, obesity, a history of depression, traumatic brain injury, and a family history of AD presents for a routine check-up. Despite being aware of her risk factors, the patient struggles with maintaining a healthy lifestyle due to socioeconomic constraints and a demanding job.



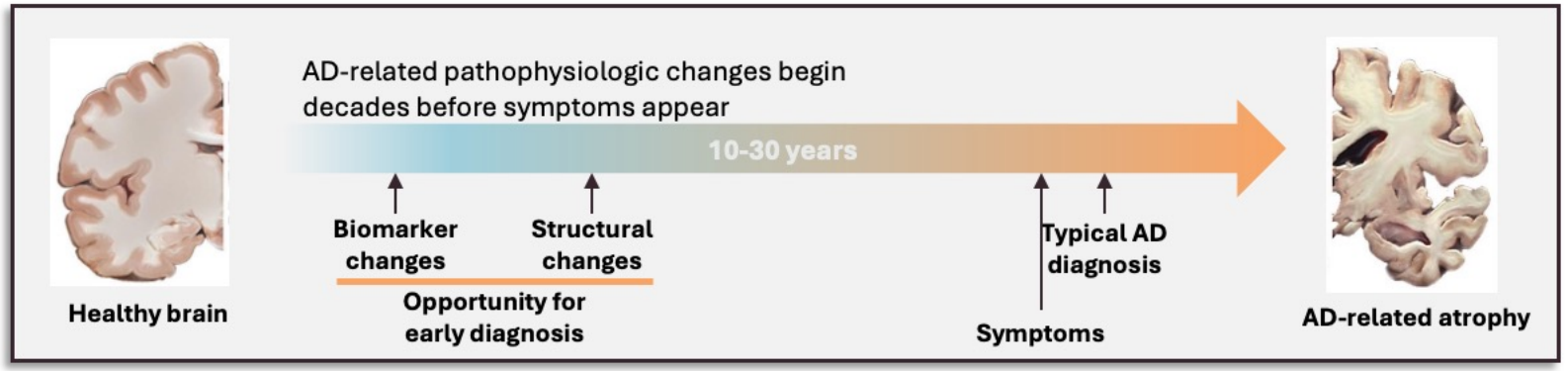
The Challenge of AD

- New course-modifying medicines will be most effective if administered early
- Current screening and diagnosis: Too little, Too late
  - 10% community elderly have undetected dementia
  - Primary care physicians fail to diagnose 33% of mild dementias
  - Diagnostic accuracy hovers around 75%

	Sensitivity	Specificity
Probable AD	81%	70%
Possible AD	93%	47%

Solomon PR, et al. Identifying Dementia in the Primary Care Practice. *Int Psychogeriatr*. 2000;12(4):483-493; Löppönen M, et al. Diagnosing cognitive impairment and dementia in primary health care -- a more active approach is needed. *Age Ageing*. 2003;32(6):606-612; Knopman DS, et al. Practice parameter: diagnosis of dementia (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2001;56(9):1143-1153.

Importance of Early AD Diagnosis

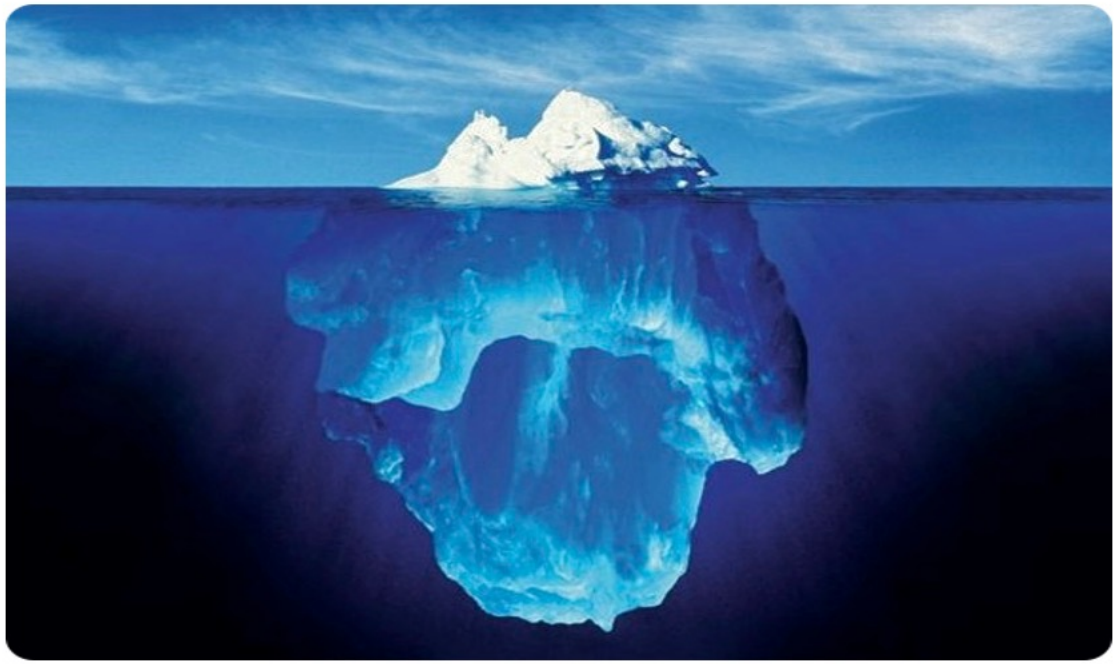


- AD has long asymptomatic and prodromal periods
- Symptoms, once present, are often minimized, misattributed, or ignored
- Early diagnosis can:
  - Improve the use of AD disease-modifying therapies (DMTs) to slow disease progression
  - Allow for the application of lifestyle interventions to slow progression
  - Increase the chances of clinical trial eligibility and participation
  - Provide additional time for patients and care partners to plan for the future

Younes L, et al. Identifying Changepoints in Biomarkers During the Preclinical Phase of Alzheimer's Disease. *Front Aging Neurosci.* 2019;11:74; Atri A. The Alzheimer's Disease Clinical Spectrum: Diagnosis and Management. *Med Clin North Am*. 2019;103(2):263-293; Rasmussen J, Langerman H. Alzheimer's Disease - Why We Need Early Diagnosis. *Degener Neurol Neuromuscul Dis*. 2019;9:123-130.

Why Prevention

- Inadequacies of current treatments
- Considerable data on risk markers
- Recognition of sub-disorder conditions



Rationale for Prevention Strategies

- Protecting intact neurons will be more feasible than repairing damaged ones
- Estimated **one-third** of risk for accelerated brain aging stems from genetic factors
- Minimal risk and general value of healthy lifestyle changes support initiating prevention strategies prior to receiving results from randomized clinical trials

Rowe JW, Kahn RL. *Successful Aging*. New York, NY: Pantheon; 1998; Small GW. What we need to know about age related memory loss. *BMJ*. 2002;324 (7352):1502-1505; Thoenen E. *An Overview of Dementia: The Growing Crisis in West Virginia*. West Virginia Department of Health and Human Resources; 2005. https://dhhr.wv.gov/HSC/publications/A_Z_Index/Documents/Dementia/Dementia_2011.pdf. December 11, 2024.

What is a Sufficient Cognitive Assessment in MCI?

Bedside exams lack precision

- Overlap with both normal cognition and dementia
- Very insensitive with respect to prognosis

Neuropsychological testing is helpful but not always available, expensive

- Characterization of persons with MCI according to cognitive domain(s) involved and degree of abnormality adds to prediction of decline

Evaluating MCI (Mild Cognitive Impairment). Harvard Health Publishing — Harvard Medical School. December 7, 2023. https://www.health.harvard.edu/mind-and-mood/evaluating-mci-mild-cognitive-impairment.

The Brain at Perimenopause

Structural and Functional Changes

- Gray matter volume (GMV) decreases in certain brain regions during perimenopause but may recover post-menopause
- Functional MRI studies indicate altered spontaneous brain activity, particularly in regions related to cognitive function and memory, such as the superior frontal gyrus and lingual gyrus
- Multi-modal MRI studies have revealed changes in brain structure, function, and perfusion during perimenopause
    - These changes are implicated in symptoms such as headaches, depression, insomnia, and cognitive decline

Energy Metabolism

- Hypometabolic state, which may increase the risk of neurodegenerative diseases
- Reduced cerebral glucose metabolism and mitochondrial efficiency

Cognitive and Mood Changes

- Women in this stage often experience deficits in verbal memory and increased risk of depressive symptoms
- Elevated monoamine oxidase A (MAO-A) levels during perimenopause may contribute to oxidative stress and apoptosis, further influencing mood and cognitive function

Mosconi L, et al. Menopause impacts human brain structure, connectivity, energy metabolism, and amyloid-beta deposition. *Sci Rep*. 2021;11(1):10867; Brinton RD, et al. Perimenopause as a neurological transition state. *Nat Rev Endocrinol*. 2015;11(7):393-405; Mosconi L, et al. Perimenopause and emergence of an Alzheimer's bioenergetic phenotype in brain and periphery. *PLoS One*. 2017;12(10):e0185926; Rekkas PV, et al. Greater Monoamine Oxidase A Binding in Perimenopausal Age as Measured With Carbon 11–Labeled Harmine Positron Emission Tomography. *JAMA Psychiatry*. 2014;71(8):873-879; Weber MT, et al. Cognition and mood in perimenopause: a systematic review and meta-analysis. *J Steroid Biochem Mol Biol*. 2014;142:90-98; Halpain S, et al. Loss of 3H-corticosterone binding capacity in hippocampal slices maintained in vitro. Brain Res Bull. 1986;16(2):167-170. He L, et al. Altered Spontaneous Brain Activity in Women During Menopause Transition and Its Association With Cognitive Function and Serum Estradiol Level. *Front Endocrinol* (*Lausanne*). 2021;12:652512.

Health Considerations and Opportunities at Perimenopause/Menopause

Health Assessment for Women at Midlife

- Cardiovascular disease risk (blood pressure and lipids)
- History and narrative concerning menopausal signs/symptoms
- Urogenital/Sexual health (consider local hormonal/non-hormonal therapy)
- Cancer screening: breast check, cervical cancer screening, mammogram, colonoscopy
- Metabolic (waist-hip circumference, fasting blood glucose and A1c)
- Lifestyle screening and interventions
- Mental health screening

Harlow SD, et al. Women's midlife health: the unfinished research agenda. *Womens Midlife Health*. 2023;9(1):7; Thomas HN, Thurston RC. A biopsychosocial approach to women's sexual function and dysfunction at midlife: A narrative review. *Maturitas*. 2016;87:49-60; Faubion SS. Routine screening tests for women as they enter midlife and beyond. Mayo Clinic. January 19, 2022. https://mcpress.mayoclinic.org/women-health/routine-screening-tests-for-women-as-they-enter-midlife-and-beyond/. Accessed December 11, 2024.

The Brain and Neuroendocrine Aging

More than two-thirds of AD patients are women

- *Age-standardized dementia prevalence is higher in women*
  - *Female-to-male ratio = 1.69 (1.64–1.73)*
- *The neurophysiological impact of estrogen decline during menopause is emerging as the main basis for the higher prevalence of AD in females*
- Only 0.5% of neuroscience studies look at women's health
  - Early 1990s — hypothalamus was observed to be double in size in postmortem brains
- Estrogen is neuroprotective and impacts the aging trajectory of the female brain
- Many of the changes in the brain occurring in the midlife woman are similar to those that occur in AD
  - Structural
  - Energetic
  - Inflammatory

Mosconi L, et al. Menopause impacts human brain structure, connectivity, energy metabolism, and amyloid-beta deposition. *Sci Rep*. 2021;11(1):10867

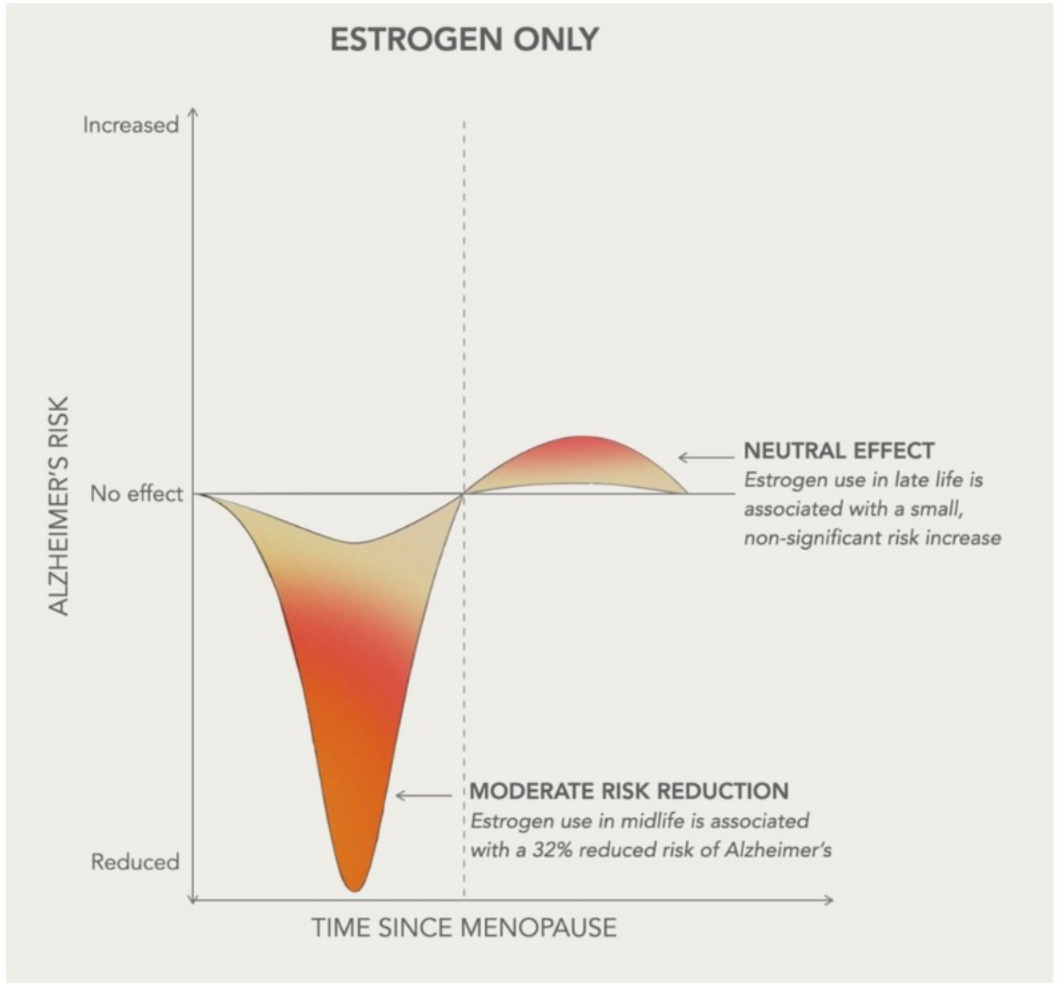
MHT and the Brain

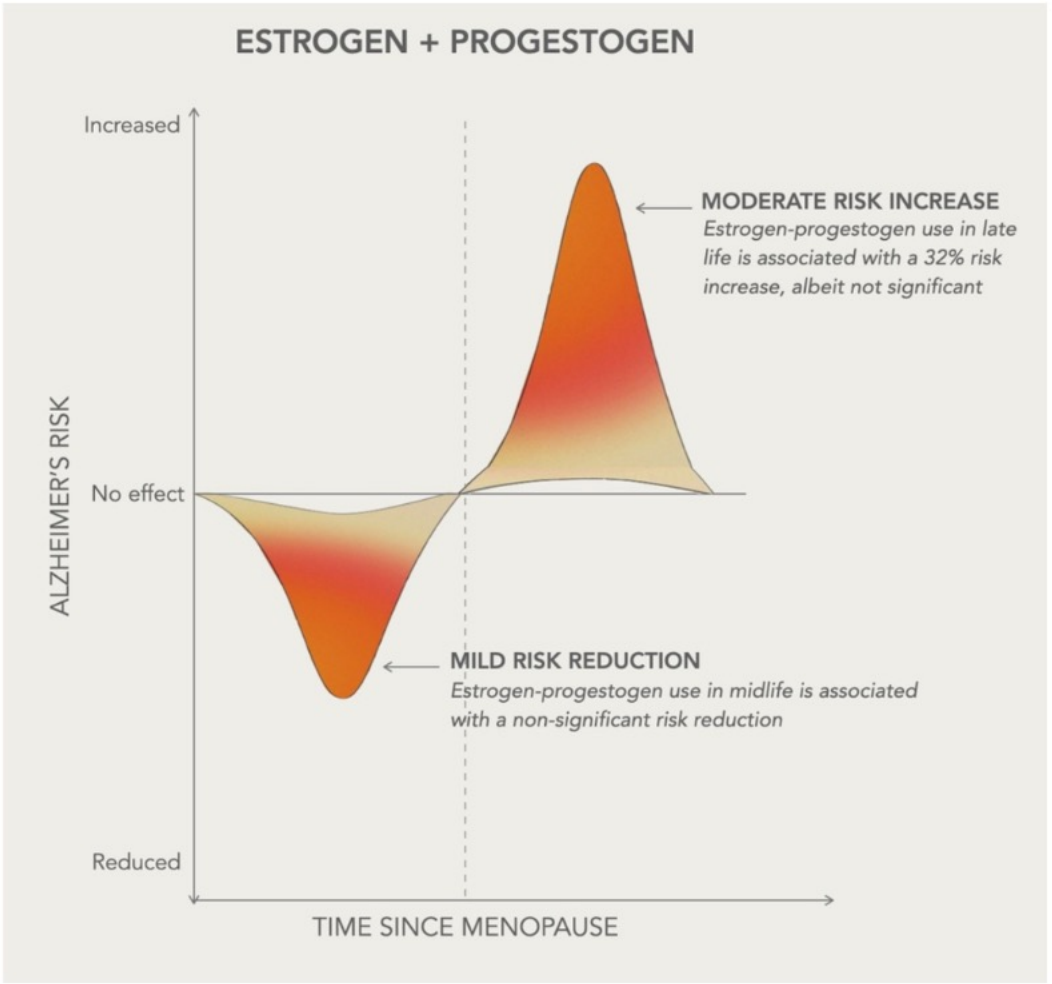
A "critical window" for neuroprotection was first proposed by Sherwiln and Maki in 2006: hormone replacement therapy (HRT) impact on brain health is dependent on timing of initiation of HRT — the sooner the better, and later is detrimental

- Further statistical analysis reveals that HRT was protective for brain health, but only if initiated within 5 years of menopause
- This critical window for HRT and neuroprotection has been observed in other studies, such as the Kaiser Permanente study from UCSF and the LAWs study, which reported that those who started HRT within three years of menopause scored higher on cognitive tests than those who never used HRT, and significantly higher than users who initiated HRT later in life
- Multiple other studies provide support for the critical time frame hypothesis of HRT and neuroprotection
    - Stratification of the data into current and former HRT users indeed revealed a lower risk of AD in favor of previous use

Maki PM. *Neuroscience*. 2006;138(3):1027-1030; Shao H, et al. *Neurology*. 2012;79(18):1846-1852; Whitmer RA, et al. *Ann Neurol*. 2011;69(1):163-169; Khoo SK, et al. *Climacteric*. 2010;13(3):259-264; Espeland MA, et al. *JAMA Intern Med*. 2013;173(15):1429-1436; Espeland MA, et al. *J Gerontol A Biol Sci Med Sci*. 2017;72(6):838-845; Girard R, et al. *Sci Rep*. 2017;7:44917; Dunkin J, et al. *Psychoneuroendocrinology*. 2005;30(3):284-296. ; https://www.ucsf.edu/news/2011/02/98174/estrogen-therapys-link-dementia-risk-depends-age-when-taken-study-finds. Accessed December 11, 2024.

MHT and Dementia





https://www.frontiersin.org/files/Articles/1260427/fnagi-15-1260427-HTML/image_m/fnagi-15-1260427-g008.jpg. Accessed December 11, 2024.

Estrogen and Dementia

Recommendations advise against estrogen use for dementia prevention, but data is emerging on this topic.

- 2022 Danish study by Løkkegaard and colleagues
- 2019 Finnish observational study
  - Very small increased AD risk, especially when using combination hormones long-term
- 2003-2004, the WHIMS clinical trials
  - Further research is needed to clarify this topic
  - Treatment of perimenopausal/menopausal women with estrogen should be individualized
  - Attention should be made to APOE4 status when considering hormone support
- HRT use should account for genotype, cardiovascular health, education, age, dose, and treatment duration, until risk factors influencing HRT effects are better understood or alternative treatments improve

WHIMS, Women's Health Initiative Memory Study.

Rocca WA, Faubion SS. Estrogen and dementia. *Maturitas*. 2022;165:120-121; Mangione CM, et al. Hormone Therapy for the Primary Prevention of Chronic Conditions in Postmenopausal Persons: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2022;328(17):1740-1746. Kang JH, Grodstein F. Postmenopausal hormone therapy, timing of initiation, APOE and cognitive decline. *Neurobiol Aging*. 2012;33(7):1129-1137. Mills ZB, Faull RLM, Kwakowsky A. Is Hormone Replacement Therapy a Risk Factor or a Therapeutic Option for Alzheimer's Disease?. Int J Mol Sci. 2023;24(4):3205. Published 2023 Feb 6.

APOE4 and MHT

- Higher AD risk and progression necessitates a more focused preventive approach in women
- **It has been demonstrated that HRT can have a beneficial effect on a range of cognitive function tests and cognition-related regional brain volumes in women with *APOE4***
  - *APOE4* MHT users had larger entorhinal cortex and amygdala volumes compared to MHT users
  - Scored higher in the RBANS delayed memory index
  - The earlier the age of MHT initiation, the larger the hippocampus volume — an association only observed in women with *APOE4*
- UK BIOBANK analysis (age = 40 to 69 years)
  - Early HRT use (oral and transdermal) was associated with less evident brain aging in APOE4 carriers only

RBANS, Repeatable Battery for the Assessment of Neuropsychological Status.

Saleh RNM, et al. Hormone replacement therapy is associated with improved cognition and larger brain volumes in at-risk APOE4 women: results from the European Prevention of Alzheimer's Disease (EPAD) cohort. *Alzheimers Res Ther*. 2023;15(1):10.

Late MHT and Increased Tau

Association of age at menopause and HRT use with tau and β-amyloid positron emission tomography (PET)

- HRT use in the setting of high Aβ is associated with elevated tau PET levels
- Late HRT initiation exhibited an elevated tau PET signal compared with females who initiated HRT proximal to menopause onset
- Findings suggest HRT is safe when used close to menopause onset and support the timing hypothesis, which proposes that intervention, if initiated late, increases risk for progression to AD dementia
- Tau deposition may underlie the pre-established association between late HRT intervention and AD dementia

Coughlan GT, et al. Association of Age at Menopause and Hormone Therapy Use With Tau and β-Amyloid Positron Emission Tomography. *JAMA Neurol*. 2023;80(5):462-473.

Prognosis of MCI

- A risk state for progression to dementia
  - 10% to 20% of people aged 65 or older with MCI develop dementia over a one-year period
- Not all MCI progresses
- Sometimes, improvement can occur
- Probability of progression is a function of:
  - Age
  - Cognitive status at time of diagnosis
  - Presence of abnormal biomarkers

National Institute on Aging. What Is Mild Cognitive Impairment? April 12, 2021. https://www.nia.nih.gov/health/memory-loss-and-forgetfulness/what-mild-cognitive-impairment; Campbell NL, et al. Risk factors for the progression of mild cognitive impairment to dementia. *Clin Geriatr Med*. 2013;29(4):873-893.

Brain-Healthy Strategies

1. **Diet**: eat well (MIND Diet)
2. **Controlling cerebrovascular risk factors**: manage blood pressure, blood sugars/diabetes, cholesterol, weight/body composition; and avoiding head trauma/concussions, strokes, smoking, brain toxins (including many drugs and some supplements and medications)
3. **Managing stress** and promoting relaxation responses
4. **Adopting relatively "positive" perspectives**, attitudes and a life purpose
5. **Connecting with others and your inner self**: being socially and emotionally engaged
6. **Exercising your brain**: challenging our brains to be active, with formal and informal education and activities (e.g. learning a new language or playing games and engaging in hobbies that are "mentally effortful), and to engage in life-long learning
7. **Participating in research**: get involved in research studies/programs that are right for you and that may lead to impactful breakthroughs — many studies are seeking healthy volunteers; these programs can be mentally stimulating can track how you are doing over time;
8. AND #1: **Being physically active and exercising regularly**

Livingston G, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet*. 2024;404(10452):572-628.

Genes that Increase Risk of AD

- Apolipoprotein E epsilon 4 allele
  - About 25% of people carry one copy of *APOE4*, and 2% to 5% carry two copies
  - Carriers of one E4 allele have three-fold risk, carriers of two E4 alleles have 10 to 30 times the risk of developing AD by age 75 compared to those not carrying E4 alleles
- Mutations causing overproduction of toxic Abeta peptide
  - Presenilin 1 and 2 (*PSEN1* and *PSEN2*)
  - Amyloid Precursor Protein (*APP*)
  - *ABCA7*
- Regulates clearance of Abeta in the brain
  - *CLU*
- Neuroinflammation
  - *CR1*
  - *PICALM*

National Institute on Aging. Alzheimer's Disease Genetics Fact Sheet. March 1, 2023. https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/alzheimers-disease-genetics-fact-sheet.

Deterministic Genes

- Autosomal dominant pattern
- Represent < 1% of total AD patients
- Multiple familial mutations
  - *APP*
  - *PSEN1*
  - *PSEN2*
- Trisomy 21 — Down Syndrome
  - *APP* gene is on chromosome 21

National Institute on Aging. Alzheimer's Disease Genetics Fact Sheet. March 1, 2023. https://www.nia.nih.gov/health/alzheimers-causes-and-risk-factors/alzheimers-disease-genetics-fact-sheet.

Developments in Lab Testing

For use in patients with cognitive decline

- **Labcorp**
  - **ATN profile**: β Amyloid 42/40 Ratio; Phosphorylated Tau 181 (pTau-181); Neurofilament Light Chain (NfL)
  - P-tau217 testing available
- **Quest Diagnostics**
  - **AD-Detect**: Amyloid Beta 42/40 Ratio
  - ApoE Isoform testing
  - pTau-181
- **PrecivityAD2**
  - Aβ42/40 ratio, *ApoE* genotype, pTau217
  - Direct to consumer, not FDA approved, cost approximately $1250

Alzheimer's Association. Alzheimer's Disease Blood Tests Could Improve Diagnosis in Primary Care, Speed Recruiting for Research and Reduce Wait Times. July 28, 2024. https://aaic.alz.org/releases-2024/blood-tests-alzheimers-biomarkers.asp. Accessed December 11, 2024. Labcorp. ATN Profile: For and Beyond Alzheimer's Disease. September 18, 2024. https://www.labcorp.com/atn-profile-and-beyond-alzheimers-disease. Accessed December 11, 2024. Quest Diagnostics. Quest AD-Detect®, Beta-Amyloid 42/40 Ratio, Plasma. October 2023. https://testdirectory.questdiagnostics.com/test/test-guides/TS_AD_Detect_BetaRatioPlasma/quest-ad-detect. Accessed December 11, 2024. Precivity. C_2N Diagnostics Introduces the PrecivityAD2™ Blood Test. November 29, 2024. https://precivityad.com/news/c2n-diagnostics-introduces-the-precivityad2-blood-test. Accessed December 11 2024.

Developments in Lab Testing

- Phosphorylated tau217
  - Highly correlates with amyloid PET
  - Comparable with CSF biomarkers, with longitudinal trajectory increasing with worsening brain atrophy and declining cognitive performance
- %p-tau217: ratio of phosphorylated tau217 to non-phosphorylated tau is clinically equivalent to CSF biomarkers and correlates with brain imaging
- Highly accurate blood test for Alzheimer's disease is similar or superior to clinical CSF tests

Ashton NJ, et al. Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology. *JAMA Neurol*. 2024;81(3):255-263; Barthélemy NR, et al. Highly accurate blood test for Alzheimer's disease is similar or superior to clinical cerebrospinal fluid tests. *Nat Med*. 2024;30(4):1085-1095.

Amyloid PET

- Evaluates β-amyloid neuritic plaque density
- Currently for use in patients with cognitive impairment
- Examples of these radiopharmaceuticals include:
  - Florbetapir F18 injection
  - Florbetaben F18 injection
  - Flutemetamol F18 injection
- Only performed at specialized imaging centers
- Medicare coverage per Medicare Administrative Contractors (MACs) varies regionally

Alzheimer's Association. For Healthcare Professionals | Frequently asked questions about beta-amyloid imaging. July 28, 2024. https://www.alz.org/media/Documents/health-care-pros-faqs-beta-amyloid-imaging.pdf; Johnson KA, et al. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *J Nucl Med*. 2013;54(3):476-490; Centers for Medicare & Medicaid Services. Beta Amyloid Positron Emission Tomography in Dementia and Neurodegenerative Disease — Decision Memo. October 13, 2023. https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=308.

Redefining Alzheimer's: Biomarker vs Clinical

- Accuracy of clinical diagnosis of AD is 30% to 50% compared to autopsy
- Amyloid β is an imperfect biomarker
- Implications of labeling people with AD in a presymptomatic stage!
- 10% of 50-year-olds test amyloid positive on PET scans, >50% of 80-year-olds

Dubois B, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. *Lancet Neurol*. 2021;20(6):484-496; Johnson KA, et al. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *Alzheimers Dement*. 2013;9(1):e-16.

Leveraging AD Biomarkers for Patient Selection

Currently recommended AD biomarkers for identification of anti-Aβ treatment candidates

CSF
Aβ42/40, Aβ42/total tau, or Aβ42/p-tau

Imaging
Elevated Aβ on visual read of PET

- Good concordance between CSF and PET for Aβ plaque burden
- Tau PET results can support diagnosis and help predict treatment benefit, but should not be used in isolation for treatment decision-making
- Limitations include invasiveness of CSF collection, lack of access to advanced imaging, and costs of imaging

Rapidly emerging and newly validated biomarkers for AD

Blood
Aβ42:40, p-tau, NfL, or GFAP

- May be useful for diagnosis and monitoring treatment response
- Not yet recommended for use in isolation for treatment decision-making
- Must be interpreted within the context of medical history, clinical examination, cognitive testing, and other biomarker results
- More cost effective relative to CSF and imaging approaches

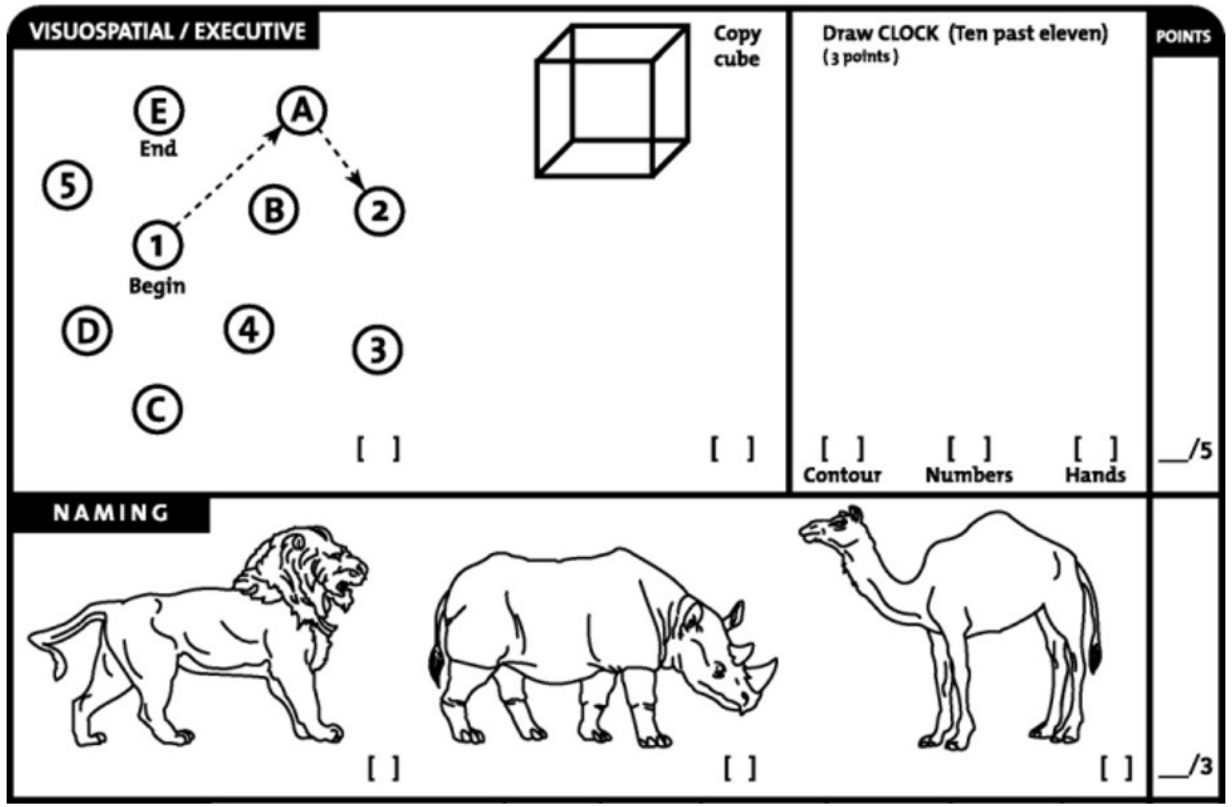
Cummings J, et al. Aducanumab: appropriate use recommendations Update. *J Prev Alzheimers Dis*. 2022;9(2):221-230. Cummings J, et al. Lecanemab: appropriate use recommendations. *J Prev Alzheimers Dis*. 2023;10(3):362-377. Angioni D, et al. Blood biomarkers from research use to clinical practice: what must be done? A report from the EU/US CTAD Task Force. *J Prev Alzheimers Dis*. 2022;9(4):569-579. Hansson O, et al. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimers Dement*. 2022;18(12):2669-2686.

AD Rating Scales

- General Practitioner assessment of Cognition (GPCOG)
  - https://gpcog.com.au/
- Montreal Cognitive Assessment (MoCA)
  - https://mocacognition.com/
- Saint Louis University Mental Status exam (SLUMS)
  - https://www.slu.edu/medicine/internal-medicine/geriatric-medicine/aging-successfully/pdfs/slums_form.pdf
- Mini Mental State Exam (MMSE)
- Clinical Dementia Rating Scale (CDR)

Fasnacht JS, et al. Conversion between the Montreal Cognitive Assessment and the Mini-Mental Status Examination. *J Am Geriatr Soc*. 2023;71(3): 869-879.

Montreal Cognitive Assessment (MoCA)



MEMORY	Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes.		FACE	VELVET	CHURCH	DAISY	RED	No points
		1st trial						
		2nd trial						
ATTENTION	Read list of digits (1 digit/ sec.).	Subject has to repeat them in the forward order [ ] 2 1 8 5 4						__/2
		Subject has to repeat them in the backward order [ ] 7 4 2						
Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors		[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B						__/1
Serial 7 subtraction starting at 100		[ ] 93	[ ] 86	[ ] 79	[ ] 72	[ ] 65		__/3
		4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**						
LANGUAGE	Repeat : I only know that John is the one to help today. [ ]							__/2
	The cat always hid under the couch when dogs were in the room. [ ]							
Fluency / Name maximum number of words in one minute that begin with the letter F		[ ] ____ (N ≥ 11 words)						__/1
ABSTRACTION	Similarity between e.g. banana - orange = fruit	[ ] train – bicycle	[ ] watch - ruler					__/2
DELAYED RECALL	Has to recall words WITH NO CUE	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only	__/5
Optional	Category cue							
	Multiple choice cue							
ORIENTATION	[ ] Date	[ ] Month	[ ] Year	[ ] Day	[ ] Place	[ ] City		__/6

© Z.Nasreddine MD Version 7.0 www.mocatest.org Normal ≥ 26 / 30

Administered by: _____

TOTAL __/30

Add 1 point if ≤ 12 yr edu

Montreal Cognitive Assessment (MoCA). https://mocacognition.com.

Clinical Dementia Rating Scale (CDR)

CLINICAL DEMENTIA RATING (CDR):	0	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 material retained; new material rapidly lost	Severe memory loss; only fragments remain
Orientation	Fully oriented	Fully oriented except for slight difficulty with time relationships	Moderate difficulty with time relationships; oriented for place at examination; may have geographic disorientation elsewhere	Severe difficulty with time relationships; usually disoriented to time, often to place	Oriented to person only
Judgment & Problem Solving	Solves everyday problems & handles business & financial affairs well; judgment good in relation to past performance	Slight impairment in solving problems, similarities, and differences	Moderate difficulty in handling problems, similarities, and differences; social judgment usually maintained	Severely impaired in handling problems, similarities, and differences; social judgment usually impaired	Unable to make judgments or solve problems
Community Affairs	Independent function at usual level in job, shopping, volunteer and social groups	Slight impairment in these activities	Unable to function independently at these activities although may still be engaged in some; appears normal at first glance	No possibility of independent function outside home Appears well enough to be taken to functions outside a family home	Appears too ill to be taken to functions outside a family home
Home and Hobbies	Life at home, hobbies, and intellectual interests well maintained	Life at home, hobbies, and intellectual interests 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 ability to do things in home

Clinical Dementia Rating (CDR) Scale. MDCalc.com. https://www.mdcalc.com/calc/10160/clinical-dementia-rating-cdr-scale.

Approved Drugs Targeting the Symptoms of AD

DRUG	MECHANISM OF ACTION	FDA-APPROVED INDICATIONS	SIDE EFFECTS
Donepezil	Cholinesterase inhibitor	Mild-to-severe Alzheimer's dementia	Nausea/vomiting Diarrhea Loss of appetite Dizziness Syncope Leg cramps Ulcers Cardiac arrhythmias
Rivastigmine		Mild-to-moderate Parkinson's dementia	
Galantamine		Mild-to-moderate Alzheimer's dementia	
Tacrine			
Memantine	NMDA antagonist	Mild-to-severe Alzheimer's dementia	Confusion Sedation Dizziness Constipation
Memantine and donepezil	Fixed-dose combination: NMDA antagonist and cholinesterase inhibitor		

NMDA, N-Methyl-D-aspartate.

Birks J. Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev*. 2006;2006(1):CD005593; Emre M et al. Pooled analyses on cognitive effects of memantine in patients with moderate to severe Alzheimer's disease. *J Alzheimers Dis*. 2008;14(2):193-199; Homma A, et al. Donepezil treatment of patients with severe Alzheimer's disease in a Japanese population: results from a 24-week, double-blind, placebo-controlled, randomized trial. *Dement Geriatr Cogn Disord*. 2008;25(5):399-407.

Overview of Approved and Investigational AD DMTs

DRUG	TARGET	STATUS	INDICATION	DOSING	EFFICACY IN PHASE 3 RCTs	SAFETY IN PHASE 3 RCTs
Aducanumab	Aβ plaques	Accelerated approval granted in 2021	Early symptomatic AD (MCI or mild dementia)	10 mg/kg IV every 4 weeks	Slowed functional and cognitive decline relative to placebo in patients with MCI or mild dementia due to AD (EMERGE only; no difference in ENGAGE)	ARIA-E (26%-36%), brain microhemorrhage (16%-20%), superficial siderosis (10%-16%), headache (18%-21%)
Lecanemab	Aβ plaques and protofibrils	Full approval granted in 2023	Early symptomatic AD (MCI or mild dementia)	10 mg/kg IV every 2 weeks	Slowed functional and cognitive decline relative to placebo in patients with MCI or mild dementia due to AD	Infusion-related reactions (26%), ARIA-H (14%), ARIA-E (13%), headache (11%)
Donanemab	Aβ plaques	Full approval granted in 2024	N/A	700 mg (first 3 doses) then 1 400 mg IV every 4 weeks until Aβ plaque level is under cutoff	Slowed functional and cognitive decline relative to placebo **and** increased Aβ clearance relative to aducanumab in patients with MCI or mild dementia due to AD	ARIA-E (24%), ARIA-H (20%), headache (14%), infusion-related reaction (9%)

Aβ, amyloid β; ARIA-E, amyloid-related imaging abnormalities with edema; ARIA-H, amyloid-related imaging abnormalities with hemorrhage; IV, intravenous; N/A, not applicable, RCTS, randomized control trial.

Budd Haeberlein S, et al. Two Randomized Phase 3 Studies of Aducanumab in Early Alzheimer's Disease. *J Prev Alzheimers Dis*. 2022;9(2):197-210; van Dyck CH, et al. Lecanemab in Early Alzheimer's Disease. *N Engl J Med*. 2023;388(1):9-21; Sims JR, et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. *JAMA*. 2023;330(6):512-527; Salloway S, et al. TRAILBLAZER-ALZ 4: topline study results directly comparing donanemab to aducanumab on amyloid lowering in early, symptomatic Alzheimer's disease. *BJPsych Open*. 2023;9(Suppl 1):S67.

Clinical Implementation Model for Anti-Aβ Therapies

TREATMENT INITIATION

- Assess clinical status (i.e., MCI or mild dementia)
- Confirm AD etiology with biomarkers
- Review medical history
- Determine risk for amyloid-related imaging abnormalities (ARIA)
- Engage in shared decision-making discussion regarding care goals

DRUG ADMINISTRATION

- Ensure access to drug
- Develop standardized order sets and protocols
- Identify infusion facilities/referral mechanisms
- Prepare for administrative burdens (e.g., prior authorizations, coverage appeals)

TREATMENT MONITORING

- Develop safety assessment plan
- Track treatment response (e.g., clinical testing, biomarker testing)
- Follow recommendations for complications (e.g., ARIA protocols)

Ramanan VK, et al. Antiamyloid Monoclonal Antibody Therapy for Alzheimer Disease: Emerging Issues in Neurology. *Neurology*. 2023;101(19):842-852.

Amyloid-Related Imaging Abnormalities (ARIA)

- *ApoE4* carriers have higher risk of ARIA
- **Edema** or sulcal effusions (ARIA-E): 24% treatment, 2% placebo
  - Zero *ApoE4* alleles: 15%
  - One *ApoE4* allele: 23%
  - Two *ApoE4* alleles: > 40%
- **Microhemorrhages** and superficial siderosis (ARIA-H): 21% treatment, 14% placebo
- Most common early in treatment
- 70% are asymptomatic — detected by surveillance MRIs
- Boxed warning particularly for *ApoE4* homozygotes

Roytman M, et al. Amyloid-Related Imaging Abnormalities: An Update. *AJR Am J Roentgenol*. 2023;220(4):562-574; Régy M, et al. The role of dementia in the association between APOE4 and all-cause mortality: pooled analyses of two population-based cohort studies. *Lancet Healthy Longev*. 2024;5(6):e422-e430; Fortea J, et al. APOE4 homozygozity represents a distinct genetic form of Alzheimer's disease. *Nat Med*. 2024;30(5):1284-1291.

ARIA Symptoms

Common

Headache

Confusion

Visual changes

Dizziness

Nausea

Gait difficulty

Severe

Seizures

Status epilepticus

Focal neurologic deficits

Malignant HTN

Intracerebral hemorrhages
> 1 cm (some fatal)

Vukmir RB. Amyloid-related imaging abnormalities (ARIA): diagnosis, management, and care in the setting of amyloid-modifying therapy. *Ann Clin Transl Neurol*. 2024;11(7):1669-1680.

Facilitating Access to Anti-Aβ Therapies

- In many communities, limited access to neurologists, AD specialists, and dementia care resources requires collaborative care efforts

- Clinics should develop pathways and processes to address new clinical and administrative burdens
  - Prior authorizations, denials, and appeals
  - Increased requests for evaluation and information from patients and care partners
  - Administration (1-hour infusion) and monitoring

MEDICARE COVERAGE

In 2023, CMS announced Medicare coverage of anti-Aβ therapies, with full FDA approval for people who meet the following criteria:

- Medicare enrollment
- Diagnosis of MCI or mild dementia due to AD
- Prescription issued by a clinician participating in CMS registry with a clinical team and follow-up care

CMS, Centers for Medicare & Medicaid Services.
Ramanan VK, et al. Antiamyloid Monoclonal Antibody Therapy for Alzheimer Disease: Emerging Issues in Neurology. *Neurology*. 2023;101(19):842-852; CMS. CMS announces new details of plan to cover new Alzheimer's drugs. June 22, 2023. Accessed September 21, 2023. https://www.cms.gov/newsroom/fact-sheets/cms-announces-new-details-plan-cover-new-alzheimers-drugs.

CMS Coverage of Amyloid Monoclonal Antibody Drugs

Requirements for coverage:

- Cognitive assessment documenting MCI or mild AD
- Confirm amyloid via amyloid PET, CSF, and/or blood tests
- Report patient's baseline clinical status on cognition and function assessments to CMS via the dedicated CMS CED submission portal every six months for up to 24 months
- Report patient's use of anti-platelet and/or anti-coagulation therapy and whether the patient has developed new ARIA since the last assessment data submission

CED, coverage with evidence development.

CMS. Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD). September 10, 2024. https://www.cms.gov/medicare/coverage/coverage-evidence-development/monoclonal-antibodies-directed-against-amyloid-treatment-alzheimers-disease-ad. Accessed December 11, 2024.

Appropriate Use Criteria

- Align closely with clinical trial inclusion/exclusion criteria
- Only studied in narrow patient population
  - Age 50 to 90
  - MMSE 22 to 30 (MoCA > 15)
  - BMI 17 to 35
  - < 2 lacunar strokes
- Frequent MRI surveillance
- Implementation is a lift, even in academic centers with experience

Leisher S, et al. Amyloid-Lowering Monoclonal Antibodies for the Treatment of Early Alzheimer's Disease. *CNS Drugs*. 2023;37(8):671-677.

Anti-Amyloid Monoclonal Antibodies-Summary

- Very expensive
- Difficult to select appropriate patients, perform appropriate testing, and prescribe in primary care setting
- IV infusion q 2 to 4 weeks
  - Look for possible SC dosing in the future
- Only MCI and early Alzheimer patients benefit
- 30% reduction of cognitive decline, but is this clinically meaningful?
  - Equates to extending MCI phase by 7.5 months
- Similar to chemo for cancer patients
  - Provides modestly improved survival with significant toxicity (ARIA)
- Even if cost is not a consideration, hassle factor will be for most
- Treat until amyloid plaques cleared

Potential Future Drug Targets

- Oxidative stress
- Neuroinflammation
- Blood vessel architecture
- Mitochondrial dysfunction
- Neurogenesis

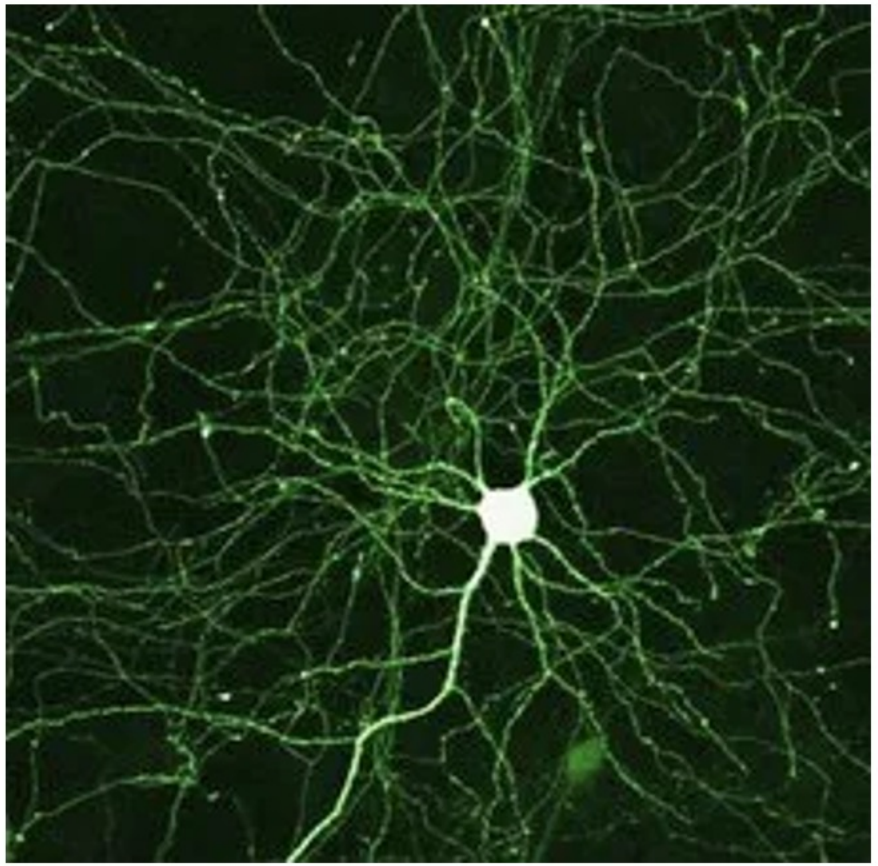
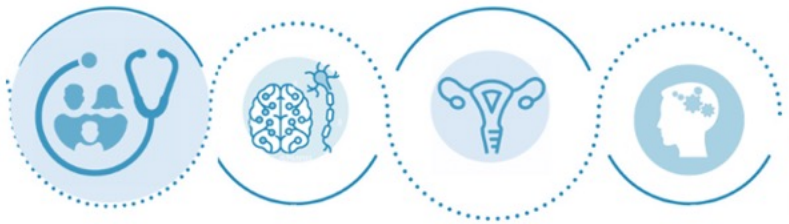


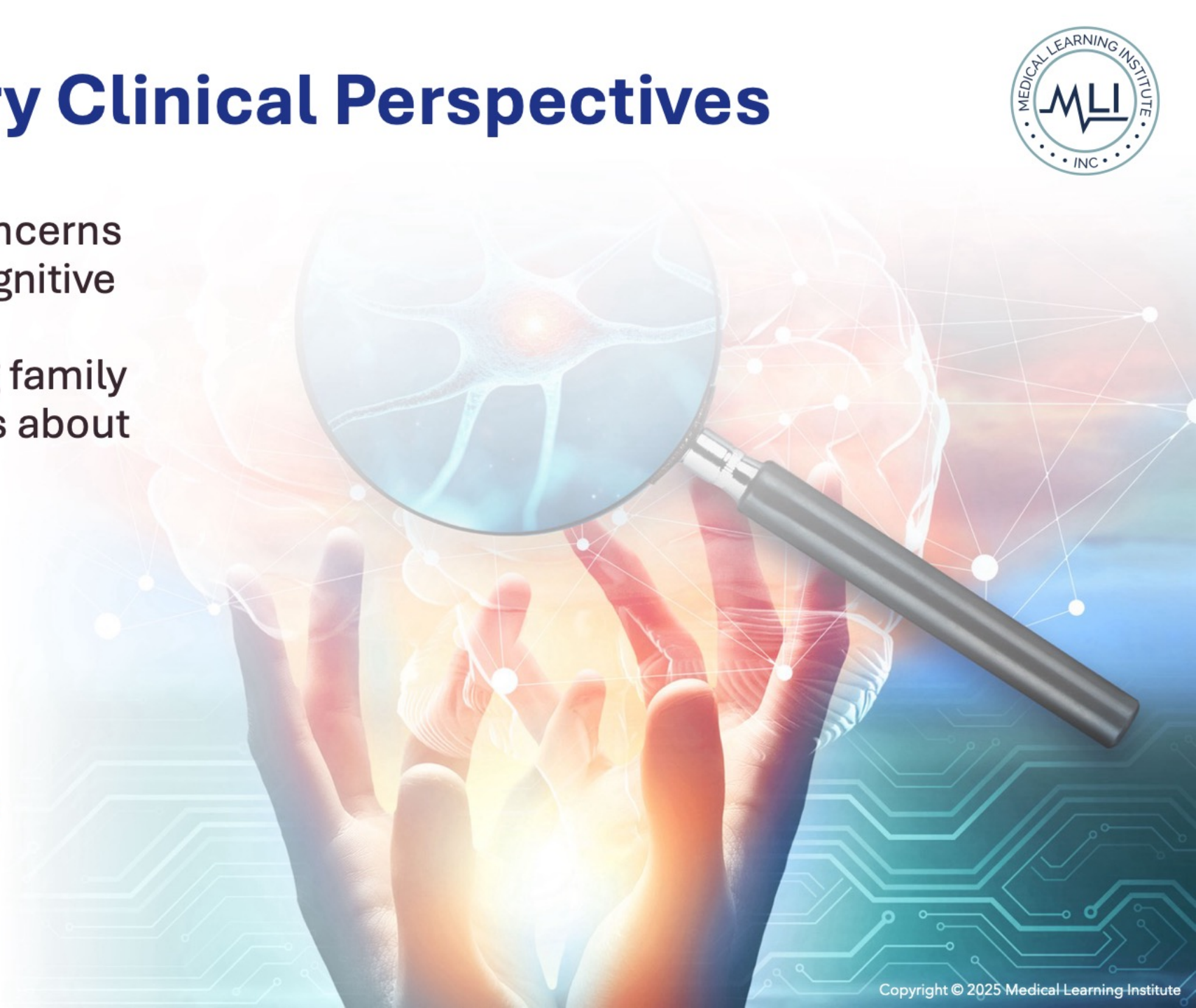
Image from: https://api.openverse.org/v1/images/e03fd63b-0d60-4b7e-b76f-58b01a7ccd60/thumb/.

Song T, et al. Mitochondrial dysfunction, oxidative stress, neuroinflammation, and metabolic alterations in the progression of Alzheimer's disease: A meta-analysis of in vivo magnetic resonance spectroscopy studies. *Ageing Res Rev*. 2021;72:101503.

Multidisciplinary Clinical Perspectives

A 62-year-old male with concerns about memory loss and cognitive impairment presents for evaluation. He has a strong family history of AD and is anxious about his future.





Timing is Critical

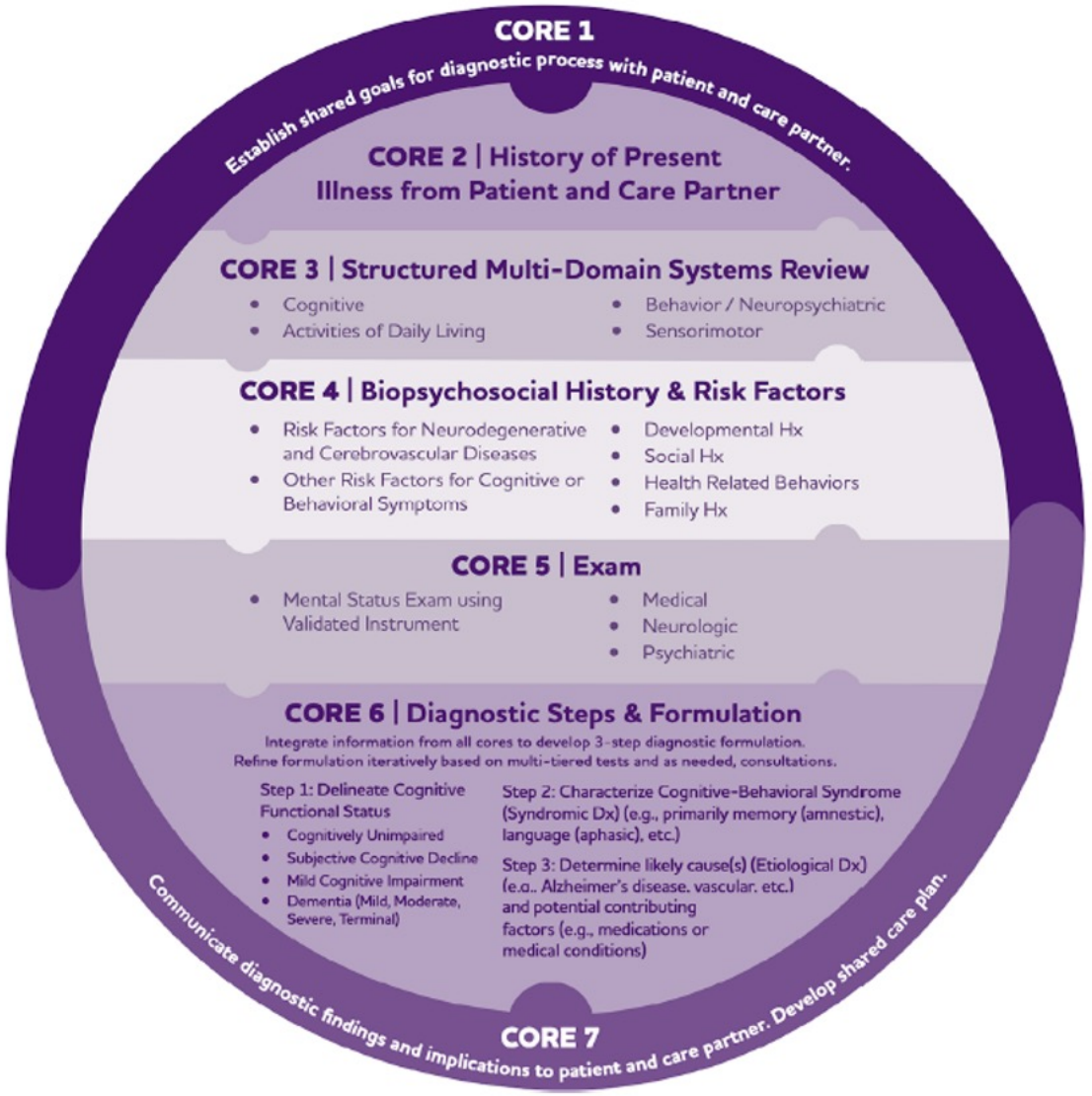
- As genetic testing advances, we may identify persons at higher risk at a young age
- Presymptomatic diagnosis and treatment is the buzz
- May need to use a cocktail of treatments targeted at various neurotoxins

The Lancet Neurology. Treatment for Alzheimer's disease: time to get ready. *Lancet Neurol*. 2023;22(6):455; Rentz DM, et al. Benefits and risks of FDA-approved amyloid-targeting antibodies for treatment of early Alzheimer's disease: Navigating clinician-patient engagement. *Alzheimers Dement*. 2024;20(11):8162-8171.

Core Elements of Evaluation of Patient with Suspected Cognitive Impairement

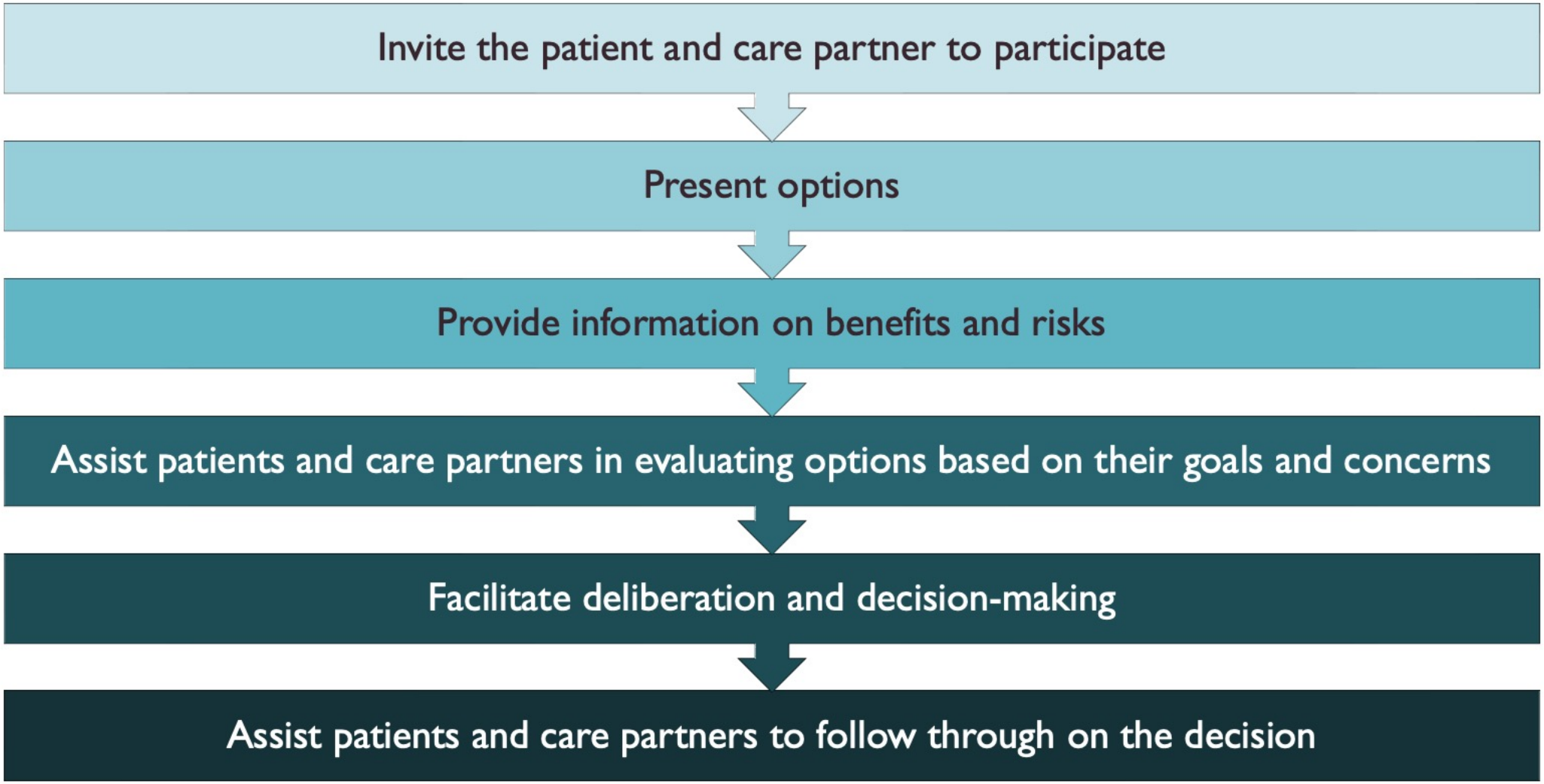
For patients who may be exhibiting symptoms and/or signs of cognitive impairment due to AD or ADRD, the three steps of the diagnostic formulation may be accomplished by following a process of seven core elements

Step 1: Delineate the cognitive functional status
Step 2: Characterize the patient's cognitive–behavioral syndrome
Step 3: Generate and narrow the differential diagnosis of the brain disease(s) or disorder(s) that is the likely cause(s) of the patient's cognitive–behavioral syndrome



Dickerson BC, Atri A, et al. Alzheimer's Association clinical practice guideline for the Diagnostic Evaluation, Testing, Counseling, and Disclosure of Suspected Alzheimer's Disease and Related Disorders (DETeCD-ADRD): Executive summary of recommendations for primary care. *Alzhimer's Dement*. 2024;1-31.

Involving the Patient and Their Care Partners: Shared Decision-Making



National Learning Consortium. Shared decision-making fact sheet . December 2013. Accessed 4/10/2024. www.healthit.gov/sites/default/files/nlc_shared_decision_making_fact_sheet.pdf.

The "Other" Patient in the Room… Family Caregivers

- In 2022, over 11 million family and friends provided 18 billion hours of unpaid care to those with Alzheimer's and other dementias. That care had an estimated economic value of $339.5 billion

- Caregivers are prone to depression, grief, fatigue, and social and relationship problems
- Caregiver stress is related to premature institutionalization

Alzheimer's Association. 2023 Alzheimer's Disease Facts and Figures Report: At a Glance Statistics. 2023. https://alz.org/media/Documents/Facts-And-Figures-2023-At-A-Glance-Stats-Fact-Sheet.pdf. Accessed December 11, 2024.

Stigma and Stereotypes

- **Family:** may not want to talk about the disease, avoid interaction
- **Friendships:** refusal to believe diagnosis, withdrawal from that person's life — abandonment and isolation
- People may approach wife/husband/caregiver rather than the patient themself
- Encourage patients to:
  - Be open and direct
  - Communicate the facts
  - Seek support and stay connected
  - Don't be discouraged
  - Be part of the solution

Alzheimer's Association. Overcoming Stigma. 2024. https://www.alz.org/help-support/i-have-alz/overcoming-stigma.

Patient and Care Partner Support

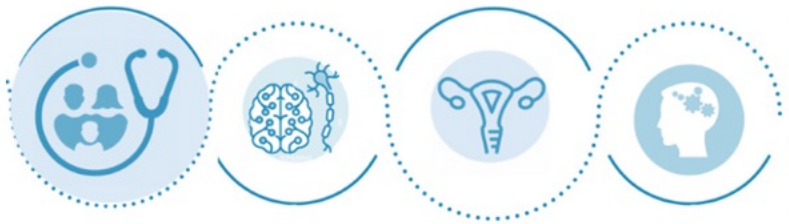
- Alzheimer's Association
  - www.alz.org
  - 24/7 helpline 800.272.3900
- NIH
  - www.alzheimers.gov
- CDC
  - Helping Alzheimer’s Caregivers (cdc.gov)
- Alzheimer’s Foundation of America
  - Alzheimer's Foundation of America | Resources for Alzheimer’s and Dementia Caregivers (alzfdn.org)

AAFP Physician Resources

- AAFP Cognitive Care Kit
  - Cognitive Care | AAFP
- AAFP Dementia free CME course
  - Dementia and Alzheimer's Disease Care Training | AAFP

Multidisciplinary Clinical Perspectives

A 75-year-old female and her daughter are concerned about recent memory issues. The patient is resistant to discussing cognitive health with her HCP due to fear and stigma.

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