

Road Map to Dementia Diagnosis Physician Edition



As the average age of Americans increases, so does the risk for developing Alzheimer's disease (AD). Unfortunately, there is no cure for AD. In June 2021, a disease modifying treatment called aducanumab (Adhulem) was approved by the FDA for patients diagnosed with AD, the first drug to be approved for AD in 18 years. Aducanumab is an antibody that targets a protein called amyloid. Amyloid accumulates in the brains of Alzheimer's disease patients, and it is thought to contribute to the cognitive decline in Alzheimer's disease. Aducanumab helps patients' immune systems remove the amyloid deposits from the brain.

While this new medication offers hope, it may not be the right medication for all patients suffering from this disease and research indicates the medication is more effective for those with very mild disease. Close monitoring and evaluation are needed. Please find additional information to reference in this booklet.

Treatments to manage symptoms have been available for some time, yet not all patients benefit fully from these treatments. Physicians need to understand how to diagnose patients accurately and quickly. The sooner we can detect changes associated with AD the sooner we can intervene.

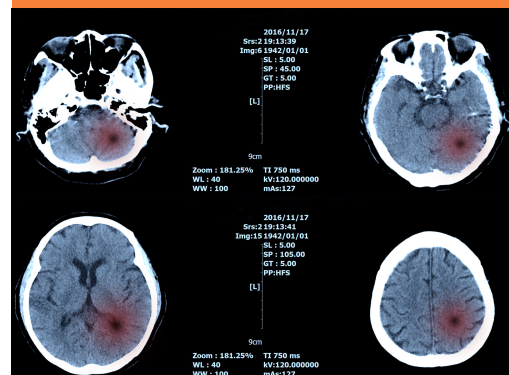
In this booklet, you will learn how to evaluate and manage someone living with Alzheimer's disease and understand how and when to implement treatment and strategies to manage symptoms.



Aging & Memory Loss Road Map Series for Physicians

I. Dementia Diagnosis Version II

II. Behavioral Management



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MASSACHUSETTS
Alzheimer's Disease
Research Center



Center for
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Mass General Brigham

Current recommended diagnostic assessments for Alzheimer's disease

Clinical Diagnostic Criteria for Dementia

- Dementia is a chronic progressive syndrome consisting of cognitive, behavioral and functional dysfunction
- Symptoms interfere with daily functioning
- Represents a decline from previous abilities
- Not explained by delirium or primary psychiatric condition
- Cognitive impairment is assessed by history (patient/caregiver) and exam ("bedside" or neuropsychological testing)
- Cognitive or behavioral impairment of 2 or more domains: memory, attention/executive function, visuospatial function, language, and behavior

Initial Evaluation for Suspected Dementia

Localize cognitive dysfunction

- Focal, multifocal, or diffuse
- Cortical or subcortical
- Pattern of deficits corresponds with a neurodegenerative clinical syndrome

Establish time course

- Insidious onset and slow progression: Neurodegenerative disease
- Rapid progression: Prion disease, autoimmune/inflammatory disease, atypical neurodegenerative disease
- Static time course or fluctuations without clear progression: Psychiatric or general medical illness

Dementia Diagnostic Assessments

- "Bedside" assessment: tests that can increase detection of cognitive impairment
- Brief Screening Tests (<5 minutes): Mini-Cog (3-item recall test for memory and a simply scored clock drawing test) and AD8 (AD8 contains 8 questions for the patient and/or caregiver that test for memory, orientation, judgment, and function)
- Intermediate Screening Tests (10-20 minutes): Montreal Cognitive Assessment (MoCA, tests memory, orientation, attention, executive function, visuospatial function, and language; targets mild cognitive impairment (MCI) and mild dementia), Mini-Mental State Examination (MMSE, tests memory, orientation, attention, visuospatial function, and language; targets mild to moderate dementia), and Blessed Dementia Rating Scale, IMC subscale (tests memory, orientation, and attention; targets mild to moderate dementia)
- Comprehensive Tests (30-45 minutes; usually performed by dementia specialists): Addenbrooke's Cognitive Exam (ACE, tests memory, orientation, attention, visuospatial function, and language; targets MCI and mild dementia), Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery (includes the MMSE and other tests of memory, attention, visuospatial function, and language; targets MCI and mild dementia), Clinical Dementia Rating (CDR, Relies on questions for caregiver and patient; tests orientation, memory, judgment and problem solving, instrumental and basic activities of daily living; provides dementia staging: cognitive normal, MCI, mild dementia, moderate dementia, and severe)
- Physical exam: Parkinsonism, localizing features, motor neuron disease features

Neuropsychological Testing

Performed by neuropsychologists; 2-4 hours of comprehensive cognitive testing in all domains; most useful for MCI, mild dementia or for atypical presentations.

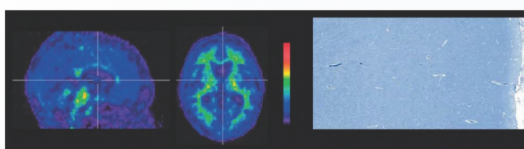
- Labs: CSF (routine, A β 1-42, tau,14-3-3), blood (B12, TSH, CBC, electrolytes, LFTs), urinalysis
- Brain imaging
- Brain Structure: MRI (CT)
- Brain Function: FDG-PET (SPECT), fMRI (primarily a research tool)
- Molecular imaging of pathology: Amyloid PET imaging (F-18 agents, approved by FDA for clinical use in MCI or dementia but not covered by insurance; primarily used in research), Tau PET (not yet approved by FDA; used only in research)
- Genetic testing (family history suggestive of autosomal dominant inheritance: PS1, PS2, APP)*

*These genetic mutations are associated with early-onset dementia which occurs between a person's 30s and mid-60s and accounts for about 1% of all people living with Alzheimer's disease. Source (NIH)



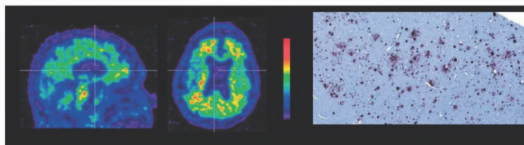
18F-Florbetapir PET amyloid imaging correlates well with post-mortem findings

Low amyloid on PET and autopsy



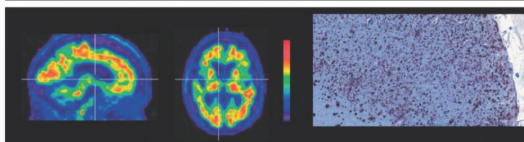
Visual rating:
Sensitivity 92%
Specificity 100%

Intermediate amyloid on PET and autopsy



Clark et al. JAMA 2011;

High amyloid on PET and autopsy



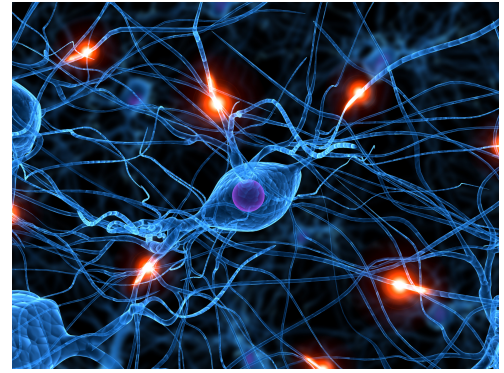
Clark et al. *Lancet Neurol* 2012

Differential Diagnosis of Dementia

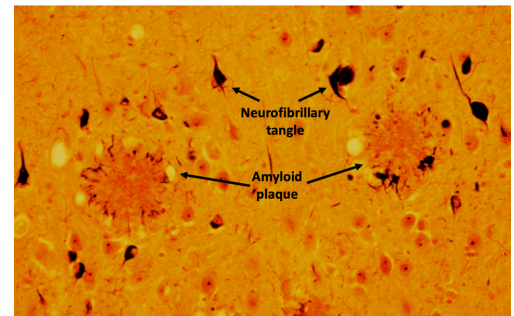
- Vascular
- Infectious
- Toxic
- Autoimmune/inflammatory
- Metabolic
- Iatrogenic
- Neoplastic
- Structural
- Genetic
- Psychiatric
- Degenerative

Alzheimer's Disease (AD) Facts

- Most common cause of dementia
- Typical onset in early 70's
- Progressive neurodegenerative disease
 - Insidious clinical progression over years
 - Typically begins with impaired short-term memory, sense of direction, and praxis
 - Eventually affects general cognition, behavior, and daily functioning
- >5 million people in U.S. have a diagnosis of AD dementia (Alzheimer's Association 2012)
- 20 million more at risk over next 30 years
⇒ Prevalence doubles every 5 years
- Cost estimates: > \$150 billion/year
- 1.5x more prevalent in Hispanics, 2x in African Americans



Neuron

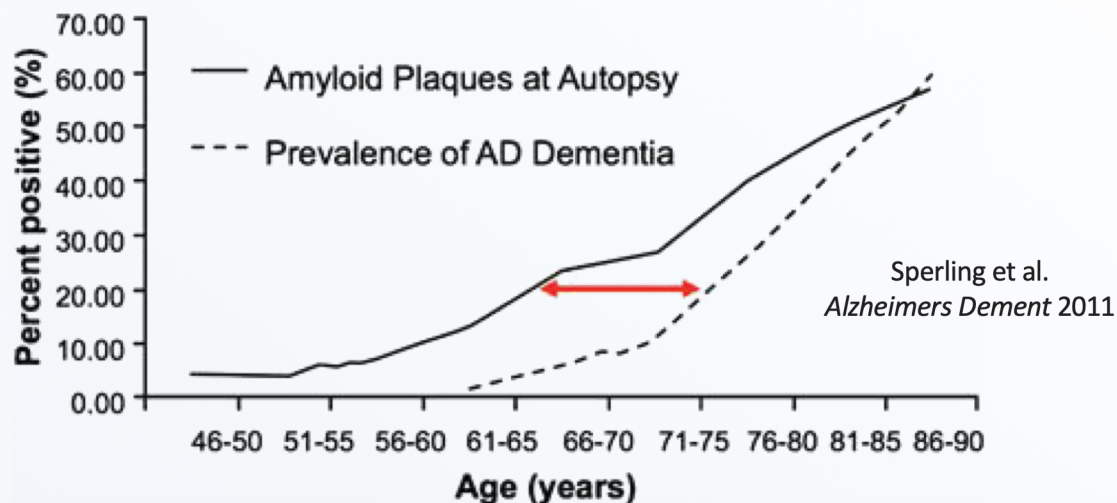


Diagnosing AD Early

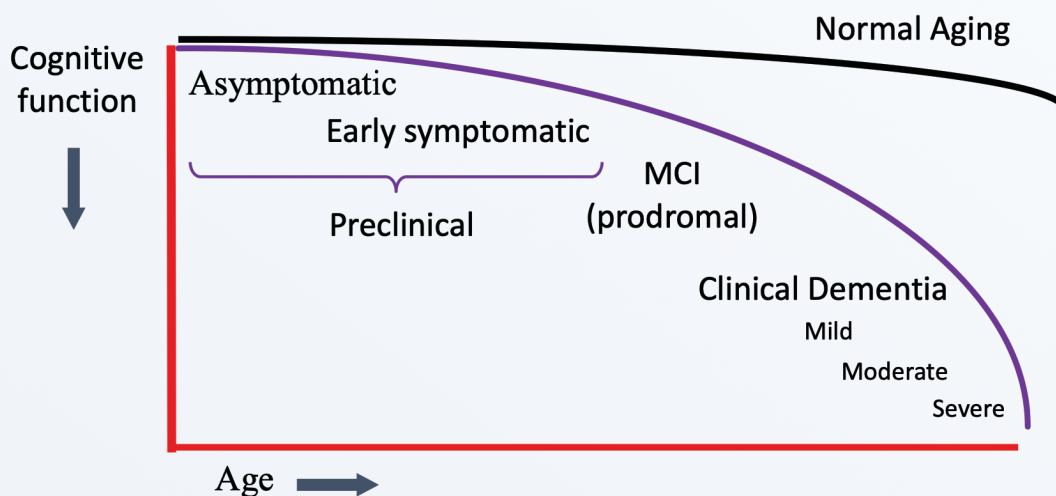
- The underlying pathological changes begin 10-15 years prior to a clinical diagnosis
 - Using disease-modifying drugs may be most effective during this time
- Mild Cognitive Impairment (prodromal AD): Mild impairment in one or more cognitive domains with intact or mild decline in instrumental activities of daily living (IADL) (ex: managing the finances)
 - Precursor to dementia (mostly AD): 10-15% progress to dementia annually (Petersen 1999)
- Preclinical AD is a research diagnosis for individuals who are asymptomatic or minimally symptomatic, not yet meeting criteria for AD and who have biomarker evidence of underlying AD pathology (amyloid, tau, and neurodegeneration).

TEMPORAL LAG OF ABOUT 10 YEARS BETWEEN AMYLOID ACCUMULATION AND ONSET OF DEMENTIA

Appearance of Plaques vs. Dementia



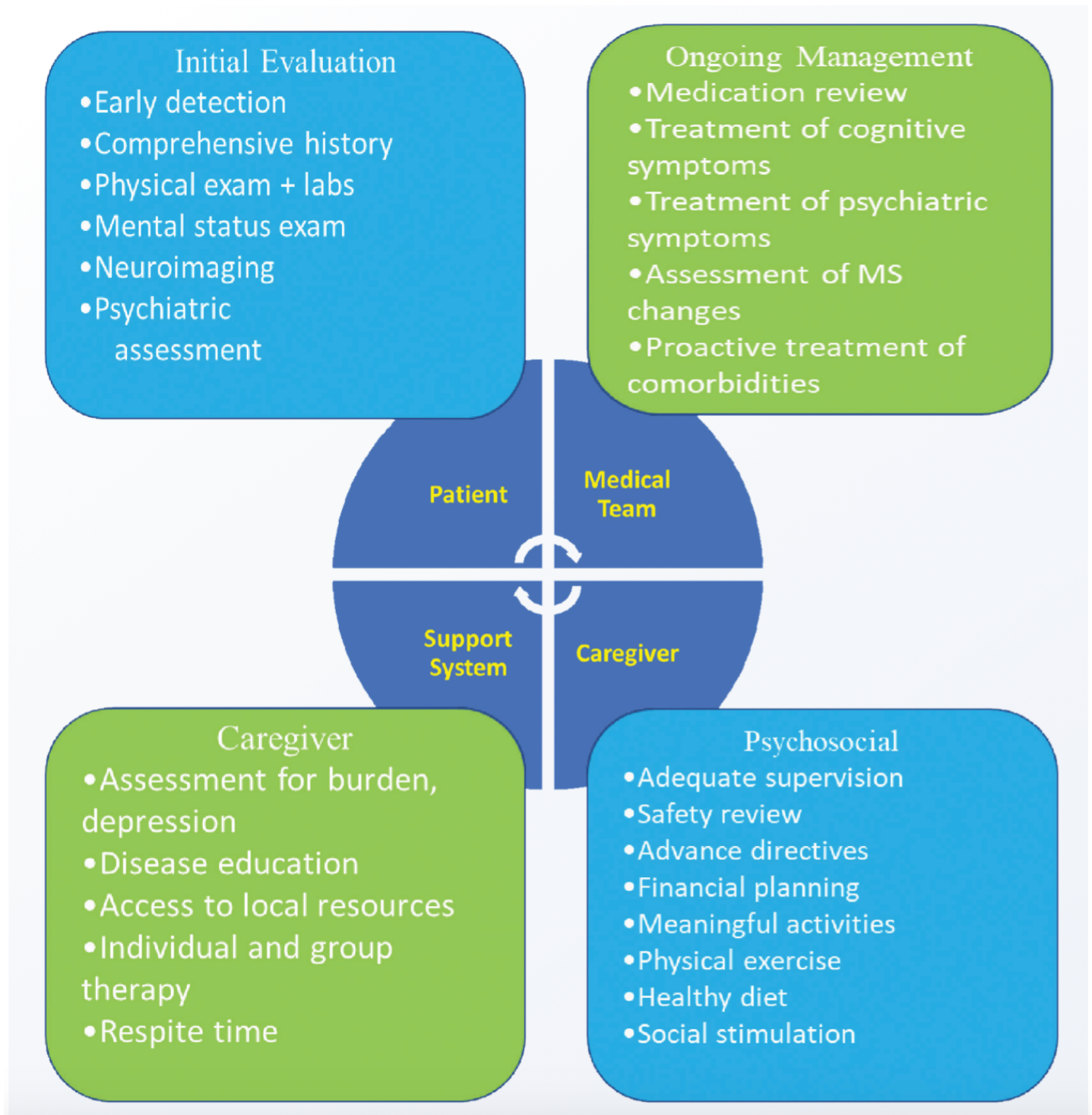
ALZHEIMER DISEASE TRAJECTORY



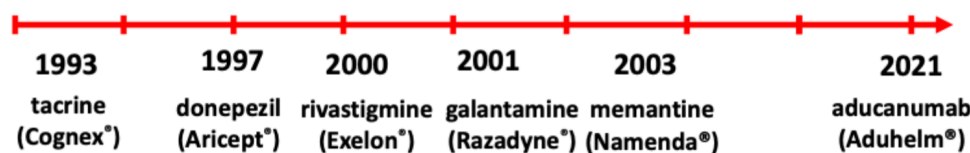
Modified from Sperling et al. *Alzheimers Dement* 2011

Multiple Components of Dementia Management

Helping patients and caregivers manage dementia takes a multi-pronged approach. Below is a diagram courtesy of the Alzheimer's Association depicting the various aspects involved:



FDA approved medications for AD dementia



Cholinesterase-inhibitors (ChE-1): donepezil, rivastigmine, galantamine, tacrine* (no longer clinically used)

- All FDA approved for treating mild to moderate AD dementia
- Donepezil has also been FDA approved for treatment of severe AD dementia (2006)
- Galantamine available as a generic since 2009; donepezil, rivastigmine since 2010

NMDA (glutamate) receptor antagonist: memantine

- FDA approved for treatment of moderate to severe AD dementia (generic 2015)

AD Dementia Medications: Symptomatic Benefits

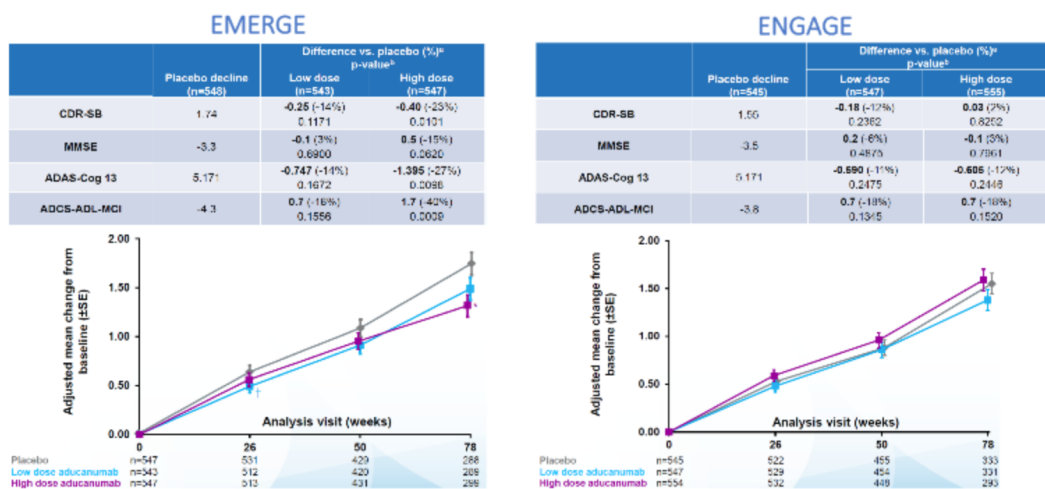
Although we do not have a cure for AD or medications that modify the underlying disease process and its trajectory, the FDA approved medications have symptomatic benefits.

- ChE-I and Memantine: have been shown in multiple randomized, double-blind, placebo-controlled trials of AD dementia to provide modest but clinically significant improvements to groups of participants in:
 - Daily functioning, cognition, neuropsychiatric symptoms, caregiver burden (and potentially saving money)
- Individual results vary
 - Highly variable effects across time between and within individuals

The FDA approved aducanumab (Aduhelm) in the accelerated approval program requiring Biogen to conduct a post-approval phase 4 trial within 9 years. Modest clinical benefit was seen in one phase 3 trial in a subset of patients with very mild disease but not in the other phase 3 trial, and this topic continues to be debated. The FDA's decision on approval was based primarily on the biological removal of amyloid plaque in the brain. To see the FDA decision information visit www.fda.gov and for additional information for patients and family, as well as medication availability at the Mass General Brigham, visit the www.madrc.org "Announcements" page.

AD Dementia Medications: Symptomatic Benefits (Continued)

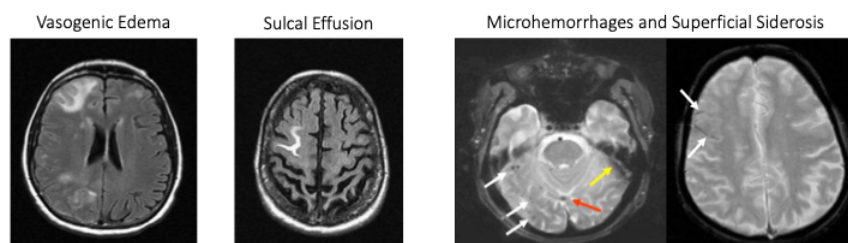
Aducanumab FDA accelerated approval 6/7/21 Phase 3 Trials Clinical Outcomes in MCI/very mild AD dementia



Since aducanumab works by helping the immune system remove amyloid deposits from the brain, some patients may experience an exaggerated immune response in the brain. If this occurs, it may cause blood vessel leakiness leading to localized brain swelling, small spots of bleeding in the brain, or both. These side effects can be seen using MRI imaging of the brain and are called amyloid-related imaging abnormalities (ARIA). As a result, patients receiving aducanumab will require regular monitoring with MRI scans. During the clinical trials, trial patients (~35%) who developed ARIA-E (edema) had clearing of the focal brain swelling within 2-3 months and most did not develop symptoms. Another potential side effect is an allergic response during the infusion of aducanumab. The treatment must be closely monitored. Monitoring guidelines are currently being developed by institutions who will offer treatment and patient advocacy groups like the Alzheimer's Association www.alz.org.

Amyloid-Related Imaging Abnormalities (ARIA)

- Amyloid antibody treatments have been associated with ARIA
- ARIA-E refers to vasogenic edema or sulcal effusion; ARIA-H refers to microhemorrhages or superficial siderosis
- In ENGAGE and EMERGE, approximately 35% of participants taking high-dose and 25% of those taking low-dose treatment experienced ARIA-E, compared with 2.5% of those taking placebo



Haeblerlein et al. CTAD 2019; Sperling et al. *Alzheimers Dement* 2011

Treatment of other dementias

- Rivastigmine FDA approved for treatment of Parkinson's disease with dementia (PDD) since 2007
- Off-label use of all ChE-I for PDD and dementia with Lewy bodies (DLB)
- There is no FDA approved drug for treatment of vascular dementia (VaD)
 - ChE-I are used off label for VaD or mixed AD/VaD dementia based on a positive donepezil trial (Roman 2005) and a positive and a partially positive galantamine trial (Erkinjuntti 2002, Auchus 2007)
- No FDA approved drug for frontotemporal dementia (FTD)
- To date, only one drug (aducanumab) has been approved by the FDA for the treatment of mild cognitive impairment (MCI)



Lifestyle Modifications

Healthy Diet: Eating a Mediterranean diet reduces risk of developing AD dementia and slows existing cognitive decline

Physical exercise

- Exercise 3 or more times per week or vigorous exercise 1 hour per week reduces risk of developing AD dementia

Controlling vascular risk factors

- Aggressive control of hypertension (SBP<120) has been shown to reduce the risk of progression to MCI in the SPRINT MIND trial (Williamson 2019)

Cognitive training

- Most studies have shown improvement in performance of the cognitive tasks used for training but not other cognitive domains or IADL. However, some studies have shown that cognitive training may reduce decline in reasoning, processing speed, and IADL.

Enhance social activity

- Interacting with others may help preserve memory and processing speed

Sleep (7-9 hours/night)

- Can help consolidate memories and may help clear amyloid from the brain

Why is research vital?

Clinical trials offer hope for many people and are an opportunity to help researchers find better treatments for others in the future.

People participate in research for a variety of reasons. Healthy research participants and patients say they take part in clinical trials to help others and to contribute to moving the science forward, or to receive access to a possible new treatment.

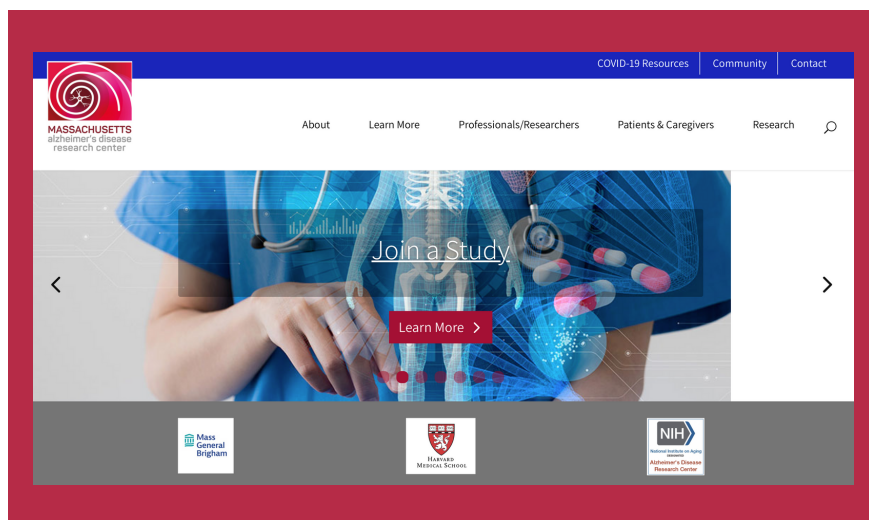
At Mass General Brigham, we conduct two major types of clinical research studies: Observational or natural history studies and Interventional or therapeutic clinical trials.

In observational studies, participants undergo clinical assessments such as memory and thinking tests and/or brain imaging. Researchers at CART and MADRC are working on developing more sensitive cognitive tests, biomarkers, and neuroimaging techniques like functional MRI and PET scans to detect early brain changes related to AD, and to differentiate these changes from normal aging.

In therapeutic clinical trials, participants receive an experimental drug or a placebo to test potential new therapies to treat AD. CART is currently enrolling research participants in multiple studies, including ones for older individuals with normal cognition, participants living with MCI or mild AD.

Currently available research studies

At Mass General Brigham, we conduct several studies for individuals who are cognitively normal or have been diagnosed with MCI, AD or non-AD dementia. Please visit the “Join a Study” page on our website at www.madrc.org, for additional information.



In addition to on-site research studies, a web-based observational study called the “APT Web Study” (must be cognitively normal and at least 50 years old) is currently enrolling. For additional information, visit: <https://www.aptwebstudy.org/en/welcome>

Who we are



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Where we work

Center for Alzheimer Research & Treatment (CART)

The Center for Alzheimer Research and Treatment (CART) is affiliated with the Department of Neurology and the Center for Brain/Mind Medicine at Brigham and Women's Hospital and Harvard Medical School. Its mission is two-fold: to assess promising new therapies for the prevention and treatment of AD through clinical trials, and to improve early diagnosis of AD by employing more sensitive clinical evaluations, biomarkers, and neuroimaging techniques.



Massachusetts Alzheimer's Disease Research Center (MADRC)

The Massachusetts Alzheimer's Disease Research Center's (MADRC) mission is to support new research and to enhance ongoing research by bringing together behavioral, biomedical, and clinical science investigators, to enrich the effectiveness of AD research and, ultimately, to improve health care delivery.

The Center has three functions: (1) Conducting multi-disciplinary research, (2) training scientists and clinicians, (3) teaching and/or transferring new information concerning AD and related disorders.

The MADRC Outreach, Recruitment & Engagement (ORE) Core increases public awareness about the importance of AD clinical research, educates the community about current advances in early AD and other neurodegenerative diseases, and supports recruitment and retention for MADRC-affiliated clinical research. The MADRC is based at Massachusetts General Hospital.



Our Goal:

The goal of Building a Road Map to support diagnosis and care for individuals living with MCI, AD and related dementias is to provide primary care physicians with tools to support, diagnose and manage the care of patients; to build a referral partner network that will support access to early diagnosis and treatment, and to provide information about community services and research opportunities. We are working together to find a cure for AD and related dementias.

Care at Brigham & Women's Hospital

At Brigham and Women's Hospital, the Clinical Care Program of the Alzheimer's Disease Center (ADC), which is part of the [Center for Brain/Mind Medicine](#) and the Division of Cognitive and Behavioral Neurology, provides comprehensive evaluation and treatment for this complex disease. The care spans all aspects of a patient's life. The multidisciplinary team of specialists in behavioral neurology, neuropsychiatry, geriatric psychiatry, neuropsychology, and social work address the cognitive, emotional and behavioral components of AD during each stage of the illness.

The Division of Cognitive and Behavioral Neurology provides comprehensive diagnostic and evaluative services for patients with the following neurologic conditions:

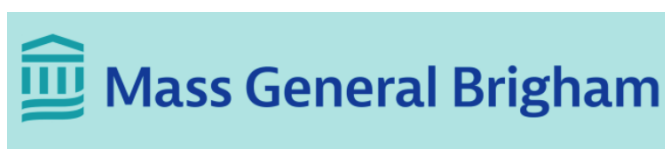
- AD
- Non-Alzheimer dementias
- MCI
- Frontotemporal Dementia
- Autism and Asperger Syndromes
- Learning disabilities
- Attention Deficit Hyperactivity Disorder

The Division of Cognitive and Behavioral Neurology also treats patients experiencing cognitive and neuropsychiatric difficulties, secondary to the following conditions:

- Parkinson's disease
- Traumatic brain injury
- Cerebrovascular disease
- Brain tumors and other central nervous system cancers
- Seizures and epilepsy

Care at Massachusetts General Hospital

The [Memory Disorders Division](#) at Massachusetts General Hospital (MGH) provides comprehensive diagnostic and treatment services for people with AD and other types of dementia, such as Frontotemporal Dementia or Dementia with Lewy bodies. These services are provided at specialized outpatient clinics, including the Memory Disorders Unit, the Frontotemporal Disorders Unit, the Normal Pressure Hydrocephalus clinic, and the Lewy Body Dementia Unit. MGH also has the [Multicultural Assessment & Research Center](#) with culturally and linguistically appropriate neuropsychological services for diverse adult patients with brain disorders..



Additional Programs at Massachusetts General Hospital (MGH)

- The [Frontotemporal Disorders Unit](#) at MGH specializes in comprehensive diagnosis and treatment for Frontotemporal focal dementia syndromes and disorders. Their aim is to develop better knowledge about, diagnosis of, and treatment for all forms of Frontotemporal focal dementia and related focal dementia syndromes.
- The [Lewy Body Dementia Unit](#) at MGH, a Lewy Body Dementia Association Research Center of Excellence, coordinates clinical care and research for patients living with Dementia with Lewy bodies.
- The [Psychology Assessment Center](#) at MGH provides neuropsychological and psychological assessment for individuals, including Spanish speakers.

Other Resources for Providers

[Rapid Diagnostic Clinic](#) at Brigham and Women's Hospital: designed to improve access to earlier diagnosis for patients interested in research participation at the Center for Alzheimer Research (CART) and Treatment and to support physicians in need of diagnostic assistance.

For more information, please email BWHBehavioralNeurology@bwh.harvard.edu or submit referrals via EPIC to the BWH Neuro BWH CART pool with important information such as patient's DOB, MRN, and medications.

MADRC has **educational programs for professionals** that can be offered virtually or in-person. Physician-specific programs are offered through our Road Map education series, and via customized programs by our research team members.

The Road Map professional series includes the following programs:

- [Road Map to Dementia Diagnosis Management](#)
- [Road Map to Behavioral Management](#)

For information about the Road Map series, contact:

Lenore Jackson Pope: ljackson-pope@bwh.harvard.edu or (617) 525-8381

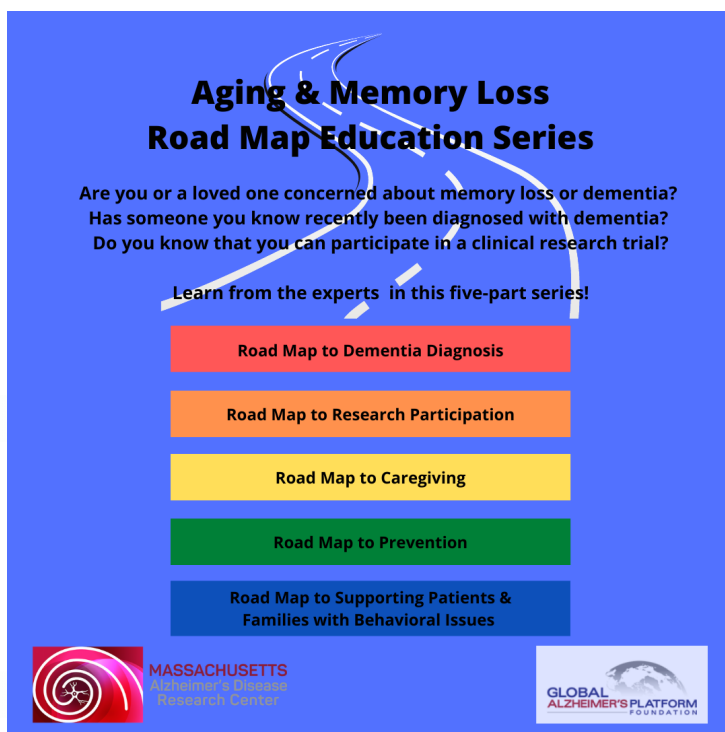
Resources for patient and caregiver support

Caregiver & Patient Support Resources

- [Alzheimer's Association](#): 800-272-3900 (24/7 helpline)
- [American Association for Retired Persons \(AARP\)](#)
- [National Institute on Aging \(NIH\)](#): 800-438-4380
- [Alzheimer's Foundation of America](#): 866-232-8484
- [Lewy Body Dementia Association](#): 800-539-9767
- [Association for Frontotemporal Degeneration](#): 866-507-7222

The MADRC **Aging & Memory Loss, Road Map Education Series** provides community education on the following topics:

- [Road Map to Dementia Diagnosis](#)
- [Road Map to Research Participation](#)
- [Road Map to Caregiving](#)
- [Road Map to Prevention](#)
- [Road Map to Supporting Patients & Families With Behavioral Issues](#)




**Aging & Memory Loss
Road Map Education Series**

Are you or a loved one concerned about memory loss or dementia?
Has someone you know recently been diagnosed with dementia?
Do you know that you can participate in a clinical research trial?

Learn from the experts in this five-part series!

- Road Map to Dementia Diagnosis
- Road Map to Research Participation
- Road Map to Caregiving
- Road Map to Prevention
- Road Map to Supporting Patients & Families with Behavioral Issues

 MASSACHUSETTS
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Research Information

- [ClinicalTrials.gov](#)
- [Alzheimer's Association Trial Match](#)
- [Center for Clinical Research Participation Information \(CICSRP\)](#)

National Clinical Trials Information

Participating in research will significantly help us find more effective treatments for Alzheimer's disease and related dementias. The following resources provide information about clinical trials:

- National Institute on Aging - Alzheimer's Disease Education and Referral Center: 800-438-4380
- Alzheimer's Association Trialmatch: 800.272.3900
- Alzheimer's Prevention Network

Brigham & Women's Hospital
Center for Alzheimer Research & Treatment
www.bwhcart.org



Massachusetts General Hospital
Massachusetts Alzheimer's Disease Research Center
www.madrc.org



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