

A Road Map to Diagnosis



Physician edition

As the average age of Americans increases over time, the risk for developing Alzheimer's disease will rise too. Unfortunately, there is no cure for Alzheimer's disease and the last drug to be approved by the FDA was in 2003.

To help reduce patients' chances of facing this harsh reality, we as physicians need to understand how to diagnose them more accurately and quickly. The sooner we detect significant changes in one's memory, the sooner we can intervene.

In this booklet, you will learn how to evaluate and manage someone with dementia.

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

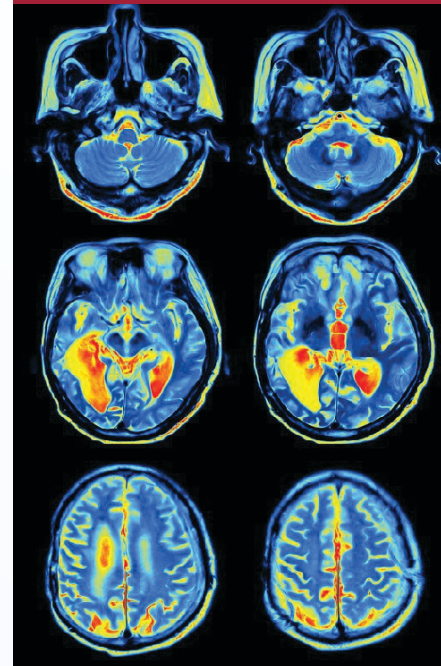
- Insidious onset and slow progression: Neurodegenerative disease
- Rapid progression: Prion disease, autoimmune/inflammatory disease, atypical neurodegenerative disease
- Static time course or fluctuations without clear progression: Psychiatric or general medical illness

Aging & Memory Loss Road Map Series

I. Dementia Diagnosis

II. Research Participation

III. Caregiving



Contents:

Current recommended diagnostic assessments for Alzheimer's disease	1
Alzheimer's disease	3
Multiple Components of AD management.....	5
FDA Approved medications for AD dementia	6
AD Dementia Medications: Symptomatic Benefits	6
Lifestyle modifications	6
Why research is vital?.....	7
Currently available research studies.....	7
Who we are	8
Where we work	9
Care at BWH and MGH.....	10
Resources	11-12



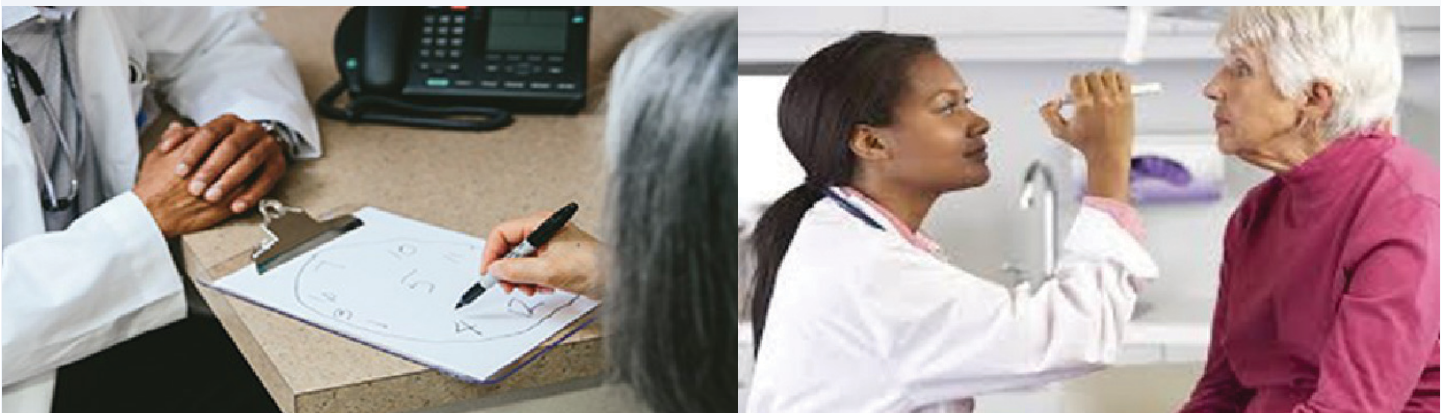
Dementia Diagnostic Assessments

- “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 to 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; target MCI and mild dementia), Clinical Dementia Rating (CDR, Relies on questions to 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 or mild dementia or for atypical presentations

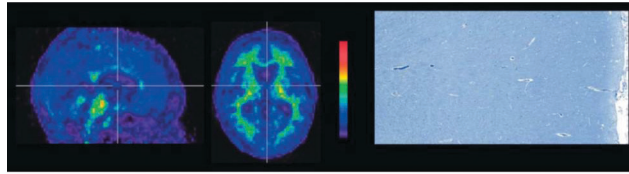
- Labs: CSF (routine, A β 1-42, tau, 14-3-3), blood (B12, TSH, CBC, electrolytes, LFTs), urinalysis
 - Brain imaging
- ⇒ Brain Structure: MRI (CT)
- ⇒ Brain Function: FDG-PET (SPECT), fMRI (primarily a research tool)
- ⇒ Molecular imaging of pathology: Amyloid PET imaging (F-18 agents, approved by FDA for clinical use in MCI or dementia but not covered by insurance; primarily used in research), Tau PET (not approved by FDA yet; 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 between a person’s 30s and mid-60s and accounts for about 1% of all people with Alzheimer’s disease. *Source (NIH)*



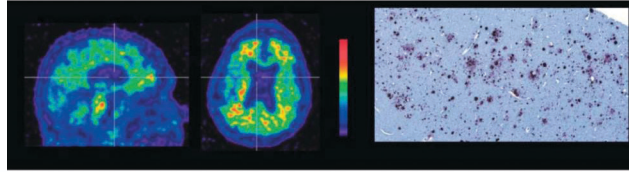
18F-Florbetapir PET amyloid imaging correlates well with post-mortem findings

Low amyloid on PET and autopsy



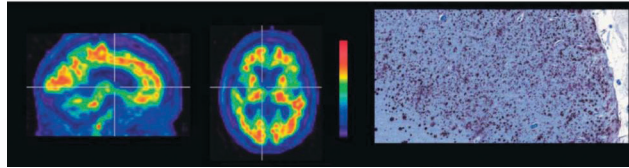
Visual rating:
Sensitivity 92%
Specificity 100%

Intermediate amyloid on PET and autopsy



Clark et al. JAMA 2011;

High amyloid on PET and autopsy



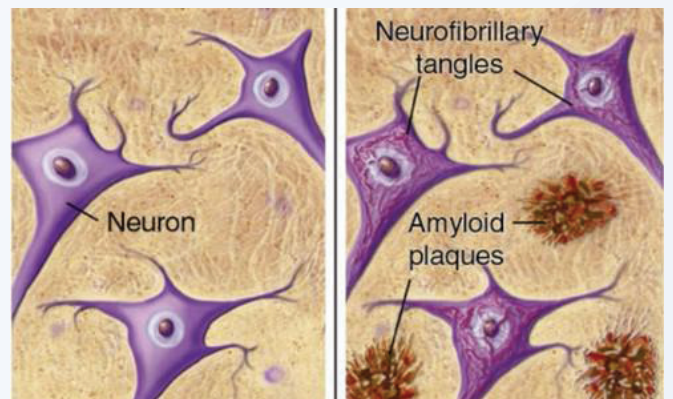
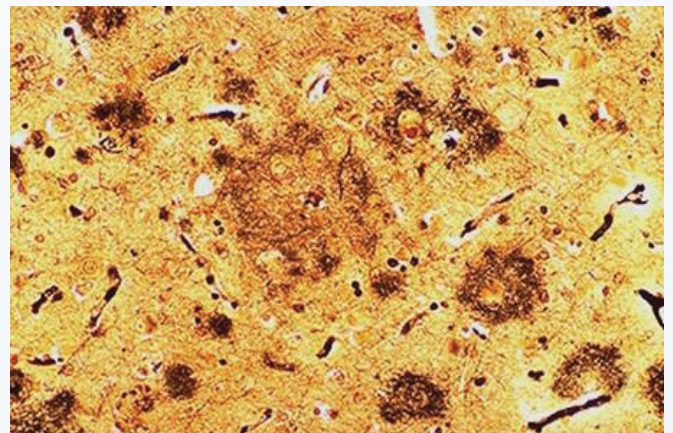
Clark et al. *Lancet Neurol* 2012

Differential Diagnosis of Dementia

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

Alzheimer's disease

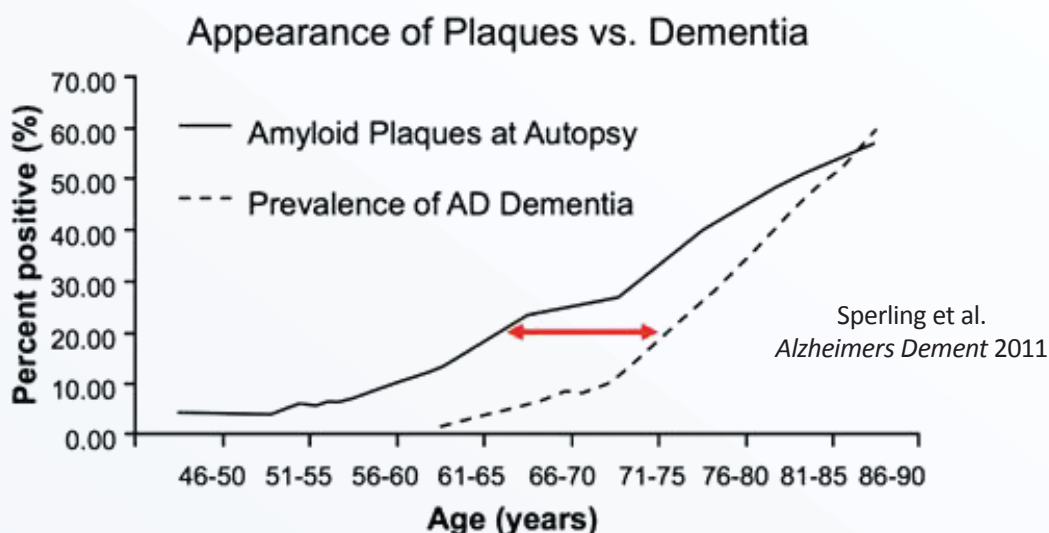
- Most common cause of dementia
- Typical onset in early 70's
- Progressive neurodegenerative disease
- ⇒ Insidious clinical progression over years
- ⇒ Typically begins with impaired short-term memory, sense of direction, and praxis
- ⇒ Eventually affects general cognition, behavior, and daily functioning
- >5 million people in U.S. carry 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



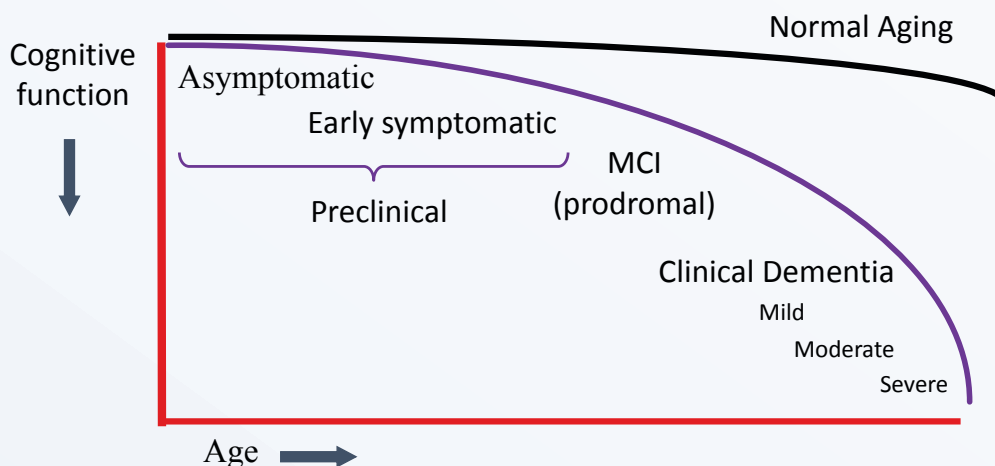
Diagnosing AD early

- The underlying pathological changes begin 10-15 years prior to clinical diagnosis
- ⇒ Using disease-modifying drugs during this period may be most effective
- 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 meeting criteria for AD yet, 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

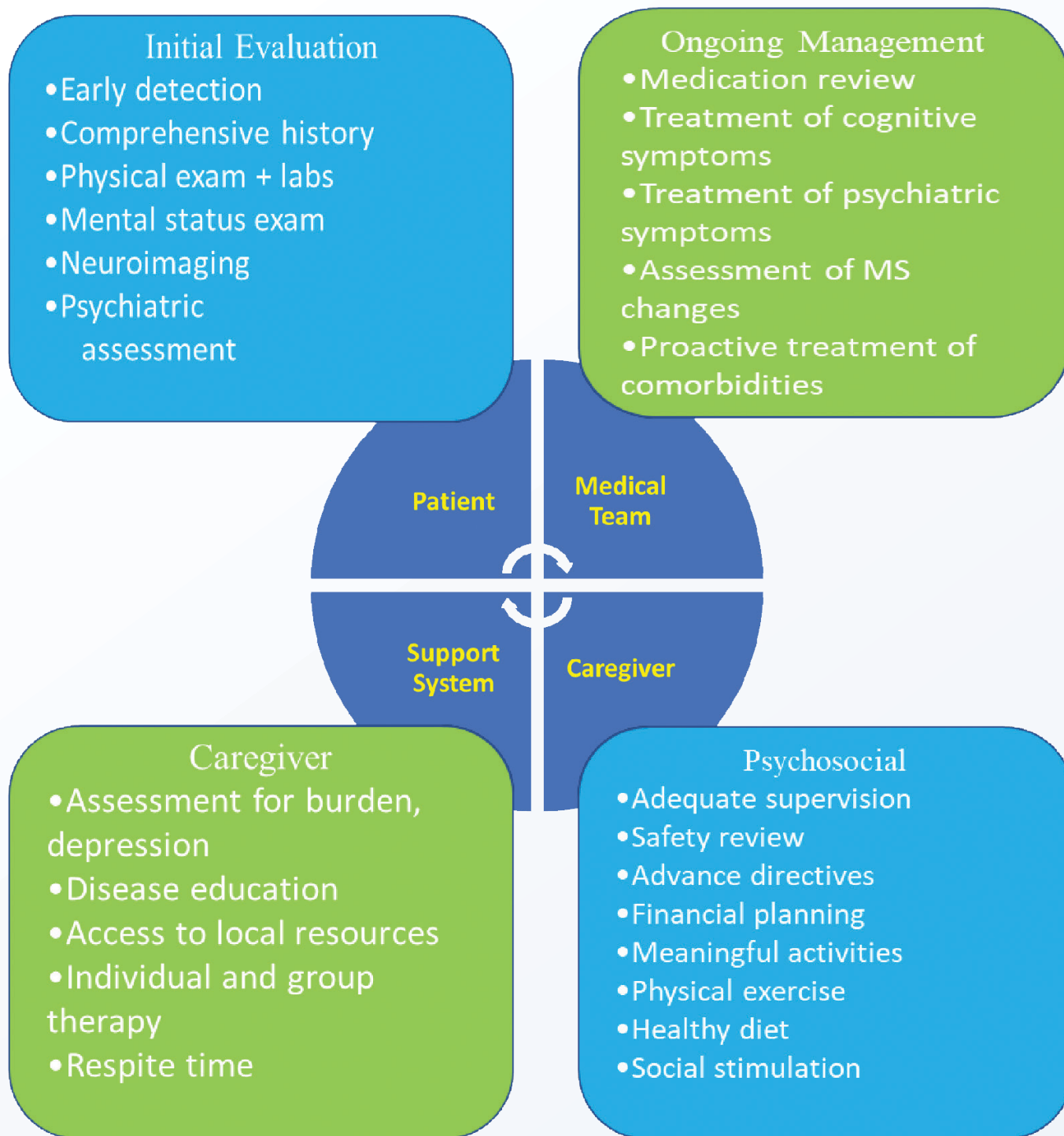


ALZHEIMER DISEASE TRAJECTORY



Multiple Components of Dementia Management

There are multiple components to managing patients with dementia and their caregivers. Below is a diagram courtesy of the Alzheimer's Association depicting the various aspects involved:



FDA Approved medications for AD dementia



- **Cholinesterase-inhibitors (ChE-I):** donepezil, rivastigmine, galantamine, tacrine * (no longer clinically used)
 - o All FDA approved for treatment of mild to moderate AD dementia
 - o Donepezil also FDA approved for treatment of severe AD dementia (2006)
 - o Galantamine available as a generic since 2009; donepezil, rivastigmine since 2010
- **NMDA (glutamate) receptor antagonist:** memantine
 - o 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:
 - o Daily functioning, cognition, neuropsychiatric symptoms, caregiver burden (and potentially saving money)
- Individual results vary
 - o Highly variable effects across time between and within individuals

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)
 - o 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)
- No FDA approved drug for 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**
 - o 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**

- o 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**

- o Interacting with others may help preserve memory and processing speed

- **Sleep (7-9 hours/night)**

- o 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 volunteers and patients say they participate in clinical trials to help others and to contribute to moving the science forward, or to receive access to a possible new treatment.

At Brigham and Women's Hospital Center for Alzheimer Research and Treatment (CART) and the Massachusetts Alzheimer's Disease Research Center (MADRC), 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 new potential therapies to treat AD. CART is currently enrolling participants in multiple studies, including studies for older individuals with normal cognition, participants with MCI or mild AD dementia.

Currently available research studies

At BWH and MGH, we have 5 clinical trials, 5 observational imaging studies, and 22 observational studies for individuals who are cognitively normal or diagnosed with MCI, AD or non-AD dementia.

In addition to on-site research studies, a web based observational study named "APT Web Study"(must be cognitively normal and at least 50 years old) is currently enrolling. <https://www.apwebstudy.org/en/welcome>



Who We Are



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Where We Work

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 these patients, and to build a referral partner network that will support access to early diagnosis and treatment, as well as information about community services and research opportunities.

We are working together to fight AD and related dementias.

Center for Alzheimer Research and 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.



CART Staff

Massachusetts Alzheimer's Disease Research Center (MADRC)

The Massachusetts Alzheimer's Disease Research Center (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, 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.



Members of the ORE core of MADRC and CART

Care at Brigham and 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 at the new Hale Building for Transformative Medicine, provides comprehensive evaluation and treatment for this complex disease. The care provided 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 that are secondary to the following conditions:

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

Can dementia be cured? *We have not yet found a cure for any type of dementia, but there is ongoing research of drugs, vaccines and other treatments.*

Care at Massachusetts General Hospital



The Memory Disorders Unit at Massachusetts General Hospital 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. There is also a Memory Disorders Unit clinic with Spanish speakers to provide comprehensive care to the Hispanic/Latino community.

Additional programs at Massachusetts General Hospital:

- The **Frontotemporal Disorders Unit** at Massachusetts General Hospital 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. Email MGHFTDUnit@partners.org or call 617-726-5571.

- The **Lewy Body Dementia Unit** at Massachusetts General Hospital coordinates clinical care and research for patients with Dementia with Lewy bodies. It is a Lewy Body Dementia Association Research Center of Excellence. To contact the MGH Lewy Body Dementia Unit please call **617-726-5532**.
- The **Psychology Assessment Center** at Massachusetts General Hospital provides neuropsychological and psychological assessment for individuals, including Spanish speakers. Contact the Psychology Assessment Center for further information at **617-726-3647**.

Memory Disorders Unit
Massachusetts General Hospital

Phone: (617) 726-1728

Fax: (617) 726-4104

Other Resources for Providers

- **Rapid Diagnostic Clinic (at Brigham and Women’s Hospital):** designed to improve access to earlier diagnosis for patients interested in re-search participation at the Center for Alzheimer Research and Treatment and to support physicians in need of diagnostic assistance.

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

Caregiver Resources

- Alzheimer’s Association:
www.alz.org/care
 1-800-272-3900 (24/7 helpline)
- American Association for Retired Persons (AARP):
<http://bit.ly/2EJrP9J>
- National Institutes on Aging:
[http:// bit.ly/2nESqO7](http://bit.ly/2nESqO7)

Research Information

- Clinical Trials.gov:
www.clinicaltrials.gov
- Alzheimer’s Association Trial Match:
www.alz.org/trialmatch
- Center for Clinical Research Participation Information (CICSRP):
www.ciscrp.org

Resources for Patient and Caregiver Support

Alzheimer’s Association: The premier source of information for advocacy, research, support programs, and education.

- 24/7 Helpline: *1-800-272-3900*
- MA/NH Chapter contact: *617-868-6718*

Alzheimer’s Foundation of America: Direct services and educational resources to patients and caregivers.

- National Toll-Free Helpline: *1-866-232-8484*

Association for Frontotemporal Degeneration (ATFD): www.theaftd.org

- Helpline *1-866-507-7222*

Lewy Body Dementia Association (LBDA): www.lbda.org

- LBD Caregiver Link *1-800-539-9767*



National Institute on Aging: Alzheimer’s Disease Education and Referral Center (ADEAR): The latest dementia related news and publications on diagnosis, treatment, care, and research.

- www.nia.nih.gov/health/alzheimers
- Toll-Free Helpline: 1-800-438-4380

National Clinical Trial Information

You or a loved one’s participation in research studies will significantly help in the search for more effective treatments for AD and related dementias. The following resources provide information about a range of national clinical trials:

National Institute on Aging: Alzheimer’s Disease Education and Referral Center (ADEAR):

Toll-free contact: 1-800-438-4380

Alzheimer’s Association TrialMatch: 24-hour Helpline 1-800-272-3900

Alzheimer Prevention Network: alzpreventionnetwork.org

Brigham and Women’s Hospital

Massachusetts General Hospital



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