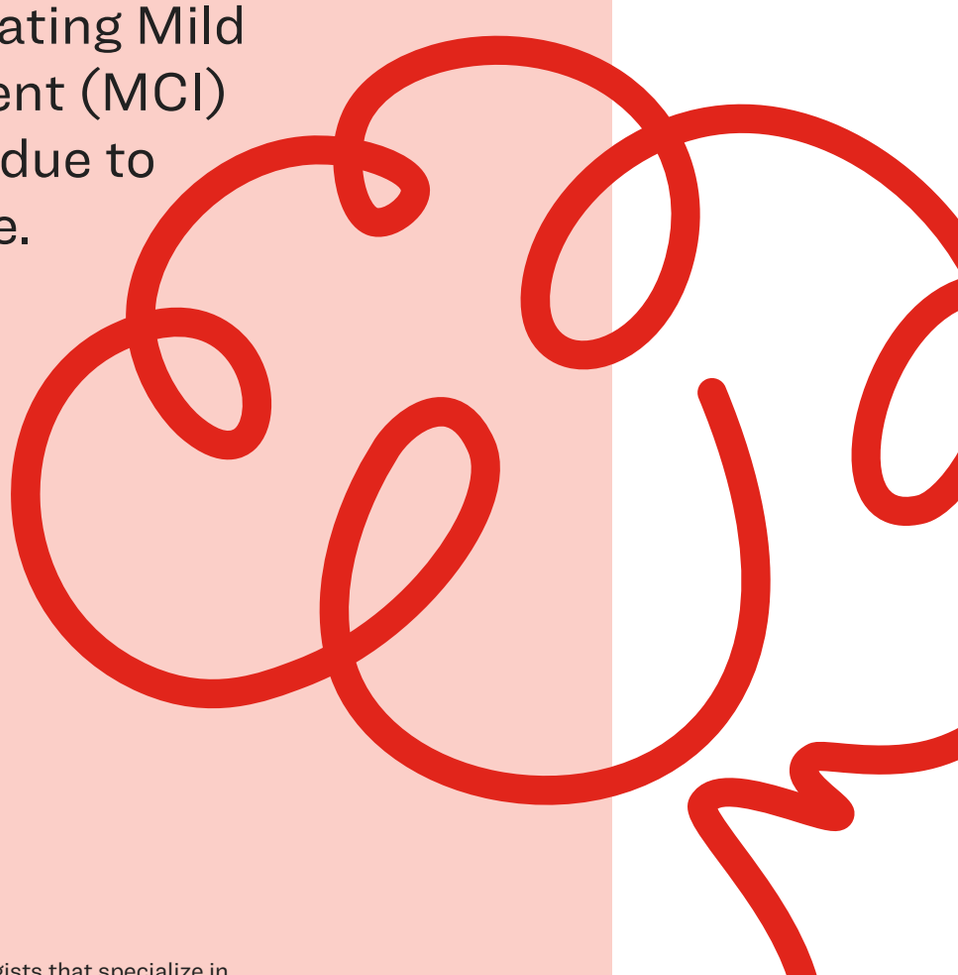
Lilly
A MEDICINE COMPANY

Early Symptomatic Alzheimer's Disease: **A Patient Care Pathway**

A practice guide for primary care providers and dementia specialists[a], offering guidance on detecting, assessing, diagnosing, and treating Mild Cognitive Impairment (MCI) and mild dementia due to Alzheimer's disease.



[a]Dementia specialists also encompass neurologists that specialize in Alzheimer's disease care.

Content

This guide offers a step-by-step framework for dementia specialists and primary care providers to detect, assess, diagnose, and treat early symptomatic Alzheimer's disease.

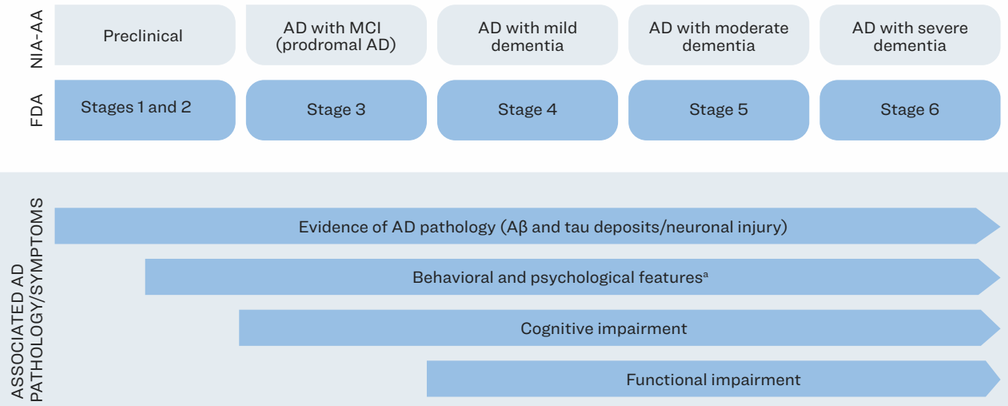
The goal is to adapt the communication to the various steps of the care pathway and optimize patient outcomes.

Early Symptomatic Alzheimer's Disease: What, Why, and How

Alzheimer's disease (AD) is the most common cause of dementia, becoming more prevalent as the global population of people 65 years and older age is increasing.[1]

It is a progressive, neurodegenerative disease in which patients experience increasing cognitive, functional, and behavioral impairments.[1]

AD continuum[1]



[a]One important behavioral and psychological feature to consider is mild behavioral impairment, a clinical construct that describes the emergence of sustained and impactful neuropsychiatric symptoms that may occur in patients ≥50 years old prior to cognitive decline and dementia.

Note: There are additional naming conventions available, and these are just two examples.

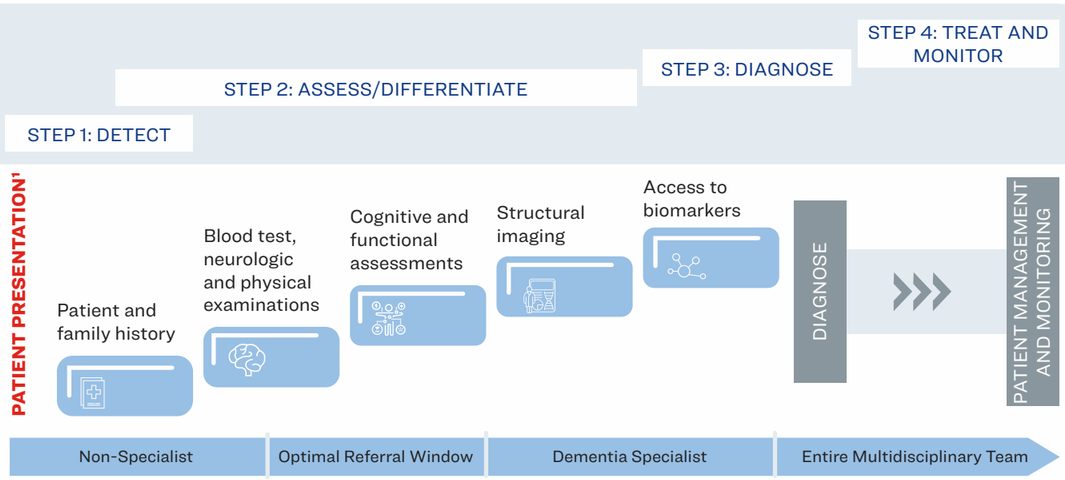
Given the complex nature of AD, a multidisciplinary team approach is necessary to ensure timely and accurate diagnoses for patients suspected of having or living with AD.[1]

This approach, which begins with primary care and extends through various specialists such as dementia experts, neurologists, and other healthcare providers, can be seen as a **patient care pathway.**

Why is early diagnosis important?[1,2]

- Provides clarity for the patient
- Gives patients and families time to plan ahead and access support systems
- Enables early treatment, which can slow disease progression and help maintain independence for longer

Patient Care Pathway



Note: Exact practice for individuals in a collaborative care team may vary based on many factors, including expertise and resources.

Goals of the four steps[1,3]

Detect:
Learn to recognize the most common signs and symptoms of AD.

Assess and Differentiate:
Gain insights into the most common assessments.
Learn to rule out other conditions, possibly reversible, such as depression or vitamin deficiencies.

Diagnose:
Learn how to detect the clinical evidence and biomarker confirmation for a diagnosis of early symptomatic AD.

Treat:
Develop an individualized management plan for the patients living with early symptomatic AD.

Recommended[a] roles and responsibilities in the patient care pathway [1]

The circle ● and triangle ▲ will represent primary care providers and dementia specialists, respectively, throughout the rest of this document.

● Primary care providers

- Detect early signs and symptoms of AD
- Perform an initial assessment, including risk factors and medical history
- Evaluate the differential diagnosis, as other conditions may have similar presentations

▲ Dementia specialists

- Further evaluation with clinical and biomarker assessments to determine underlying etiology
- Confirm the diagnosis, and develop a patient-focused management and follow-up plan
- Provide the patient with additional support resources

[a]This is based on the guidelines by Alzheimer's Association (2024) and study by Porsteinsson et al. (2021), which takes a US perspective, and this may vary regionally.

Step 1: Detecting Alzheimer's Disease ●

Have you covered everything?[1]

Symptoms affecting cognition? | Changes in behavior? | Any psychological changes in state of mind? | Symptoms with a physical trait, eg, affecting gait? | Sleep disorder?

Detecting early signs and symptoms of AD is the first step of the care pathway.[1]

- Early signs of AD are often subtle and vary from person to person. They typically develop gradually as the disease progresses.
- It is important that you pay attention to subtle details and listen closely to inputs from family members or care partners, as they can provide valuable insights for recognizing early signs.
- Being aware of the most common symptoms of early symptomatic AD is important.
- Have you reviewed the patient's medication list as a potential cause of cognitive impairment?

Key symptoms linked to the early symptomatic stages of AD include[1]:

	Category of Symptoms	Practical Examples to Be Aware of
Cognition	• *Short-term memory loss* • *Word-finding difficulties (anomia) or communication difficulties*	• Forgetting appointments, names, and recent events • Frequently misplacing items • Trouble finding exact words to express oneself, or loss of word meaning
Behavior	• *Withdrawal from social activities* • *Disinhibition and impulsivity*	• Inability to participate in meaningful social situations • Inappropriate social conduct such as eating from someone else's plate, or inappropriate language • Poor or decreased judgment
Psychological	• *Depression* • *Mood disturbances* • *Apathy*	• Changes in mood or personality • Feeling of helplessness and a loss of purpose in life • Loss of initiation
Physical	• *Visuospatial problems* • *Gait impairment*	• Frequent falls
Other	• *Insomnia*	• Difficulty initiating sleep • Physical discomfort or restlessness

Note: Not inclusive of all symptoms.

Step 2: Assessing and Differentiating Alzheimer's Disease

The second step of the care pathway consists of conducting several assessments to rule out potentially reversible causes, such as depression or vitamin deficiencies, and other causes of mild cognitive impairment.[1] AD can cause a wide range of symptoms, and assessments can include history and physical assessment, cognitive, functional, and behavioral assessments, and laboratory and imaging testing.[1]

History and Assessment[1,4]:

Risk factors:
- Family history of AD or related dementias in first degree relatives, age, females, *ApoE ε4* status, physical inactivity, low educational status, chronic conditions, obesity, and psychiatric conditions

Medical conditions that can affect cognition:
- Including hypertension, diabetes, stroke, Parkinson's disease, uncontrolled hypothyroidism, signs of issues with speaking or hearing, or head trauma

Prescribed medications that can impair cognition:
- E.g., sleep aids, anxiolytics, analgesics, or anticholinergics

Social history:
- Illicit drug use, exposure to heavy metals, alcoholism or chemotherapy

Physical Assessment[1]:

Mental status
- Assess for depression

Neurological assessment
- Signs that could indicate a stroke

Diet and nutrition

Review medications:
- Review medications mentioned during the initial assessment. Do any of them impair cognition?

Physical examination
- Blood pressure
- Temperature
- Pulse
- Listen to heart and lungs

Laboratory Analysis[1]:

Recommended:
- Complete blood cell count
- Blood glucose
- Thyroid-stimulating hormone
- Serum B12 and folate
- Serum electrolytes
- Liver function
- Renal function tests
- Urinalysis[5]

Recommended, if available:
- ApoE genotyping

Structural Imaging[1]:

Recommended:
- Magnetic resonance imaging (MRI)

Consideration:
- For patients with more advanced AD symptoms, consider using fluorodeoxyglucose-PET (FDG-PET)

Disclaimer: This list of tests is not exhaustive and is intended to provide a general overview only.

Engage care partners: Care partners, such as next of kin, can provide critical insights on cognitive and functional changes over time.[1]

Have you[1]

- Confirmed medical and family history?
- Reviewed medications for any cognitive impairment risks?
- Performed laboratory tests to rule out reversible causes (eg, vitamin deficiencies or hormonal imbalances)?
- Conducted a brief clinical assessment to identify cognitive and functional impairment?

Cognitive, Functional, and Behavioral Assessments[1]:

Type of Assessment	Assessment	Number of Items	Time Taken to Complete Assessment (minutes)	Scoring System	Sensitivity and Specificity	Justification
Cognitive	MMSE	30	5-10	23-24	Sensitivity: 85%–100% Specificity: 66%–100%	Requires payment to use[6]
	MoCA	12	10	<26 for MCI or dementia	Sensitivity: 78%–100% Specificity: 65%–94%	Requires a certification and payment[7]
	Mini-Cog	3-item recall with clock drawing	2-3	Recall 2/3 items clock drawing used to determine presence of cognitive deficits	Sensitivity and specificity comparable to MMSE	Brief assessment and easy to interpret, no training requirements
	AD8	8	2-3	Scores greater than 2 signify impairment	Sensitivity: 90% Specificity: 68%	Brief assessment for cognitive impairment
	IQCODE	16 or 26	10	Scores greater than 3.44 signify impairment	Sensitivity: 76%–100% Specificity: 65%–86%	Measures decline from premorbid level
Functional	FAQ	10 categories	5[a]	0–3 scale (0=normal; 3=dependent)	Sensitivity: 90% Specificity: 83%	Highly reliable assessment
Behavioral	GDS	15 or 30	5-10	≥5 suggestive of depression; ≥10 significant of depression[a]	No data available	Reliable assessment for depression (often associated with dementia; symptoms may overlap)
	NPI-Q	12	5	0-3 scale (0=none; 3=severe)	Sensitivity: 86% Specificity: 76%	Brief and reliable assessment

[a]Personal communication.

Step 3: Diagnosing Alzheimer's Disease

Once the assessment is completed and other conditions have been ruled out, the third step of the care pathway is to diagnose AD. This is made by evaluating the clinical, cognitive, functional, and neuropathological evidence or biomarkers. There is a strong concordance between CSF biomarkers and amyloid PET in AD. They can be used interchangeably.[1] The next step is confirmation of neuropathological hallmarks such as amyloid and tau with or without neurodegeneration.

Notice:
Access to these tools and their reimbursement status can differ depending on where you live. It is important to verify the availability and local practice environment.

Imaging Biomarkers[1,8]

Amyloid PET Scanning

- Visualizes β-amyloid plaques in the brain using specific tracers
- Considerations: This should be used alongside clinical assessments for a reliable AD diagnosis, as PET scans alone cannot definitively diagnose the disease
- Limitations: The accuracy of amyloid PET depends on the observer's experience, and the presence of amyloid plaques in various conditions can also complicate the interpretation

Fluid Biomarkers (CSF Testing)[1,8]

Cerebrospinal fluid Biomarker Analysis

- Can detect changes in AD biomarkers, such as amyloid (Aβ42 and Aβ42/40) and tau levels (P-tau and T-tau), which is indicative of amyloid accumulation and neurodegeneration
- Consideration: Elevated T-tau is not specific to Alzheimer's

Tip: There are appropriate use criteria available to help identify suitable patients for CSF biomarker analysis

Note on Emerging Diagnostic Tools[1]:

Since the availability of amyloid PET is limited globally, new technologies and advances are needed to identify the underlying pathophysiology of AD. The most likely up-and-coming tools are blood-based and CSF biomarkers, such as the blood-based plasma biomarkers P-tau181 and P-tau217.
Blood-based biomarkers are being investigated as a diagnostic option, additionally, they may prove to be a more cost-effective diagnostic tool in the near future.[9]

Step 4: Treating Alzheimer's Disease

The final and fourth step of the care pathway is to determine the best management plan, including possible treatment options, for the patient. This should be personalized and based on earlier steps to address specific risk factors and symptoms. The management plan can consist of a combination of the following categories.

Diet and Lifestyle Changes[10,11,12,13]:

- A diet consisting of fish, chicken, fruits, spices (such as curcumin, cinnamon, and curry pepper), low-fat foods, vegetables, nuts, olive oil, and whole grain products
- It is recommended to stop smoking and drink alcohol to a minimum

Cognitive Training[10,11]:

- Simple memory exercises (eg, recalling recent conversations or identifying familiar faces), word searches, and practice with organizing daily tasks (eg, planning a simple schedule or meal)
- The patient can be reminded of details such as the upcoming events, using conversational cues or a calendar

Exercise[4]:

- Physical activities like walking are cognitively engaging
- A randomized clinical trial found that exercise, and relevant lifestyle changes, improved cognition in people at-risk for cognitive decline

Care Partner Training[14]:

Educational programs are available for care partners. They help improve patients':
- cognitive benefits
- functional benefits
- health-related quality-of-life benefits

Pharmacologic Treatment[15]:

Based on the AD staging and eligibility factors, clinicians can prescribe:
- Symptomatic treatments that may help lessen or stabilize symptoms for a limited time by affecting certain chemicals involved in carrying messages among and between the brain's nerve cells
- Disease-modifying therapies, such as Amyloid-targeting therapy (ATT), can slow the decline in memory, thinking, and function inpatients living with AD by influencing the underlying biological processes of the disease

Keep in Mind That[1]

The goal of the management plan is to preserve the patient's cognitive abilities and for the patient to maintain independence in their daily activities for as long as possible. Regular, ongoing monitoring is important to follow the disease progression and adjust the management plan accordingly.
In early symptomatic AD, non-pharmacological therapies are commonly used, alongside medications when appropriate.

Tips for Communicating with a Patient Living with Alzheimer's Disease

Patients living with AD may experience a range of symptoms that can affect their communication abilities. This can manifest in many ways, for example[16]:

- Frequently forgets words
- Frequently use or repeat certain words or phrases
- Often loses their train of thought
- Often describes items instead of calling them by name
- Participates less in conversations

To accommodate these changes and to increase the success of detecting and diagnosing AD, it is necessary to adjust the approach to communication. This page provides some key communication tips that may increase your success and the patient's experience.

Key Communication Tips[16,17,18]

Best Practices in Communicating a Diagnosis of AD[a]

- Discuss the preferred method of communication
- Confirm patient understanding using tools such as the Teach Back method
- Tailored conversations may encourage patient participation in shared decision-making
- Care partners can provide perspective on clinical history and support with future patient care
- Be patient, listen, and give the patient time to speak
- At least 15-20 min are recommended for the diagnostic disclosure
- Step-up empathy languages can enhance information sharing and foster trust

[a]This resource was developed by Eli Lilly and Company and Dr. Sharon Cohen, MD, and Prof. Katherine Rankin, PhD, who are experts in Alzheimer's Disease. This work was inspired by established peer-reviewed research but created based on the participants' perspectives and opinions as well as from data on file from multiple Lilly advisory settings.

For more resources on best practices to communicate a diagnosis to a patient living with AD, please visit the following link:

medical.lilly.com

Abbreviations

Aβ=Amyloid Beta; AD=Alzheimer's disease; AD8=Ascertain Dementia 8-item; APOE=Apolipoprotein E; ATT=Amyloid Targeting Therapy; CSF=Cerebrospinal Fluid; FAQ=Functional Activities Questionnaire; FDA=Food and Drug Administration; FDG-PET=Fluorodeoxyglucose-Positron Emission Tomography; GDS=Geriatric Depression Scale; IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly; MCI=Mild Cognitive Impairment; Mini-Cog=Mini Cognitive Assessment Instrument; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; MRI=Magnetic Resonance Imaging; NIA-AA=National Institute of Aging and Alzheimer's Association; NPI-Q=Neuropsychiatric Inventory Questionnaire; P-tau=Phosphorylated tau; PET=Positron Emission Tomography; T-tau=Total-tau.

References

[1] Porsteinsson AP, Isaacson RS, Knox S, Sabbagh MN, Rubino I. Diagnosis of early Alzheimer's disease: clinical practice in 2021. *J Prev Alzheimers Dis.* 2021;8(3):371-386.

[2] Rasmussen J, Langerman H. Alzheimer's disease - why we need early diagnosis. *Degener Neurol Neuromuscul Dis.* 2019;9:123-130.

[3] Clinical practice guidelines & evidence. Alzheimer's Disease and Dementia. 2024. https://www.alz.org/professionals/health-systems-medical-professionals/clinical-practice-guidelines-and-evidence. (Accessed April 04, 2025).

[4] Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and management of dementia: review. *JAMA.* 2019;322(16):1589-1599.

[5] Atri A, Dickerson BC, Clevenger C, 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. *Alzheimer's Dement.* 2024; 1-32.

[6] Kalish VB, Lerner B. Mini-Mental State Examination for the Detection of Dementia in Older Patients. *American Family Physician.* 2016;94(11):880-881. https://www.aafp.org/pubs/afp/issues/2016/1201/p880.html

[7] MoCA Montreal - Cognitive Assessment. MoCA Montreal - Cognitive Assessment. http://www.mocatest.org

[8] Blennow K, Zetterberg H. Biomarkers for Alzheimer's disease: current status and prospects for the future. *J Intern Med.* 2018;284(6):643-663.

[9] Palmqvist S, Tideman P, Mattsson-Carlgren N, et al. Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary Care. *JAMA*. 2024;332(15):1245-1257

[10] InformedHealth.org [Internet]. 2006-Alzheimer's disease: learn more – non-drug interventions for Alzheimer's disease. Institute for Quality and Efficiency in Health Care (IQWiG). https://www.ncbi.nlm.nih.gov/books/NBK279355/ (Updated Mar 29, 2022. Accessed October 22, 2024).

[11] Fertalova T, Ondriova I. Non-pharmacological treatment of Alzheimer's. In: Redirecting Alzheimer Strategy - Tracing Memory Loss to Self Pathology. *IntechOpen*; 2019.

[12] Yang JJ, Keohane LM, Pan XF, et al. Association of healthy lifestyles with risk of Alzheimer disease and related dementias in low-income black and white Americans. *Neurology.* 2022;99(9):e944-e953.

[13] Wilcox S, Sharkey JR, Mathews AE, et al. Perceptions and beliefs about the role of physical activity and nutrition on brain health in older adults. *Gerontologist.* 2009;49 Suppl 1:S61-S71.

[14] Sanjuán M, Navarro E, Calero MD. Caregiver training: evidence of its effectiveness for cognitive and functional improvement in older adults. *J Clin Nurs.* 2023;32(5-6):736-748.

[15] Treatments. Alzheimer's Association. https://www.alz.org/alzheimers-dementia/treatments/medications-for-memory (Accessed October 22, 2024).

[16] Communication and Alzheimer's. Alzheimer's Association. https://www.alz.org/help-support/caregiving/daily-care/communications (Accessed October 22, 2024).

[17] Baile WF, Buckman R, Lenzi R, Glober G, Beale EA, Kudelka AP. SPIKES-A six-step protocol for delivering bad news: application to the patient with cancer. *Oncologist.* 2000;5(4):302-311.

[18] Yen PH, Leasure AR. Use and effectiveness of the teach-back method in patient education and health outcomes. *Fed Pract.* 2019;36(6):284-289.

A MEDICINE COMPANY

Notes