Detection and Diagnosis of Early Symptomatic Alzheimer's Disease in Primary Care

Dani Cabral, MD; Thomas O. Obisesan, MD, MPH

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KEY TAKEAWAYS

- Alzheimer's disease (AD) is commonly seen in primary care settings, and primary care clinicians (PCCs) are often the first to encounter patients presenting with cognitive impairment.[1]
- Despite the high prevalence of AD in individuals aged 65 years and older, diagnosis is often delayed or missed, resulting in delayed treatment and negative impacts on patients, care partners, and health care systems.[3]
- Current diagnosis of AD is clinical-neuropathologic based both on clinical presentation as well as underlying neuropathology.[2]
- PCCs are critical in the detection and initial evaluation of patients with early symptomatic AD.[2]

FACULTY

Dani Cabral, MD, Assistant Professor, Departments of Neurology and Psychiatry, University of Arizona, Tucson.

Thomas O. Obisesan, MD, MPH, Professor of Medicine and Geriatrics, Department of Medicine, Howard University, Washington, DC.

DISCLOSURES

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INTRODUCTION

Alzheimer's disease (AD) is a chronic, progressive neurodegenerative disease that affects cognition, behavior, and function.[1,2] AD is a highly prevalent disease in the United States and presents a continually increasing health care challenge as the size of the aging population grows.[3] The population of Americans aged 65 years and older is projected to increase from 58 million in 2022 to 82 million in 2050, resulting in a higher number of individuals with AD and other dementias, as the risk for dementia increases with advancing age.[3] Mortality rates are higher in people with dementia due to AD, and AD is the fifth-leading cause of death for people in the United States aged 65 years and older (2021 data).[3] Inaccurate, delayed, or generalized diagnoses (eg, dementia unspecified) can result in less time for care planning, inappropriate or insufficient disease management, higher health care costs and utilization, and a negative impact on the individual's and care partner's mental and physical health. Estimates suggest that diagnosing AD in the early stages could save approximately $7 trillion in medical and long-term care costs, based on patients who were alive in 2018 and would develop AD.[3]

Despite the substantial and increasing burden of AD, patients remain underdiagnosed by clinicians in multiple settings, including primary care.[3] Outside research, a high proportion of patients who meet the diagnostic criteria for AD are not diagnosed; eg, as many as 8 million people in the US may have undiagnosed mild cognitive impairment (MCI) (though not all individuals with MCI develop dementia).[1] Based on claims data, of those patients covered by Medicare with a diagnosis of AD or other dementia, only half were made aware of their diagnosis by their clinician.[2] Delayed diagnosis and underdiagnosis can result in potential harms, necessitating a change in approach to early evaluation and diagnosis of AD.[3]

Primary care clinicians (PCCs) are often the first to encounter patients with symptoms of cognitive impairment that could be detected during a routine medical visit.[1] The current diagnostic process to evaluate patients presenting with cognitive decline is complex and varies across healthcare settings.[4,5] It is vital for PCCs to recognize early signs and symptoms of AD, use appropriate assessment tools, and refer patients with suspected AD for further workup, including imaging and biomarker testing; this could potentially result in earlier disease management.[1,2,6] The focus of this article

will be on early symptomatic AD, which is inclusive of MCI due to AD and mild dementia due to AD.

CASE STUDY

A 67-year-old Black woman presents to her PCC for an annual wellness visit. She reports cognitive concerns she has been having for the past year. She works part-time as an insurance agent and has noticed some difficulty managing multiple tasks associated with her job. She is feeling more stress than in the past about completing tasks accurately. Her supervisor has not mentioned anything related to her work performance, but her husband has noted she seems more stressed at home. The patient denies any recent changes in mood or sleep and has no other identifiable new psychosocial stressors.

Current medications: lisinopril 20 mg once daily, atorvastatin 10 mg once daily.
Past medical history: hypertension, hyperlipidemia, osteoarthritis.
Social history: She lives with her husband and has 3 grown children. She occasionally drinks alcohol (1 to 2 drinks per week) and does not use tobacco products or recreational drugs. She exercises 3 days per week for 60 minutes at a gym.
Family history: The patient's mother was diagnosed with dementia in her 70s and died at age 78 of stroke. Her father died at age 70 of a myocardial infarction. She has 2 siblings aged 69 and 74 years with no known cognitive or neurologic issues.
Physical exam: Blood pressure 128/86 mm Hg, heart rate 68 beats per minute, other vital signs stable, body mass index 28 kg/m^2, no focal neurologic findings.
Cognitive testing in the office[1]: The Montreal Cognitive Assessment (MoCA) score is 25 (out of 30); the patient missed all 5 points on delayed recall. The MoCA Memory Index Score (MIS) is 8 (out of 15). The patient does not have depression as assessed by the Patient Health Questionnaire-9 (PHQ-9).
Laboratory evaluation: Complete blood count, comprehensive metabolic panel, thyroid-stimulating hormone, vitamin B12, and glycated hemoglobin (HbA1c) are all unremarkable.
Imaging: Brain magnetic resonance imaging (MRI) without gadolinium contrast shows mild diffuse atrophy with mild bihippocampal atrophy and mild subcortical white matter hyperintensities. Ventricular size is consistent with diffuse brain atrophy.

The patient in the case scenario is referred by her PCC for evaluation by a neurologist based on history, cognitive testing, and brain imaging suggestive of MCI due to AD. The patient denied symptoms (other than those previously stated) and did not present with signs of other types of dementia. The neurologist ordered an amyloid positron emission tomography (PET) scan that was consistent with a diagnosis of MCI due to AD, thus confirming the initial diagnostic impression of the PCC.

PREVALENCE OF AD AND UNMET NEED

Prevalence of AD

Recent estimates suggest that 6.9 million adults aged 65 years and older in the US have AD, which is about 1 in 9 individuals in that age group.[3] Additionally, low proportions of patients with dementia (11%) or AD (24%) have cognitive testing documented in electronic medical records within the 5 years before diagnosis, contributing to potential underreporting of cognitive symptoms and further raising concerns for underdiagnosis.[7,8]

Early-onset AD is defined as AD occurring in individuals younger than 65 years of age and is relatively rare; it is not the focus of this discussion.[3] The lifetime risk for AD is higher for women than men (1 in 5 vs 1 in 10, respectively).[3] Additionally, Black older adults are twice as likely and Hispanic older adults are 1 to 1.5 times as likely to have AD and other dementias compared with White older adults.[3] Black and Hispanic populations are often diagnosed later at more advanced stages.[3,9] These facts underscore the need for a timely and accurate diagnosis across population groups.

Unmet need in AD

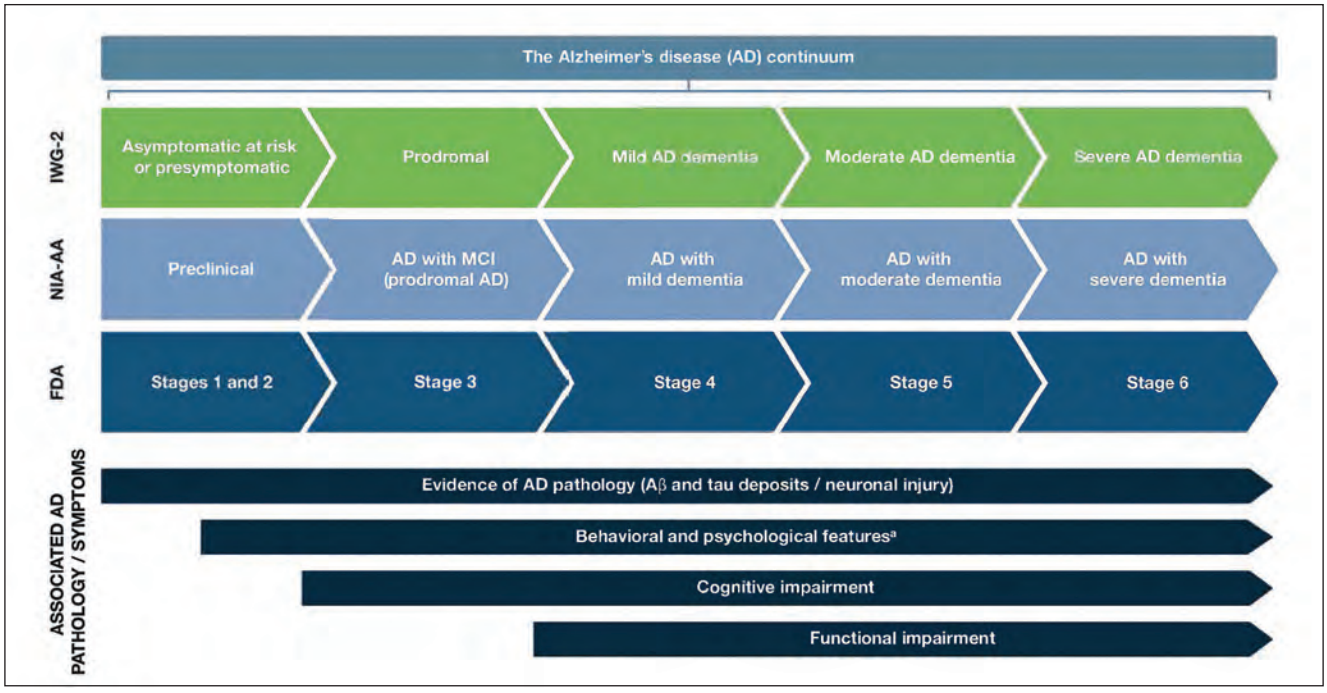
Underdiagnosis of AD is most common in the early stages of the disease when symptoms are mild, leading to low rates of MCI diagnosis.[3] Estimates suggest that as few as 8% of older Americans who have MCI receive a formal diagnosis.[3] Furthermore, rates of dementia misdiagnosis are estimated to be as high as 35% in specialty clinics, especially when biomarkers are not used.[10] Historically, AD diagnosis has been one of exclusion, made usually in the later stages of the disease, and therefore, years after the initial development of symptoms.[1] Many conditions may have more overt symptoms than early symptomatic AD, competing for clinicians' attention during clinic visits.

The benefits of early AD diagnosis for patients, care partners, and clinicians include an explanation of signs and symptoms the patient is experiencing, time for care partners to adjust to their role, opportunities for early intervention, better management of symptoms, and postponement of advanced care needs.[5,11,12]

AD DEFINITIONS AND STAGES

AD follows a progressive continuum, and staging terminology varies based on the professional organization, government authority, or group that develops models of AD progression. However, they all agree on the presence and detection of pathology and the timing and severity of clinical features across the disease continuum (**FIGURE 1**).[1] According to the National Institute on Aging—Alzheimer's Association (NIA-AA), there is a long asymptomatic phase in which clinical manifestations of cognitive or functional decline are

FIGURE 1. The Alzheimer's disease continuum and stages according to clinical and research classifications[1]



Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; FDA, Food and Drug Administration; IWG, International Working Group; MCI, mild cognitive impairment; NIA-AA, National Institute on Aging—Alzheimer's Association.

The AD continuum can be classified into different stages from preclinical AD to severe AD dementia; the nomenclature associated with each stage varies between the different clinical and research classifications. This figure provides a summary of the different naming conventions that are used within the AD community and the symptoms associated with each stage of the continuum.

[a]Mild behavioral impairment is a 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.

Source: 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. Figure licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution, and reproduction. The license can be viewed at this link: https://creativecommons.org/licenses/by/4.0/legalcode

not evident; however, AD pathology may be present for 10 to 20 years before symptom onset.[1,13] Patients may then progress to MCI due to AD, where cognition is impacted but their ability to complete instrumental activities of daily living (iADLs) and basic activities of daily living (ADLs) are essentially preserved.[1,13] ADLs include core daily tasks such as eating, dressing, and bathing, while iADLs are more complex tasks, such as preparing meals, managing finances, and doing housework.[14] Once patients progress to mild dementia due to AD, functional impairment in iADLs becomes more evident and then progressively worsens over time. During the next phases of AD, the disease impacts ADLs, and patients become increasingly dependent and require more advanced care.[1,13]

RISK FACTORS FOR AD

Knowledge of risk factors associated with AD may support more timely detection. Lifestyle risk factors for AD include a sedentary lifestyle, poor diet, stress, poor sleep, social isolation, loneliness, and smoking. Environmental factors, such as air pollution and adverse social determinants of health, may also have an impact.[3,12] Chronic diseases, such as diabetes, hypertension, and overweight or obesity, are correlated with an increased risk for dementia.[3,12]

Genetic risk factors for AD have also been identified. The most well-known and common genetic risk factor associated with AD is the apolipoprotein E (*APOE*) gene. *APOE*-e4 is correlated with an increased risk for developing AD.[3] Notably, individuals with 1 copy of *APOE*-e4 (heterozygous) are at higher risk for AD, and those with 2 copies of *APOE*-e4 (homozygous) are at even higher risk.[3] Among patients aged 65 to 69 years, the risk for dementia by the early to mid-80s is estimated to be up to 7% with no copies of *APOE*-e4, up to 16% with 1 copy, and up to 40% in those with 2 copies.[3] The number of copies of *APOE*-e4 also plays a role in inheritance patterns.[3] Other genes have also been shown to increase the risk for AD, particularly in very rare and early-onset forms of AD.[3]

NEUROPATHOLOGY OF AD

AD is characterized by 2 underlying neuropathologic hallmarks: amyloid plaques and tau neurofibrillary tangles

(NFTs). Extracellular beta-amyloid plaques and intracellular NFTs accumulate over time, leading to inflammation, synaptic dysfunction, and progressive neurodegeneration. Amyloid plaques form 10 to 20 years prior to symptom onset, whereas NFTs develop 5 to 10 years prior to cognitive symptoms.[1,3,13]

Historically, prior to progress with in vivo biomarkers, the diagnosis of AD was considered either clinical (using primarily clinical data) or neuropathologic (formulated postmortem by demonstrating corresponding neuropathologic changes). However, recent guidance supports the concept of a clinical-neuropathologic diagnosis.[2,15] Thus, an accurate diagnosis of AD requires clinical evaluation of history, risk factors, signs and symptoms, physical examination, and cognitive assessment, as well as biomarker testing to identify underlying neuropathologic changes.[2] Due to variable accessibility and specificity of testing, biomarker testing is often conducted after the patient has been referred to a dementia care specialist and can include amyloid PET scans, cerebrospinal fluid (CSF) testing, and/or plasma analysis.[2]

CLINICAL AND NEUROPATHOLOGIC DIAGNOSIS OF AD

PCCs are often the first health care providers in a multidisciplinary care team to see patients presenting with cognitive impairment. This enables them to identify early symptomatic AD at the first signs and symptoms of cognitive decline.[2] Distinguishing between deficits in ADLs and iADLs can help identify early symptomatic AD.[14] The level of functional impairment related to iADLs is a core clinical distinction between MCI and dementia.[14]

However, due to insidious and variable presentations, distinguishing changes associated with normal cognitive aging vs MCI or mild dementia due to AD can be difficult (**TABLE**).[2,16] Newness and worsening of symptoms over time are suggestive of dementia. Additional challenges and barriers to AD diagnosis in primary care include time constraints among PCCs and clinic staff; difficulty in accurately identifying AD pathology; the tendency among patients, care partners, and clinicians to dismiss or deny symptoms as part of the normal aging process; and the stigma associated with an AD diagnosis.[1,2,5,17,18]

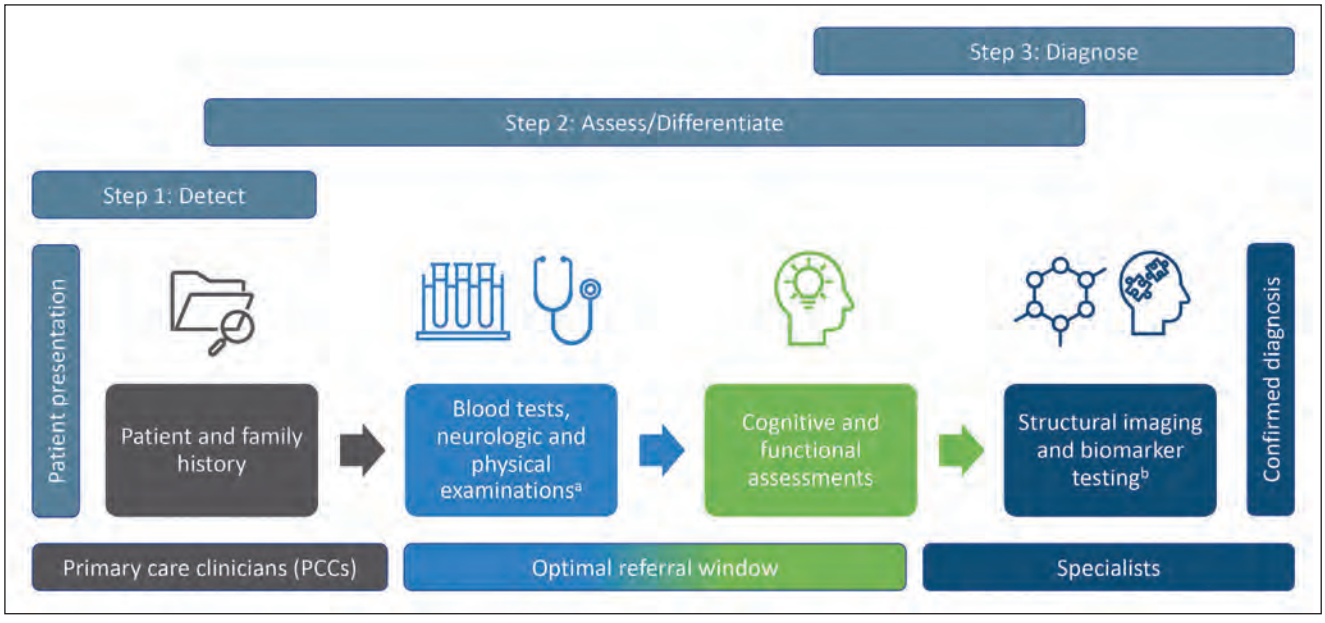
The differential diagnosis in evaluating patients with suspected AD is challenging. There are mimickers of AD including other neurodegenerative diseases, insomnia, untreated depression, excessive alcohol use, and certain medications. AD is the most common type of dementia, accounting for an estimated 60% to 80% of cases.[3] Vascular dementia accounts for 5% to 10% of cases, an estimated 5% of patients with dementia have Lewy body disease, and Parkinson disease accounts for about 3.6% of cases of dementia.[3] Mixed dementias are frequently observed in research studies and clinical practice, and more than 50% of patients with AD have mixed dementia.[3] By age 85, 85% of patients with any type of dementia will have a second type.[3]

The varied presentations of dementia pose challenges in accurately diagnosing AD because the dementia etiology is often multifactorial.[3] In fact, most individuals with neuropathology of AD also have a coexisting non-AD neuropathology, such as Lewy body disease.[3] Thus, it is not always clear which etiology or pathology is predominantly contributing to clinical symptoms.[3] As such, detection of AD neuropathology and associated neurodegenerative disease through structural imaging and biomarkers has emerged as a key component of the diagnostic workup.[1,2] The need for a multifaceted and holistic assessment warrants involvement of a multidisciplinary team and may include a thorough evaluation by a specialist for certain patients.[1]

TABLE. Examples of cognitive signs and symptoms due to normal aging vs dementia[2,16]

Signs of normal aging	Signs of dementia
May not recall information as quickly they used to	Having difficulty, or an inability, to learn new information (or having trouble with familiar tasks and following directions)
Sometimes forgetting names or appointments but remembering them later	Forgetting recently learned information and increasingly needing to rely on memory aids (eg, reminder notes); asking the same questions repeatedly
Occasionally needing help to use microwave settings or record a television show	Have difficulty driving to a familiar location, organizing a grocery list, or remembering the rules of a favorite game
Sometimes having trouble finding the right word	May have trouble naming a familiar object or use the wrong name (eg, calling a watch a "hand clock"); may stop in the middle of a conversation not knowing how to continue
Making a bad decision once in a while	Making poor judgments frequently
Missing a monthly payment once	Persistent problems managing bills
Forgetting which day it is and remembering it later	Losing track of the date or time of year
Losing things from time to time	Misplacing things frequently and being unable to find them

FIGURE 2. Example algorithm of a diagnostic pathway for AD[1]



[a]Basic blood work and examination to help rule out alternative or reversible causes of cognitive impairment; may also include genetic testing.

[b]Might include MRI or amyloid PET imaging, CSF testing, and/or plasma biomarker testing.

Source: Porsteinsson AP, et al. *J Prev Alzheimers Dis*. 2021;8(3):371-386.

Guidelines for AD detection and diagnosis have been proposed that can be applied in primary care.[1,2] One recent example of a diagnostic algorithm is shown in **FIGURE 2**. Most often—in up to 70% of cases—evaluation of cognition is prompted by cognitive complaints, so PCCs are in the best position to take action and further investigate when patients report these symptoms or when they are evident through objective measures and observations.[4] PCCs can also play a critical role in proactively asking cognition and memory-related questions to assess changes over time.

Other strategies for establishing an early, accurate AD diagnosis include initial screening using standardized assessment tools and questionnaires such as the Montreal Cognitive Assessment (MoCA), the Mini-Mental State Examination (MMSE), and the Mini-Cog.[1] These tools can be used during a routine clinic visit, such as a Medicare annual wellness visit, which includes an assessment of cognition.[2,6]

Clinicians should also consider cultural aspects of AD diagnosis and care, as the increased risk for dementia among socially disadvantaged racial and ethnic groups is directly influenced by social and physical environments.[3] These factors can also influence diagnosis of AD, resulting in a higher rate of missed diagnoses among Black and Hispanic older adults compared with White older adults.[3]

When discussing cognitive concerns with a patient, asking certain questions of patients and family members or informants may be helpful in initially distinguishing between a suspected diagnosis of early symptomatic AD and other, potentially treatable causes of cognitive decline. Such questions might include the following[1]:

- What does a typical day look like? Are there changes to mood or forgetting/misplacing things? Is there frequent repetition of questions?
- Is there more trouble or less confidence with organizing, multitasking, or completing tasks that were previously done without difficulty?
- Have you noticed any changes in personality or behavior?
- Have you (the family member) had to take over for certain tasks that are no longer possible or require additional effort (eg, managing finances, organizing medications and appointments)?
- Have there been any recent acute illnesses, surgeries, or medication changes that could impact memory (eg, use of general anesthesia, urinary tract infection, antihistamines and other anticholinergics, sedative hypnotics, or narcotics)?
- Have there been any:
  - Recent falls?
  - Changes in sleep (quality, duration, any nighttime events)?
  - Vision or hearing problems?

Variability in coverage of diagnostics, including amyloid PET, CSF, and plasma tests, is a limitation of these approaches in detection and diagnosis. The adoption of biomarker tests

has historically been relatively low and slow due to challenges with availability, cost, reimbursement, and PCC confidence in interpretation. However, tests for specific biomarkers, such as β-amyloid, total tau, and phosphorylated tau, are becoming increasingly available clinically and can be used to help distinguish between different disorders and neurodegenerative diseases.[4,19]

CONCLUSION

AD is a common and profoundly burdensome disease that is frequently underdiagnosed and misdiagnosed, resulting in delays in diagnosis and disease management. PCCs are often the first to encounter patients with signs and symptoms of cognitive impairment and play a crucial role in establishing a diagnosis of early symptomatic AD through collaboration with specialists and other multidisciplinary care team members. The current diagnosis of AD is clinical-neuropathologic—based both on clinical presentation as well as biomarker findings—and both aspects are needed to support timely and accurate diagnosis to help enable appropriate disease management.

For more information and additional resources on detection and diagnosis of AD, as well as patient communication, readers are encouraged to visit the Alzheimer's Association clinical resources page (https://www.alz.org/professionals/health-systems-medical-professionals/clinical-resources) or Alzheimers.gov (https://www.alzheimers.gov/professionals/health-care-providers). ●

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