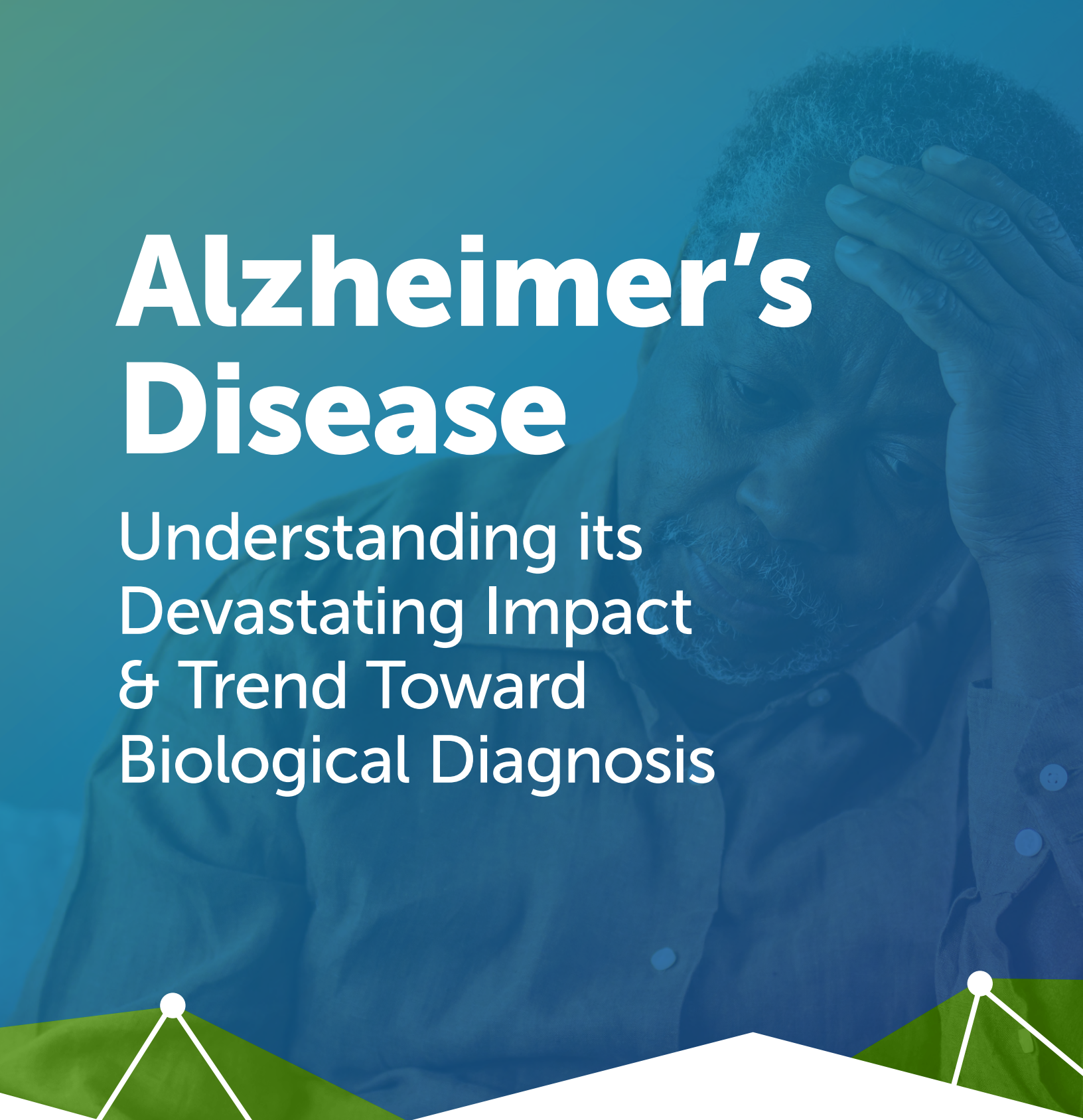

Alzheimer's Disease

Understanding its Devastating Impact & Trend Toward Biological Diagnosis

A Clinical Proceedings White Paper

November 2024

Clinical Neurological Society of America

About the Clinical Neurological Society of America

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CNSA is led by a volunteer board of directors who, like the society's members, hail from across the country and treat patients with a range of neurologic conditions.

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Alzheimer's Disease as a Cause of Dementia

Alzheimer's disease affects nearly 7 million Americans,[1] a number that is predicted to more than double by 2060.[2] Dementia is a general term denoting impairment in cognition leading to interference in daily activities. Alzheimer's disease is the most common cause of dementia.

> "Patients often come into my office thankful that they have a diagnosis of dementia instead of Alzheimer's disease. Many patients and families don't realize that Alzheimer's disease is a cause of dementia."
>
> **–Scott Turner, MD**

Alzheimer's disease is distinguished from other forms of dementia by deposition and accumulation of two proteins in certain areas of the brain:[1]

- **Amyloid-beta:** a protein that accumulates abnormally outside nerve cells and in the walls of small blood vessels in the brain
- **Tau:** a protein that forms tangles inside nerve cells

The progressive accumulation of these proteins with aging is accompanied by the death of neurons, brain atrophy, and worsening of Alzheimer's disease symptoms.[3,4]

Common causes of dementia[1] *(% of total cases)*	
Alzheimer's disease*	60-80%
Vascular dementia	5-10%
Hippocampal syndrome	3-13%
Frontotemporal dementia	3-10%
Dementia with Lewy bodies	5%
Parkinson's disease	<4%

**Most people also have brain changes associated with at least one other cause of dementia[5] (called mixed pathology or mixed dementia)*

Alzheimer's Disease Stages

Alzheimer's disease progresses along a continuum that is grouped into three broad stages: preclinical, mild cognitive impairment, and dementia. Historically, these stages have been based on the severity of symptoms and the extent to which they interfere with daily activities. The stages have varying durations, and it can be difficult to determine when a person passes from one stage to the next.[6]

Today, the stages of Alzheimer's disease are increasingly defined by biological changes in proteins (amyloid-beta and tau) and neurodegeneration.[7] These biological changes are described in more detail later in this paper in the Diagnosis section.

Clinical Continuum of Alzheimer's Disease[1]

Preclinical

No symptoms but biological changes in the brain

May occur up to 20 years before symptoms appear

Mild Cognitive Impairment

Very mild symptoms that may not interfere with daily activities

Mild Dementia

Symptoms interfere with complex daily activities

Moderate Dementia

Symptoms interfere with basic daily activities

Severe Dementia

Symptoms interfere with all daily activities

Impact of Alzheimer's Disease on Cognition, Behavior, and Functioning

Memory and cognition

Often, the first sign of Alzheimer's disease is memory loss, especially involving recently learned information. People may have difficulty remembering appointments or may ask the same question repeatedly. Another common early sign involves difficulty planning and following through with daily activities such as cooking meals or paying bills.[1]

Confusion and poor judgment may occur as the disease progresses. People may find it difficult to remember the date or may be confused about where they are and how they got there. Sometimes people get into financial difficulties by over-spending, not paying bills, or falling prey to scams.

Subjective cognitive impairment versus mild cognitive impairment

Subjective cognitive impairment is defined as patient reported cognitive decline without evidence of objective impairment on formal cognitive testing. Mild cognitive impairment is defined as cognitive decline with objective evidence on formal cognitive testing, without functional impairment. A portion of patients do progress from subjective cognitive impairment to mild cognitive impairment and later dementia.[8,9]

Eventually, people with Alzheimer's disease may have trouble recognizing family members and friends and lose the ability to communicate.[1]

Behavioral and psychological symptoms

Nearly all people with Alzheimer's disease experience neuropsychiatric symptoms.[11] Depression, anxiety, and apathy are among the most common and often appear early in the disease.[12] Agitation is also common and persistent and may manifest as repeating questions, arguing or complaining, hoarding, pacing, becoming upset easily, and crying out inappropriately.[13] Sleep disturbances frequently disrupt family life, as do wandering or rummaging, including at night.

Delusions (persistent false beliefs) can lead people with Alzheimer's disease to accuse others of actions such as stealing, posing as someone else (i.e., an imposter), or trying to harm them. Hallucinations may also occur—sensory perceptions in the absence of external stimulation, such as seeing a person or animal who is not there.

The behavioral and psychological symptoms of dementia are often extremely difficult for caregivers to handle and may lead to early placement in care facilities.[14,15]

> "The mental health issues tend to be very disruptive for families and patients and can be the key factor that allows patients to stay home versus needing an extra level of care and support."
>
> **–Ryan Darby, MD**

Functional impairment and quality of life

In the early stages, people with Alzheimer's disease begin to experience problems with complex (also called instrumental) activities of daily living, such as driving, taking daily medications correctly, shopping, cooking, and finances. As the disease progresses, people become unable to complete basic tasks with multiple steps such as getting dressed. They may find it difficult to participate in social activities and begin withdrawing. In the later stages of Alzheimer's disease, people often have difficulty walking, speaking, and swallowing, and eventually require assistance from caregivers for most or all activities of daily living.

Quality of life is a subjective experience of wellbeing that can be assessed by people with Alzheimer's disease themselves or by their caregivers. People with Alzheimer's disease often rate their quality of life lower if they experience daytime sleepiness and depression, while caregivers typically rate quality of life lower as the person's cognition and independence decrease.[16]

Impact of Alzheimer's Disease on Caregivers

Caregivers provide a wealth of physical and emotional support for people with Alzheimer's disease. Assistance may initially involve helping with daily activities such as shopping, cleaning, preparing meals, providing transportation, making doctor's appointments, paying bills, and taking medications as prescribed.

As the disease progresses, caregivers may assist with bathing, dressing, feeding, walking, and transfers to and from chairs, bed, and the toilet. Caregivers also coordinate care, provide emotional support, and work with health care providers to manage behavioral symptoms such as aggression, wandering, agitation, anxiety, and sleep difficulties.

Caregiving duties can be exhausting and have major implications for caregivers' health.[1] Caregivers who report high levels of caregiving strain are more likely to die than those who report no or moderate strain.[18]

Caregiver Reporting of Burnout Symptoms:[17]	
Extreme stress	58%
Sleep deprivation	47%
Increased social isolation from friends and family	43%
Increased alcohol/ marijuana use	36%
24-hour care of the patient	23%

> “Especially in the later stages of Alzheimer’s disease, a clinic visit is not just between the physician and patient. You have to touch on how the people are doing around the patient. If the caregiver is not doing well, they are not going to be able to take care of the patient.”
>
> **–James Eaton, MD**

> “Many caregivers are older and can have injuries that affect their mobility. All of a sudden, they face challenging choices of not being able to care for their loved one anymore or doing so at the expense of their own health.”
>
> **–Ryan Darby, MD**

Caregiver support is extremely important in Alzheimer’s disease. This includes not only caregiver support groups and assistance from social workers, but also individualized support because caregivers vary in their orientation and needs.

> “We have partnered with a caregiver support program that was initially working with oncologists. This group offers individual counseling to caregivers, which is important because caregivers vary in their responses—some are extremely disturbed by their loved one’s decline, whereas others are more resilient. We definitely need more of these programs.”
>
> **–Marissa Natelson Love, MD**

Race, ethnicity, geographic location, and socioeconomic status play a major role in the care and support services available to caregivers.[19] The Alzheimer’s Association has issued guidelines to address health disparities for Alzheimer’s caregivers, which include increasing diversity in dementia care, sensitivity to cultural norms, and many other practices that will hopefully improve inequalities.[20]

Factors impacting care and support services for caregivers

- ⚠ Race
- ⚠ Geographic Location
- ⚠ Ethnicity
- ⚠ Socioeconomic Status

Economic Burden of Alzheimer's Disease

Costs to patients and families

The cost of Alzheimer's disease to patients and families is alarming. In the United States, patients and families spend nearly 20% of their income on caregiving expenses, including medical and personal care for those with Alzheimer's disease and respite care services.[21] These out-of-pocket costs for Alzheimer's disease amount to $91 billion annually.[1]

The costs of Alzheimer's disease can also be indirect, involving financial scams or money mismanagement.

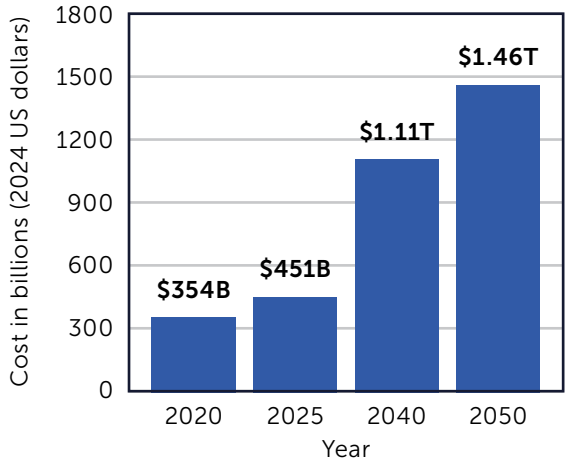
> "I learned of a patient who was handling the financial side of his family business. The patient's errors in judgment led to loss of this business that his family had built up for generations. In this case, the patient's impaired memory and decision making had a large impact even before the family recognized his dementia."
>
> **–Mary Ellen Koran, MD**

Placement of a loved one in a care facility dramatically increases costs. According to the National Council on Aging, the average monthly cost of residential memory care in an assisted living facility is $6,160 per month,[22] although costs can be nearly twice that much depending on the facility, state, and level of care needed. These costs are prohibitive for many families.

> "Patients and families often have to liquidate all of their assets in order to get Medicaid to cover nursing home care."
>
> **–Marissa Natelson Love, MD**

Health care system costs

Total Projected Costs of Alzheimer's Disease in the US[23]



In the United States, Alzheimer's disease and other dementias cost $354 billion in 2024 dollars—a figure that is expected to increase to more than $1.4 trillion in 2050.[23] Medicare and Medicaid pay about two-thirds of these costs.

The total lifetime cost of care for each person with dementia is estimated at nearly $400,000.[1] In the United States alone, unpaid caregivers—mostly family members—provide more than 18 billion hours of care per year for people with dementia. These contributions are valued at nearly $350 billion per year.[1]

Diagnosis of Alzheimer's Disease

Clinical diagnosis of Alzheimer's disease

Historically, the diagnosis of Alzheimer's disease has been based on clinical symptoms and difficulties with activities of daily living. These problems typically trigger people to visit their physician. Patients may be diagnosed with mild cognitive impairment if they show objective impairment in cognition that is not impairing their function.[24] As cognition worsens and the disease interferes with daily activities, dementia may be diagnosed.

> "Even though mild cognitive impairment is not a new concept, people are still confused by it. Mild cognitive impairment is often an early stage of Alzheimer's disease that precedes mild dementia on the Alzheimer's continuum."
>
> **–Scott Turner, MD**

The clinical diagnosis of Alzheimer's disease is made using a variety of different tools.[25] Medical histories can help rule out other potential causes of symptoms, such as medication side effects, and neurological exams can identify potential factors contributing to dementia, such as stroke. Various cognitive and functional tests are also used. These tests and procedures are typically accompanied by brain imaging to assess evidence of stroke, structural brain damage, tumor, and other alternate causes of dementia.[1]

Toward a biological diagnosis of Alzheimer's disease

The brain changes in Alzheimer's disease begin about 15-20 years before signs and symptoms are evident.[1,4] Such changes are not detectable by family members or neurologists using clinical or neurological exams. However, early brain changes can be detected using imaging techniques or via assessment of various body fluids and tissues. These methods evaluate biological markers, or biomarkers, of Alzheimer's disease.

> "Many other diseases, like cancer for example, rely on a biological diagnosis. This allows early intervention before the cancer progresses and spreads to other areas of the body. Biological diagnosis of Alzheimer's is similarly important because it will allow us to intervene before the disease progresses to the advanced stages. Alzheimer's disease has been challenging because we can't just take tissue samples from the brain for testing, but now we have new imaging and blood-based tests that allow for easier, earlier diagnosis."
>
> **–Mary Ellen Koran, MD**

Various biomarkers of Alzheimer's disease have been identified, including those that detect amyloid-beta protein deposits, tau protein tangles, and neurodegeneration. These are known by the acronym ATN. High levels of amyloid-beta and/or tau biomarkers in the brain, accompanied by neurodegeneration, are closely linked to Alzheimer's disease.[4,28]

Cognitive and Functional Assessments for Alzheimer's Disease

Commonly used cognitive and functional assessments for Alzheimer's disease include:

- Montreal Cognitive Assessment (MoCA)
- Mini-Mental State Examination (MMSE)
- Functional Activities Questionnaire (FAQ)

The MoCA is particularly useful for detecting early Alzheimer's disease, at the stage of mild cognitive impairment.[26] The test takes approximately 10-12 minutes to administer and is scored on a scale of 0 to 30.

Interpretation of MoCA scores (range 0-30):[27]	
Normal cognitive performance	26-30
Mild cognitive impairment	18-25
Moderate impairment*	10-17
Severe impairment	0-9

MoCA=Montreal Cognitive Assessment

**Scores of 17 and below are usually considered to indicate dementia.*

Detection of Biomarkers for Early Alzheimer's Disease

Currently, biomarkers for early Alzheimer's disease are detected in the brain using imaging techniques or in cerebrospinal fluid (CSF) and blood using laboratory tests.

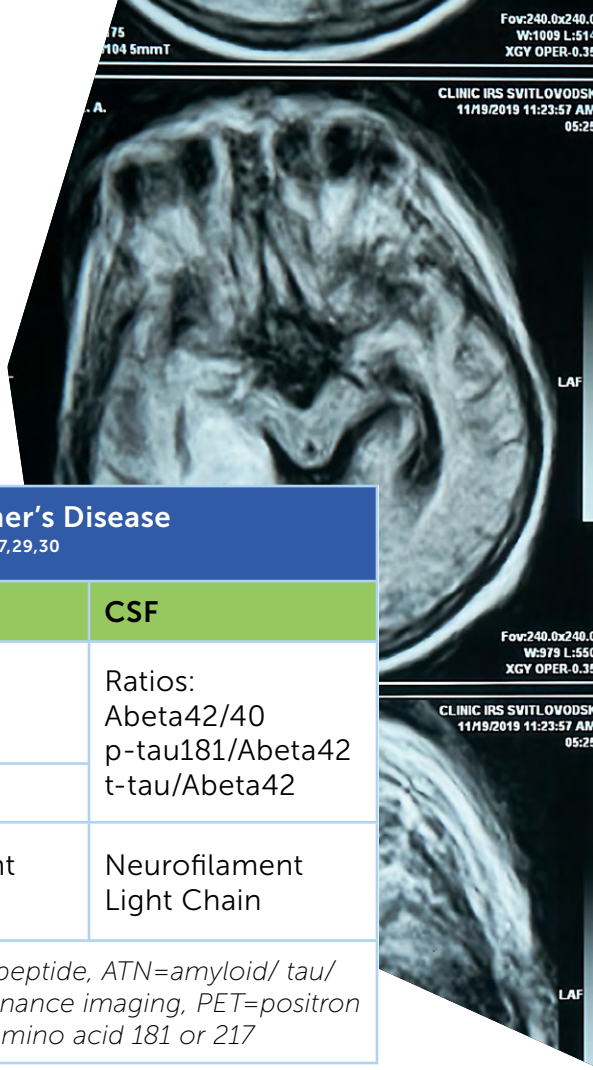


Table. Example Biomarker Tests for Alzheimer's Disease According to the ATN Classification[7,29,30]

Biomarker	Imaging	Blood	CSF
Amyloid-beta deposition	Amyloid PET	Ratio: Abeta42/40 p-tau217	Ratios: Abeta42/40 p-tau181/Abeta42 t-tau/Abeta42
Tau tangles	Tau PET		
Neurodegeneration	FDG-PET Anatomic MRI	Neurofilament Light Chain	Neurofilament Light Chain

Abeta42/40=amyloid-beta 42 amino acid peptide/40 amino acid peptide, ATN=amyloid/ tau/ neurodegeneration, FDG=flurodeoxyglucose, MRI=magnetic resonance imaging, PET=positron emission tomography, p-tau181/p-tau217=tau phosphorylated at amino acid 181 or 217

Imaging biomarkers

The main imaging techniques used for assessing Alzheimer's disease are positron emission tomography (PET) and magnetic resonance imaging (MRI).

Amyloid PET. Amyloid PET techniques assess the presence of amyloid-beta protein deposition in the brain—the earliest appearing pathological biomarker for Alzheimer's disease.[7] The compounds available for amyloid PET in the US are 18F-florbetapir, 18F-flutemetamol, and 18F-florbetaben.[30] These compounds are radiotracers that bind to amyloid-beta deposits in the brain and emit a small amount of light that can be imaged.

FDG-PET. 18F-fluorodeoxyglucose (FDG)-PET measures brain glucose metabolism, a marker of brain activity. Decreased glucose metabolism in certain brain areas is associated with Alzheimer's disease[31] and can be useful for differentiating among different causes of dementia.[32] FDG-PET is currently approved to help differentiate frontotemporal lobar degeneration and Alzheimer's.

MRI. MRI can detect structural brain changes in Alzheimer's disease such as loss of brain volume or decreased cortical thickness due to neurodegeneration, specifically in the hippocampi.[7] MRI is also useful for assessing vascular brain injury and several other potential causes or contributors to dementia.

CSF biomarkers

Laboratory tests of CSF for Alzheimer's disease primarily evaluate ratios of amyloid-beta and tau proteins. Amyloid-beta 42 (Abeta42) is a 42-amino acid peptide that is prone to forming abnormal aggregates.[33] CSF levels of Abeta42 are often assessed in relation to total tau protein (t-tau), tau phosphorylated at amino acid 181 (p-tau181), or amyloid-beta 40 (Abeta40).

Neurofilament light chain (NfL) is a protein that forms the cytoskeleton of neurons and is released in response to injury or disease. High levels of NfL in the CSF are associated with Alzheimer's disease but also with other conditions, making this a nonspecific indicator of neuronal injury.

Blood biomarkers

Blood tests for Alzheimer's disease are evolving rapidly and currently vary in their performance and validation.[30] Blood tests have major advantages over CSF and imaging due to their accessibility, acceptability, and cost-effectiveness. These features will likely make blood tests useful for screening, with positive results to be followed by imaging or CSF testing.

Blood tests evaluate some of the same biomarkers as do CSF tests, including the Abeta42/40 ratio and NfL. Newer blood tests examine the levels or percentage of tau phosphorylated at amino acid 217 (p-tau217), and other blood-based biomarkers are in development.[34]

> "Eventually, blood tests will be very useful in determining whether or not someone has Alzheimer's disease pathology in the brain, and then imaging tests, particularly those for tau, will help us determine where in the brain the pathology is concentrated, which correlates with symptoms and may help us better target treatment."
>
> **–Mary Ellen Koran, MD**

Barriers to early diagnosis

Although the aforementioned methods are available for early diagnosis of Alzheimer's disease, important barriers interfere with their use.[30] Many health care professionals are not aware of these tests, whereas others do not know how to obtain them or interpret the results. Individual techniques and tests for Alzheimer's disease biomarkers also have specific limitations:

- **CSF testing** is invasive, costly, and not readily accessible. Patients are often reluctant to undergo the procedure, and a limited number of specialists are willing to perform it.
- **PET and MRI** require specialized equipment and experts for the interpretation of results. These tests are time consuming and expensive. Although the reimbursement processes can be complicated, the Centers for Medicare and Medicaid Services recently expanded coverage of amyloid PET imaging for Alzheimer's disease that is designed to increase access.[35]
- **Blood tests** are the newest tests available and there are some questions regarding generalizability and validity.

> "An important observation about the biomarker tests is that they have been developed on the people who participate in research—who are primarily White and socioeconomically advantaged. Researchers are trying to include more diverse populations, including Blacks, for whom the blood biomarker tests might have different thresholds."
>
> **–Marissa Natelson Love, MD**

An additional barrier to early diagnosis of Alzheimer's disease can be the time it takes to diagnose the disease clinically. Primary care physicians in the US have limited time to spend with patients, and Alzheimer's disease diagnosis typically involves a careful history from the patient and a reliable historian, a neurological exam, and psychological testing.

Another challenge is that people with cognitive or memory problems may be reluctant to see a physician either because they are not aware of their problems or do not want to acknowledge them. They may not want to have their cognitive and behavioral difficulties discussed due to embarrassment or fear of stigma.

Finally, ethical difficulties may arise for younger people who receive a biological diagnosis of Alzheimer's disease, which may be a barrier to early diagnosis. Questions such as whether the result should be disclosed to an employer, implications for long-term care and life insurance, and family planning have not yet been fully considered.

Prevention and Treatment of Alzheimer's Disease

Lifestyle factors

Lifestyle changes are now widely recommended for reducing the risk of Alzheimer's disease. The Centers for Disease Control and Prevention reports that the following lifestyle factors substantially increase the risk of Alzheimer's disease: hypertension, physical inactivity, obesity, diabetes, depression, smoking, hearing loss, and binge drinking.[36] People who have 4 or more of these risk factors fare especially poorly. Similarly, a cross-sectional study of US adults found that 41% of dementia cases were attributable to 12 risk factors, with the highest being hypertension, obesity, and physical inactivity.[37] Risk was considerably higher for Black and Hispanic adults than for White and Asian adults. Studies are ongoing worldwide to evaluate the effects of integrated lifestyle interventions on dementia risk.[38]

> "I tell my patients that cardiovascular health, exercise, and sleep quality are all extremely important—they are good brain behaviors. Nevertheless, many patients balk when I say that their goal should be 150 minutes of exercise per week."
>
> **–James Eaton, MD**

Symptomatic treatments

Symptomatic treatments for Alzheimer's disease target the symptoms and signs rather than the underlying cause of the disease. Various medications are used for the symptoms and signs of Alzheimer's disease.[38]

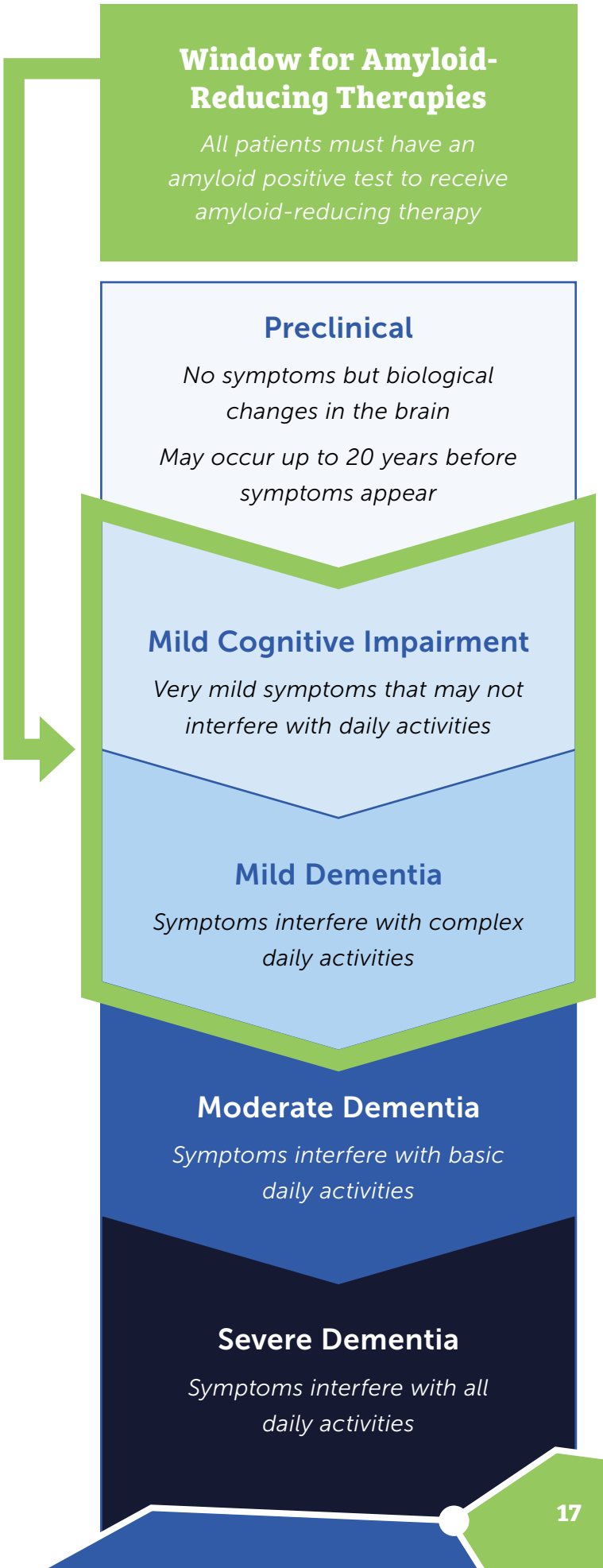
Memory and cognition. The main classes of medications approved for the treatment of memory and cognition in Alzheimer's disease are acetylcholinesterase inhibitors and the N-methyl-D-aspartate (NMDA) receptor antagonist memantine. These medications are the current standard for treatment.

Behavioral and psychological symptoms. Selective serotonin reuptake inhibitors (SSRIs) such as citalopram have been studied and found effective for agitation in Alzheimer's disease.[39] Atypical antipsychotic drugs are only used to treat the behavioral and psychological symptoms of dementia, such as agitation and psychosis, that lead to safety concerns when safer treatments and non-drug strategies have failed. Brexpiprazole was recently FDA approved for the treatment of agitation in Alzheimer's disease.[40]

Sleep problems. Sleep difficulties in Alzheimer's disease can be treated by optimizing sleep hygiene, such as having a regular bedtime and keeping the room dark. Melatonin is often used to help with sleep initiation. Dual orexin antagonists such as suvorexant can be used for patients who do not respond to nonpharmacologic interventions.

Disease-modifying treatments: Amyloid-reducing therapies

Several amyloid-reducing therapies have recently gained traditional FDA approval for use in the US. These medications, lecanemab and donanemab, are monoclonal antibodies directed against aggregated forms of amyloid-beta.[41,42] Lecanemab and donanemab are covered



by Medicare for use in people who have verified amyloid-beta pathology (through either PET imaging or CSF biomarker diagnosis) and mild cognitive impairment or mild dementia.

Given that these medications are approved for use in early Alzheimer's disease, early diagnosis has become more critical. People who have progressed to moderate dementia no longer qualify for these medications. Conversely, people who are amyloid-beta positive on biomarker tests but do not show any symptoms are also not currently candidates for the amyloid-reducing therapies. Patients who cannot get MRI scans and those on anticoagulant medications are also ineligible for amyloid-reducing therapy according to the appropriate use recommendations.[43]

High demand for these therapies is requiring adjustments in the health care system. Clinics are hiring additional administrative and case managers to assist with Medicare billing, insurance requirements such as prior authorization, and patient/family counseling related to the medication's high financial costs.

Conclusion

Alzheimer's disease is the most common cause of dementia in the elderly and is characterized by abnormal deposits of amyloid-beta and tau proteins in the brain. The disease has a devastating impact on a person's memory, cognition, behavior, and activities of daily living, and its progressive nature means that people require ever-increasing assistance from caregivers. Caregivers themselves experience extreme stress and health problems as a result of caregiving demands. In addition, the financial costs of Alzheimer's disease are exorbitant and are borne by patients and their families, as well as society.

Although the diagnosis of Alzheimer's disease is often made clinically based on symptoms, the field is moving toward a biological diagnosis that permits detection of the disease in earlier stages. Biomarkers for Alzheimer's disease can be evaluated via imaging techniques such as PET and MRI or in body tissues or fluids such as CSF and blood. With the availability of amyloid-reducing therapies, detection of Alzheimer's disease in its early stages is now critical. The field is undergoing rapid and dramatic changes with the introduction of blood tests for Alzheimer's disease biomarkers and the increased use of advanced imaging for the detection of early disease.

CNSA's Clinical Proceedings

The Clinical Neurological Society of America has 50 years of experience bringing together leading experts and clinical neurologists for educational programming. CNSA's Clinical Proceedings—a white paper series—are informational resources intended to raise awareness and address unmet needs in neurology. CNSA recognizes the expert panel members who contributed to the development of this white paper.

Marissa Natelson Love, MD
Chair

Ryan Darby, MD

James Eaton, MD

Mary Ellen Koran, MD

Scott Turner, MD

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