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The Alzheimer's Disease Landscape

An overview of disease continuum and early diagnosis

Alzheimer's disease (AD): prevalence and aetiology[1]

AD is a progressive neurologic disorder caused by damaged neurons in the brain

As of 2023, an estimated 6.7 million Americans aged 65 and older are living with Alzheimer's dementia

This figure is expected to increase to 13.8 million by 2060

The brain and neuronal communication are affected in AD

The brain is the main organ in the central nervous system and controls various processes such as sensory perception, movement, thoughts, and memories

Nerve cells, or neurons, are involved in signal transduction and are critical for the appropriate functioning of the brain

Neuronal communication occurs through chemical interaction at the synapse

Changes occurring outside neurons in AD

- The amyloid beta (Aβ) protein is derived from the Aβ precursor protein, a transmembrane glycoprotein
- The build-up of Aβ plaques outside neurons affects neuronal communication

Changes occurring inside neurons in AD

- Tau proteins are microtubule-associated proteins present inside neurons
- The accumulation of abnormal tau proteins inside neurons can affect the normal functioning of the cells

Other changes occurring in the brain

- Brain atrophy – loss of functional neurons and the connections between them
- Neuroinflammatory reaction of microglia and astrocytes
- Decrease in the ability to utilize glucose by brain cells

Clinical stages based on the AD continnum[1]

The AD continuum describes the progression of the disease from unnoticeable cognitive impairment to clinically definite cognitive decline that cause memory problems and, eventually, severe physical impairment

Preclinical AD

- Non-pathological levels of Aβ proteins
- Undetectable symptoms of memory loss or cognitive decline

AD-mild cognitive impairment

- Mild cognitive impairment due to AD
- Noticeable mild cognitive decline

AD dementia

- Presence of AD biomarkers combined with impaired mental cognition
- Can be mild, moderate, or severe

The level of biomarkers are not correlated to clinical severity

Pathophysiological changes may begin many years before clinical manifestation and the length of each stage varies depending on age, gender, genetics, and other factors

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Classification of AD

The traditional classification of AD diagnosis[2,3]

The initial framework is based on biomarkers and guidelines for the diagnosis of AD were limited to the presence or absence of behavioural and cognitive clinical symptoms

Amyloid/Tau/Neurodegeneration (AT(N)) classification: A clinical–biological construct for AD diagnosis[2,3]

Efficient biomarkers to study AD-related pathological changes

- Aβ status can reflect AD-related pathological changes in the brain during the early phase of AD
- A+T+N– profile refers to the presence of Aβ and tau biomarkers but lack of neurodegeneration
- A+T+N+ profile indicates an advanced stage of AD
- AT(N) biomarker-based classification can enable the assessment of varying degrees of AD abnormalities and pathology

ATNIVS system[2]

Inflammatory (I), vascular (V), α-synuclein (S) can be used to classify AD in future

There is a need to establish and define cut-off points for neuroimaging and fluid-based biomarkers

Current limitations and challenges of the AT(N) framework for clinical trials[2]

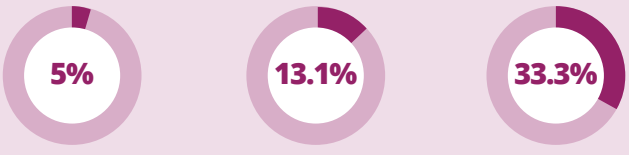
- Undefined cut-off points for neuroimaging and fluid biomarkers
- Non-standardised clinical endpoints and outcome measures across independent multicentre studies

- Inadequate evidence on clinical validity for regulatory approval and adoption
- Regional variations in biomarker testing guidelines

Risk factors associated with AD

Age[1]

- Age is an important risk factor for AD
- AD-related dementia across different age groups



65–74 years | 75–84 years | >85 years

Genetics and family history[1]

- Several genes are known to increase AD risk; in 2022, 31 new genes involved in AD pathophysiology were identified
- *APOE-e4* gene is a risk factor of late-onset AD
- Genetic defects associated with Down syndrome increase the risk of AD
- Dominantly inherited AD is a known risk factor
- Individuals born to a parent with AD or who have a sibling with AD are at a greater risk

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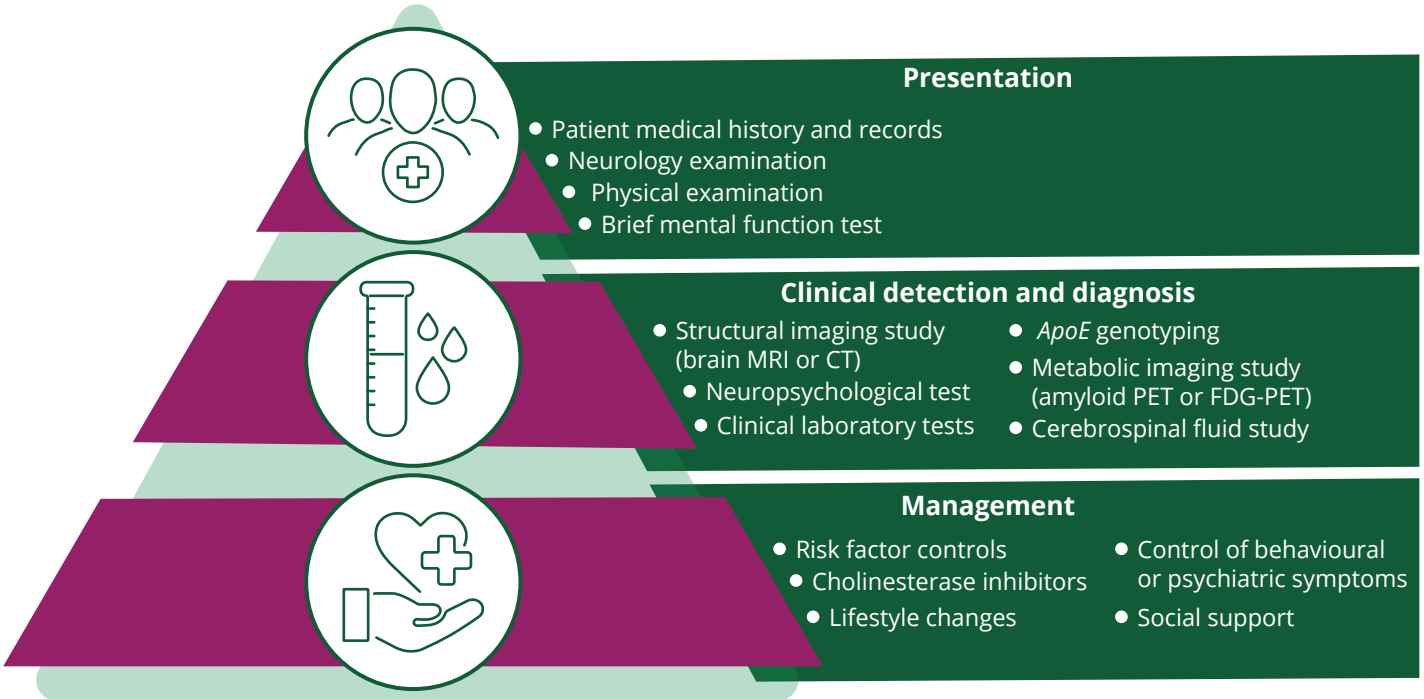
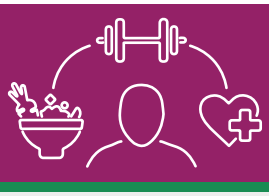
Modifiable risk factors of AD[1]

Importance of early diagnosis[4]

Presentation → Clinical detection and diagnosis → Management





The early and accurate diagnosis of AD can help the patients to follow and incorporate appropriate treatment regimens and lifestyle changes, ultimately increasing their overall quality of life

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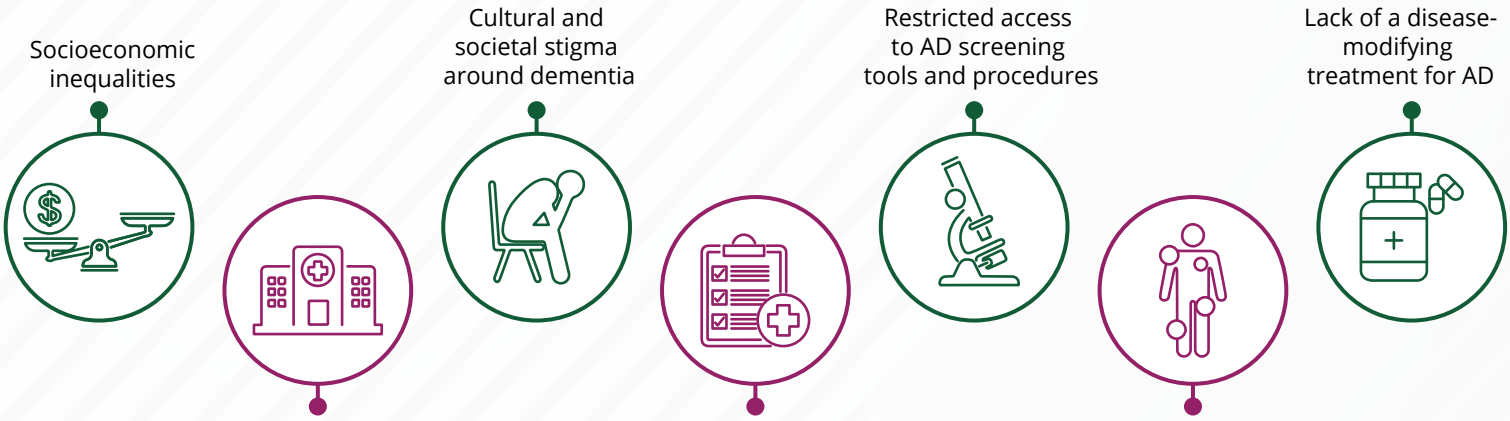
Barriers to the diagnosis of AD

There are numerous challenges in improving the testing, diagnosis, and care of patients with AD[5]



The healthcare setup of a country and its policies around dementia-related issues are important in addressing the challenges around the diagnosis of AD

Solutions to the challenges in AD diagnosis[5]

- Extensive research into the development and validation of novel and affordable biomarkers
- Increased involvement of external support agencies to share the treatment burden
- Increased access and appropriate use of cognitive evaluation tests in individuals from marginalised sections of society
- Raising awareness through educational campaigns on the risks of dementia and the need for an early diagnosis
- Use of inclusive and collaborative healthcare models with adequate training in AD diagnosis and treatment protocols
- Specialised training and education for healthcare providers on the appropriate use and interpretation of AD biomarkers

Key messages

- **Best practice AD care necessitates memory conversations at the onset of symptoms and the use of new diagnostic techniques to ensure an appropriate diagnosis**
- **A knowledgeable healthcare team that includes specialists to diagnose the disease, monitor disease progression, and provide individualised care plans is crucial**

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2. Hampel, H., Cummings, J., Blennow, K., Gao, P., Jack, C. R., Jr, & Vergallo, A. (2021). Developing the ATX(N) classification for use across the Alzheimer disease continuum. *Nature Reviews Neurology, 17*(9), 580–589.
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5. Kerwin, D., Abdelnour, C., Caramelli, P., Ogunniyi, A., Shi, J., Zetterberg, H., & Traber, M. (2022). Alzheimer's disease diagnosis and management: Perspectives from around the world. *Alzheimer's & Dementia*: *Diagnosis, Assessment & Disease Monitoring, 14*(1), e12334.

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