Acta Biomed 2023; Vol. 94, N. 2: e2023046 DOI: 10.23750/abm.v94i2.15444

Early Detection of Alzheimer's disease by using the Latest Techniques

Shmmon Ahmad[1], Moh Aijaz[2], Mumtaz Ahmad[2], Abdul Hafeez[1], Mohammad Asif[3], Ashok Kumar[1], Anmar Al-Taie[4], Mohamamd Anas Ansari[2]

[1]Glocal School of Pharmacy, Glocal University, Saharanpur, India.
[2]School of Pharmacy, Graphic Era Hill University, Dehradun India
[3]Era College of Pharmacy, Era University, Lucknow, India.
[4]Department of Clinical Pharmacy, Faculty of Pharmacy, Istinye University, Istanbul, Turkey
Corresponding Author: Shmmon Ahmad, Glocal School of Pharmacy, Glocal University, Saharanpur, India, Email: shmmon@gmail.com.

Abstract: Alzheimer's disease (AD) is a prevalent neurodegenerative disease affecting cognitive functions and is particularly common among elderly people worldwide. It is considered incurable, and its symptoms progressively deteriorate over time. Early detection of AD is critical for developing new and effective treatment strategies. Dementia causes irreversible damage to brain neurons, leading to changes in brain structure that can be analyzed through multifractal frameworks. This study focuses on developing an efficient computing technique to pre-process and classify AD, especially in the early stages. The development of additional non-invasive and cost-effective tools for identifying individuals in the preclinical or early clinical stages of AD is necessary. These tools can aid in early detection and potentially more effective therapeutic and preventative strategies for AD. Large clinical trials are necessary to validate these tools before implementing them in clinical practice. This review will summarize and highlight the most promising screening tools, including neuropsychiatric, clinical, blood, and neurophysiological tests.

Keywords: Alzheimer's disease, biomarker, Machine learning algorithms, Imaging technologies, Neuroimaging

Introduction

Alzheimer's disease (AD) is a prevalent form of neurodegenerative brain disease that affects a large portion of the population. It is responsible for up to 75% of all cases of dementia, which is a major cause of death. AD leads to a progressive decline in cognitive abilities and memory loss [1] [2].

Alzheimer's disease (AD) is the primary cause of dementia in the elderly and affects over 35 million individuals worldwide. The aging population in developed countries implies that AD will become an epidemic unless prevention or cure therapies are developed. Unfortunately, most experimental interventions aimed at modifying the disease have failed to show clinical benefits in people with symptomatic AD. This failure is likely due to administering the drugs too late in the AD neuropathological processes. It is essential to identify biomarkers that are sensitive to preclinical or early clinical stages of AD to facilitate earlier treatment and potentially more effective therapeutic strategies. The potential benefits of starting treatment in the preclinical stage of AD are unknown and are being evaluated in ongoing treatment trials [3] [4].

Diagnosis

Currently, the clinical diagnosis of Alzheimer's disease (AD) involves a specialized clinic and requires various tests, including a medical examination, neuropsychological testing, neuroimaging, cerebrospinal fluid (CSF) analysis, and blood examination. However, this process is neither cost nor time-effective, and with the aging global population, there is an expected increase in AD cases and an insufficient number of specialized clinics to meet the growing demand. While CSF and neuroimaging markers are considered gold standards for assessing patients in vivo, they are invasive, expensive, and not suitable as frontline screening or diagnostic tools. Inaccuracies in identifying early AD and mild cognitive impairment (MCI) have been observed in nonspecialist clinicians, making it essential to find clinically useful screening and diagnostic tools [3][5]. As a result, there is a growing demand for noninvasive and cost-effective tools to identify individuals in the preclinical or early clinical stages of Alzheimer's disease (AD). These tools could enable frontline identification, with subsequent clinical, CSF, and neuroimaging analyses in specialized clinics. The ability to predict the risk of developing AD would be a valuable asset for healthcare systems, allowing for early intensive lifestyle consultations and pharmacological interventions for high-risk individuals. Recent findings in

neuropathology, biochemistry, and neuroimaging have shown that AD biomarkers can be detected in the brains and CSF of cognitively healthy elderly individuals, supporting the relevance of early diagnosis of AD [3] [6].

In individuals with Alzheimer's disease (AD), changes in the brain occur due to two main factors:
(1) the accumulation of beta-amyloid protein fragments outside of neurons, leading to the formation of plaques.

(2) the accumulation of protein tau inside neurons, leading to the formation of tangles over time.

The accumulation of beta-amyloid plaques between neurons at synapses occurs gradually, while tau tangles disrupt the transport of essential molecules inside neurons, leading to the loss of communication between neurons. As a result, irreversible changes occur in the brain, including atrophy or shrinkage in the frontal lobes, temporalparietal, and hippocampus due to cell loss, which is believed to occur when microglia fail to perform their functions. The severity of dementia, particularly AD, is classified into seven stages according to the Global Deterioration Scale (GDS), which helps to predict the primary degenerative process of dementia and its stages [1] [7].

In this review, we will provide a summary and analysis of the most promising and innovative screening and diagnostic tools for early detection of AD, with a focus on non-invasive and cost-effective methods. In addition to established clinical, CSF, and neuroimaging diagnostics, we will examine the utility of novel neuro psychometric, clinical, blood, and neurophysiological tests in identifying individuals in the preclinical or early clinical stages of AD. These tools have the potential to revolutionize the way AD is diagnosed and treated, providing earlier interventions and improved outcomes for patients.[3][6]

The importance of an early diagnosis

Historically, a diagnosis of AD has been one of exclusion, and one only made in the latter stages of disease; however, the disease process can take years to play out, exacting a significant toll on the patient, caregiver, and healthcare system along the way[8]. Absolutely, early detection and diagnosis of AD is crucial for improving patient outcomes and reducing the burden on the healthcare system. Primary care providers (PCPs) play a crucial role in identifying early symptoms of AD and referring patients for further evaluation and diagnosis. PCPs should have access to reliable and validated screening tools to assess cognitive impairment in their patients, and be knowledgeable about the appropriate referral pathways to specialists for further diagnostic evaluation. Moreover, PCPs can also play a role in educating patients and their families about the early signs and symptoms of AD, and the importance of early detection and management. This can include lifestyle modifications, such as exercise and a healthy diet that may help reduce the risk of developing AD or delay its onset. PCPs can also work with patients and their families to develop care plans that address the complex medical and social needs of patients with AD [8] [9].

An accurate diagnosis of Alzheimer's dementia is crucial for appropriate management and planning for the future. In addition to a doctor's exam, other diagnostic tools may be used to assist in the diagnosis of Alzheimer's. These may include neuropsychological testing, brain imaging studies such as MRI or PET scans, and blood tests to rule out other potential causes of cognitive decline. It is important to note that early detection and diagnosis of Alzheimer's can help to optimize treatment outcomes and improve quality of life for both the individual with Alzheimer's and their loved ones [10] [11].

Strategy for early detection of Alzheimer’s disease

Diagnosing Alzheimer's disease typically involves multiple diagnostic procedures rather than relying solely on one. Medical professionals use a variety of tools and approaches, often seeking input from specialists such as neurologists, neuropsychologists, geriatricians, and geriatric psychiatrists. To confirm an Alzheimer's diagnosis or eliminate other potential causes of symptoms, brain scans are often conducted using magnetic resonance imaging (MRI), computed tomography (CT), or positron emission tomography (PET). However, in some cases, particularly in the early stages, diagnostic assessments may not reveal Alzheimer's disease, and additional testing may be required. Additionally, the progression from a healthy state to Alzheimer's disease can span several years, with patients initially experiencing mild cognitive impairment (MCI) before gradually transitioning to Alzheimer's. Not all individuals with MCI will develop Alzheimer's disease, and various techniques such as medical imaging and blood plasma spectroscopy can be used to predict the likelihood of conversion [1] [12].

Episodic memory tests

Episodic memory is the cognitive domain that is most severely affected in Alzheimer's disease (AD) and in its prodromal stages, including amnestic mild cognitive impairment (aMCI). Various tests can be used to evaluate episodic memory, such as the Logical Memory subtest from the Wechsler Memory Scale, the California Verbal Learning Test (CVLT-II), and the Free and Cued Selective Reminding Test (FCSRT). Studies have compared these tests and found that CVLT is more sensitive to preclinical changes in episodic memory. The FCSRT's free recall has been more predictive than the Wechsler Logical Memory immediate recall in identifying individuals with memory

complaints who developed incident AD over 2 to 4 years. In addition, the FCSRT has been the most sensitive and specific test for diagnosing prodromal AD among standardized neuropsychological batteries in other studies. The FCSRT was also better at predicting the likelihood of an AD-like cerebrospinal fluid (CSF) profile among MCI subjects than the Wechsler Logical Memory delayed recall [3] [13].

Clinical tests Assessment of subjective memory complaints

In terms of cognitive decline, it's important to distinguish between objective deficits measured with specific neuropsychological tests and subjective memory complaints (SMC) reported by individuals or informants (family members, caregivers, or clinicians). SMCs have gained increasing interest, with debate over their significance in preclinical AD diagnosis. Recent studies show that SMCs are associated with pathological brain amyloid burden in cognitively normal older people and increased risk for late-onset AD before any measurable cognitive decline. SMCs also exist in a pre-MCI stage, according to a study with PSEN1 E280 A mutation carriers. A recent study revealed that one-third of adults over 50 attending primary care centers with SMC were already affected by MCI, with cognitive impairment reported by informants linked to a higher MCI prevalence. Therefore, SMC may serve as an indicator of preclinical and early symptomatic AD, with information obtained from both individuals and informants crucial for screening. Diagnostic tools to assess SMC, such as the Subjective Cognitive Failures Questionnaire or simple questions about memory impairment and concerns, are noninvasive and inexpensive, making them potentially suitable as additional parameters for a broader screening of putative amyloid-positive but still cognitively healthy individuals, aside from depression and personality factors [3] [14].

Assessment of late-onset depression

It is common for people to experience depression at some point in their life, with one in five individuals affected. Similarly, dementia is a prevalent condition in late life, with the risk of developing it doubling every five years after the age of 65 and increasing up to 50% among those over 90 years old. While studies have shown that depression and late-onset dementia often coexist, it is unclear whether there is a causal relationship between the two. Research suggests that depression may be linked to the occurrence of Alzheimer's disease neuropathology in women with the presenilin-1 mutation during the preclinical phase of familial AD [15]. Depression or depressive symptoms may reflect (1) a risk factor for dementia,

(2) a prodromal phase of dementia or

(3) a consequence of the dementia neurodegenerative processes.

According to a longitudinal study conducted by Barnes and colleagues, having a personal history of depression can increase the risk of developing dementia later in life. The type of dementia may depend on when in life the depression occurs. Specifically, the study found that individuals with depressive symptoms in late-life had a twofold increase in the risk of developing Alzheimer's disease (AD), while those with symptoms in mid- and latelife had a more than threefold increase in the risk of developing vascular dementia (VaD) [3] [15].

Speech testing

Verbal communication is a complex process that requires various cognitive abilities such as memory, phonological structure knowledge, and understanding of grammar and word meaning. Language is produced spontaneously by individuals on a daily basis and can be easily recorded, making it a valuable biological sample to study. Speech deterioration has a significant impact on a person's ability to interact socially and often results in emotional changes, both of which are early signs of Alzheimer's disease. Automatic speech analysis techniques can detect these changes and do not require specialized training, making them accessible to anyone in the patient's natural environment [3] [16].

Biomarkers for earlier detection

Current diagnosis of Alzheimer's disease relies largely on documenting mental decline, at which point, Alzheimer's has already caused severe brain damage. Researchers hope to discover an easy and accurate way to detect Alzheimer's before these devastating symptoms begin.

Experts believe that biomarkers (short for "biological markers") offer one of the most promising paths. A biomarker is something that can be measured to accurately and reliably indicate the presence of disease, such as fasting blood glucose (blood sugar) level, which indicates the presence of diabetes if it is 126 mg/dL or higher [17].

Finding biomarkers will help earlier diagnosis and treatment of Alzheimer's and other forms of dementia. Several potential biomarkers are being studied for their ability to indicate early stages of Alzheimer's disease. Examples being studied include beta-amyloid and tau levels in cerebrospinal fluid (CSF) and brain changes detectable by imaging. Recent research suggests that these indicators may change at different stages of the disease process [17].

Before a biomarker can be used in medical clinics, it must be validated, in which multiple studies in large and diverse groups of people establish that it accurately and reliably indicates the presence of disease. Furthermore, the

laboratory methods used to measure the biomarker must be shown to be stable and reliable.

Currently, there are some FDA-approved tools that, when applicable, can be used to aid in diagnosis of people with symptoms of Alzheimer's or another dementia (e.g., brain imaging). Some of these tools have a wealth of research and clinical data to support their use in the clinic (e.g., biomarkers in CSF), while other emerging biomarkers are promising but still under investigation (e.g., blood tests and genetic risk profiling) [17] [18].

Biomarkers are neurochemical indicators used to diagnose Alzheimer's disease. These markers include abnormal deposits of beta-amyloid (Aβ42), which causes amyloid plaques, and the accumulation of total tau (T-tau) and phosphorylated tau (P-tau) in the cerebrospinal fluid (CSF). However, measuring biomarker levels in the same sample can vary significantly between institutions and testing platforms. Therefore, researchers are exploring brain imaging methods to enhance diagnosis and progress monitoring [1] [19].

Machine learning algorithms

Reliable early diagnosis of Alzheimer's disease (AD) is crucial for managing the disease and making therapeutic choices that can delay its progression. Machine learning (ML) techniques have been widely utilized to develop algorithms for this purpose. However, the clinical utility, interpretability, and generalizability of the classifiers across different datasets and MRI protocols are still restricted [20]. In recent studies, researchers have explored the use of machine learning algorithms to develop predictive models for classifying different stages of Alzheimer's disease (AD). The researchers applied recursive feature elimination and support vector machine (SVM) to classify various stages, including CN versus AD, MCI versus AD, and CN versus MCI, achieving accuracies of 100%, 73.68%, and 90%, respectively. They also proposed a new algorithm called "Support Vector Machine Leave-One-Out Recursive Feature Elimination and Cross-Validation" (SVM-RFE-LOO) for early detection of AD. Other researchers have also used SVM for AD detection, such as applying an artificial neural network (ANN) with MRI images to predict the transition from mild cognitive impairment (MCI) to AD with an accuracy of 89.5% [21] [22].

Deep Neural Network (DNN) learning

Several studies have utilized Deep Neural Network (DNN) learning or Convolutional Neural Network (CNN) models for the classification of dementia and Alzheimer's disease (AD). One study proposed a DEMentia NETwork (DEMNET) based on CNN to detect different stages of dementia. Another study proposed a modified LeNet model based on DNN, using MRI images for AD classification. Additionally, a volumetric CNN model based on MRI images was utilized for multi-classification tasks in another study. These studies demonstrate the potential of DNN and CNN models in accurately classifying and detecting AD and dementia [1][23] [24]

Brain imaging/neuroimaging

Neuroimaging techniques, such as magnetic resonance imaging (MRI) and positron emission tomography (PET), have proven to be valuable tools in the early detection and diagnosis of Alzheimer's disease. These techniques allow for the visualization of changes in brain structure and function, as well as the detection of abnormal protein accumulation, such as beta-amyloid and tau, which are associated with the development of Alzheimer's disease.

Ongoing research in neuroimaging is focused on developing and improving advanced brain imaging techniques that can provide even earlier and more accurate detection of Alzheimer's disease. For example, researchers are exploring the use of advanced MRI techniques, such as diffusion tensor imaging (DTI) and functional MRI (fMRI), which can provide more detailed information on changes in brain connectivity and function. Additionally, new PET imaging tracers are being developed that can specifically target and detect beta-amyloid and tau proteins in the brain, improving the accuracy of Alzheimer's diagnosis [17] [25].

Imaging technologies used in Alzheimer's research]

The different types of neuroimaging techniques are used to provide various types of information about the brain. Structural imaging methods such as magnetic resonance imaging (MRI) and computed tomography (CT) provide information about the shape, position, or volume of brain tissue. In contrast, functional imaging techniques such as positron emission tomography (PET) and functional MRI (fMRI) reveal how actively the cells in different brain regions are working by showing how much they use sugar or oxygen. Finally, molecular imaging techniques such as PET and fMRI use targeted radiotracers to detect specific cellular or chemical changes related to particular diseases. All of these techniques are constantly evolving, and ongoing research is exploring their potential for improving our understanding of Alzheimer's disease and other neurological conditions. [17][26]

Structural imaging

Structural imaging is a valuable tool for detecting Alzheimer's disease, as research has shown that the brains of individuals with the disease experience significant shrinkage over time, particularly in specific brain regions

such as the hippocampus. Standardized values for brain volume loss have been established by scientists, providing a basis for diagnosing the presence of Alzheimer's or monitoring disease progression. Today, structural imaging is commonly used as part of a standard workup for Alzheimer's, allowing doctors to assess tissue damage associated with neurodegeneration and rule out other conditions that may mimic Alzheimer's symptoms but require different treatments. By using MRI, doctors can detect a range of conditions, including tumors, strokes, trauma-related damage, or fluid build-up in the brain, as well as identify underlying conditions that may impact treatment decisions [17] [27].

Functional imaging

Additionally, functional MRI (fMRI) studies have revealed that changes in brain activity may occur long before structural changes can be seen on imaging. This suggests that functional imaging may be useful for detecting Alzheimer's at an earlier stage than structural imaging. Some studies have used fMRI to detect changes in brain activity patterns associated with Alzheimer's disease, such as decreased connectivity between brain regions involved in memory and cognitive processing. It's important to note that functional imaging is not routinely used as a diagnostic tool for Alzheimer's disease. Rather, it is primarily used for research purposes and to better understand the underlying mechanisms of the disease. [17] [28] [29].

Molecular imaging

Molecular imaging has the potential to detect biological changes associated with Alzheimer's disease even before structural or functional changes in the brain become evident. By using specific radiotracers, molecular imaging can reveal the presence of beta-amyloid plaques and tau protein tangles, two hallmark signs of Alzheimer's disease. This can help with early diagnosis and monitoring of disease progression, as well as the evaluation of potential new treatments. The use of molecular imaging in Alzheimer's disease research is still in its early stages, but it holds great promise for improving diagnosis and treatment of the disease [17] [30] [31]. Several molecular imaging compounds are being studied, and four have been approved for clinical use:

A brain scan that shows amyloid plaques in the brain of a person with Alzheimer's and a controlled brain without amyloid plaques.

1. Florbetaben (Neuraceq®), has been approved for the detection of beta-amyloid in the brain.
2. Flortaucipir F18 (Tauvid®) has been approved for the detection of tau in the brain.

That is correct. The presence of amyloid plaques in the brain is a hallmark feature of Alzheimer's disease, but it is not sufficient to diagnose the disease on its own. A diagnosis of Alzheimer's disease is usually made through a combination of medical history, physical examination, neurological tests, and laboratory tests, along with imaging tests such as PET scans, MRI, or CT scans. These tests help to evaluate the structure and function of the brain and detect any abnormalities or changes that may be indicative of Alzheimer's disease. [17].

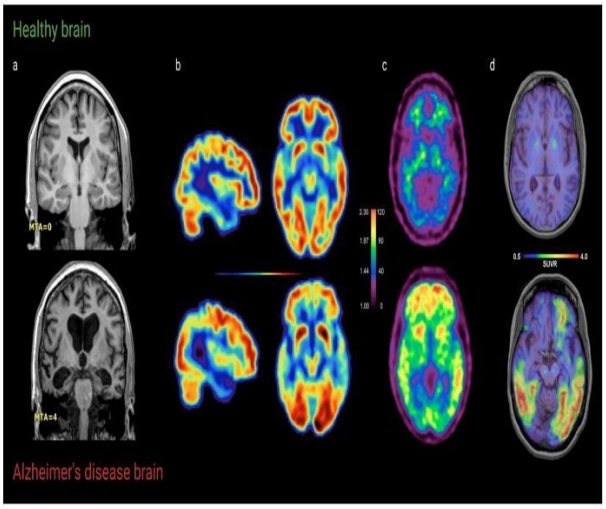

Figure 1. Neuroimages of the healthy versus the Alzheimer's disease (AD) brain. Neuroimaging with (a) structural MRI, (b) FDG-PET, (c) amyloid-PET with PiB, and (d) tau PET with 18F-AV1451 in both healthy and AD brains [32].

Blood tests

Blood tests for Alzheimer's disease are an active area of research. The development of a simple, non-invasive, and affordable blood test for Alzheimer's disease would be a game-changer in the field of Alzheimer's research and clinical practice. Blood tests could potentially allow for earlier and more accurate diagnosis of the disease, as well as monitoring of disease progression and treatment response. Some studies have identified specific blood biomarkers, including amyloid beta and tau proteins, that may be associated with Alzheimer's disease, but further research is needed to validate these findings and develop reliable blood tests for clinical use.[17] [33]

Blood tests are becoming increasingly important in the design of clinical trials and are currently being used in some specialty care centers. In the future, these tests are expected to revolutionize the diagnostic process for Alzheimer's and other types of dementia. However, it is important to use these tests in a careful and controlled manner since much more research is needed before they can be routinely used in clinical settings. Standardized and validated tests are still being developed to ensure reliable results for all individuals [17].

While there are a few blood tests currently available on the market to aid in the diagnosis of memory complaints, they do not yet have FDA approval. It is

recommended that these tests only be used by specialty care doctors who are seeing patients with memory complaints and are not recommended for individuals without cognitive or memory symptoms. These tests may predict the presence of amyloid changes in the brain or the presence of neurodegenerative disease or neuronal damage. However, they cannot be used as a stand-alone test to diagnose Alzheimer's disease or any other type of dementia and must be used in combination with other exams as part of a diagnostic workup [17].

Conclusion

The combination of an aging population and the promise of disease-modifying therapies in the near future have made the characterization of the early stages of Alzheimer's disease (AD) a topic of major research interest. The consensus within the AD community has shifted to encourage the diagnosis of AD as early as possible, enabling patients to plan their future and consider symptomatic therapies and lifestyle changes that could reduce cognitive deficits and ultimately preserve their quality of life. New potentially disease-modifying therapeutic candidates are on the horizon that could be effective in early AD by targeting and ameliorating the underlying biological mechanisms.

In this article, recent progress in understanding the evolution of early AD is reviewed, with particular reference to the symptomatic pre-dementia stage designated 'mild cognitive impairment', emphasizing work on the early cognitive profile and associated neuroimaging studies. The description of distinctive and reliable biomarkers that are now available through structural brain imaging with magnetic resonance imaging, molecular neuroimaging with positron emission tomography, and cerebrospinal fluid analyses, along with a better definition of the clinical profile of amnestic disorders that occur early in the course of the disease, make it possible to identify AD with high accuracy, even in the early stages of the disease.

Accordingly, new criteria for the diagnosis have been proposed that capture both the prodromal and the more advanced dementia stages of the disease in the same diagnostic framework.

Future diagnostic tests

Scientists are actively engaged in developing diagnostic tests that can measure biological markers of Alzheimer's disease in the brain, which may include blood tests. These tests are expected to improve diagnostic accuracy and enable early detection of the disease before the onset of symptoms. One such test that measures the levels of beta-amyloid in the blood is currently available. While genetic testing is not recommended for most individuals undergoing evaluation for Alzheimer's disease, people with a family history of early-onset Alzheimer's may consider genetic testing after consulting with a genetic counselor to fully understand the risks and benefits [34].

Declarations Ethical Approval: Not Applicable

Patients Consent: Not applicable

Conflict of Interests: Each author declares that he or she has no commercial associations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangement, etc.) that might pose a conflict of interest in connection with the submitted article.

Author Contributions: Conceptualization: All Authors; Collected the data: SA, MZ, MAD Writing original draft preparation: SA, AH; Reviewed the manuscript for important intellectual content and editing: MA, AK, AAT, and MAA; All authors have read and approved the final version of the manuscript

References

1. Y. M. Elgammal, M. A. Zahran, and M. M. Abdelsalam, “A new strategy for the early detection of alzheimer disease stages using multifractal geometry analysis based on K-Nearest Neighbor algorithm,” Scientific Reports 2022 12:1, vol. 12, no. 1, pp. 1–19, Dec. 2022, doi: 10.1038/s41598-022-26958-6.
2. S. Ahmad and A. Hafeez, “Formulation and Development of Curcumin-Piperine-Loaded SSNEDDS for the Treatment of Alzheimer’s Disease,” Mol Neurobiol, vol. 60, no. 2, pp. 1067–1082, Feb. 2023, doi: 10.1007/S12035-022-03089-7.
3. C. Laske et al., “Innovative diagnostic tools for early detection of Alzheimer’s disease,” Alzheimer’s & Dementia, vol. 11, no. 5, pp. 561–578, May 2015, doi: 10.1016/J.JALZ.2014.06.004.
4. WHO, “Dementia,” Mar. 15, 2023. https://www.who.int/news-room/factsheets/detail/dementia (accessed Mar. 28, 2023).
5. B. Dubois, G. Picard, and M. Sarazin, “Early detection of Alzheimer’s disease: new diagnostic criteria,” Dialogues Clin Neurosci, vol. 11, no. 2, p. 135, 2009, doi: 10.31887/DCNS.2009.11.2/BDUBOIS.
6. J. Weller and A. Budson, “Current understanding of Alzheimer’s disease diagnosis and treatment,” F1000Res, vol. 7, 2018, doi: 10.12688/F1000RESEARCH.14506.1.
7. “What Happens to the Brain in Alzheimer’s Disease? | National Institute on Aging,” National Institutes of Health, May 17, 2017. https://www.nia.nih.gov/health/what-happens-brainalzheimers-disease (accessed Mar. 28, 2023).
8. P. Porsteinsson and R. S. Isaacson, “Diagnosis of Early Alzheimer’s Disease: Clinical Practice in 2021,” The Journal

of Prevention of Alzheimer's Disease, vol. 8, no. 3, pp. 371–386, Jun. 2021, Accessed: Mar. 27, 2023. [Online]. Available: https://link.springer.com/content/pdf/10.14283/jpad.2021.23.pdf

9. P. McCarty and R. E. Frye, "Early Detection and Diagnosis of Autism Spectrum Disorder: Why Is It So Difficult?," Semin Pediatr Neurol, vol. 35, p. 100831, Oct. 2020, doi: 10.1016/J.SPEN.2020.100831.
10. Mayo Clinic Staff, "Diagnosing Alzheimer's: How Alzheimer's is diagnosed - Mayo Clinic," Mayo Clinic, Mar. 28, 2023. https://www.mayoclinic.org/diseasesconditions/alzheimers-disease/in-depth/alzheimers/art20048075 (accessed Mar. 28, 2023).
11. G. T. Grossberg, D. D. Christensen, P. A. Griffith, D. R. Kerwin, G. Hunt, and E. J. Hall, "The Art of Sharing the Diagnosis and Management of Alzheimer's Disease With Patients and Caregivers: Recommendations of an Expert Consensus Panel," Prim Care Companion J Clin Psychiatry, vol. 12, no. 1, 2010, doi: 10.4088/PCC.09CS00833OLI.
12. J. Perales-Puchalt et al., "Acceptability and preliminary effectiveness of a remote dementia educational training among primary care providers and health navigators," J Alzheimers Dis, vol. 89, no. 4, p. 1375, 2022, doi: 10.3233/JAD-220235.
13. Chatzikostopoulos et al., "Episodic Memory in Amnestic Mild Cognitive Impairment (aMCI) and Alzheimer's disease Dementia (ADD): Using the 'Doors and People' Tool to Differentiate between Early aMCI—Late aMCI—Mild ADD Diagnostic Groups," Diagnostics, vol. 12, no. 7, Jul. 2022, doi: 10.3390/DIAGNOSTICS12071768.
14. S. Neto and R. Nitrini, "Subjective cognitive decline: The first clinical manifestation of Alzheimer's disease?," Dement Neuropsychol, vol. 10, no. 3, p. 170, Jul. 2016, doi: 10.1590/S1980-5764-2016DN1003002.
15. L. Byers and K. Yaffe, "Depression and Risk of Developing Dementia," Nat Rev Neurol, vol. 7, no. 6, p. 323, May 2011, doi: 10.1038/NRNEUROL.2011.60.
16. D. J. Acheson and M. C. MacDonald, "Verbal Working Memory and Language Production: Common Approaches to the Serial Ordering of Verbal Information," Psychol Bull, vol. 135, no. 1, p. 50, Jan. 2009, doi: 10.1037/A0014411.
17. "Earlier Diagnosis | Alzheimer's Association." https://www.alz.org/alzheimersdementia/research_progress/earlier-diagnosis (accessed Mar. 27, 2023).
18. "FDA Permits Marketing for New Test to Improve Diagnosis of Alzheimer's disease | FDA." https://www.fda.gov/news-events/pressannouncements/fda-permits-marketing-new-testimprove-diagnosis-alzheimers-disease (accessed Mar. 29, 2023).
19. H. Hampel and K. Blennow, "CSF tau and β-amyloid as biomarkers for mild cognitive impairment," Dialogues Clin Neurosci, vol. 6, no. 4, p. 379, 2004, doi: 10.31887/DCNS.2004.6.4/HHAMPEL.
20. 20. V. S. Diogo, H. A. Ferreira, and D. Prata, "Early diagnosis of Alzheimer's disease using machine learning: a multi-diagnostic, generalizable approach," Alzheimers Res Ther, vol. 14, no. 1, pp. 1–21, Dec. 2022, doi: 10.1186/S13195-022-01047-Y/FIGURES/4.
21. G. Moya-Alvarado, N. Gershoni-Emek, E. Perlson, and F. C. Bronfman, "Neurodegeneration and Alzheimer's disease (AD). What Can Proteomics Tell Us About the Alzheimer's Brain? *," Molecular & Cellular Proteomics, vol. 15, no. 2, pp. 409–425, Feb. 2016, doi: 10.1074/MCP.R115.053330.
22. V. Patil, M. Madgi, and A. Kiran, "Early prediction of Alzheimer's disease using convolutional neural network: a review," Egyptian Journal of Neurology, Psychiatry and Neurosurgery, vol. 58, no. 1, pp. 1–10, Dec. 2022, doi: 10.1186/S41983-022-00571W/FIGURES/3.
23. D. Pan, A. Zeng, L. Jia, Y. Huang, T. Frizzell, and X. Song, "Early Detection of Alzheimer's Disease Using Magnetic Resonance Imaging: A Novel Approach Combining Convolutional Neural Networks and Ensemble Learning," Front Neurosci, vol. 14, p. 259, May 2020, doi: 10.3389/FNINS.2020.00259/BIBTEX.
24. T. J. Saleem et al., "Deep Learning-Based Diagnosis of Alzheimer's Disease," J Pers Med, vol. 12, no. 5, May 2022, doi: 10.3390/JPM12050815.
25. K. A. Johnson, N. C. Fox, R. A. Sperling, and W. E. Klunk, "Brain Imaging in Alzheimer Disease," Cold Spring Harb Perspect Med, vol. 2, no. 4, p. a006213, Apr. 2012, doi: 10.1101/CSHPERSPECT.A006213.
26. J. Bin Bae et al., "Identification of Alzheimer's disease using a convolutional neural network model based on T1-weighted magnetic resonance imaging," Scientific Reports 2020 10:1, vol. 10, no. 1, pp. 1–10, Dec. 2020, doi: 10.1038/s41598-020-79243-9.
27. Linda K McEvoy and James B Brewer, "Quantitative structural MRI for early detection of Alzheimer's disease," Expert Rev Neurother, vol. 10, no. 11, pp. 1675–1688, 2010, Accessed: Mar. 29, 2023. [Online]. Available: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3182103/pdf/nihms321994.pdf
28. G. H. Glover, "Overview of Functional Magnetic Resonance Imaging," Neurosurg Clin N Am, vol. 22, no. 2, p. 133, Apr. 2011, doi: 10.1016/J.NEC.2010.11.001.
29. K. A. Stigler and C. J. McDougle, "Structural and Functional MRI Studies of Autism Spectrum Disorders," The Neuroscience of Autism Spectrum Disorders, pp. 251–266, Jan. 2013, doi: 10.1016/B9780-12-391924-3.00017-X.
30. V. L. Villemagne, F. Barkhof, V. Garibotto, S. M. Landau, A. Nordberg, and B. N. M. van Berckel, "Molecular imaging approaches in dementia," Radiology, vol. 298, no. 3, pp. 517–530, Mar. 2021, doi: 10.1148/RADIOL.2020200028.
31. Villa, M. Lavitrano, E. Salvatore, and R. Combi, "Molecular and Imaging Biomarkers in Alzheimer's disease: A Focus on Recent Insights," J Pers Med, vol.

10, no. 3, pp. 1–32, Sep. 2020, doi: 10.3390/JPM10030061.

32. W. M. van Oostveen and E. C. M. de Lange, “Imaging Techniques in Alzheimer’s Disease: A Review of Applications in Early Diagnosis and Longitudinal Monitoring,” International Journal of Molecular Sciences 2021, Vol. 22, Page 2110, vol. 22, no. 4, p. 2110, Feb. 2021, doi: 10.3390/IJMS22042110.
33. M. A. Deture and D. W. Dickson, “The neuropathological diagnosis of Alzheimer’s disease,” Molecular Neurodegeneration 2019 14:1, vol. 14, no. 1, pp. 1–18, Aug. 2019, doi: 10.1186/S13024-019-0333-5.
34. Mayo Clinic Staff, “Alzheimer’s disease, Diagnosis,” Mayo Clinic Organigation, Mar. 08, 2023. https://www.mayoclinic.org/diseasesconditions/alzheimers-disease/diagnosis-treatment/drc20350453 (accessed Mar. 28, 2023).