RESEARCH PAPER

Current Perspectives on Alzheimer's Disease: Biomarkers, Drug Development and Future Directions

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ABSTRACT
Alzheimer's Disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia globally. Recent advances in biomarker discovery, disease-modifying therapies, and precision medicine have significantly reshaped the understanding and management of AD. This review highlights current perspectives on diagnostic biomarkers, emerging drug development strategies, and future research directions. Advances in blood-based biomarkers, neuroimaging, and artificial intelligence are enabling early detection and disease staging. Simultaneously, therapeutic development has transitioned from symptomatic management to targeting disease pathology, including amyloid-beta, tau protein, and neuroinflammation. Despite progress, challenges remain in achieving effective disease modification. Future directions emphasize personalized medicine, multimodal therapies, and early intervention strategies.
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1. INTRODUCTION

Alzheimer's disease is a chronic progressive neurodegenerative disorder, characterized by a gradual decline in memory, cognition, behavior and the ability to function independently. Alzheimer's is the most common cause of dementia and may account for 60–70% of cases. Although, older adults are primarily affected by the disorder, younger individuals may show early-onset forms of Alzheimer's disease due to genetic mutations. The increasing global incidence of Alzheimer's disease (AD) and other dementias is becoming a major medical, social, and economic burden on health care systems and caregivers as the population continues to age **[1]**.

Alzheimer's disease pathology starts several years prior to the emergence of overt clinical manifestations. In this quiet period abnormal aggregation of beta-amyloid peptides and hyperphosphorylated tau protein, results in synaptic dysfunction, neuronal damage and ascending cortical neurodegeneration. Patients may stay asymptomatic for a while, however molecular changes are continuing **[2]**. This phase is termed preclinical. Early subtler impairments in memory and executive function emerge, which progresses to mild cognitive impairment (MCI), a stage of cognitive decline on the spectrum associated with the continuum between normal aging and dementia as neuronal damage increases. The result is the dementia stage, during which cognitive dysfunction along with difficulties in language, reasoning, orientation and daily living progressively worsens to the point such that independent living becomes impossible **[3]**.

Clinically, Alzheimer disease results in a loss of short-term memory, difficulty learning new information, impaired judgment and language disturbances with disorientation, mood and behavioral symptoms. In the later stages patients lose the ability to speak, recognize family, care for themselves, and walk independently. Alzheimer's disease lays heavy emotional and financial strains on families and caregivers, often necessitating long-term support or institutional care **[4]**. The understanding of Alzheimer's disease has seen phenomenal advancements over the

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recent years with the stride of science. The understanding of AD has shifted from a purely symptomatic entity towards a biologically defined condition that may be diagnosed and treated before significant cognitive impairment occurs **[5]**. Advances in biomarkers such as cerebrospinal fluid beta-amyloid and tau measurements, positron emission tomography imaging, structural magnetic resonance imaging (MRI) and emerging blood-based biomarkers have shifted the paradigm. This allows earlier diagnosis and better disease staging with more precise patient selection for clinical trials **[6]**.

Even therapeutic research shifted trends from symptomatic relief to disease modification. Mind is presently looking into freshly produced monoclonal antibodies that target amyloid plaques, anti-tau treatments, neuroprotective therapies, anti-inflammatory tactics and customized medicine methods **[7]**. They are also considered important modalities for prevention and support, such as lifestyle interventions (physical activity, management of cardiovascular risk factors, cognitive stimulation and nutrition). Alzheimer's disease (AD) is one of the most important neurodegenerative disorders worldwide, characterized by progressive cognitive decline and neuronal loss **[8]**. The contemporary era of research emphasizes early detection with biomarker-guided diagnosis and targeted disease-modifying therapies, suggesting more hope for trajectory deceleration and outcomes.

2. BIOMARKERS IN ALZHEIMER'S DISEASE

Biomarkers have altered the approach to diagnosis, classification and management of Alzheimer´s disease (AD) by allowing for the detection of underlying pathology prior to development of significant cognitive symptoms. Diagnosis prior to genetic tests was primarily based upon clinical history, cognitive testing, and ruling out other potential causes of dementia **[9]**. On the contrary, current paradigms are moving towards biologic definitions of Alzheimer disease, based on methods to quantify amyloid deposition and tau pathways and neurodegeneration. Biomarkers are used today as central to early diagnosis, disease staging, prognosis, enrollment in clinical trial or monitoring of therapeutic response. These include cerebrospinal fluid analysis, blood tests, neuroimaging and next-generation digital or multi-omics technologies **[10]**.

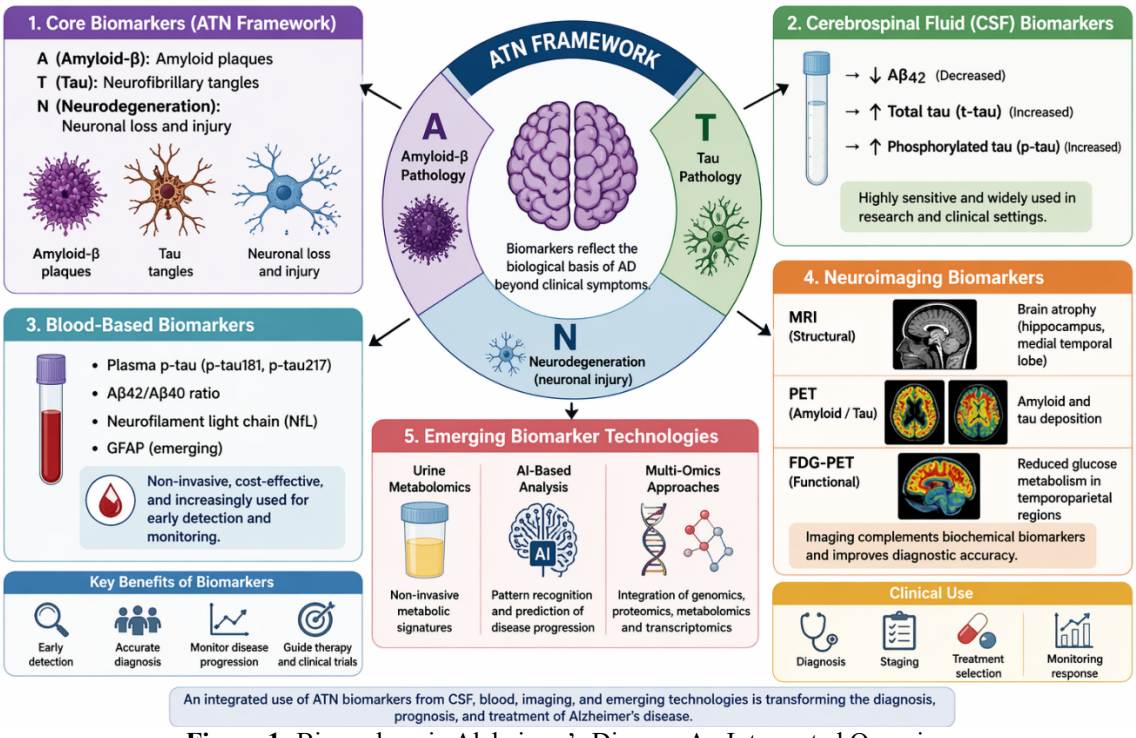

Figure 1: Biomarkers in Alzheimer's Disease: An Intergrated Overview

2.1 Core Biomarkers (Amyloid, Tau, Neurodegeneration)

The modern biomarker framework for Alzheimer's disease is based on the ATN classification system, which categorizes biomarkers into three major pathological domains **[11]**:

- A (Amyloid-β pathology)
- T (Tau pathology)
- N (Neurodegeneration or neuronal injury)

This model is grounded in the biology of Alzheimer's disease rather than clinical symptoms alone. Amyloid biomarkers represent a pathological accumulation of beta-amyloid plaques in the brain. Accumulation of pathological phosphorylated tau and neurofibrillary tangles can be reflected by Tau biomarkers **[12]**. Biomarkers of neurodegeneration indicate neuronal loss, synaptic dysfunction and brain tissue degeneration. Of

note, the ATN system has provided a unifying framework to improve stage disease and separate Alzheimer pathology from other dementias, as well as to evaluate progression of change over time in both clinical and research settings **[13]**. Emerging diagnostic frameworks, such as the new NIA-AA criteria, increasingly favour a biological definition of Alzheimer's disease where biomarker positivity may in itself indicate disease regardless of dementia status **[14]**.

2.2 Cerebrospinal Fluid (CSF) Biomarkers

Cerebrospinal fluid biomarkers remain among the most validated and widely used laboratory tools for Alzheimer's disease diagnosis. Because CSF is in close contact with the brain and spinal cord, it reflects biochemical changes occurring in the central nervous system **[15]**.

Key CSF biomarkers include:

- **Decreased Aβ42** – reflects deposition of amyloid plaques in the brain, leading to reduced soluble amyloid in CSF.
- **Increased total tau (t-tau)** – indicates neuronal injury and axonal degeneration.
- **Increased phosphorylated tau (p-tau)** – more specific marker of tau pathology and neurofibrillary tangle formation.

These biomarkers demonstrate particularly high specificity and sensitivity when given in combination. In patients who present atypically, have early-onset cognitive decline or an uncertain diagnosis, CSF testing is helpful when differentiating Alzheimer's disease from other neurodegenerative diseases. Lumbar puncture is invasive, but better techniques and acceptance have made it more common **[16]**.

2.3 Blood-Based Biomarkers

This is a salient development in the field of diagnosis of Alzheimer, and recent advances in blood-based biomarkers (BBMs) have been one of the major progressions in this area. Blood testing is less invasive, more palatable to patients, repeatable, and less expensive than CSF or advanced imaging **[17]**. In certain populations, some assays (e.g., LumiraDx) have shown sensitivities similar to or greater than 90 %. Blood biomarkers have been increasingly utilized to aid in screening, risk stratification, referral decisions, and monitoring the disease course. These tools are yet to become a routine standard of care, but primary care docs and memory clinics will have them firmly as part of their practice **[18]**.

Important blood biomarkers include:

- Plasma phosphorylated tau: especially p-tau181, p-tau217, and newer p-tau isoforms, strongly associated with Alzheimer's pathology.
- Aβ42/Aβ40 ratio: reflects amyloid processing abnormalities and plaque burden.
- Neurofilament light chain (NfL): marker of neuroaxonal injury and neurodegeneration.
- Glial fibrillary acidic protein (GFAP): may reflect astrocytic activation and early pathology.

2.4 Neuroimaging Biomarkers

Neuroimaging biomarkers characterize aspects of the underlying biology and are based on structural, molecular and functional characteristics of the brain. These techniques help deepen diagnostic confidence and complement fluid biomarkers **[19].**

Magnetic Resonance Imaging (MRI)

The use of MRI to evaluate brain atrophy, specifically the shrinkage of the hippocampus and medial temporal lobe is correlated with impairment in memory. An MRI also rules out strokes, tumors, hydrocephalus and other structural causes of cognitive decline **[20]**.

2.5 Emerging Biomarker Technologies

Advancing technologies continually broaden the future of Alzheimer's biomarker science. Urinary Metabolomics with non-invasive sampling: Assessment of metabolic profiling from urine samples may provide a biomarker for biochemical signatures associated with disease. Still investigational, this method is more appealing for screening. AI and ML can process massive biomarkers datasets, image patterns, cognitive data, longitudinal trends to refine diagnostic utility or progression prediction. AI tools probably detect subtle changes long before other methods. Multi-Omics Approaches Integrated analysis of genomics, proteomics, metabolomics and transcriptomics and lipidomic data profiles may reveal personalized disease signatures or important therapeutic targets. Multi-omics approaches provide support for precision medicine in Alzheimer's disease **[21].**

3. Drug Development in Alzheimer's Disease

Over the past two decades, drug development for Alzheimer's disease (AD) has changed substantially. For decades, the treatment strategies have mainly targeted symptomatic improvement of memory and cognition, without significantly affecting the underlining neurodegenerative process. Disease-modifying strategies have moved the research focus away from symptomatic therapies towards approaches that target the biological mechanisms of neuronal loss, including improving molecular pathology, biomarker science, genetics, and neuroimmunology. More recent examples of drug discovery now consider amyloid deposition, tau pathology, synaptic dysfunction, neuroinflammation and mitochondrial injury as well as several potentially interacting pathways. This sets the stage for a new era of personalized medicine in the treatment of Alzheimer's disease, assisted by biomarkers and novel technologies **[22]**.

Sr. No.	Category /	Examples	Mechanism of Action	Clinical Significance /

	Strategy			Limitations
1. Current Therapeutic Landscape [23]	Cholinesterase Inhibitors	Donepezil, Rivastigmine, Galantamine	Inhibit acetylcholinesterase, increasing synaptic acetylcholine levels and improving cholinergic transmission	Provide symptomatic improvement in memory and cognition; do not stop disease progression
	NMDA Receptor Antagonist	Memantine	Blocks excessive NMDA receptor activation and reduces glutamate-mediated excitotoxicity	Useful in moderate to severe AD; symptomatic benefit only
2. Disease-Modifying Therapies [24]	Anti-Amyloid Monoclonal Antibodies	Lecanemab, Donanemab	Bind amyloid-beta aggregates and promote plaque clearance	Slow disease progression in selected early-stage patients; not curative; require monitoring for ARIA
	Amyloid-Lowering Strategy	Investigational biologics and antibodies	Reduce amyloid burden and pathological accumulation	Represents shift from symptomatic care to pathology-targeted therapy
3. Targeting Tau and Neuroinflammation [25]	Tau Aggregation Inhibitors	Experimental compounds	Prevent tau misfolding, aggregation, and spread	Promising because tau correlates strongly with cognitive decline
	Anti-Tau Immunotherapy	Monoclonal antibodies, vaccines	Target extracellular or intracellular tau species	Under clinical investigation
	Anti-Inflammatory Agents	NSAID-derived and novel agents	Reduce neuroinflammation, cytokine release, and glial activation	Mixed results; active area of research
	Microglial Modulation	TREM2-targeted therapies, immune modulators	Regulate microglial function and phagocytosis	Emerging therapeutic target
4. Advanced Drug Development Approaches [26]	PROTACs	Protein degradation technologies	Direct pathogenic proteins toward proteasomal degradation	Potential for removing tau or other toxic proteins
	Dual-Target Inhibitors	Multi-mechanism small molecules	Simultaneously affect two disease pathways	May address multifactorial pathology better than single agents
	Allosteric Modulators	Receptor modulators	Bind non-active receptor sites for selective regulation	Potentially fewer adverse effects and improved specificity
5. Role of AI in Drug Development [27]	Target Identification	AI-driven discovery platforms	Analyze genomics, proteomics, imaging, and databases	Speeds identification of novel therapeutic targets
	Clinical Trial Optimization	Predictive algorithms	Improve recruitment, patient stratification, endpoint selection	Reduces cost and failure rates
	Outcome Prediction	Machine learning models	Predict treatment response and disease progression	Supports precision medicine and faster development

3.1 Current Therapeutic Landscape

It was long been the case that approved treatments for Alzheimer's disease were mostly symptomatic agents aimed at maintaining neurotransmitter function and temporarily ameliorate cognition. Such therapies are still prevalent, particularly in early or mid-stage disease progression **[28]**.

Cholinesterase Inhibitors

The main cholinesterase inhibitors are as follows: Donepezil, Rivastigmine and Galantamine. They inhibit acetylcholinesterase, raising the levels of acetylcholine in synapses. Since cholinergic neurons are strongly affected in Alzheimer's disease, improvement of daily functioning and memory/attention might be achieved through the augmentation of cholinergic transmission. Generally, the benefits are minimal and short-lived **[29]**.

NMDA Receptor Antagonist

Glutamate can induce pathological overactivation of N-methyl-D-aspartate (NMDA) receptors, which memantine blocks. This may ameliorate excitotoxic neuronal death and enhance cognition or behavior in moderate to severe disease. While these agents can ameliorate symptoms, they do not halt or reverse disease course, and neuronal degeneration continues to progress over time **[30]**.

3.2 Disease-Modifying Therapies

Of upmost significance is the recent approval of disease-modifying therapies (DMTs) for AD, which target underlying pathological processes rather than symptomatic manifestations and consequently favour a slowing of progression. Recent illustrations include: Lecanemab and Donanemab. These monoclonal antibodies bind aggregated amyloid-beta (Aβ), promoting plaque clearance from the brain **[31]**. In selected early-stage patients, data from clinical trials have shown reductions in amyloid burden as well as modest benefit on cognitive and functional decline. These therapies mark a one-in-a-century step toward the biological treatment of Alzheimer disease. These treatments may not be curative, but currently seem more likely to slow progression than restore lost function. Careful patient selection using biomarkers and adverse effect monitoring should also be used for ARIA (e.g., edema or microhemorrhage). Although limited, these agents have paved the way towards future targeted therapies **[32]**.

3.3 Targeting Tau and Neuroinflammation

While amyloid remains important, many researchers now recognize that tau pathology and neuroinflammation correlate more strongly with neuronal loss and clinical decline. Because tau tangles spread through the brain in a pattern linked to symptom progression, blocking tau pathology may offer major therapeutic benefit **[33]**.

Tau-Targeted Strategies

Emerging tau-based approaches include:

- Tau aggregation inhibitors
- Anti-tau monoclonal antibodies
- Tau phosphorylation modulators
- Microtubule stabilizers
- Gene-silencing therapies targeting tau expression

Neuroinflammation as a Target [34]

Chronic activation of microglia and astrocytes contributes to neuronal injury through cytokine release, oxidative stress, and synaptic dysfunction. Therefore, new therapies focus on:

- Anti-inflammatory agents
- Microglial modulators
- TREM2-targeted therapies
- Complement pathway inhibitors
- Immune signaling regulators

Neuroinflammation is increasingly recognized as a central driver of disease progression rather than merely a secondary response.

3.4 Advanced Drug Development Approaches

Due to the multifactorial nature of Alzheimer disease, single-target therapy may be inadequate. These new strategies seek to target several disease pathways at once **[35]**.

PROTACs: PROTACs: Proteolysis Targeting Chimeras are molecules that guide deleterious proteins to cellular degradation machinery. This technology may be used to remove toxic tau, abnormal amyloid-related proteins or any other pathogenic molecules.

Dual-Target Inhibitors: These agents are meant to hit two targets at once, such as: Amyloid + inflammation, Tau + oxidative stress and Cholinesterase + NMDA signaling. These approaches might, therefore, have a greater clinical benefit than therapy restricted to a single pathway.

Allosteric Modulators: Allosteric modulators bind to regulatory sites on receptors rather than prime active sites, enabling selective control of neurotransmission with reduced adverse liability. They focus on the cholinergic, glutamatergic and GABAergic systems **[36]**.

Gene and RNA-Based Therapies: Other novel methods including antisense oligonucleotides, RNA interference and gene editing approaches are also being explored for the control of disease-associated genes.

3.5 Artificial Intelligence in medicines development

Since then, AI has been fast revolutionizing Alzheimer's drug discovery and development **[37-39]**.

Novel Drug Targets: Using drug discovery an AI can study genomics, proteomics imaging and clinical databases to identify new molecular targets related to disease progression.

Drug Repurposing: Drug repurposing can also benefit from machine learning as it allows to have found out existing approved drugs that may possess unpredicted uses in the field of Alzheimer's yet take a shorter development time [16, 38].

AI and Clinical Trial Optimization: AI algorithms can improve patient selection, predict disease progression, and identify responders to new therapies while significantly reducing clinical trial failure rates.

Predicting Therapeutics Dynamics: Algorithms can compute efficacy, toxicity, on a biopsy-transcriptome level and predict biomarker response and subsequent progression patterns, facilitating the implementation of personalized treatment strategies. AI could also drastically shorten the long and often costly process of developing drugs for Alzheimer's by accelerating discovery and keeping expenses down **[40]**.

4. Challenges in Alzheimer's Disease Research

Although substantial advances have been made in basic neuroscience, biomarker discovery and therapeutic development for Alzheimer's disease (AD), the area remains beset by many scientific and clinical obstacles. Alzheimer disease is one of the most multifactorial and complicated neurodegenerative disease in which several pathologic mechanisms, such as amyloid accumulation, tau aggregation, synaptic disfunction, mitochondrial damage, vascular change, neuroinflammation and progressive neuronal loss sub vise each other **[41]**. As a result of this complexity, it has been challenging to develop uniformly effective treatments or predictive diagnostic models. A number of new disease-modifying therapies (DMTs) have recently come on the market; however, many restrictions still exist and formidable hurdles continue to delay advances toward prevention, cure or long-term control of disease **[42]**.

5. FUTURE DIRECTIONS

Future advances in research and treatment for Alzheimer's disease (AD) are rapidly heading toward earlier diagnosis, biologically targeted therapy, and personalized patient care. High-level SummaryTraditional methods targeting symptom relief are being superseded by strategies focused on identifying the pathological mechanism(s) of disease prior to dementia and intervening at the earliest stages of neurodegeneration **[43]**. Recent advances in genomics, biomarker science, artificial intelligence, neuroimaging, and systems biology represent a promising transformational opportunity for precision medicine. Future advances will probably rely on the combination of different diagnostic tools, personalization of therapy to individual patients, combining disease-modifying agents and lifestyle factors promoting preventive approaches. These strategies provide promise for delaying the onset, slowing the progression, and/or improving the quality of life **[44]**.

5.1 Precision Medicine

Precision medicine is expected to become a central pillar of future Alzheimer's care. Because Alzheimer's disease is biologically heterogeneous, patients differ in genetic risk, biomarker profile, progression rate, inflammatory responses, vascular burden, and treatment response. A uniform treatment model is therefore unlikely to be optimal for all individuals **[45]**.

5.2 Multimodal Biomarker Integration

Alzheimer disease itself has numerous complexities and no biomarker captures all of them. As a consequence, improved diagnostic accuracy, staging and prediction is increasingly based on the integration of multiple data sources in future diagnostic models. Integrated machine learning supported biomarker platforms may be able to detect disease sooner than any standalone test. However, multimodal systems can also assess changes in treatment response, track progression and stratify patients into biologically relevant subgroups. And this, evidently, will be the default in memory clinics and research centers **[46]**.

5.3 Early Intervention Strategies

Among the more critical aspirational targets for the future is treatment during a preclinical phase of the disease — when pathology may be present but neurodegeneration resulting in severe cognitive decline has yet to occur. As such, substantial neuronal loss has often already progressed by the time dementia becomes manifest. Prevention that may identify candidates for therapeutic intervention Screening of high-risk individuals with blood biomarkers, genetic risk assessment and digital cognitive tools. Just as preventive cardiology takes on heart disease years in advance, future therapies could begin years prior to the onset of dementia **[47]**.

5.4 Combination Therapies

Because Alzheimer's disease involves multiple pathological pathways, future treatment is likely to rely on combination therapies rather than single agents **[48]**.

Potential Combinations Include:

- Anti-amyloid + anti-tau therapies
- Neuroprotective + anti-inflammatory agents
- Synaptic enhancers + disease-modifying drugs
- Vascular therapies + metabolic interventions
- Lifestyle programs + pharmacotherapy

It is a strategy reminiscent of treatment paradigms in cancer, HIV, and cardiovascular disease where multi-target regimens frequently supersede monotherapy. Such combination regimens may protect neurons, lower levels of toxic proteins, suppress inflammation and improve cognition at once. Rational sequence of therapies based on disease stage (early preventive treatment versus later restorative strategies) will likely also become relevant **[49-51]**.

5.5 Preventive Approaches

Alzheimer's prevention has been shown to be one of the most effective mechanisms against this disease. Cognitive decline is associated to numerous modifiable risk factors, and modifying these may delay its onset or reduce lifetime risk. Yup—a lot, but here are the essential lifestyle prevention approaches: Physical activity; Mental stimulation; Diet and Nutrition; Management of hypertension, diabetes, overweight or obesity and smoking. Risk modification programs at the population-level could mitigate much of the future burden from

dementia. Delaying the onset for even a couple of years would have huge public health benefits **[52-53]**.

6. CONCLUSION

Research into Alzheimer's disease is now in the midst of a paradigm shift ushered in by transformative technologies in biomarker science, molecular neuroscience and targeted therapeutics. For approximately two decades, symptomatic management consisted primarily of cholinesterase inhibitors and memantine treatment that has been associated with only modest cognitive and functional benefits without modifying the neurodegenerative cascade. The transition from symptomatic therapy to disease modification is a major milestone in modern Alzheimer's care.

The maturation of sensitive and specific biomarkers to identify pathology prior to irreversible cognitive impairment has been one major impetus for this paradigm shift. They have transformed diagnosis, screening, staging and monitoring of therapy with cerebrospinal fluid markers, amyloid and tau PET imaging, structural MRI and most recently blood-based biomarkers such as plasma phosphorylated tau or amyloid ratios. Such tools allow for earlier identification of disease at preclinical and mild cognitive impairment states, for which treatment may be more effective.

Meanwhile, the treatment landscape is already changing with the introduction of targeted biological therapies. Monoclonal antibodies targeting amyloid-beta, such as lecanemab and donanemab, show that removal of pathological protein burden can modestly slow disease progression in selected patients, While these therapies are not a cure for Alzheimer disease nor do they reverse advanced neuronal loss, they represent evidence that it is clinically possible to modify core pathology. The horizon is even wider with the simultaneous development of tau-directed agents, anti-inflammatory therapies, neuroprotective compounds, synaptic repair strategies and gene-based approaches.

In fact, artificial intelligence and digital medicine are also evolving as strong tools to aid in Alzheimer's research. More specifically, AI-driven systems can these imaging modalities with other available forms of health information (i.e. genetics, biomarkers and clinical data) — to better diagnose, predict progression, enhance clinical trials and discover new drug targets. Such technologies could potentially reduce research costs massively and speedup therapeutic discovery.

These advances aside, though, there are still headwinds. Alzheimer's disease is biologically heterogeneous and multifactorial; diagnosis is made only after irreversible neuronal injury has occurred. Existing therapeutic approaches are only partially effective, high rates of clinical trial failure persist, and access to advanced diagnostics and therapy is still inequitable. Thus, a permanent cure continues to be out of reach.

Future directions should centre around precision medicine, in which therapy is guided by genetic background and biomarker profile as well as disease subtype and stage. This suggests that early intervention strategies targeting pathology before much neurodegeneration has occurred would be most beneficial. Second, combination therapies targeting amyloid, tau, inflammation, vascular dysfunction and synaptic loss together may be more efficacious than monotherapy. Prevention through lifestyle modifications, cardiovascular risk management and cognitive health will also continue to be crucial.

Taken together, this view may represent an emerging paradigm shift in the research of Alzheimer disease away from post-symptomatic late-stage symptomatic treatment to early biologically guided intervention. Although a complete cure remains elusive, progress in biomarkers and AI-driven diagnostics and therapeutics provides an unprecedented expectation for prevention, control, and treatment of Alzheimer's disease.

REFERENCES

1. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413-46.
2. Busche MA, Hyman BT. Synergy between amyloid-β and tau in Alzheimer's disease. *Nat Neurosci*. 2020;23(10):1183-93.
3. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer's disease: where do we go from here? *Nat Rev Neurol*. 2021;17(3):157-72.
4. Swerdlow RH. Mitochondria and mitochondrial cascades in Alzheimer's disease. *J Alzheimers Dis*. 2020;62(3):1403-16.
5. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2020. *Alzheimers Dement (N Y)*. 2020;6(1):e12050.
6. Breijyeh Z, Karaman R. Comprehensive review on Alzheimer's disease: causes and treatment. *Molecules*. 2020;25(24):5789.
7. Yiannopoulou KG, Papageorgiou SG. Current and future treatments for Alzheimer's disease. *Ther Adv Neurol Disord*. 2020;13:1756286420942067.
8. Knopman DS, Amieva H, Petersen RC, Chételat G, Holtzman DM, Hyman BT, et al. Alzheimer disease. *Nat Rev Dis Primers*. 2021;7(1):33.
9. Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chételat G, Teunissen CE, et al. Alzheimer's disease. *Lancet*. 2021;397(10284):1577-90.
10. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535-62.
11. Dubois B, Villain N, Frisoni GB, Rabinovici GD, Sabbagh M, Cappa S, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the

International Working Group. *Lancet Neurol*. 2021;20(6):484-96.

12. Dubois B, Villain N, Frisoni GB, Rabinovici GD, Sabbagh M, Cappa S, et al. Biomarkers in Alzheimer's disease: role in early and differential diagnosis. *Nat Rev Neurol*. 2023;19(11):687-704.
13. Teunissen CE, Verberk IMW, Thijssen EH, Vermunt L, Hansson O, Zetterberg H, et al. Blood-based biomarkers for Alzheimer's disease: towards clinical implementation. *Nat Rev Neurol*. 2022;18(11):643-56.
14. Hansson O, Edelmayer RM, Boxer AL, Carrillo MC, Mielke MM. The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimers Dement*. 2022;18(12):2669-86.
15. Palmqvist S, Tideman P, Cullen N, Zetterberg H, Blennow K, Dage JL, et al. Prediction of future Alzheimer's disease dementia using plasma phospho-tau combined with other accessible measures. *Nat Med*. 2021;27(6):1034-42.
16. Thijssen EH, La Joie R, Wolf A, Strom A, Wang P, Iaccarino L, et al. Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration. *Nat Med*. 2020;26(3):387-97.
17. Janelidze S, Mattsson-Carlgren N, Palmqvist S, Smith R, Beach TG, Serrano GE, et al. Plasma P-tau217 in Alzheimer's disease: relationship to other biomarkers, differential diagnosis, neuropathology and longitudinal progression to Alzheimer's dementia. *Nat Med*. 2020;26(3):379-86.
18. Ashton NJ, Pascoal TA, Karikari TK, Benedet AL, Lantero-Rodriguez J, Brinkmalm G, et al. Plasma p-tau231: a new biomarker for incipient Alzheimer's disease pathology. *Acta Neuropathol*. 2021;141(5):709-24.
19. Verberk IMW, Thijssen E, Koelewijn J, Mauroo K, Vanbrabant J, de Wilde A, et al. Combination of plasma amyloid beta(1-42/1-40) and glial fibrillary acidic protein strongly associates with cerebral amyloid pathology. *Alzheimers Res Ther*. 2020;12(1):118.
20. Verberk IMW, Slot RE, Verfaillie SCJ, Heijst H, Prins ND, van Berckel BNM, et al. Plasma amyloid as prescreener for the earliest Alzheimer pathological changes. *Ann Neurol*. 2018;84(5):648-58.
21. Verberk IMW, Laarhuis MB, van den Bosch KA, Ebenau JL, van Leeuwenstijn M, Prins ND, et al. Serum markers glial fibrillary acidic protein and neurofilament light for prognosis and monitoring in cognitively normal older adults. *Alzheimers Res Ther*. 2021;13(1):177.
22. Nakamura A, Kaneko N, Villemagne VL, Kato T, Doecke J, Doré V, et al. High performance plasma amyloid-β biomarkers for Alzheimer's disease. *Nature*. 2018;554(7691):249-54.
23. 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):371-86.
24. Frisoni GB, Altomare D, Thal DR, Ribaldi F, van der Kant R, Ossenkoppele R, et al. The probabilistic model of Alzheimer disease: the amyloid hypothesis revised. *Nat Rev Neurol*. 2022;18(10):585-99.
25. Cummings J, Lee G, Ritter A, Sabbagh M, Zhong K. Alzheimer's disease drug development pipeline: 2022. *Alzheimers Dement (N Y)*. 2022;8(1):e12295.
26. Cummings J, Apostolova LG, Rabinovici GD, Atri A, Aisen P, Greenberg S, et al. Lecanemab: appropriate use recommendations. *J Prev Alzheimers Dis*. 2023;10(3):362-77.
27. van Dyck CH, Swanson CJ, Aisen P, Bateman RJ, Chen C, Gee M, et al. Lecanemab in early Alzheimer's disease. *N Engl J Med*. 2023;388(1):9-21.
28. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023;330(6):512-27.
29. Mintun MA, Lo AC, Duggan Evans C, Wessels AM, Ardayfio PA, Andersen SW, et al. Donanemab in early Alzheimer's disease. *N Engl J Med*. 2021;384(18):1691-704.
30. Pontecorvo MJ, Siderowf A, Dubois B, Doraiswamy PM, Frisoni GB, Grundman M, et al. Association of donanemab treatment with exploratory plasma biomarkers in early symptomatic Alzheimer disease: a secondary analysis of the TRAILBLAZER-ALZ randomized clinical trial. *JAMA Neurol*. 2022;79(12):1250-9.
31. Shcherbinin S, Evans CD, Lu M, Andersen SW, Pontecorvo MJ, Willis BA, et al. Association of amyloid reduction after donanemab treatment with tau pathology and clinical outcomes. *JAMA Neurol*. 2022;79(10):1015-24.
32. Alzheimer's Association. 2024 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2024;20(5):3898-4015.
33. Nichols E, Steinmetz JD, Vollset SE, Fukutaki K, Chalek J, Abd-Allah F, et al. Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease Study 2019. *Lancet Public Health*. 2022;7(2):e105-25.

34. Xu L, Wang Y, Ma T, Zhang J, Huang Y, Wang L, et al. Global incidence trends and projections of Alzheimer disease from 1992 to 2021 and forecasts to 2050. *Alzheimers Dement*. 2025. Epub ahead of print.
35. Jack CR Jr, Therneau TM, Weigand SD, Wiste HJ, Knopman DS, Vemuri P, et al. Predicting future Alzheimer's disease progression using individual participant data from longitudinal cohorts. *Brain*. 2023;146(3):1117-30.
36. Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, Karlawish JH, et al. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force. *J Nucl Med*. 2013;54(3):476-90.
37. Ossenkoppele R, Smith R, Ohlsson T, Strandberg O, Mattsson N, Insel PS, et al. Associations between tau, Aβ, and cortical thickness with cognition in Alzheimer disease. *Neurology*. 2019;92(6):e601-12.
38. Karikari TK, Pascoal TA, Ashton NJ, Janelidze S, Benedet AL, Rodriguez JL, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modeling study using data from four prospective cohorts. *Lancet Neurol*. 2020;19(5):422-33.
39. Brickman AM, Manly JJ, Honig LS, Sanchez D, Reyes-Dumeyer D, Lantigua RA, et al. Plasma p-tau181, p-tau217, and neurodegeneration in ethnically diverse community-dwelling older adults. *JAMA Neurol*. 2021;78(11):1350-9.
40. Karikari TK, Benedet AL, Ashton NJ, Lantero Rodriguez J, Snellman A, Suárez-Calvet M, et al. Diagnostic performance and prediction of clinical progression of plasma phospho-tau217 in Alzheimer disease. *Nat Med*. 2020;26(3):387-97.
41. Suárez-Calvet M, Karikari TK, Ashton NJ, Gispert JD, Salvado G, Minguillon C, et al. Novel tau biomarkers for Alzheimer's disease. *Lancet Neurol*. 2020;19(10):880-92.
42. Hampel H, Cummings J, Blennow K, Gao P, Jack CR Jr, Vergallo A. A precision medicine initiative for Alzheimer's disease: the road ahead to biomarker-guided integrated care. *Nat Rev Neurol*. 2021;17(9):580-99.
43. Cheng F, Lu W, Liu C, Fang J, Hou Y, Handy DE, et al. Artificial intelligence and open science in discovery of disease-modifying therapeutics for Alzheimer's disease and related dementias. *Nat Rev Drug Discov*. 2024;23(4):267-89.
44. Angioni D, Cummings J, Aisen PS, Vellas B, Cammalleri V, Weiner MW, et al. Combination therapy in Alzheimer's disease drug development: a report from the EU/US CTAD Task Force. *J Prev Alzheimers Dis*. 2025. Epub ahead of print.
45. Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, Andrieu S, et al. Preclinical Alzheimer's disease: definition, natural history, and diagnostic criteria. *Alzheimers Dement*. 2016;12(3):292-323.
46. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Feldman HH, Frisoni GB, et al. A/T/N: an unbiased descriptive classification scheme for Alzheimer disease biomarkers. *Neurology*. 2016;87(5):539-47.
47. Panza F, Lozupone M, Logroscino G, Imbimbo BP. A critical appraisal of amyloid-β-targeting therapies for Alzheimer disease. *Nat Rev Neurol*. 2019;15(2):73-88.
48. Congdon EE, Sigurdsson EM. Tau-targeting therapies for Alzheimer disease. *Nat Rev Neurol*. 2018;14(7):399-415.
49. Butterfield DA, Halliwell B. Oxidative stress, dysfunctional glucose metabolism and Alzheimer disease. *Nat Rev Neurosci*. 2019;20(3):148-60.
50. DeTure MA, Dickson DW. The neuropathological diagnosis of Alzheimer's disease. *Mol Neurodegener*. 2019;14(1):32.
51. Long JM, Holtzman DM. Alzheimer disease: an update on pathobiology and treatment strategies. *Cell*. 2019;179(2):312-39.
52. Heneka MT, Golenbock DT, Latz E. Innate immunity in Alzheimer's disease. *Nat Immunol*. 2015;16(3):229-36.
53. Alzheimer's Association. 2025 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2025. Epub ahead of print.