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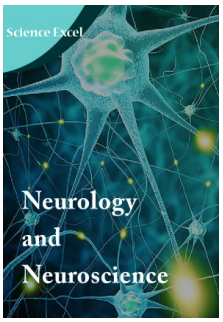
Short Communication



Dementia in the 21st Century: From Biomarkers to Disease-Modifying Therapies

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Introduction

The global prevalence of dementia has reached unprecedented levels, establishing it as one of the most significant health challenges of the 21st century. The worldwide number of individuals living with dementia is projected to reach 60–65 million in 2026. This figure reflects a sustained increase driven by population aging and demographic expansion, with projections suggesting a nearly threefold rise to approximately 190 million cases by 2050 [1–3]. Consequently, dementia—particularly Alzheimer's disease (AD)—demands urgent attention from the neurological community and healthcare professionals involved in the care of affected individuals [1–2].

The majority of cases occur in individuals over 65 years of age, with higher prevalence observed in women, partly attributable to greater life expectancy. Marked regional disparities exist, with more rapid increases projected in countries with low sociodemographic indices, particularly in Asia and Africa [2–4]. Approximately 60–70% of dementia cases are attributable to Alzheimer's disease (AD), although global prevalence estimates encompass all etiologies of dementia [1]. Epidemiological projections indicate that the overall burden will continue to rise, underscoring the need for comprehensive public health strategies focused on prevention, early diagnosis, and appropriate therapeutic management [2–3].

Significant racial and ethnic disparities persist in dementia incidence. African Americans experience approximately 27 cases per 1,000 person-years, compared with 19 cases among White Americans and 15 among Asian Americans. These differences highlight the complex interplay of biological, sociodemographic, and healthcare access factors shaping the global and national landscape of dementia [2].

Biomarkers

Over the past five years, a paradigm shift has occurred in the diagnosis of dementia driven by the development of blood-based biomarkers. Traditional diagnostic approaches—primarily cerebrospinal fluid (CSF) analysis and advanced neuroimaging—although accurate, have been limited by high costs and restricted accessibility. These limitations are particularly consequential for older adults and populations in low-resource settings, where early detection is critical [5–6].

The emergence of minimally invasive plasma biomarkers now offers transformative potential for large-scale screening and early therapeutic intervention. Plasma phosphorylated tau at threonine 217 (p-tau217) has emerged as one of the most promising biomarkers, demonstrating outstanding diagnostic performance, with area under the receiver operating characteristic curve (AUC) values exceeding 0.93 and a positive predictive value of approximately 91% for detecting Alzheimer's disease (AD) pathology [6–7]. Notably, p-tau217 can identify pathological changes 15–20 years before the onset of clinical symptoms, with plasma concentrations increasing by more than 8.5% annually during the preclinical phase [6].

Recent approval by the U.S. Food and Drug Administration (FDA) of a plasma p-tau217/Aβ1–42 ratio test for the early detection of cerebral amyloid pathology in symptomatic individuals over 55 years of age represents a major advance in accessible and minimally invasive diagnostics [8].

Additional plasma biomarkers further enhance diagnostic precision. The beta-amyloid 42/40 ratio correlates with cerebral amyloid plaque burden, while p-tau181 is strongly associated with amyloid pathology and may predict incipient cognitive decline in presymptomatic individuals [9]. Neurofilament light chain (NfL) serves as a marker of neuroaxonal injury and helps differentiate AD

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from non-degenerative conditions. Glial fibrillary acidic protein (GFAP) reflects astrocytic activation and neuroinflammatory processes [5–8–9].

Collectively, these biomarkers enable earlier diagnosis, improved patient stratification, longitudinal disease monitoring, and evaluation of therapeutic response—capabilities that are essential in the emerging era of precision medicine.

Disease-Modifying Therapies

After decades of largely unsuccessful clinical trials, the field of Alzheimer's disease therapeutics has achieved its first meaningful breakthroughs in disease-modifying treatments. Lecanemab and donanemab—humanized IgG1 monoclonal antibodies targeting aggregated β-amyloid species—have demonstrated significant clinical efficacy in phase 3 trials, slowing cognitive decline by approximately 27% to 36% compared with placebo over an 18-month period [10].

Both agents have received regulatory approval in multiple jurisdictions, including the United States, the United Kingdom, the European Union, China, and Japan, between July 2024 and August 2025. These approvals represent a milestone in the treatment of early Alzheimer's disease.

Importantly, these therapies provide clinical support for the amyloid cascade hypothesis. Beyond amyloid plaque reduction, treatment has been associated with downstream effects on phosphorylated tau, glial fibrillary acidic protein (GFAP) reactivity, and markers of neurodegeneration such as total tau and neurofilament light chain. Donanemab, in particular, has demonstrated efficacy in patients at earlier biological stages of disease, defined by tau pathology on positron emission tomography (PET), underscoring the importance of timely intervention [11].

Despite these advances, the implementation of anti-amyloid therapies presents substantial challenges. Appropriate patient selection requires comprehensive evaluation, including standardized cognitive assessment, confirmation of elevated cerebral amyloid burden, apolipoprotein E (APOE) ε4 genotyping, and baseline brain magnetic resonance imaging (MRI) to exclude alternative causes of cognitive impairment [10]. Treatment protocols involve monthly or bi-monthly intravenous infusions over 12–18 months, accompanied by serial MRI monitoring.

Adverse effects associated with anti–β-amyloid monoclonal antibodies include amyloid-related imaging abnormalities (ARIA), which may present as vasogenic edema (ARIA-E) or cerebral microhemorrhages and hemosiderin deposition (ARIA-H). Although often asymptomatic, ARIA can produce headache, confusion, nausea, seizures, or focal neurological deficits. The risk is significantly higher in carriers of the APOE ε4 allele, necessitating careful radiologic surveillance during treatment [10–11].

The high cost of these biologic agents, the logistical demands of their administration, uncertainties regarding long-term durability of benefit, and questions surrounding optimal patient selection have sparked ongoing debate about their cost-effectiveness, real-world value, and equitable access [12].

Future Horizons

The coming decade is poised to transform dementia therapeutics, shifting from a predominantly single-pathway focus toward multimodal and precision-based strategies. Multiple investigational therapies for Alzheimer's disease (AD) are currently under evaluation, with research increasingly extending into the asymptomatic preclinical stages of the disease continuum [10].

The AHEAD study is assessing lecanemab in cognitively unimpaired individuals with elevated cerebral amyloid levels, potentially paving the way for true preventive interventions [10]. Parallel efforts are targeting tau pathology, which represents a critical therapeutic frontier. Passive anti-tau immunotherapies and small-molecule inhibitors of tau aggregation are actively under investigation [13]. Given the strong correlation between phosphorylated tau accumulation and cognitive decline, combination strategies targeting both amyloid and tau may ultimately yield greater clinical benefit than monotherapy approaches [14].

Beyond amyloid and tau, immunomodulatory strategies designed to enhance microglial-mediated clearance of aggregated proteins are being developed, alongside neuroprotective interventions aimed at mitigating oxidative stress and chronic neuroinflammation [13]. These approaches reflect a growing recognition of dementia as a multifactorial and biologically heterogeneous disorder.

Precision medicine frameworks offer a particularly promising paradigm for addressing this complexity. The integration of fluid biomarkers, genetic profiling, advanced neuroimaging, and digital phenotyping may enable individualized risk stratification and therapeutic tailoring.

Technological innovation will further accelerate this evolution. Nanotechnology-based drug delivery systems are being engineered to improve blood–brain barrier penetration and therapeutic bioavailability [12]. In parallel, artificial intelligence (AI)–driven platforms are expediting target discovery, biomarker integration, and patient stratification, facilitating more efficient clinical trial design and personalized treatment selection [15].

Conclusion

The field of dementia research is undergoing a historic transformation. Blood-based biomarkers now enable increasingly accurate and accessible early diagnosis, while disease-modifying therapies have demonstrated, for the first time, measurable clinical benefit in altering the trajectory of Alzheimer's disease.

Yet these advances also redefine the responsibilities of clinicians, researchers, and health systems. The next phase will require integrated strategies that combine biomarker-driven early detection, multimodal therapeutic approaches, equitable access to emerging treatments, and individualized care models grounded in precision medicine.

The central challenge of the coming decade is not only scientific innovation but implementation. Translating these breakthroughs into sustainable, globally accessible care will determine whether dementia remains an inexorable cause of cognitive decline or evolves into a condition that is increasingly preventable, treatable, and manageable.

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