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VIEWPOINTS

Primary progressive dementia in 2026: beyond amyloid, towards biomarker-guided and equitable care. A viewpoint from Croatia and resource-constrained health systems

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Dementia caused by primary neurodegenerative disease, traditionally termed "primary progressive dementia" in our region, affected an estimated 57 million people worldwide in 2019, a figure projected to approach 153 million by 2050, with the steepest increases in low- and middle-income countries (LMICs). Recent years have transformed the field. Alzheimer disease is now defined biologically; plasma phosphorylated tau 217 approaches the diagnostic accuracy of cerebrospinal fluid and positron emission tomography; and two anti-amyloid monoclonal antibodies, lecanemab and donanemab, have shown that removing amyloid modestly slows decline in early disease, at the price of amyloid-related imaging abnormalities, intensive monitoring and high cost. At the same time, the failure of semaglutide in two large phase 3 trials, the high frequency of mixed pathologies, and the frequent dissociation between amyloid burden and clinical state remind us that amyloid is a necessary but insufficient part of the story. In this viewpoint we argue that neurodegeneration is better understood as a progressive failure of neuronal networks, in which collapse of intracellular transport, impaired clearance and regulated cell death converge, than as a single-protein disease. We then consider what the new diagnostic and therapeutic tools mean for health systems with limited resources, drawing on Croatian experience: a strong research tradition, scarce imaging capacity, care that rests largely on families, and a national dementia plan still under development. We propose that blood biomarkers, task-sharing with primary care and population-wide risk-factor reduction, rather than costly infusions, should be the first priorities for LMICs and resource-constrained European systems.

1. Introduction: a growing and shifting burden

Few conditions illustrate the limits of modern medicine as clearly as the dementias caused by primary neurodegeneration, the progressive and so far irreversible loss of memory, thinking and judgement that arises without an identifiable external cause such as stroke, trauma, infection or a tumour. In Croatian clinical tradition this group has often been called "primary

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progressive dementia", as opposed to symptomatic dementias that accompany other diseases. The term is useful at the bedside, but it now needs to be reconciled with an international vocabulary that has changed rapidly.

The scale of the problem is not in doubt. The Global Burden of Disease analysis estimated that 57.4 million people were living with dementia in 2019 and forecast 152.8 million by 2050.[1] Contrary to a widespread perception, the fastest growth is not expected in the wealthy countries of the West but in North Africa, the Middle East and sub-Saharan Africa, where populations are ageing quickly and cardiovascular and metabolic risk factors are rising.[1] The global cost of dementia was estimated at 1.3 trillion US dollars in 2019, about half of which is informal care provided by families, predominantly women.[2] In many high-income countries the age-specific incidence of dementia has in fact declined over recent decades, a finding attributed to better education and vascular risk control.[3] The rise in absolute numbers is therefore driven mainly by population ageing and growth, and the burden is shifting towards the countries least prepared to carry it.

This viewpoint summarises where the field stands in late 2026, revisits mechanistic questions that remain open, and asks what the new tools mean for LMICs and for resource-constrained European health systems such as Croatia's.

2. What we mean by primary progressive dementia today

Clinically, dementia is still diagnosed when cognitive decline interferes with independence in everyday life, a threshold that in Croatian law loosely corresponds to loss of legal capacity and the need for a guardian. Mild cognitive impairment (MCI) describes objectively measured decline that does not yet compromise independence. Not all people with MCI progress, and the clinical syndrome alone predicts the underlying pathology poorly.

The most important conceptual shift of recent years is the move from a syndromic to a biological definition. The 2024 revised criteria of the Alzheimer's Association workgroup define Alzheimer disease by the presence of core biomarkers of amyloid and tau pathology, regardless of symptoms, and stage the disease biologically and clinically.[4] The same framework recognises biomarkers of co-pathology, including α-synuclein seed amplification assays in cerebrospinal fluid, vascular injury and markers of nonspecific neurodegeneration such as neurofilament light chain.[4] The proposal is contested: classifying cognitively unimpaired, amyloid-positive people as having a disease raises clinical, ethical and economic questions, because many will never develop dementia in their lifetime. For clinicians in our region, the practical message is that "primary progressive dementia" is not one disease but a family of proteinopathies (amyloid-β, tau, α-synuclein, TDP-43) that frequently coexist in the same brain, particularly in the oldest patients.

Dementia is also not an inevitable consequence of ageing. The 2024 Lancet Commission identified 14 modifiable risk factors across the life course, including low education, hearing loss, hypertension, diabetes, smoking, obesity, physical inactivity, depression, social isolation, excessive alcohol use, traumatic brain injury, air pollution, and, newly added, high LDL cholesterol and untreated vision loss, which together account for an estimated 45% of dementia cases.[3] These are risk factors rather than causes, and none alone is decisive; the difference matters, but so does the fact that their combined weight is large and, in principle, modifiable.

3. Amyloid: necessary, but not sufficient

Amyloid plaques were the first lesion described by Alois Alzheimer and have dominated the field for four decades. Two observations from amyloid positron emission tomography (PET), first with the Pittsburgh compound B and later with fluorinated tracers, have long tempered the amyloid hypothesis: a substantial proportion of cognitively unimpaired older people carry a heavy amyloid load, and a meaningful proportion of people clinically diagnosed with Alzheimer-type dementia have little or no amyloid. In the latter group, alternative or co-existing pathologies such as limbic-predominant TDP-43 encephalopathy, Lewy body disease, hippocampal sclerosis and cerebrovascular disease are common. The cerebrospinal fluid profile of Alzheimer disease, with low amyloid-β42 (or a low amyloid-β42/40 ratio) and elevated phosphorylated and total tau, reflects sequestration of amyloid in plaques and release of tau from injured neurons.

The anti-amyloid monoclonal antibodies have answered part of the question. In the CLARITY AD trial, lecanemab reduced brain amyloid and slowed decline on the Clinical Dementia Rating Sum of Boxes (CDR-SB) by 0.45 points, about 27%, over 18 months in early Alzheimer disease.[5] In TRAILBLAZER-ALZ 2, donanemab slowed decline by roughly a third on integrated cognitive and functional scales, with greater benefit in participants with lower tau burden.[6] Both drugs are now authorised in the United States and, with restrictions related to apolipoprotein E (*APOE*) ε4 status, in the European Union. Their principal hazard is amyloid-related imaging abnormalities (ARIA): vasogenic oedema and microhaemorrhages, which are usually asymptomatic but occasionally severe and, rarely, fatal.[5,6] The risk is highest in *APOE* ε4 homozygotes and in people with cerebral amyloid angiopathy, in whom amyloid is deposited in vessel walls; removal of vascular amyloid appears to weaken already fragile vessels.

Removing amyloid therefore slows, but does not stop, neurodegeneration, and the absolute clinical effect is modest, amounting to a delay of several months over 18 months of treatment. This confirms that amyloid is causally involved, at least early in the cascade, but also that once tau pathology has

spread through cortical networks the degenerative process becomes largely independent of amyloid. This is consistent with the view that amyloid is an important trigger and marker, rather than the sole executor, of neuronal loss.

4. Beyond amyloid: transport failure, network disconnection and cell death

If amyloid is not the whole story, where should we look? Two cellular processes appear consistently. The first is failure of intracellular transport. Tau stabilises axonal microtubules, the "roads" along which mitochondria, synaptic vesicles and neurotransmitter machinery are carried; α-synuclein regulates synaptic vesicle trafficking. When these proteins misfold, detach and aggregate, transport fails and synapses are deprived of what they need. The second is failure of clearance, both intracellular (the autophagy–lysosomal system) and extracellular (microglial phagocytosis, perivascular and glymphatic drainage). We and others have argued that these two processes are not independent but feed each other in a vicious circle.

A third perspective, which the author has developed with colleagues as a theoretical model, concerns the network. Neurodegenerative syndromes do not spread randomly; they follow large-scale, functionally connected brain networks, so that the clinical picture reflects the network first affected.[7] Neurons depend on synaptic activity and on trophic support delivered through their connections; a neuron, or a subnetwork, that loses its connections with the rest of the network becomes redundant and is eliminated by regulated cell death, as is well documented for motor and sensory neurons that lose their targets. On this view, neurodegeneration may partly represent the programmed elimination of disconnected, initially healthy neurons, which would also explain why biological tests rarely predict the process before it begins. Who "decides" that a network has become irretrievably disconnected remains unknown; highly connected hub structures such as the thalamus and brainstem nuclei, which degenerate early in several proteinopathies, are plausible candidates.

Recent data refine the classical emphasis on apoptosis. In human neurons transplanted into mouse brains exposed to amyloid, neuronal loss occurred through necroptosis, a programmed inflammatory form of cell death driven by the long non-coding RNA *MEG3*, and could be prevented by blocking the necroptotic pathway.[8] Whatever the precise mode, the message is the same: neuronal death in neurodegeneration is regulated, which makes it, at least in principle, pharmacologically modifiable. Croatian research has contributed to this mechanistic agenda; for example, work from Zagreb has linked haplotype-tagging polymorphisms of the tau gene *MAPT* to cerebrospinal fluid biomarkers, neuropsychological performance and *APOE* genotype in a Croatian cohort.[9]

The therapeutic pipeline now reflects this broader view. Of 138 drugs in 182 trials registered in 2025, the majority were disease-targeted and addressed some 15 distinct processes, including tau, inflammation, synaptic function, metabolism and neuroprotection.[10] Not all promising ideas survive testing: oral semaglutide, a glucagon-like peptide-1 receptor agonist supported by strong epidemiological and preclinical signals, did not slow progression in the two phase 3 EVOKE trials in early Alzheimer disease.[11] Negative results of this quality are valuable, and they caution against translating observational associations directly into therapy.

5. Diagnosis moves into the blood

For decades the proof of a primary degenerative process rested on functional imaging (perfusion single-photon emission computed tomography and fluorodeoxyglucose PET) and, later, on amyloid PET and cerebrospinal fluid analysis. These remain valuable, but they are expensive, unevenly distributed and, in the case of lumbar puncture, often declined. The most consequential advance for health systems with limited resources is therefore not a drug but a blood test.

In a Swedish study of more than 1,200 patients, a plasma test combining phosphorylated tau 217 with the amyloid-β42/40 ratio identified Alzheimer pathology with about 90% accuracy in both primary and secondary care, whereas the accuracy of primary care physicians and dementia specialists using standard assessment was 61% and 73%, respectively.[12] In 2025 the Alzheimer's Association issued its first clinical practice guideline on blood-based biomarkers, recommending that tests with at least 90% sensitivity and 75% specificity may be used for triage, and those with at least 90% sensitivity and 90% specificity may substitute for PET or cerebrospinal fluid in specialist care.[13] A systematic review of real-world clinical populations confirmed the consistently high performance of plasma phosphorylated tau 217, with more variable results for glial fibrillary acidic protein and neurofilament light chain, and noted the near absence of data from non-European populations.[14]

Two cautions apply. Many commercial assays do not yet meet the guideline thresholds, and plasma concentrations are influenced by chronic kidney disease, body mass and comorbidity, which are common in older patients in LMICs. Blood tests are intended for symptomatic patients evaluated by clinicians, not for screening of asymptomatic people, in whom a positive result carries uncertain prognostic meaning and considerable psychological weight.

6. Prevention: the most scalable intervention

If 45% of dementia is attributable to modifiable factors,[3] prevention is the only intervention that can be delivered at the scale of the problem. The US POINTER trial randomised 2,111 older adults at increased risk to

a structured or a self-guided multidomain lifestyle programme combining physical activity, Mediterranean-style diet, cognitive and social engagement and cardiovascular risk monitoring. Global cognition improved in both groups, slightly more with the structured programme.[15] The effect is small at the individual level but potentially large at the population level, and it builds on the Finnish FINGER model that has been adapted in more than 60 countries. Treating hypertension, hearing loss, vision loss and diabetes, avoiding smoking and reducing air pollution are measures that health systems in LMICs already know how to deliver, and they bring benefits well beyond the brain.

7. The view from low- and middle-income countries

Most people with dementia live in LMICs, yet most evidence, trial participants and infrastructure come from high-income countries. In many LMICs the majority of people with dementia never receive a diagnosis, specialist services are concentrated in capital cities, and antibody therapy is effectively unavailable. Even in wealthy systems, anti-amyloid treatment requires biomarker confirmation, repeated magnetic resonance imaging for ARIA surveillance, *APOE* genotyping and infusion capacity; in an LMIC context these requirements, rather than the drug price alone, are prohibitive.

We therefore suggest a pragmatic sequence for resource-constrained systems. First, invest in timely clinical diagnosis by primary care physicians and nurses using brief validated instruments, supported by referral pathways. Second, introduce validated plasma biomarkers at regional level to separate Alzheimer disease from other causes and to reduce dependence on PET.[12-14] Third, embed risk-factor reduction in existing programmes for hypertension, diabetes and healthy ageing.[3,15] Fourth, support families, who provide most dementia care,[2] through education, respite and social protection. Disease-modifying therapies should be introduced selectively, in centres able to monitor safely, and accompanied by registries that generate local data. Equally important is the participation of LMIC populations in biomarker validation and clinical trials, without which the new diagnostic thresholds may not transfer reliably.[14]

8. The Croatian experience

Croatia is classified as a high-income country, but its per-capita health expenditure is among the lower in the European Union and its dementia care shares many features with LMIC settings. Estimates suggest that between 80,000 and 100,000 people in Croatia live with dementia, most of them undiagnosed or diagnosed late. Specialist diagnosis is concentrated in university centres in Zagreb, Split, Rijeka and Osijek; amyloid PET is scarcely available; and cerebrospinal fluid biomarker analysis is offered by a small number of laboratories, including those connected to the Croatian Institute for Brain Research, whose basic and translational work on tau and Alzheimer

pathology has been internationally recognised.[9] Places in nursing homes and specialised dementia units are insufficient, and the burden of care falls overwhelmingly on families.

There have nevertheless been important civil-society and professional initiatives. The national Alzheimer association, the Referral Centre of the Ministry of Health for Alzheimer's Disease and Old Age Psychiatry, and local communities have developed dementia-friendly initiatives, memory cafés and caregiver education.[16] In 2020 the Croatian Parliament unanimously adopted conclusions calling for a national dementia strategy, and in 2023 the Ministry of Health convened a working group to prepare a national action plan. Turning these commitments into a funded, operational plan with measurable targets for diagnosis rates, caregiver support and prevention remains the central task.

With the European authorisation of lecanemab and donanemab, Croatian neurologists now face the same questions as their colleagues across Central and Eastern Europe: which patients qualify, who will pay, and whether MRI and infusion capacity can be found without displacing other services. In our view, the most rational first step is to make blood-based biomarkers and standardised clinical pathways available nationally, so that eligible patients can be identified quickly and the far larger number of patients who are not eligible still receive an accurate diagnosis, symptomatic treatment and planned care. Symptomatic drugs remain part of that care: cholinesterase inhibitors such as donepezil are indicated from the mild stage onwards, and memantine, an NMDA receptor antagonist, in moderate to severe disease, alone or in combination.

9. Conclusions and priorities

The tools of 2026 are better than anything available a decade ago: a biological definition of Alzheimer disease, accurate blood tests, the first therapies that modify the disease course, and evidence that lifestyle and vascular risk reduction protect cognition. None of these resolves the fundamental question of why neurons in specific networks begin to fail, and the modest effect of amyloid removal suggests that the decisive events lie deeper, in intracellular transport, clearance and the regulated death of disconnected neurons. For LMICs and resource-constrained systems such as Croatia's, the priorities are clear: diagnose earlier and more accurately with affordable tools, prevent what can be prevented, support caregivers, generate local data and introduce costly therapies only where they can be delivered safely. Dementia is not only a scientific challenge but also a test of whether health systems can distribute progress fairly.

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