2024 YEAR END COMPILATION • VOLUME 1

insights & Implications

Understanding Breakthroughs in Brain Health

A compilation of the insights and implications of key scientific articles from 2024 with important impact on primary care for brain health.

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Understanding Breakthroughs in Brain Health

Introduction

Welcome to the inaugural issue of *Insights & Implications: Understanding Breakthroughs in Brain Health*! This series is designed to provide the most recent scientific brain health research that can be implemented in primary care practice. *The GSA KAER Toolkit for Brain Health* provides additional resources supporting primary care teams with early detection of cognitive impairment and accurate diagnosis of dementia and is available at geron.org/brainhealth and KAERbrain.org.

The emergence of new approaches to detect and treat dementia, combined with an aging population, has placed renewed emphasis on brain health in primary care practice. With new tools becoming available that can facilitate early diagnosis and interventions for dementia, primary care providers have opportunities to improve care trajectories for their patients. However, remaining abreast of new literature remains an ongoing challenge for busy clinicians.

The new *Insights & Implications: Understanding Breakthroughs in Brain Health* series provides a compilation of the insights and implications of key scientific articles from 2024 with important impact on primary care for brain health. Articles address topics ranging from emerging biomarkers to strategies to support caregivers. The first five articles in this inaugural issue address detecting and diagnosing Alzheimer's disease; the second group of five articles focuses on treatment and care. The article selection process aimed to identify literature that presents findings that are actionable by primary care providers and was guided by an expert advisory board. Stay tuned for future issues. Feedback may be provided to KAER@geron.org.

This publication is available on geron.org/brainhealth

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contents

Detecting Impaired Cognition and Diagnosing Alzheimer's Disease

Revised Criteria for Diagnosis and Staging of Alzheimer's Disease: Alzheimer's Association Workgroup

insights

This article presents an updated framework for diagnosing and staging Alzheimer's disease (AD) that uses objective criteria and a biological definition of the disease. This biological definition is integrated with a clinical staging framework to address relationships between clinical and biological AD stages. The update builds on the 2018 National Institute on Aging and Alzheimer's Association's (NIA-AA's) research framework and reflects advances in biomarker testing.

The revised definition is based on AD neuropathologic change (ADNPC)—biological processes that begin while people are asymptomatic. The definition includes two groups of biologic changes. Early-changing biomarkers (amyloid positron emission tomography [PET], cerebrospinal fluid biomarkers, and blood-based biomarkers [phosphorylated tau 217]) are grouped into Core 1. Later-changing biomarkers that can be used for disease staging and prognosis are grouped into Core 2.

According to the framework, a diagnosis of AD can be made using abnormal Core 1 biomarkers alone, with sufficient diagnostic accuracy to inform clinical decision-making. Biological staging can be used to distinguish the severity of AD pathology independent of clinical symptoms.

implications

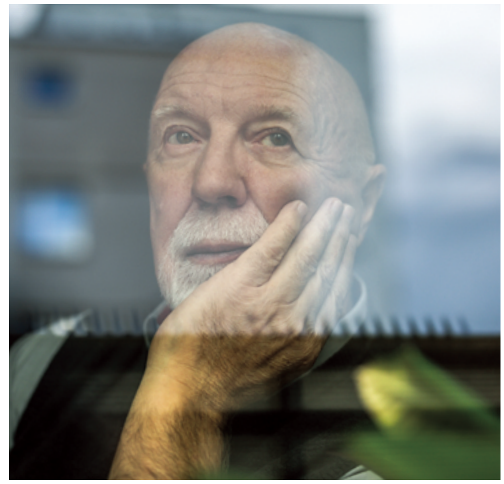
With the approval of new therapies that target AD pathology early in the course of the disease, there is a need to identify patients who could best benefit from these therapies. Blood-based biomarker detection for AD has increased the accessibility of biological diagnosis of AD. This revised framework aims to integrate this objective biological information into routine AD diagnosis and staging to support early and accurate identification of AD and inform therapy decisions. In addition to helping to determine therapy eligibility, biologic information can help assess disease progression risk and individualize symptomatic therapies.

These diagnostic criteria are not intended as practice guidelines; rather, they should be used as general principles to inform decision-making. Considerations for applying these diagnostic criteria include limits in sensitivity, uncertainty about establishing cut-points, and possible confounding factors, such as comorbidities. Clinical judgment should always be employed when applying diagnostic frameworks based on biomarker tests.

Blood-based biomarker detection for AD has increased the accessibility of biological diagnosis of AD.

Jack CR Jr, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement*. 2024;20(8):5143-5169. doi:10.1002/alz.13859

Detection and Diagnosis of Early Symptomatic Alzheimer's Disease in Primary Care



Underdiagnosis of early AD is common, especially in underserved populations, and many people are unaware they have cognitive impairment. Further misdiagnosis is common; more than half of individuals with AD also have another form of dementia (mixed dementia). Limited appointment time, stigma, symptom denial, and insufficient biomarker access contribute to underdiagnosis. Underdiagnosis results in delayed treatment and negative impacts on patients, caregivers, and health care systems.

insights

Early and accurate diagnosis of Alzheimer's disease (AD) can enable timely diagnosis, care planning, and potential treatment interventions. It can significantly reduce long-term care costs and improve patient outcomes. Primary care providers (PCPs) are often the first to observe early cognitive changes during routine visits and play a crucial role in identifying and diagnosing early AD, including mild cognitive impairment.

Careful evaluation is needed to distinguish normal aging from pathological decline. The diagnostic approach should consider both clinical signs and biomarker evidence (e.g., from amyloid positron emission tomography [PET], cerebrospinal fluid, or blood tests). Common tools in primary care include the Montreal Cognitive Assessment (MoCA), Mini-Mental State Examination (MMSE), and Mini-Cog.

implications

PCPs can improve early detection and diagnosis. A comprehensive, patient-centered approach—including clinical assessments, biomarkers, and interdisciplinary care—can lead to earlier intervention and better outcomes for patients and caregivers alike.

Strategies that can enhance early AD detection include routine cognitive screenings, which can be incorporated during Medicare annual wellness visits. Improved access to biomarker testing and expanded training for its use are recommended. PCPs can also form and enhance collaborations with specialists to confirm and manage diagnoses.

Cabral D, Obisesan TO. Detection and diagnosis of early symptomatic Alzheimer's disease in primary care. *Fed Pract.* 2024;41(Suppl 6):S7-S12. doi:10.12788/fp.0530

Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary Care

insights

This study investigated the use of a blood test to detect Alzheimer's disease (AD). The test was based on the ratio of plasma phosphorylated tau 217 (p-tau217) relative to non–p-tau217 (expressed as a percentage of p-tau217) combined with the amyloid-β42 and amyloid-β40 plasma ratio (the amyloid probability score 2 [APS2]). To assess the ability of the test to detect AD in clinical practice, the use of this blood-based biomarker test was assessed in 1,213 patients with cognitive symptoms in primary and secondary care settings.

The test was found to have high diagnostic accuracy (88%–92%) in detecting AD and outperformed standard clinical evaluations by primary care physicians (61% accuracy vs. 91%) and dementia specialists (73% accuracy vs. 91%). The test performed consistently in both primary and secondary care settings, with similar positive predictive value and negative predictive value.

implications

Anti-amyloid immunotherapy has been approved by the US Food and Drug Administration as a therapy for patients with early symptomatic AD. Because this approach should only be initiated in patients with confirmed amyloid pathology, testing is needed to identify appropriate candidates for these novel medications. Currently available testing methods include assessments of biomarkers in cerebrospinal fluid (CSF) and/or the use of positron emission tomography (PET) scans. Access to both modalities is limited in primary care settings, which is a barrier to the initiation and effective use of anti-amyloid immunotherapies.

The use of a blood test for early AD detection, rather than the use of CSF testing or PET scans, could improve timely access to accurate diagnosis and facilitate the identification of patients for whom new anti-amyloid therapies are appropriate. The diagnostic accuracy of the test in this study indicates that it has potential as a suitable biomarker test for this purpose in primary and secondary care. In the future, primary care providers may be able to use a blood test, such as this one, to evaluate patients to determine whether they are appropriate candidates for anti-amyloid immunotherapy.

Caution is always important when interpreting the results of biomarker tests for AD. Results should be interpreted within the clinical context because in some patients with early AD pathology, cognitive symptoms could be caused by other conditions.

Palmqvist S, Tideman P, Mattsson-Carlgren N, et al. Blood Biomarkers to Detect Alzheimer Disease in Primary Care and Secondary Care. *JAMA*. 2024;332:1245-1257. doi:10.1001/jama.2024.13855

Considerations for Widespread Implementation of Blood-Based Biomarkers of Alzheimer's Disease

insights

This article discusses key considerations and consensus recommendations from The Global CEO Initiative on Alzheimer's Disease BBM Workgroup for integrating blood-based biomarkers (BBMs) into clinical practice for Alzheimer's disease (AD) diagnosis and management.

BBMs offer a less invasive, more accessible, and cost-effective alternative to traditional diagnostic methods such as cerebrospinal fluid analysis and positron emission tomography (PET) imaging. They have the potential to facilitate earlier detection of AD pathology, enabling timely intervention and better patient outcomes. The authors identified several challenges to clinical implication, including:

- **Lack of Standardized Guidelines.**
  There is an absence of consistent protocols for cognitive assessment and interpretation of BBM test results.
- **Limited Understanding of Test Characteristics.**
  Further research is needed to fully comprehend the sensitivity, specificity, and predictive value of BBMs across diverse populations. There is a need for more research on real-world use of BBMs to ensure that findings can be generalized to all populations.
- **Ethical Considerations.**
  Managing the implications of BBM test results, especially in asymptomatic individuals, raises ethical questions regarding disclosure and psychological impact.

implications

To support effective integration into clinical practice, the authors call for the development of evidence-based guidelines, with standardized procedures for the use of BBM testing in practice. Health care providers will require comprehensive training programs regarding recommended strategies for implementing BBM testing, as well as interpreting and applying test results. There is also a need for educational programs that are designed for the patient and the general population. There is a need for multi-stakeholder collaborations with patients, caregivers, health care providers, and policymakers to address current challenges and facilitate adoption in a manner that improves patient care. In the meantime, primary care providers can seek emerging information and continuing education programs as they work to remain abreast of this evolving field.

Mielke MM, Anderson M, Ashford JW, et al. Considerations for widespread implementation of blood-based biomarkers of Alzheimer's disease. *Alzheimers Dement.* 2024;20:8209-8215. doi:10.1002/alz.14150

Non-Literacy Biased, Culturally Fair Cognitive Detection Tool in Primary Care Patients with Cognitive Concerns: A Randomized Controlled Trial

insights

This article introduces the 5-Cog, a brief, culturally sensitive and easy-to-use cognitive assessment tool. This tool is paired with clinical decision support embedded within the electronic medical record. The goal of the 5-Cog paradigm (i.e., the assessment tool and clinical decision support) is to improve dementia diagnosis in primary care settings, particularly among racially diverse and socioeconomically disadvantaged populations.

In the current study, the 5-Cog paradigm was evaluated in a sample of 1,201 older adults with cognitive concerns who lived in socioeconomically disadvantaged neighborhoods; 94% of participants were Black or Hispanic, 72% were women. The study evaluated whether the use of the 5-Cog paradigm could enhance dementia-related care actions, such as new diagnoses of mild cognitive impairment (MCI) or dementia, initiation of relevant investigations, prescriptions, or specialist referrals.

Compared with a control group, patients who were evaluated with the 5-Cog paradigm experienced a significant increase in dementia care actions (e.g., identification of MCI, specialist referral, and additional clinical evaluation). The 5-Cog paradigm was received positively by patients and staff and there were no noted adverse events. The authors concluded that the 5-Cog paradigm significantly improved the diagnosis and management of patients with cognitive concerns in primary care settings.

implications

Dementia can be challenging to diagnose in some primary care environments, especially among specific patient populations, which may be due in part to the characteristics of existing assessment tools. Limitations associated with existing cognitive assessment tools include length and the need for specialized skills to administer them. Furthermore, many commonly used cognitive tests were developed in white populations and do not adequately account for cultural differences or health inequities. The 5-Cog is a brief assessment tool that may help triage patients with cognitive concerns and improve care for dementia in populations experiencing health disparities through increased symptom detection. The test can be administered by nonphysician personnel with minimal training in less than five minutes.

The goal of the 5-Cog paradigm is to improve dementia diagnosis in primary care settings, particularly among racially diverse and socioeconomically disadvantaged populations.

Verghese J, Chalmer R, Stimmel M, et al. Non-literacy biased, culturally fair cognitive detection tool in primary care patients with cognitive concerns: a randomized controlled trial. *Nat Med.* 2024;30):2356-2361. doi:10.1038/s41591-024-03012-8

Dementia Risk Reduction, Treatment, and Care

Dementia Prevention and Treatment: A Narrative Review

insights

This article provides a comprehensive overview of current evidence regarding modifiable risk factors for dementia and the percentage of dementia cases that are attributable to each factor:

- Less education (7.1%)
- Hearing loss (8.2%)
- Traumatic brain injury (3.4%)
- Hypertension (1.9%)
- Alcoholism (0.8%)
- Obesity (0.7%)
- Smoking (5.2%)
- Depression (3.9%)
- Social isolation (3.5%)
- Physical inactivity (1.6%)
- Diabetes (1.1%)
- Air pollution (2.3%)

Together, these risk factors account for 39.7% of all dementia cases. The article notes that, while no randomized clinical trials have proven conclusively that interventions targeting these modifiable risk factors can prevent or delay dementia, addressing them may offer additional health benefits.

In addition, the article reviews nonpharmacologic and pharmacologic interventions for individuals with dementia. Behavioral and psychological symptoms are best addressed through individualized, nonpharmacologic strategies. Psychotropic medications for treating these symptoms have limited efficacy and are associated with increased risks, including mortality and cognitive decline.

Other medications may have a role in treating dementia. Cholinesterase inhibitors (e.g., donepezil, rivastigmine, and galantamine) or an *N-methyl-D-aspartate* receptor antagonist (memantine) are approved as therapies for Alzheimer's disease (AD) and may be used off-label for other types of dementias. Additionally, anti-amyloid immunomodulators have shown modest effects in slowing cognitive and functional decline in mild cognitive impairment or mild dementia due to AD.

The article also notes that it is important for primary care providers to address the needs and well-being of caregivers, whose roles are crucial in providing comprehensive dementia care.

implications

There are several modifiable risk factors that account for a substantial proportion of dementia cases and primary care providers have opportunities to work with individuals with and without dementia to address these risk factors. Several potentially valuable interventions can be initiated in midlife or later that may have beneficial effects for reducing risk or slowing the onset of dementia. Appropriate use of pharmacotherapy, particularly anti-amyloid immunomodulators, may slow or delay cognitive or functional decline in individuals with mild cognitive impairment or mild AD. The needs of caregivers must also be considered when addressing care plans for people with dementia.

Reuben DB, Kremen S, Maust DT. Dementia prevention and treatment: a narrative review. *JAMA Intern Med*. 2024;184:563-572. doi:10.1001/jamainternmed.2023.8522

Dementia Prevention, Intervention, and Care: 2024 Report of the *Lancet* Standing Commission

insights

The *Lancet* Commission on Dementia Prevention, Intervention, and Care's update to its 2020 report suggests that nearly half of dementia cases could be prevented by addressing modifiable risk factors with 14 specific actions. These actions are based on available evidence concerning 14 modifiable risk factors for dementia (less education, head injury, physical inactivity, smoking, excessive alcohol consumption, hypertension, obesity, diabetes, hearing loss, depression, infrequent social contact, vision loss, high cholesterol, and air pollution). The 14 specific actions are to:

- Encourage educational and cognitively stimulating opportunities.
- Detect and treat hearing loss.
- Treat depression.
- Encourage the use of helmets and head protection.
- Promote exercise and active lifestyles.
- Stop smoking.
- Identify hypertension and maintain systolic blood pressure of 130 mm Hg or less.
- Detect and treat high LDL cholesterol from midlife.
- Maintain a healthy weight and treat obesity.
- Reduce alcohol consumption.
- Prioritize age-friendly and supportive community environments and housing.
- Reduce social isolation by participating in activities and living with others.
- Screen for and treat vision loss.
- Minimize exposure to air pollution.

The article stresses that prevention efforts, especially efforts to address lifestyle factors, should begin early in life and continue throughout the lifespan to maximize cognitive and physical health. It also notes that anti-amyloid drugs offer some hope for slowing cognitive decline in AD, but their long-term effects and accessibility remain uncertain. Finally, for people who are diagnosed with dementia, postdiagnosis interventions, including caregiver support, neuropsychiatric symptom management, and physical health maintenance, can improve quality of life.

implications

This report provides new and compelling evidence that untreated vision loss and high LDL cholesterol are additional risk factors for dementia. It indicates that dementia risk can be reduced through interventions that address risk factors, many of which can be addressed in primary care settings (although some recommendations require policy-level actions). Interventions that primary care providers can implement include those that address cardiovascular health, sensory impairments, and lifestyle changes.

Livingston G, Huntley J, Liu KY, et al. Dementia prevention, intervention, and care: 2024 report of the Lancet standing Commission. *Lancet*. 2024;404(10452):572-628. doi:10.1016/S0140-6736(24)01296-0

Dementia Ideal Care: Ecosystem Map of Best Practices and Care Pathways Enhanced by Technology and Community

insights

To help address barriers and gaps in dementia care the Dementia Ideal Care Map presents a unified and comprehensive framework aimed at improving care for people with dementia. It summarizes more than 200 best practices, almost 100 technology tools, other infrastructure, and enhanced care pathways in a single comprehensive diagram. Topics in the ecosystem map include psychosocial interventions, care partner support, awareness of community-based organizations, risk reduction, initial detection, diagnosis, ongoing medical care, governmental activities, payers, health systems, businesses, data, research, and training.

To help address barriers and gaps in dementia care the Dementia Ideal Care Map presents a unified and comprehensive framework aimed at improving care for people with dementia.

Key features of the Dementia Ideal Care Map include:

- Comprehensive care pathways that outline a holistic approach to dementia care, encompassing all stages of the disease and addressing the needs of both people with dementia and their caregivers.
- Use of digital health solutions to enhance care delivery, communication, and support for people with dementia.
- Roles of community resources and social support systems in providing comprehensive care.

implications

Recognizing that existing best practices are often fragmented and focus on specific stages or groups within the patient journey, the authors sought to create an integrated, actionable tool for risk reduction, detection, care, and promoting quality of life. The map is applicable to a wide range of stakeholders—in addition to medical interventions, the ecosystem map includes a broader set of interventions, including nonpharmacologic and psychosocial approaches, the role of family and friend care partners, and the role of community, employers, and governments.

Primary care providers can use this map as a component of their self-assessments and continuous quality improvement efforts. Furthermore, they can share it with people with dementia and other stakeholders to support comprehensive interventions and address barriers and gaps in care.

Dombrowski W, Mims A, Kremer I, et al. Dementia ideal care: ecosystem map of best practices and care pathways enhanced by technology and community. *J Alzheimers Dis.* 2024;100:87-117. doi:10.3233/JAD-231491

Mapping a Better Future for Dementia Care Navigation

insights

This report from the Alzheimer's Association examines how people with dementia and their caregivers navigate the health care system and introduces care navigation as an approach to improve outcomes and reduce caregiver burden.

People with dementia and their caregivers often face stress, confusion, and inadequate support while trying to coordinate care across primary care providers, specialists, social services, and community resources. They report difficulty navigating care systems, securing appointments, coordinating between doctors, and accessing respite services.

Dementia care navigation is an emerging approach that provides "strengths-based support across the illness continuum and settings to mitigate the impact of dementia through collaborative problem solving and coaching." It includes both medical (e.g., medication management, provider coordination) and nonmedical (e.g., behavioral support, community resource connection) services. Principles emphasize evidence-based person- and family-centered, culturally responsive care, with well-defined roles for all team members to help address barriers for persons living with dementia.

The Centers for Medicare & Medicaid's (CMS's) GUIDE model, which launched in July 2024, aims to provide comprehensive dementia care management aligned with the dementia care navigation process. It offers person-centered assessments, 24/7 support, and care navigators to assist patients and caregivers. Importantly, it also introduces an alternative payment model to promote financial sustainability.

implications

Dementia care navigation offers a person-centered, scalable model to improve dementia care. Programs such as GUIDE represent important steps but broader health system changes are needed to ensure widespread access, consistent training, and long-term sustainability.

Primary care providers can help to advance dementia care navigation by supporting initiatives that aim to:

- Formalize navigator roles within health systems.
- Improve training for navigators, especially around dementia.
- Expand access through programs like GUIDE and beyond.
- Enhance visibility and caregiver awareness of navigation support.
- Leverage technology (e.g., 24/7 helplines, apps) to create direct connections to navigators.

Alzheimer's Association. Special report: Mapping a better future for dementia care navigation. *Alzheimers Dement.* 2024;20(5):3772-3821. doi:10.1002/alz.14425

Defining Benefit: Clinically and Biologically Meaningful Outcomes in the Next-Generation Alzheimer's Disease Clinical Care Pathway

insights

This article presents a framework for redefining meaningful benefit in the management of Alzheimer's disease (AD). The authors explain that observable and meaningful outcomes of therapies can be both clinical and biological. Importantly, biological changes (detected through biomarkers) have potential value in assessing the impact of interventions because they are associated with the evolving pathophysiology of AD before clinical symptoms emerge. Thus, they have a role for early detection and evaluation of responses to therapy. However, because many cognitive and functional assessments in current use are not sensitive enough to detect biological changes in early disease stages, they do not capture these benefits.

To address these gaps, the authors propose the concept of a Minimum Biologically and Clinically Important Difference (MBCID) measure to evaluate a wider range of impacts. The proposed MBCID framework would capture outcomes that are most important to patients and caregivers, which include preserved memory, daily function, quality of life, and delayed loss of independence. (Outcome expectations would vary depending on the stage of AD development and progression.) In addition, the MBCID would account for changes in biomarkers (e.g., amyloid-beta, phosphorylated tau, neurofilament light), which are predictive of disease progression and can reflect therapeutic effects at earlier stages of AD.

implications

This review advocates for a paradigm shift in how the benefits of therapies for AD are evaluated. It emphasizes the need to integrate clinical symptoms, patient experiences, and biological data into outcome assessments to support precision medicine in AD care. Regarding current clinical care, the authors emphasize the importance of shared decision-making and incorporating patient values into developing care plans for people with AD.

Elhage A, Cohen S, Cummings J, et al. Defining benefit: clinically and biologically meaningful outcomes in the next-generation Alzheimer's disease clinical care pathway. *Alzheimers Dement.* 2025;21:e14425. doi:10.1002/alz.14425

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