Bridging the Gap Across Biomarker and AI/M Innovations to Clinical Implications: A White Paper on Challenges and Collaborative Solutions for Chronic Brain Disorders

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Abstract

The emergence of artificial intelligence and machine learning (AI/ML), along with novel biomarker platforms for diagnosis, staging and prognosis advances significantly the medical field. On the other hand, it poses considerable challenges regarding their integration into clinical practice and accessibility to patients. Thus, adaptation of the new medical products and advanced technologies into clinical care remains the current hurdle. This editorial discusses the critical barriers hindering the implementation of effective and efficient care opportunities for patients with chronic brain disorders with a specific emphasis on Alzheimer's disease and related dementias (AD/ADRD). Topics examined include the challenges affecting patients, providers, and other stakeholders, including issues related to data standardization, regulatory constraints, and economic obstacles. This paper seeks to foster innovation and collaboration among policymakers, the insurance and pharmaceutical industries, healthcare providers, and innovations developers to bridge the gap between biomarker discoveries and machine learning approaches and their real-world applications.

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Introduction

Background and Importance

Chronic brain disorders such as Alzheimer's and other dementias (AD/ADRD) represent a significant burden to healthcare systems worldwide. With the aging population, the prevalence of these disorders is escalating at the same pace, necessitating advanced diagnostic tools and treatment options. Biomarkers and AI/ML are poised to deliver early detection, disease stage, and more accurate prognosis to facilitate personalized treatment, yet multiple challenges impede their adoption into mainstream clinical practice (1).

Scope of the Issue

To bridge this gap, we must address the developmental, logistical, ethical, and financial challenges impacting the implementation of biomarker and AI/ML applications in diagnostics and treatment, especially in complex healthcare systems and amidst the social and political climate of the country and worldwide.

Current Barriers to Effective Care

Data Collection and Standardization

Incorporating biomarkers into healthcare requires standardized data collection, semantic consistency, harmonization of datasets across multiple projects, and integration across various healthcare systems (2, 3). Current issues in data collection, including data disparity, challenged interoperability, inconsistent methodologies, and data harmonization of various datasets, limit the efficacy of biomarkers, thwart the potential of advanced analytics, and make replicability challenging. Moreover, human diversity presents another level of challenge as, populations at the point of care may differ socio-demographically from those studied in prospective clinical trials. Effective biomarkers should reflect disease progression accurately within a well-defined clinical and demographic group of patients. In addition, these biomarkers often lack standardization, making them challenging to implement consistently across national clinics and more so globally (1).

Regulatory and Ethical Challenges

Regulation and ethical considerations present additional challenges to developing and implementing novel technologies primed to impact outcomes (4). Lack of regulatory

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harmonization, particularly for AI/ML tools, complicates their validation and adoption (5). Different agencies may have different requirements, complicating the development and acceptance of new approaches to development (6). The plethora of possible biomarkers and ML technologies may need to be clarified. Additionally, ethical concerns such as privacy risks, potential algorithmic bias, and data ownership issues require ongoing consideration and refinement to safeguard patients and providers alike (7).

Economic Barriers and Reimbursement

Limited economic incentives and reimbursement models hinder the adoption of innovative biomarkers platforms and advanced AI/ML pipelines in clinical settings; moreover, financial resources are lacking in clinical settings, challenging adoption by providers, especially those in smaller practice settings. Payers, including public and private insurance entities, are slow to adapt and implement the new medical products including, assay platforms and computational technologies, without established economic evidence of long-term savings and improved outcomes. Additionally, developing new diagnostic tools, and their International Classification of Diseases codes and corresponding payment codes (Current Procedural Terminology) is critical to aligning clinical innovations with reimbursement frameworks (8, 9). Addressing these financial and structural barriers is essential to foster widespread adoption (10).

Impact of These Barriers on Stakeholders

Patients and Families

For patients with brain disorders, delayed diagnosis, misdiagnosis, and limited treatment options hasten disease progression, worsen prognosis and impact their quality of life. A lack of reliable, widely available, and accessible biomarkers can prolong diagnostic journeys, delaying crucial interventions. For families, this translates to increased caregiving and economic burdens, greater emotional strain, and lower quality of life (11, 12).

Healthcare Providers

Providers face challenges in training and retraining on new biomarker and AI/ML tools, often without adequate support. Medical education curricula often don't include the level of training requisite to allow providers to be receptive to these new tools. The overload of emerging data and the lack of clear clinical guidelines lead to uncertainty in decision-making, creating a gap between biomedical research advancements and real-world clinical practice (12-15).

Systemic and Economic Consequences

Healthcare systems bear increased costs as delayed diagnosis leads to advanced disease stages requiring more intensive treatment, often with more marginal impact. The lack of early interventions driven by biomarkers and AI/ML exacerbates healthcare expenses, impacting providers and payers who struggle with budget constraints and resource allocation (16-18). Failure to implement timely, well-documented and evidence-based research advances may prolong the unnecessary disease burden and reduce the productivity of members of the greater community (patients and caregivers).

Engaging Key Stakeholders to Address Barriers

Government and Regulatory Bodies

Policymakers can foster innovation by streamlining regulatory pathways for biomarker and AI/ML tools. Cross-agency collaboration and the creation of harmonized data standards would expedite approval processes and encourage adoption. Supporting translational research initiatives will also close the gap between innovation and clinical adoption (4, 12, 19, 20).

Insurance and Payers

Insurance companies can transform healthcare by updating reimbursement policies to support innovative diagnostic and treatment approaches. Moreover, more agile processes incorporating leeway for novel, impactful advanced medical products should be adopted. Payers can create incentives for preventive and precision medicine, including cost-effective biomarker testing and aligning economic goals with improved patient outcomes.

Pharmaceutical Biotech and Academia Partnerships

Pharmaceutical companies can collaborate with translational neuroscientists and technology developers and healthcare institutions to co-develop biomarker tools, making AI/ML applications more robust and clinically useful. Data-sharing partnerships between academia, pharma and biotech industries can accelerate biomarker discovery and validation, benefiting early detection efforts (4).

Healthcare and Technology Developers

Healthcare providers and technology developers need to work in tandem to ensure that AI/ML models are accessible, reliable, and integrated into existing clinical workflows (5). Technology companies should seek to hire clinical leadership able to be involved in use case selection, deployment strategy, change management, clinical validation and outcome testing (21). Developing intuitive and adaptable platforms for biomarkers that can handle real-time data will be essential for practical, widespread usage (22).

Case Studies or Hypothetical Scenarios

In this section we highlight successful examples of biomarker integration in clinical settings. Most prominent are AI-driven imaging biomarkers have We will give examples from imaging-, blood- and AI- based biomarkers that shown promise in identifying Alzheimer's disease pathology years before clinical symptoms appear, which could allow for early interventions and tailored treatment plans. Amongst, most prominent are AI-driven imaging biomarkers outlined below.

AI-Driven Imaging Biomarkers

Amyloid PET Imaging

AI-enhanced amyloid PET imaging has shown remarkable accuracy in detecting AD pathology years before symptom onset. For example, researchers at West Virginia University have developed AI tools that can detect AD in its early stages using metabolic biomarkers (23). These tools achieved over 90% accuracy in detecting AD from brain scans, significantly improving upon traditional methods (24).

Retinal Imaging

A novel deep learning framework called Eye-AD has been developed to detect Early-onset Alzheimer's Disease (EOAD) and Mild Cognitive Impairment (MCI) using optical coherence tomography angiography (OCTA) images of retinal microvasculature. This non-invasive method demonstrated superior performance:

- EOAD detection: AUC = 0.9355 (internal data), AUC = 0.9007 (external data)
- MCI detection: AUC = 0.8630 (internal data), AUC = 0.8037 (external data)

MRI-Based Biomarkers

GE HealthCare is leading the PREDICTOM project, which aims to develop a digital platform that aggregates biomarker data and uses AI algorithms to generate risk assessments and early diagnoses of AD [17]. This project focuses on identifying scalable and cost-effective early biomarkers, including imaging biomarkers from MRI.

Blood-Based Biomarkers

Plasma Biomarkers

Recent advancements have led to the development of blood-based biomarkers for AD diagnosis (25-27). The most promising measures include:

- Aβ42/Aβ40 ratio
- Phosphorylated tau (p-tau) at different sites, including p-tau181 and p-tau217

These plasma biomarkers have shown acceptable performance in detecting amyloid pathology, potentially allowing for more accessible and less invasive early diagnosis.

Recently, the FDA approved an AD diagnostic blood test, based on pTau217/ß-Amyloid 1-42 Plasma Ratio measures that can predict the presence of amyloid plaques. This test increases diagnostic accessibility as it is less expensive and considerably not invasive in comparison to imaging- and CSF- based biomarkers. However, like the other biomarker tests, it relies mainly on Aβ and p-tau fragments pathologies as core markers; thus, its performance is limited particularly prior to the beginning of neurodegeneration and atrophy, and the main associated risks are false positive and false negative test results. Furthermore, this blood test is intended only for patients who are cognitively impaired.

AI-Enhanced Clinical Tools

icobrain aria

The U.S. Food and Drug Administration (FDA) recently granted clearance to icometrix for icobrain aria, the first AI software approved for detecting, measuring, and grading amyloid-related imaging abnormalities (ARIA) (28).

This tool significantly improves the accuracy of radiologists' ARIA assessments, enhancing the safety of amyloid-targeting therapies for AD patients.

ADappt

The Alzheimer Biomarkers in Daily Practice project developed a web-based tool called ADappt. This tool calculates personalized risk estimates of progression from mild cognitive impairment to dementia, helping clinicians interpret biomarker results and engage patients in shared decision-making regarding diagnostic testing (29).

These examples demonstrate the significant progress made in integrating AI-driven biomarkers into clinical settings for early AD detection and personalized treatment planning. As these platforms and technologies continue to evolve, they promise to revolutionize AD diagnosis and management, potentially leading to earlier interventions improved disease prognosis and patient outcomes and ultimately opportunities for delay onset and preventative medicine.

Future Scenarios

Imagine a healthcare setting where diagnostic and prognostic biomarkers integrated with AI/ML allow providers to diagnose, monitor and treat brain disorders preemptively, thus significantly reducing cognitive decline. Such a system could prioritize preventive care, improving millions' long-term outcomes.

Recommendations for Action

To further address these challenges and foster collaborative solutions, we recommend meeting with key stakeholders, including policymakers, healthcare providers, insurance payers, pharmaceutical, biotech and academic leaders, and technology developers of biological assays and AI/ML analytical pipelines. This meeting would provide a platform to:

1. **Discuss Challenges and Outlooks into Resolutions**: Share insights on current barriers and identify areas where collaboration can drive impactful change.
2. **Establish Workgroups:** Form dedicated workgroups that address specific challenges, such as data standardization, regulatory harmonization, and economic incentives for AI/ML and biomarker adoption.
3. **Create Action Plans:** Develop actionable roadmaps for pilot programs, funding mechanisms, and multi-sector initiatives that bridge the gap between innovation and clinical practice.

Policy Recommendations

Governments, health care and drug discovery regulators should prioritize data standardization, transparency in AI models, and multi-sector partnerships. Recommendations include developing certifications for validated biomarker tools and implementing cross-border data-sharing frameworks to harmonize clinical applications across regions.

Implementation Framework

Pilot programs for testing biomarker assays and AI applications in various clinical settings within diverse population should be created and deployed nationally and internationally. These pilot studies should include feedback loops to refine technologies based on real-world data, ensuring continuous improvements in biomarker efficacy.

Long-term Goals

Ongoing collaboration between sectors, sustained funding, and incentives for innovation will be essential to create a sustainable framework for biomarker and AI/ML integration. This collaborative approach would support the development of advanced diagnostic tools, making precision medicine more accessible and feasible for chronic brain disorder patients.

Conclusion and Call to Action

Summary of Benefits

Addressing these barriers will improve diagnostic accuracy, treatment personalization, and patient outcomes, while also reducing costs for healthcare systems and the burden on caregivers. The unified adoption of biomarker tests and AI/ML has the potential to transform the field of AD/ADRD and more broadly the spectrum of neurodegenerative diseases, allowing for earlier and more effective interventions (refs).

Envisioning the Impactful Next Steps for Stakeholders

We call on stakeholders to contribute to a unified action plan, prioritizing policies that support biomarker and AI/ML integration, encourage financial investments in translational research, and develop public awareness campaigns. By working together, we can close the gap between scientific innovation and clinical impact for chronic brain disorders.

Appendices

Additional Resources

Include references to recent studies, policy frameworks, and case studies discussed in this paper.

Glossary of Terms

Definitions of biomarkers, AI/ML, neurodegenerative diseases, and other key terms for accessibility.

Conflict of interest

Drs. Khachaturian, Pinho, and Alphs have nothing to disclose

Ethical standards

Ethical standards guiding the development of this editorial perspective include transparency in discussing methodologies and interpretations, a commitment to objectivity in presenting arguments and full disclosure of any potential conflict of interest. The authors aim to uphold honesty, provide reliable analysis and commentary respect intellectual property, and present a balanced reflection of the field, shaped by the collective insights and professional judgment of all contributors.

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