J Prev Alz Dis 2024;5(11):1180-1182
Published online September 26, 2024, http://dx.doi.org/10.14283/jpad.2024.167

Editorial

# Amplifying Efficiency and Accuracy in Dementia Drug Development

*O. Lerch[1,2], S.Z. Levine[1,3], S. Sivakumaran[1,4], M.W. Lutz[1,5], O. Chiba-Falek[1,5], N. Mazer[1,7], M. Bairu[1,8], I.R.J. Hebold Haraldsen[1,9], P.M. Rossini[1,10], P.J. Snyder[1,11], J. Bouteiller[1,12], Z.S. Khachaturian[1,13], A.S. Khachaturian[1,13,14,15,*]*

1. International Neurodegenerative Disorders Research Center, Prague, Czech Republic; 2. Second Faculty of Medicine, Charles University, Motol University Hospital, Memory Clinic, Department of Neurology, Prague, Czech Republic; 3. University of Haifa, Faculty of Social Welfare and Health Sciences, School of Public Health, Haifa, Israel; 4. Critical Path Institute, Tucson, AL, United States of America; 5. Duke University School of Medicine, Department of Neurology, Durham, NC, United States of America; 6. Duke University, Neurology, Durham, AL, United States of America; 7. NAM Consulting, Basel, Switzerland; 8. Bio Usawa Inc, Kigali, Rwanda; 9. Oslo University Hospital, Department of Neurology, Oslo, Norway; 10. IRCCS San Raffaele Roma, Department of Neuroscience and Neurorehabilitation, Rome, Italy; 11. University of Rhode Island, Rhodes Island, AL, United States of America; 12. Viterbi School of Engineering & Keck School of Medicine University of Southern California, Alfred E. Mann Department of Biomedical Engineering, Los Angeles, AL, United States of America; 13. Campaign to Prevent Alzheimer's Disease, Potomac, Maryland, United States of America; 14. Brain Watch Coalition, Rockville, MD, United States of America; 15. University of Las Vegas, Nevada, National Supercomputing Institute & Dedicated Research Network, Las Vegas, Nevada, United States of America; *On behalf of the International Neurodegenerative Disease Research Center (INDRC) Scientific Advisory Board

*Corresponding Author:* Ara Khachaturian, Campaign to Prevent Alzheimer's Disease, USA, ara@pad2020.org

Authors, reviewers, and readers of peer-reviewed journals, such as the Journal of Prevention of Alzheimer's Disease, fully understand the burden of neurodegenerative disorders. Descriptions often note global estimates of dementia incidence, high long-term care costs, challenges to detection or diagnosis outside of specialty clinic populations, an inadequate healthcare workforce, fragmented healthcare services, and the prolonged, uncompensated, and variable nature of caring for cognitive, behavioral, and functional impairments imposed on people living with dementia. Since the late 20th century, the mission of the global dementia research enterprise has been to keep everyone functionally independent and autonomous for as long as possible before requiring expensive and often long-lasting personal care. Yet despite this focus, a question remains: does the current research environment have the capacity and resources to deliver effective, timely, and accurate interventions to individuals living with the specter of dementia?.

Intensive research still seeks effective treatments to slow the progression of dementing disorders (1, 2). Over the last decade, 95 Phase II and III Alzheimer's disease (AD) clinical trials (3) have been unsuccessful. The total cost of these trials was estimated to be approximately 42.5 billion USD. The most significant costs (up to 57%) were incurred during Phase III of clinical development (4). The cost of AD drug development is comparatively higher than that in other fields (5). The average drug development cost in the dementia field is 5.6 billion USD, and the process takes approximately 13 years from preclinical studies to approval by the FDA (6). This compares unfavorably with an estimated cost of cancer treatment development of 793.6 million USD per agent (7) or 2.8 billion USD per agent among all other therapeutic areas in the pharmaceutical industry (8).

Aduhelm (aducanumab), approved by the FDA in June 2021 and not by the European Medicines Agency in December 2021, faced significant post-approval challenges. In addition to concerns stemming from its accelerated approval pathway, which raised questions about the sufficiency of the clinical evidence supporting its efficacy and safety, limited adoption in clinical care was due to high costs and risks like amyloid-related imaging abnormalities (ARIA). Medicare's restricted coverage to clinical trials further limited its use, ultimately leading to its commercial failure (9, 10). Leqembi (lecanemab) is more accepted, but its efficacy, cost, and additional monitoring costs for serious side effects have slowed initial access (11). The recently FDA-approved Kisunla (donanemab, July 2024) might offer more benefits. Still, with uncertain future coverage decisions and healthcare system preparedness, it may need to overcome similar access challenges (12) (13).

Except for these three recent approvals, there are many other reasons why many new dementia interventions fail to gain market access. Among these are the long preclinical stage and progressive nature of the disease, inadequate drug dosing or penetration through the blood-brain barrier, insufficient target engagement, inadequate patient stratification and trial enrollment, suboptimal trial design, the choice of suboptimal clinical outcome measures, long trial duration increasing the risk of losing patients, the need for extensive enrollments involving multiple sites and tightly coordinated project management, or erroneous treatment targets (14-16).

The multifactorial nature of Alzheimer's disease (AD) and Alzheimer's disease-related dementias (ADRD) presents significant challenges, particularly in capturing the complexity of heterogeneity in AD/ADRD, selective neuronal vulnerability, and specificity of affected brain regions (17-19). The use of the word—multifactorial—is often a rhetorical concept, context-specific and variably related to "complex" or "lots of things".

Neurobiologically, the multifactorial concept may describe how AD/ADRD impacts different molecular

*Received August 28, 2024*
*Accepted for publication September 11, 2024*

components, cells, and/or brain regions, with certain hierarchical levels exhibiting differential susceptibility to degeneration (20, 21). Meanwhile, the balance and timing between risk (modifiable or non-modifiable), protective or resilience factors—across the lifespan—that define the delicate boundaries between biologically defined and clinically defined disease is poorly understood (22). Clinically, the concept may translate to describe diverse symptom presentations, risk factors, and patient progression patterns (23-25). On a social and public policy level, the concept may characterize the complexity of creating effective public health strategies or equitable care practices for a disease that manifests differently across populations and environments.

Regardless of research context—basic/translational, clinical/population, or social/public policy—the multiple "factors" in AD/ADRD comprise admixtures of relevant constructs and parameters. The reader is asked to stipulate, to some degree, that these "factors" are sometimes challenging to define, replicate, or validate, and these "factors" sometimes lack a broad consensus gold standard. The inherent complexity of using these "factors" in global research collaborations contributes to systematic and random errors in brain research. Unsurprisingly, these errors influence the high variance directly impacting AD/ADRD clinical trials and observational study results.

## A Potential for Reducing Variance Using Proteomics and Transcriptomics?

The A-T-N framework, along with advances in genomics and the use of biomarkers—spanning imaging, fluid-based, and digital modalities—has significantly enhanced the ability to predict individual treatment responses in Alzheimer's Disease and Alzheimer's Disease-Related Dementias (AD/ADRD) randomized controlled trials (RCTs)(26, 27). Various strategies have been employed to address the high variance in these measures, such as increasing research volunteer sample sizes and extending follow-up periods to improve the internal and external validity of results. Additionally, study sample stratification based on genetic or phenotypic characteristics of risk and resilience factors has become a key design feature to enhance data accuracy further. Yet, integrating proteomics and transcriptomics holds the promise of refining RCT design and conduct by offering deeper insights into disease mechanisms and treatment effects at a molecular level.

Proteomics and transcriptomics are emerging as transformative tools in developing clinical interventions for AD/ADRD. These advanced methodologies allow for the comprehensive analysis of proteins and gene expression profiles, providing far more precise, cost-effective, and efficient insights than traditional approaches. Initially employed in basic research, proteomics and transcriptomics are now finding applications in clinical settings, enhancing the capacity to design personalized treatments. By examining the entire protein and RNA landscapes of patients, these techniques offer highly accurate data and predictive insights for individual patient profiles.

Adopting proteomics and transcriptomics in AD/ADRD drug development faces significant challenges, primarily from data sparsity and insufficient sample sizes. The complexity of dementing disorders requires extensive, well-characterized datasets to identify and validate potential biomarkers and therapeutic targets accurately. However, obtaining sufficiently powered genetic data is difficult, particularly when focusing on specific disease manifestations. Additionally, the lack of diversity in available datasets further complicates the development of effective treatments, as most studies have historically relied on European ancestry data. Such information is unlikely to apply globally because the forecasted most significant dementia burden is mainly in nations not of European origin. Also, there is also a critical need for standardized methods to ensure data harmonization and interoperability, which is essential for collaborative research efforts and maximizing the utility of available data. Addressing these challenges is vital for advancing precision medicine approaches in AD and improving the success rates of new drug development.

Advanced computational technologies may present transformative and unknown opportunities for advancing analytical methods in proteomics and transcriptomics in AD/ADRD drug discovery that should be explored further. High-performance computing (HPC) maximizes computational capabilities to tackle complex, large-scale problems across basic science, clinical research, and industry. Quantum computing leverages the principles of quantum mechanics that could be used to analyze and model rapidly the complex interactions of proteins and gene expressions and aid in identifying biomarkers and predicting biological pathways. Artificial intelligence and machine learning (AI/ML) driven analytics could analyze large-scale proteomics and transcriptomics datasets, identifying patterns and predicting disease-related biomarkers. Additionally, model-based approaches representing the A-T-N framework's pathophysiological mechanisms may contribute to this effort (28).

## Establishing a Pathway for Consensus

The editors of The Journal of Prevention of Alzheimer's Disease, Vitality, Medicine & Engineering, Frontiers in Molecular Medicine, and the Scientific Advisory Board of the International Neurodegenerative Disease Research Center are interested in convening a workgroup to explore these topics more thoroughly and invite readers and potential collaborators to comment on this work. This effort seeks to understand additional opportunities and challenges in using proteomic and transcriptomics for 1) the discovery, qualification, and validation of novel

technologies to diagnose, assess, monitor or treat AD/ADRD

2) the deployment, implementation, and adoption of regulatory-approved technologies to diagnose, assess, monitor or treat AD/ADRD

The work group aims to survey and review those methods and processing protocols that can ultimately identify better intervention-responder patterns, establish a network of researchers and laboratories with the required expertise, and foster non-competitive collaborations with sponsors and developers of AD/ADRD interventions and diagnostic technologies.

*Conflict of interest:* The authors are all members of the INDRC Scientific Advisory Board and have no relevant financial conflicts of interest to report.

## References


1. Khachaturian ZS, Khachaturian AS. The Paradox of Research on Dementia-Alzheimer's Disease. J Prev Alzheimers Dis. 2016;3(4):189-91.
2. Khachaturian ZS. Prospects for Effective Treatment of the Dementia-Alzheimer Syndrome: A Renewed Odyssey in Search of the Magic Elixir. J Prev Alzheimers Dis. 2017;4(4):215-7.
3. Kim CK, Lee YR, Ong L, Gold M, Kalali A, Sarkar J. Alzheimer's Disease: Key Insights from Two Decades of Clinical Trial Failures. J Alzheimers Dis. 2022;87(1):83-100.
4. Cummings JL, Goldman DP, Simmons-Stern NR, Ponton E. The costs of developing treatments for Alzheimer's disease: A retrospective exploration. Alzheimers Dement. 2022;18(3):469-77.
5. Cummings J, Reiber C, Kumar P. The price of progress: Funding and financing Alzheimer's disease drug development. Alzheimers Dement (N Y). 2018;4:330-43.
6. Scott TJ, O'Connor AC, Link AN, Beaulieu TJ. Economic analysis of opportunities to accelerate Alzheimer's disease research and development. Ann N Y Acad Sci. 2014;1313(1):17-34.
7. Prasad V, Mailankody S. Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval. JAMA Intern Med. 2017;177(11):1569-75.
8. DiMasi JA, Grabowski HG, Hansen RW. Innovation in the pharmaceutical industry: New estimates of R&D costs. J Health Econ. 2016;47:20-33.
9. Knopman DS, Jones DT, Greicius MD. Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE trials as reported by Biogen, December 2019. Alzheimers Dement. 2021;17(4):696-701.
10. Sabbagh MN, Cummings J. Open Peer Commentary to "Failure to demonstrate efficacy of aducanumab: An analysis of the EMERGE and ENGAGE Trials as reported by Biogen December 2019". Alzheimers Dement. 2021;17(4):702-3.
11. 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.
12. Jonsson L, Wimo A, Handels R, Johansson G, Boada M, Engelborghs S, et al. The affordability of lecanemab, an amyloid-targeting therapy for Alzheimer's disease: an EADC-EC viewpoint. Lancet Reg Health Eur. 2023;29:100657.
13. Lilly's Kisunla™ (donanemab-azbt) Approved by the FDA for the Treatment of Early Symptomatic Alzheimer's Disease [press release]. PR Newswire, July 2, 2024 2024.
14. Pappalettera C, Carrarini C, Miraglia F, Vecchio F, Rossini PM. Cognitive resilience/reserve: Myth or reality? A review of definitions and measurement methods. Alzheimers Dement. 2024;20(5):3567-86.
15. Mehta D, Jackson R, Paul G, Shi J, Sabbagh M. Why do trials for Alzheimer's disease drugs keep failing? A discontinued drug perspective for 2010-2015. Expert Opin Investig Drugs. 2017;26(6):735-9.
16. Yiannopoulou KG, Anastasiou AI, Zachariou V, Pelidou SH. Reasons for Failed Trials of Disease-Modifying Treatments for Alzheimer Disease and Their Contribution in Recent Research. Biomedicines. 2019;7(4).
17. Ferreira D, Verhagen C, Hernandez-Cabrera JA, Cavallin L, Guo CJ, Ekman U, et al. Distinct subtypes of Alzheimer's disease based on patterns of brain atrophy: longitudinal trajectories and clinical applications. Sci Rep. 2017;7:46263.
18. Murray ME, Graff-Radford NR, Ross OA, Petersen RC, Duara R, Dickson DW. Neuropathologically defined subtypes of Alzheimer's disease with distinct clinical characteristics: a retrospective study. Lancet Neurol. 2011;10(9):785-96.
19. Scheltens NME, Tijms BM, Koene T, Barkhof F, Teunissen CE, Wolfsgruber S, et al. Cognitive subtypes of probable Alzheimer's disease robustly identified in four cohorts. Alzheimers Dement. 2017;13(11):1226-36.
20. Bellenguez C, Kucukali F, Jansen IE, Kleineidam L, Moreno-Grau S, Amin N, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. Nat Genet. 2022;54(4):412-36.
21. Tijms BM, Vromen EM, Mjaavatten O, Holstege H, Reus LM, van der Lee S, et al. Cerebrospinal fluid proteomics in patients with Alzheimer's disease reveals five molecular subtypes with distinct genetic risk profiles. Nat Aging. 2024;4(1):33-47.
22. Pappalettera C, Carrarini C, Cappa S, Caraglia N, Cotelli M, Marra C, et al. Challenges to identifying risk versus protective factors in Alzheimer's disease. Nat Med. 2024.
23. Nations DoEaSAU. World Population Prospects 2024 2024 [Available from: https://www.un.org/development/desa/pd/sites/www.un.org.development.desa.pd/files/undesa_pd_2024_wpp_2024_advance_unedited_0.pdf.
24. Devi G, Scheltens P. Heterogeneity of Alzheimer's disease: consequence for drug trials? Alzheimers Res Ther. 2018;10(1):122.
25. van der Veere PJ, Hoogland J, Visser LNC, Van Harten AC, Rhodius-Meester HF, Sikkes SAM, et al. Predicting Cognitive Decline in Amyloid-Positive Patients With Mild Cognitive Impairment or Mild Dementia. Neurology. 2024;103(3):e209605.
26. Jack CR, 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.
27. Khachaturian AS, Hayden KM, Mielke MM, Tang Y, Lutz MW, Gustafson DR, et al. Future prospects and challenges for Alzheimer's disease drug development in the era of the NIA-AA Research Framework. Alzheimers Dement. 2018;14(4):532-4.
28. Mazer NA, Hofmann C, Lott D, Gieschke R, Klein G, Boess F, et al. Development of a quantitative semi-mechanistic model of Alzheimer's disease based on the amyloid/tau/neurodegeneration framework (the Q-ATN model). Alzheimers Dement. 2023;19(6):2287-97.




How to cite this article: O. Lerch, S.Z. Levine, S. Sivakumaran, et al. Editorial: Amplifying Efficiency and Accuracy in Dementia Drug Development. J Prev Alz Dis 2024; http://dx.doi.org/10.14283/jpad.2024.167