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Commentary

Unraveling the Tau Puzzle: A Brief Discussion on Biomarkers in Alzheimer's Disease

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Abstract. This commentary provides an in-depth analysis of a recently published systematic review on 'Biomarkers of Tau Pathology in Alzheimer's Disease', elucidating insights into its implications for the field. This meta-analysis highlights the potential of plasma and CSF p-tau 181/231 as promising, non-invasive, and cost-effective diagnostic tools for patients suffering from AD continuum. The study comprehensively reviews the diagnostic potential of these p-tau isoforms, shedding light on their role in the precision diagnosis of Alzheimer's disease. Here we discuss the significance of these findings and the methodological nuances, emphasizing broader implications for advancing personalized medicine in neurodegenerative disorders.

Keywords: Alzheimer's disease, biomarkers, precision medicine, tau pathology

A recently published systematic review developed by Li et al. [1] presents a timely and comprehensive exploration of the diagnostic potential of phosphorylated tau (p-tau) in Alzheimer's disease (AD). The exploration of biomarkers, particularly p-tau offers promising diagnostic potential and insights into the intricate relationship between tau pathology and cognitive decline. However, it is crucial to emphasize the broader implications on personalized medicine in the real-world context of neurodegenerative disorders.

Furthermore, as the pursuit of reliable biomarkers gains momentum, this commentary seeks to explore and discuss the nuanced aspects of the study and underscore its implications for the broader field [1].

The meta-analysis adeptly synthesizes a multitude of studies, encompassing diverse populations and methodologies. By focusing on p-tau in both plasma and cerebrospinal fluid (CSF), the authors contribute valuable insights into the intricate relationship between tau pathology and cognitive decline. Notably, the inclusion of studies utilizing various analytical methods, such as enzyme-linked immunosorbent assay, single-molecule array technology, and immunomagnetic reduction, adds a layer of complexity to the discussion, prompting further exploration of standardization in methodologies. In consideration of the growing importance of imaging biomarkers in this scientific field, their integrated

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implementation with other biomarkers like fluid p-tau, along with those currently under study, demands rigorous regulation and standardization to guarantee harmonized and efficient utilization [2, 3].

The study's findings regarding differential levels of both plasma and CSF p-tau181 and p-tau231 across AD, mild cognitive impairment, and healthy controls underscore the potential of these biomarkers in aiding early diagnosis and prognosis. Such insights are particularly crucial in the evolving landscape of AD research and personalized medicine, where timely intervention holds the key to effective management. This is especially relevant in the context of emergent therapies, such as monoclonal antibodies.

About selected biofluids and techniques, current gold standard diagnostic biomarkers mainly involve positron emission tomography (PET) radiotracers and CSF biomarkers [4]. These biomarkers, while demonstrating a high accuracy in determining disease status, possess an invasive nature and are associated with high costs. In this context, there has been a growing scientific interest in plasma biomarkers as reflected in this manuscript, which highlights their potential as non-invasive alternatives in diagnosis, follow up, monitoring and to assess the possible treatment benefit [5].

In consequence, the knowledge of blood biomarkers for AD has exponentially increased in recent years. But also, biases in the clinical evaluation of blood biomarkers have been identified [6], including: (i) limited studies with appropriate biomarker validation methods; (ii) few studies designed to address specific use contexts from the start; (iii) inappropriate study designs (incorrect outcome measures and prospective studies with unsuitable intervals); (iv) many assays conducted without validation cohorts; (v) unpublished failures in cross-validation (publication bias); and (vi) insufficient studies providing relevant statistics to assess the biomarker effectiveness as a clinical screening or diagnostic tool (e.g., AUC, correlations with reference biomarker, sensitivity and specificity, PPV and PNV figures, and related statistics).

To avoid these issues, the Alzheimer's Association has recently reported several recommendations to carry out the necessary studies [7]. Evaluating the blood biomarkers in real-world cohorts; conducting large-scale observational trials; pre-defining cut-off values; analyzing follow-up samples; having available reference standards (e.g., CSF biomarkers); and performing the development, validation, and patient management in specialized memory clinics are some of the endpoints that would allow for the future acceptance of blood biomarkers as a clinical diagnostic tool.

Furthermore, the Alzheimer's Association has recently underscored the importance of the diagnostic and prognostic revolution facilitated by plasma biomarkers, both for AD diagnosis and for enhancing the design of interventional trials [7]. However, also stresses the necessity for further research before the widespread adoption of plasma biomarkers and already advocates for the use of plasma biomarkers as screening tools to identify individuals likely to exhibit AD pathological changes for inclusion in trials evaluating disease-modifying therapies, provided that the AD status is subsequently confirmed using PET or CSF gold-standard techniques [8].

Related to that, it is imperative to acknowledge the inherent limitations discussed by the authors, including the evolving diagnostic criteria and potential publication bias underscoring the need for cautious interpretation and further investigation. Although biomarkers offer substantial promise for advancing early diagnosis and treatment, none of them has shown results robust enough to be translated into routine clinical practice for which requires careful scrutiny, adherence to scientific rigor, and validation of global accessibility [9].

These scientific advancements in AD and mild cognitive impairment research may foresee a continuous reconceptualization of the disease, introducing a myriad of bioethical and legal considerations directly influencing in the real-world personalized medicine [10]. This is primarily rooted in the potential adverse consequences associated with early diagnosis and the lack of effective treatments in persons labeled as 'affected patients'. Such circumstances may increase uncertainty, anxiety, and stigmatization in those who may never develop dementia [11].

Conversely, leveraging biomarkers in a clinical research setting has the potential to enhance research endeavors aimed at developing and monitoring new treatments, refining patient selection processes, refining outcome measurements and drug approvals. Nevertheless, it may stand as a potent tool for obtaining a precise diagnosis in individuals already experiencing established dementia [12]. However, it should never be used as the sole diagnostic tool; rather, it should be considered as a complement in the diagnosis process and regarded as a mandatory tool to initiate treatment.

It is crucial to understand the role of the physician within the clinical process (diagnosis, follow-up, and

accompaniment); a role that will never be replaced by a biomarker or laboratory test.

In conclusion, the review by Li et al. [1] illuminates the promising potential of novel isoforms and sources of p-tau as a diagnostic marker for AD. While recognizing its benefits, it is imperative to approach these findings with a discerning eye striking a nuanced balance between optimism and realism, considering study limitations and ethical considerations as biomarkers progress in AD research and personalized medicine. Further research is required to investigate clinical, legal, and bioethical aspects to elucidate strategies for mitigating potential abuses and misinterpretations of biomarker results.

AUTHOR CONTRIBUTIONS

Yahveth Cantero-Fortiz (Conceptualization; Writing - original draft; Writing - review & editing); Amanda Cano (Writing -review & editing); Merce' Boada (Conceptualization; Writing - original draft;Writing - review & editing).

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CONFLICT OF INTEREST

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REFERENCES

[1] Li Z, Fan Z, Zhang Q (2024) The associations of phosphorylated tau 181 and tau 231 levels in plasma and cerebrospinal fluid with cognitive function in Alzheimer's disease: A systematic review and meta-analysis. *J Alzheimers Dis* **98**, 13-32.

[2] Izmailova ES, Maguire RP, McCarthy TJ, Müller MLTM, Murphy P, Stephenson D (2023) Empowering drug development: Leveraging insights from imaging technologies to enable the advancement of digital health technologies. *Clin Transl Sci* **16**, 383-397.

[3] Cano A, Esteban-de-Antonio E, Bernuz M, Puerta R, García-González P, de Rojas I, Olivé C, Pérez-Cordón A, Montrreal L, Núñez-Llaves R, Sotolongo-Grau Ó, Alarcón-Martín E, Valero S, Alegret M, Martín E, Martino-Adami PV, Ettcheto M, Camins A, Vivas A, Gomez-Chiari M, Tejero MÁ, Orellana A, Tárraga L, Marquié M, Ramírez A, Martí M, Pividori MI, Boada M, Ruíz A (2023) Plasma extracellular vesicles reveal early molecular differences in amyloid positive patients with early-onset mild cognitive impairment. *J Nanobiotechnol* **21**, 54.

[4] Cummings J, Isaacson R, Schmitt F, Velting D (2015). A practical algorithm for managing Alzheimer's disease: What, when, and why? *Ann Clin Transl Neurol* **2**, 307-323.

[5] Zetterberg H (2019) Blood-based biomarkers for Alzheimer's disease — An update. *J Neurosci Methods* **319**, 2-6.

[6] O'Bryant SE, Mielke MM, Rissman RA, Lista S, Vanderstichele H, Zetterberg H, Lewczuk P, Posner H, Hall J, Johnson L, Fong YL, Luthman J, Jeromin A, Batrla-Utermann R, Villarreal A, Britton G, Snyder PJ, Henriksen K, Grammas P, Gupta V, Martins R, Hampel H; Biofluid Based Biomarker Professional Interest Area (2017) Blood-based biomarkers in Alzheimer disease: Current state of the science and a novel collaborative paradigm for advancing from discovery to clinic. *Alzheimers Dement* **13**, 45-58.

[7] Hansson O, Edelmayer RM, Boxer AL, Carrillo MC, Mielke MM, Rabinovici GD, Salloway S, Sperling R, Zetterberg H, Teunissen CE (2022) The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimers Dement* **18**, 2669-2686.

[8] Flier WM van der, Scheltens P (2022) The ATN framework—moving preclinical Alzheimer disease to clinical relevance. *JAMA Neurol* **79**, 968-970.

[9] Dubois B, von Arnim CAF, Burnie N, Bozeat S, Cummings J (2023) Biomarkers in Alzheimer's disease: Role in early and differential diagnosis and recognition of atypical variants. *Alzheimers Res Ther* **15**, 175.

[10] Epelbaum S, Genthon R, Cavedo E, Habert MO, Lamari F, Gagliardi G, Lista S, Teichmann M, Bakardjian H, Hampel H, Dubois B (2017) Preclinical Alzheimer's disease: A systematic review of the cohorts underlying the concept. *Alzheimers Dement* **13**, 454-467.

[11] Whitehouse PJ (2019). Ethical issues in early diagnosis and prevention of Alzheimer disease. *Dialogues Clin Neurosci* **21**, 101-108.

[12] Gregory S, Saunders S, Ritchie CW (2022) Science disconnected: The translational gap between basic science, clinical trials, and patient care in Alzheimer's disease. *Lancet Healthy Longev* **3**, e797-e803.