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Review Article

The future of blood-based biomarkers for Alzheimer's disease

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J. Q. Trojanowski may accrue revenue in the future on patents submitted by the University of Pennsylvania wherein he is co-inventor, and he received revenue from the sale of Avid to Eli Lily as co-inventor on imaging-related patents submitted by the University of Pennsylvania. M. A. Karsdal owns stock in Nordic Bioscience. Karsdal and K. Henriksen may accrue revenue from a patent submitted by Nordic Bioscience wherein they are inventors. K. Blennow has served on advisory boards for Innogenetics, Belgium. S. E. O'Bryant has a patent pending on a blood-based biomarker tool for the detection of Alzheimer's disease. M. Sjögren is Chief Medical Officer of DiaGenic ASA, is a shareholder of AstraZeneca, and has stock options in DiaGenic ASA and UCB Pharma. A. Lönneborg has stock and stock options in DiaGenic ASA. W. Hu may accrue revenue in the future on patents submitted by Emory University wherein he is inventor.

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Abstract

Treatment of Alzheimer's disease (AD) is significantly hampered by the lack of easily accessible biomarkers that can detect disease presence and predict disease risk reliably. Fluid biomarkers of AD currently provide indications of disease stage; however, they are not robust predictors of disease progression or treatment response, and most are measured in cerebrospinal fluid, which limits their applicability. With these aspects in mind, the aim of this article is to underscore the concerted efforts of the Blood-Based Biomarker Interest Group, an international working group of experts in the field. The points addressed include: (1) the major challenges in the development of blood-based biomarkers of AD, including patient heterogeneity, inclusion of the "right" control population, and the blood–brain barrier; (2) the need for a clear definition of the purpose of the individual markers (e.g., prognostic, diagnostic, or monitoring therapeutic efficacy); (3) a critical evaluation of the ongoing biomarker approaches; and (4) highlighting the need for standardization of preanalytical variables and analytical methodologies used by the field.

Keywords: Blood; Plasma; Serum; Biomarkers; Alzheimer's disease

1. Introduction

Despite intensive efforts, there are no disease-modifying treatments approved for Alzheimer's disease (AD), with many notable trial failures making global headlines. The potential reasons for failures are numerous [1–3]. Discussions center on several possibilities: (1) study design (e.g., trials are too short; include advanced patients, thus minimizing the possibility of demonstrating clinical impact), (2) study compounds (i.e., low efficacy, addressing incorrect target/mechanism), and/or (3) lack of biomarkers to enroll the "right" patients into the trials (i.e., early-stage patients in whom disease modification is still possible) [2]. The latter notion is based on data that show pathology precedes clinical symptoms by years, and that currently available clinical outcomes, even ones used as clinical end points, show significant variation [2,4–10]. As a result, efforts toward identifying biomarkers of early pathological changes, as well as biomarkers indicative of neuronal protection, have intensified [11]. It is anticipated that the development and validation of biomarkers will greatly facilitate the identification of novel and effective treatment and preventative strategies for this devastating disease. The Blood-Based Biomarker Interest Group is an international working group of leading AD scientists from academia and industry that was created to survey the existing landscape and identify current needs to enable the field to progress forward.

The focus on blood-based AD biomarkers has grown exponentially during the past decade. Established biomarkers of AD from cerebrospinal fluid (CSF) and neuroimaging are highly accurate, but barriers to clinical implementation exist. Amyloid β peptide 42 (Aβ1–42), total tau protein, and hyperphosphorylated tau protein levels in CSF are well-characterized biomarkers of AD [4,12], and can serve as diagnostic markers with a substantial sensitivity and specificity, and thereby allow identification AD vs. comparable but cognitively normal elderly [12,13]. In addition, these biomarkers have also shown prognostic potential because they were able to separate subjects with mild cognitive impairment (MCI) who progressed to AD from those who did not [13,14]. However, the lumbar puncture required to collect CSF samples is considered an invasive practice in several countries and has from a negative public perception [15,16], thereby limiting the utility of these markers as front-line screeners. In addition, sampling at multiple time points to monitor carefully treatment efficacy, disease onset, or risk is limited and might impact biomarker levels [17].

On the other hand, neuroimaging approaches, such structural magnetic resonance imaging (MRI) of specific brain regions (i.e., hippocampus), amyloid tracer imaging (i.e., Pittsburgh compound B and florbetapir [18]), 18C-fluorodeoxyglucose, and functional MRI have been studied extensively. Neuroimaging biomarkers provide prognostic value for conversion from MCI to AD, because MCI patients who are Aβ positive are highly likely to progress, whereas those who are Aβ negative are not [18,19]. A major limitation to Pittsburgh compound B is its short half-life (about 20 minutes), which limits a broader application [20], but is not as significant of a limitation with florbetapir F18 [21]. Positron emission tomography (PET) is cost prohibitive in routine settings, including screening into clinical trials. Similar limitations apply to many of the neuroimaging approaches; however, a detailed description of them is beyond the scope of this review, and we refer to others [3,4,22]. In summary, the recognized and traditional biological markers obtained from CSF and neuroimaging are nearing and have reached clinical application (florbetapir F18 received Food and Drug Administration approval in the United States in 2012); however, these approaches still have significant limitations [16]. These biomarkers still provide needed information about disease stage and dementia type, and applying them in tandem with blood-based biomarkers is likely to improve their usefulness further, especially if the blood-based measurement can provide information about rate of disease progression [16].

The attractiveness of blood-based biomarkers is further underscored by two additional points. First, AD is already and continues to become more and more global [22], and