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Opinion

Commercialisation of Biomarker Tests for Mental Illnesses: Advances and Obstacles

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Substantial strides have been made in the field of biomarker research for mental illnesses over the past few decades. However, no US FDA-cleared blood-based biomarker tests have been translated into routine clinical practice. Here, we review the challenges associated with commercialisation of research findings and discuss how these challenges can impede scientific impact and progress. Overall evidence indicates that a lack of research funding and poor reproducibility of findings were the most important obstacles to commercialization of biomarker tests. Fraud, pre-analytical and analytical limitations, and inappropriate statistical analysis are major contributors to poor reproducibility. Increasingly, these issues are acknowledged and actions are being taken to improve data validity, raising the hope that robust biomarker tests will become available in the foreseeable future.

Trends

Substantial advances have been made in the field of biomarker research for mental illnesses.

However, no FDA-cleared blood-based biomarker tests have been translated into clinical applications.

A personal account of challenges associated with commercialisation of research findings is reported.

The major obstacles and challenges encountered in the field are briefly discussed.

The Disease Burden of Mental Illness and the Problem of Diagnosis

The Organisation for Economic Co-operation and Development (OECD) data suggest that one in two people will experience mental ill-health at some point in their life, yet only half of these patients are in treatment. Mental illnesses account for over 20% of total disability in OECD countries [1]. The direct and indirect costs of mental ill-health can exceed 4% of gross domestic product (GDP), which amounted to a staggering US$1.8 trillion of mental health spending for all OECD countries in 2013 and the numbers are increasing [1]. The WHO also estimates that mental illnesses, especially depression, will become the most debilitating disorders worldwide by 2030, overtaking cardiovascular disease [2].

The costs of depression alone in the European Union (EU) were estimated at €91,914 billion in 2010, affecting more than 30 million people. Most costs (€53,996 billion) are indirect, such as lost work productivity due to sick leave and early retirement [3,4]. Over 95% of patients with depression present with cognitive symptoms, such as concentration difficulties, indecisiveness, and/or forgetfulness, which can have a significant impact on the quality of life and the ability to function professionally and socially [5]. Workers with depression report on average 5.6 h per week of total health-related lost productivity time [6]. The longer depression remains untreated, the more debilitating the condition becomes, which in turn leads to an even greater strain on national disability funds [7]. Data from the UK show that every £1 invested in the early diagnosis and treatment of depression at work yields a cross-sector return of £5 [8]. The provision of adequate treatment for depression allows patients to resume work on average 70 days earlier and patients with depression who receive adequate treatment have a 76% remission rate [7]. However, more than half of patients do not achieve an adequate response following the first

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antidepressant treatment and remission rates are progressively lower for each successive treatment step (36.8% after the first treatment, decreasing to 13% after four treatment switches) [9]. One of the major problems affecting the effective treatment of mental disorders is that there are often long delays between onset of symptoms and clinical intervention due to late or inaccurate diagnosis, which can lead to a more severe and more difficult to treat disease course and worse outcome. In the case of depression, underdiagnosis is a common occurrence within the primary care setting, with only about 47% of patients correctly diagnosed by general practitioners [10].

Another example is schizophrenia, which currently represents the fifth leading cause of disability worldwide among individuals aged between 15 and 44 years [11]. It is one of the most chronic and debilitating psychiatric disorders [12] and is characterised by a prodromal or ultra-high risk (UHR) phase preceding the first onset of the illness. UHR individuals typically present with nonspecific behavioural abnormalities and subtle cognitive and affective changes [13]. Importantly, not all individuals meeting the UHR criteria develop schizophrenia. It is estimated that approximately 20–30% of these individuals eventually develop the illness over a 2–3-year period [14]. Consequently, the problem of delayed diagnosis is particularly difficult for UHR individuals who later develop schizophrenia and, therefore, has become a major focus of psychiatric research. Although UHR individuals are assessed using structured clinical interviews evaluating disturbances in perception, thought processing, language, and attention [15], these approaches are unable to accurately identify the schizophrenia converters. Studies have consistently shown that early diagnosis of schizophrenia would be beneficial and would improve outcome, especially if this could be achieved before or during the prodromal stages. It has also been established that shorter periods of untreated psychosis are linked to better patient outcomes [16]. However, there is concern that an incorrect diagnosis could result in unnecessary treatment and stigma since approximately 70% of individuals who fulfil UHR criteria do not develop schizophrenia [15].

In the absence of a biological disease understanding of psychiatric disorders, one of the major limitations associated with the symptom-based diagnosis of mental illnesses is that it is still based on clinical interviews with no objective tests. Most psychiatrists now acknowledge that the diagnoses of mental illnesses, such as schizophrenia, bipolar disorder, and depression, are umbrella terms for etiologically distinct conditions that present with similar symptoms and, therefore, misdiagnosis and subsequent inappropriate and ineffective treatment are common problems. Furthermore, currently used diagnostic manuals, *Diagnostic and Statistical Manual of Mental Disorders* (5th edn) (DSM-5) and *International Classification of Diseases* (*Ver. 10*) (ICD-10) [17], conceptualise that mental disorders are distinct disease entities with distinct pathologies that can be diagnosed by operational sets of criteria based on signs and symptoms. However, it is unlikely that specific symptoms are linked to defined disease pathways [18]. For example, patients with neurological, traumatic, infectious, and metabolic disorders can present with symptoms similar to those in schizophrenia [19,20]. A further complication is that many clinicians do not even use a classification system to establish a diagnosis. Instead, they reach a diagnosis based on experience and personal views, rather than by adhering to guidelines or criteria of a diagnostic system.

The issues outlined above collectively highlight the pressing need to develop readily accessible non-invasive molecular tests to aid in faster, earlier, and more accurate diagnosis of mental illnesses, particularly in the time-restrained primary care setting. The goal to search for peripheral biomarkers in psychiatric disorders is not restricted to their ease of accessibility, but also stems from the mounting evidence showing parallel changes in the central nervous system (CNS) and the periphery [21,22]. Proteomic studies investigating circulating biomarkers in psychiatric illnesses [21,23] have provided convincing evidence for alterations in immune and/or inflammatory response [24–31], the endocrine system [26,32], and metabolism [21,33,34]. However,