



## Towards a blood-based diagnostic panel for bipolar disorder



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### ABSTRACT

**Background:** Bipolar disorder (BD) is a costly, devastating and life shortening mental disorder that is often misdiagnosed, especially on initial presentation. Misdiagnosis frequently results in ineffective treatment. We investigated the utility of a biomarker panel as a diagnostic test for BD.

**Methods and findings:** We performed a meta-analysis of eight case-control studies to define a diagnostic biomarker panel for BD. After validating the panel on established BD patients, we applied it to undiagnosed BD patients. We analysed 249 BD, 122 pre-diagnostic BD, 75 pre-diagnostic schizophrenia and 90 first onset major depression disorder (MDD) patients and 371 controls. The biomarker panel was identified using ten-fold cross-validation with lasso regression applied to the 87 analytes available across the meta-analysis studies.

We identified 20 protein analytes with excellent predictive performance [area under the curve (AUC)  $\geq 0.90$ ]. Importantly, the panel had a good predictive performance (AUC 0.84) to differentiate 12 misdiagnosed BD patients from 90 first onset MDD patients, and a fair to good predictive performance (AUC 0.79) to differentiate between 110 pre-diagnostic BD patients and 184 controls. We also demonstrated the disease specificity of the panel.

**Conclusions:** An early and accurate diagnosis has the potential to delay or even prevent the onset of BD. This study demonstrates the potential utility of a biomarker panel as a diagnostic test for BD.

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## 1. Introduction

Bipolar disorder (BD) is a devastating mental disorder characterised by remitting and relapsing episodes of depression and (hypo)mania, which can also include psychotic symptoms. Disease onset commonly occurs in late adolescence or early adulthood, affecting men and women equally. BD has a lifetime prevalence of 1.0% for bipolar I disorder and 1.1% for bipolar II disorder (Merikangas et al., 2007).

Diagnosis of BD is based upon operationalized criteria with the aim to identify BD mood symptoms and patterns. The initial presentation of BD overlaps with either the depressive features of major depressive disorder (MDD) or the manic psychotic features of schizophrenia (SCZ). As most individuals seek psychiatric treatment for depressive symptoms at the onset of the disorder, the condition is frequently misdiagnosed because the subsequent (hypo)manic episode cannot be anticipated (Colom et al., 2006; Vieta et al., 2009). Ghaemi et al. estimated that the average delay for BD patients to be correctly diagnosed was 7.5 years (Ghaemi et al., 1999). An MDD misdiagnosis of BD patients is commonly associated with inappropriate antidepressant treatment that can precipitate (hypo)manic symptoms, worsening the outcome for the BD patient.

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Extensive research into neuroimaging based biomarkers and genetic risk factors, has not resulted in a diagnostic test for routine clinical use. However, gene expression studies in monocytes from BD patients have identified 22 discriminating inflammatory genes in a whole genome analysis (Padmos et al., 2008). In addition, a proof of concept whole-genome gene expression study demonstrated the value of blood biomarkers for predicting BD disease state (Le-Niculescu et al., 2009). The most promising finding comes from a case–control study with ‘never-medicated’ BD patients, where a 10-gene model predicted the patient group with 89% sensitivity and 75% specificity ( $p < 0.001$ ) (Clelland et al., 2013). In this study, we adopted a proteomics based approach to evaluate the potential of a diagnostic biomarker blood test for BD. After defining the biomarker panel and the validation in established BD patients, we applied the test to pre-diagnostic BD patients and controls, as well as first onset MDD patients, including patients who later developed (hypo)manic symptoms. We also tested the specificity of the panel.

## 2. Methods

This study consists of discovery, validation and application stages. In the discovery stage, we defined a mood-state-independent diagnostic biomarker panel for BD in a meta-analysis of eight independent case–control studies from five different clinical centres. The eight studies include a total of 158 established BD patients and 143 controls. In the validation stage, we attempted to validate the predictive performance of the diagnostic biomarker panel in a case–control study consisting of a further 66 established BD patients and 44 controls. Finally, in the application stage, we applied and evaluated the predictive performance of the diagnostic biomarker panel in undiagnosed BD patients and tested the disease specificity of the panel.

### 2.1. Study participants

#### 2.1.1. Discovery stage

Patients were recruited in four clinical centres in Germany (Cologne, Magdeburg, Münster and Würzburg) and one in the Netherlands (Rotterdam). The recruitment inclusion and exclusion criteria were similar for all eight case–control studies. The criteria required male and female participants to be within the age range of 18–60 years, have a body mass index (BMI) between 18 and 40 kg/m (Colom et al., 2006), and test negative for recreational drug screening at the time of sampling (Table 1). BD was diagnosed according to criteria of the International Classification of Diseases – 10 (ICD-10) by a trained psychiatrist in a clinical setting. Severity of symptoms was assessed using standard questionnaire based rating scales [Hamilton Depression Rating Scale (HAM-D), Young Mania Rating Scale (YMRS) and Montgomery–Åsberg Depression Rating Scale (MADRS)]. At the clinical centre in Würzburg, BD (Table 1) was diagnosed by two trained psychiatrists and the diagnosis was confirmed by the Operational Criteria Checklist for Affective and Psychotic Illness (OPCRIT). In all clinical centres, both bipolar I and bipolar II disorder patients were recruited. The BD patients were in one of the following mood states at the time of sample collection: depressed, mixed affective, hypomanic, manic or euthymic (Table 1). Age and sex matched controls from similar geographical areas, with a similar socioeconomic background were recruited with a maximum delay of four weeks. The exclusion criteria included a record of mental illness (only applied to controls), diagnosis of coronary heart disease or cardiac insufficiency, autoimmune disorders, acute or chronic infections or treatment with immunosuppressive or immunomodulating drugs or antibiotics, other neuropsychiatric disorders or chronic terminal diseases

affecting the brain, like cancer or hepatic and renal insufficiency, alcohol or drug addiction. No clinical assessment of controls was conducted. Patients and controls were fasting for at least two hours prior to blood sample collection. The study procedures and protocols received approval from the respective local ethical committees and informed written consent was obtained from all participants.

#### 2.1.2. Validation stage

We tested the predictive performance of the diagnostic biomarker panel identified in the discovery stage in a further case–control study from Würzburg in Germany (Table 1). Clinical assessments, exclusion and inclusion criteria were as described for the discovery studies.

#### 2.1.3. Application stage

We evaluated the predictive performance of the diagnostic biomarker panel in three nested case–control studies, two from the US Department of Defense Serum Repository (DoDSR) and one from the Netherlands Study of Depression and Anxiety (NESDA). For the two nested case–control studies from the military, sera were obtained from the US Department of Defense Serum Repository (DoDSR), which contains over 55 million serum specimens remaining from mandatory HIV test samples of military personnel (Perdue et al., 2015; Rubertone and Brundage, 2002). Data and sera retrieval were performed by the Armed Forces Health Surveillance Center (AFHSC) and coordinated by the Military New-Onset Psychosis Project (MNOPP) investigators at the Walter Reed Army Institute of Research (WRAIR) (Niebuhr et al., 2008). The medical and demographic data were provided by the Defense Medical Surveillance System (DMSS), AFHSC, United States Department of Defense (US DoD), Silver Spring, Maryland (data range from 1989 to 2006; released in 2007 and 2008) and serum specimens were retrieved from the DoDSR, AFHSC, US DoD (Silver Spring, MD, USA; specimens range from 1988 to 2006, released in 2007 and 2008). Sera were then transferred to the Johns Hopkins School of Medicine (Baltimore, MD, USA) prior to testing. Samples were then selected from 185 individuals who presented with psychiatric symptoms within 30 days after the blood collection and who later received a DSM-IV diagnosis of either BD or SCZ (MNOPP). Control subjects were selected from the DMSS records of active duty military service population with no inpatient or outpatient psychiatric disorder diagnoses. All data were previously collected for other purposes, and analyses were conducted on de-identified data. As only de-identified data were utilised, informed consent waivers were granted by the WRAIR Institutional Review Board (for additional information please see Supplementary Material 1). The third nested case–control study was drawn from NESDA, which is an ongoing longitudinal cohort study including 2,981 participants aged 18 through to 65 years (Penninx et al., 2008). Patients from the NESDA were recruited from three clinical sites in the Netherlands (Amsterdam, Groningen and Leiden) (Penninx et al., 2008). A four-hour baseline assessment included written questionnaires, interviews, a medical examination, a cognitive computer task and collection of blood and saliva samples. Furthermore extensive information about key (mental) health outcomes was gathered. Serum from a subset of 1701 participants was profiled. We analysed 368 controls and 102 recent onset MDD patients, 12 of which were diagnosed with BD within two years of the baseline interview (Table 1).

Informed and written consent was given by all participants, and the study protocols, analysis of samples and test methods were approved by the local Institutional Ethics Review Boards and were in compliance with the Standards for Reporting of Diagnostic Accuracy.

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