Chapter 1

Biomarkers in bipolar disorder: an overview

Estela Salagre and Eduard Vieta
Bipolar and Depressive Disorders Unit, Hospital Clinic, University of Barcelona, IDIBAPS, CIBERSAM, Barcelona, Spain

1.1 Introduction

Bipolar disorder (BD) is a chronic and recurrent disorder with an estimated lifetime prevalence of 2.4% (Carvalho, Firth, & Vieta, 2020). It is characterized by mood swings between mania or hypomania and depression (Vieta, Berk, & Schulze, 2018). The *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), encompasses five subtypes of BDs under the category "bipolar and related disorders," including bipolar I, bipolar II, or cyclothymic disorders, which differ in clinical course, prognosis, and therapeutic management (Carvalho, Firth, et al., 2020).

The peak incidence of BD occurs during the second and third decades of life, yet the first psychopathological manifestations can appear in childhood or adolescence (Vieta, Berk, et al., 2018; Vieta, Salagre, & Grande, 2018). This means that BD usually arises during a sensitive period of life, when a person typically achieves their developmental, educational, and occupational milestones, which are often negatively affected by the disorder (Carvalho, Firth, et al., 2020). In fact, BD is a major cause of disability in young people due to its detrimental impact on daily functioning (Jansen, Magalhães, Tavares Pinheiro, Kapczinski, & Silva, 2012; Vieta, Berk, et al., 2018). BD is also associated with other negative outcomes, such as cognitive decline and increased mortality, particularly from suicide and cardiovascular disease (Vieta, Berk, et al., 2018).

Hence, an early and accurate diagnosis and an adequate treatment are critical to achieve better outcomes in BD. To this day, though, the diagnosis of BD remains purely clinical, based on clinical information involving signs, symptoms, and course of illness that is gathered through clinical interviews and then confronted with the established diagnostic criteria, with no objective biological measure available to validate it (Frey, Andreazza, & Houenou, 2013).

Biomarkers in Bipolar Disorders. DOI: https://doi.org/10.1016/B978-0-12-821398-8.00012-6

Treatment selection is a purely clinical decision, too. However, given the complexity and heterogeneity of BD in terms of clinical presentation, treatment response and illness course, clinicians would benefit from the identification of objective biological markers (or biomarkers) to improve diagnosis accuracy and guide treatment selection in a more personalized way (Frey et al., 2013; Vieta, 2015).

In this chapter we will provide an overview of the field of biomarkers in BD. First, the concept of biomarker and the steps needed for the discovery and validation of a biomarker will be presented, followed by a discussion of the rationale for incorporating biomarkers in the management of BD. Then, we will detail the different categories of biomarkers and their potential use in BD, along with some examples. Finally, the limitations and future directions of the biomarker field in BD will be considered.

1.2 Biomarker definition and rationale for biomarkers in bipolar disorder

According to the FDA-NIH Biomarker Working Group, a biomarker is defined as an objective measure that can be used as "an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions" (FDA-NIH Biomarker Working Group, 2020). Accordingly, a biomarker is different from a clinical outcome assessment, that would be an evaluation of how an individual feels or functions (FDA-NIH Biomarker Working Group, 2020). Biomarkers, for instance, can be morphological (neuroanatomical changes, alterations in connectivity, etc.) cellular or molecular (DNA, inflammatory markers, proteome, etc.). They can be measured from peripheral tissues, such as blood, urine, stool samples or cerebrospinal fluid, or through imaging techniques (Frey et al., 2013; Knorr, Simonsen, & Roos, 2019).

The process of discovering and validating biomarkers is presented in Fig. 1.1. This process aims to generate new biomarkers that can be incorporated into daily clinical practice and that are compliant with the requirements of the Health Authorities [European Medicine Agency (EMA) or Food and Drug Administration (FDA)] (Davis, Aghaeepour, & Ahn, 2020). For that, a biomarker needs to be reproducible, reliable, sensitive, and robustly detected, as well as associated with the outcome of interest (Davis et al., 2020; Frey et al., 2013). Moreover, it needs to be easy to measure and interpret and acceptable to the patient (Frey et al., 2013).

The first step in the process of developing a biomarker is the recognition of the need for it and the definition of the target pathogenic process or therapeutic response that the biomarker should highlight, followed by the discovery of candidate biomarkers (Davis et al., 2020). For that, a previous understanding of either the pathophysiological processes underlying the condition of interest or the mechanism of action of the treatment of interest is

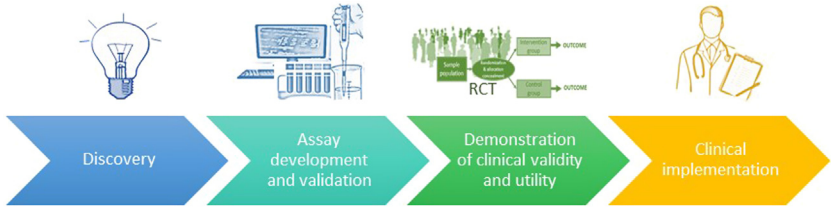

FIGURE 1.1 The process of discovering and validating a biomarker. The stages of biomarker development include biomarker discovery, assay development and analytical validation, demonstration of the clinical validity and utility of the candidate biomarker and clinical implementation. *Biomarker discovery* starts with an "hypothesis generation," that is, establishing the need for biomarkers for a particular use, defining the target biological process (pathogenic process, pharmacological response, etc.) that the biomarker should highlight and identifying potential candidates. Then, the study design (setting, sample collection, data collection, data analysis) and the *assay development* to analyze the candidate biomarkers follows. Once a biomarker is identified and the detection method or prototype assay is optimized, the *analytical validation* of the assay is required. This process evaluates how accurately and reliably does the assay or technology measure the biomarker of interest. It involves establishing if the sensitivity, specificity, accuracy, and precision of the test are acceptable, as well as other relevant performance characteristics (e.g., specimen collection or handling and storage procedures). Robust analytical performance is also needed before a biomarker can be considered for clinical use. That means that different sites running the same assay to identify the biomarker of interest should obtain highly concordant results. Then, the *clinical validity and utility* of the biomarker needs to be proved through the application of the analytically validated assay within a prospective clinical trial. Clinical validity refers to the ability of the biomarker to acceptably identify, measure, or predict the outcome of interest while its clinical utility evaluates if its use results in an improvement on the patients' outcomes. Finally, the *clinical implementation* of a biomarker depends on its cost-effectiveness and on the approval of regulatory agencies.

required so that ideal candidate biomarkers can be identified (Frey et al., 2013).

Considering this premise, one of the major barriers for the discovery of biomarkers in BD has been the scarce data on the potential biological pathways involved in the etiopathogenesis of this disease. However, the recent technological advances are changing this scenario, allowing for a deeper understanding of the pathophysiology of BD. Increasingly advanced genetic techniques are giving some clues on the genetic underpinnings of BD (Andlauer, Guzman-Parra, & Streit, 2019; Courtois, Schmid, & Wajsbrot, 2020; Stahl, Breen, & Forstner, 2019). Furthermore, a growing body of evidence suggests that, besides the traditional hypothesis of the imbalance in the monoamine neurotransmitter systems, BD might be associated with an alteration in the neuroendocrine system, the endocannabinoid system, and the modulation of synaptic and neural plasticity (Navarrete, García-Gutiérrez, & Jurado-Barba, 2020; Vieta, Berk, et al., 2018). Mitochondrial dysfunction, neuroinflammation, oxidation, and epigenetic changes are other cellular and molecular alterations that are thought to modify neuronal interconnectivity and thus to play a role in the development of BD (Vieta, Berk,

et al., 2018). The relationship between microbiota–gut–brain–axis and BD is also being examined, although this field of research is still in its infancy (Salagre, Vieta, & Grande, 2017; Vindegaard, Speyer, Nordentoft, Rasmussen, & Benros, 2020).

On the basis of this theoretical framework regarding the etiopathogenesis of BD, several studies have attempted to identify molecular/peripheral (Carvalho, Solmi, & Sanches, 2020; Jiménez-Fernández et al., 2020), neuroimaging (Ching, Hibar, & Gurholt, 2020; Vai, Bertocchi, & Benedetti, 2019), and genetic (Stahl et al., 2019) biomarkers related to these biological pathways (Fig. 1.2). The search for new biomarkers, in turn, gives more insight on the biological underpinnings of BD (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium., 2018; Yuan, Chen, Xia, Dai, & Liu, 2019). Examples of putative peripheral biomarkers in BD are neurotrophins, involved in cell growth and survival and synaptic plasticity (Grande, Fries, Kunz, & Kapczinski, 2010; Mora, Portella, & Piñol-Ripoll, 2019; Yuan et al., 2019); pro- and antiinflammatory

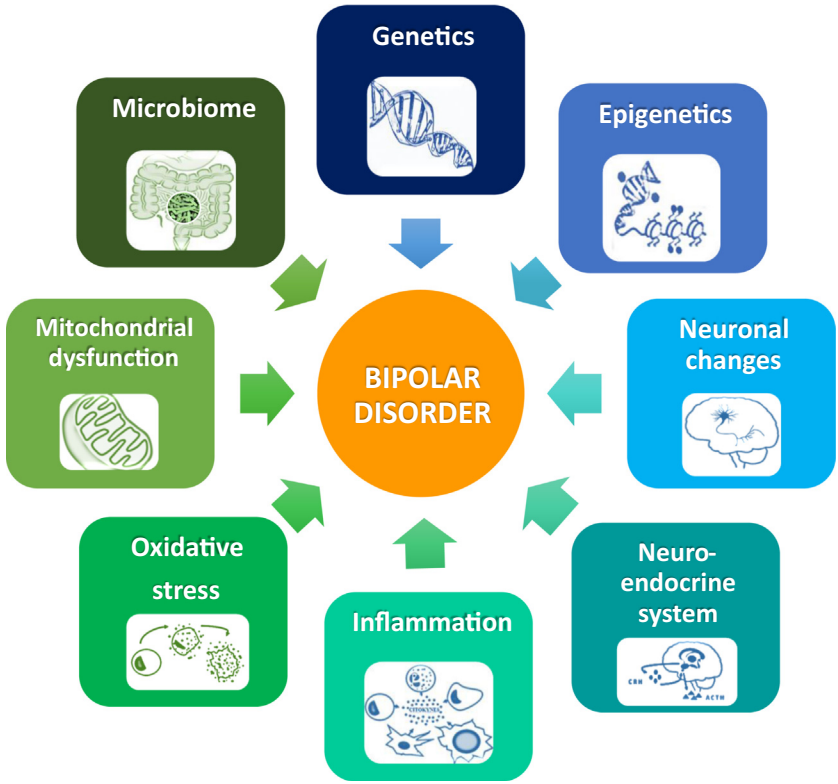

FIGURE 1.2 **Example of putative biological pathways involved in the etiopathogenesis of bipolar disorder and related to emerging biomarkers.**

cytokines, involved in inflammatory pathways (Carvalho, Solmi, et al., 2020; Yuan et al., 2019); molecular markers of oxidative stress (Jiménez-Fernández et al., 2020); or cell-free mitochondrial DNA (Jeong, Dimick, & Sultan, 2020). Neuroimaging biomarkers can include macro- or microstructural brain changes, alterations in brain activation or connectivity or alterations in brain biochemistry (Frey et al., 2013; Teixeira, Salem, Frey, Barbosa, & Machado-Vieira, 2016). Genetic polymorphisms or microRNAs (miRNAs) are examples of genetic biomarkers (Frey et al., 2013; Fries, Carvalho, & Quevedo, 2018).

1.3 Biomarker categories and potential uses in bipolar disorder

Biomarkers can be used in research and clinical practice for various assessments. Depending on their potential clinical use, biomarkers are divided in different categories (Davis et al., 2015; Singh & Rose, 2009). Davis et al. (2015) proposed the following separate categories of biomarkers for neuropsychiatric diseases: risk, diagnosis or trait, state or acuity, stage, prognosis, and treatment response (Fig. 1.3). Each of them will be described in detail below. Of note, one biomarker can fit in more than one category (Davis et al., 2015). For instance, it has been suggested that telomere length could be useful as a risk biomarker but also as a treatment response biomarker (Powell, Dima, Frangou, & Breen, 2018; Squassina, Pisanu, & Congiu, 2016).

1.3.1 Risk biomarkers

Risk biomarkers indicate the potential for developing a disease in an individual who does not currently have any clinically apparent manifestation of the illness (FDA-NIH Biomarker Working Group, 2020). Therefore, in BD, they could be useful to identify those asymptomatic individuals who present an increased vulnerability to develop BD or to monitor healthy people in order to detect early signs of the disease. Considering that BD is a highly heritable and polygenic disease (Carvalho, Firth, et al., 2020), biomarkers of genetic susceptibility could potentially identify individuals at risk for BD. To date, genome-wide association studies (GWAS) have identified several common genetic risk variants for BD (Hou, Bergen, & Akula, 2016; Stahl et al., 2019). However, while these variant alleles in genes or polymorphisms may confer susceptibility to BD, they are not deterministic (Gordovez & McMahon, 2020). Both genetic and environmental factors contribute to the development of BD (Carvalho, Firth, et al., 2020) and epigenetic mechanisms are thought to mediate in the interaction between the two (Fries, Walss-Bass, Soares, & Quevedo, 2016). miRNAs are connected to epigenetic mechanisms and they appear to be important in the onset and development

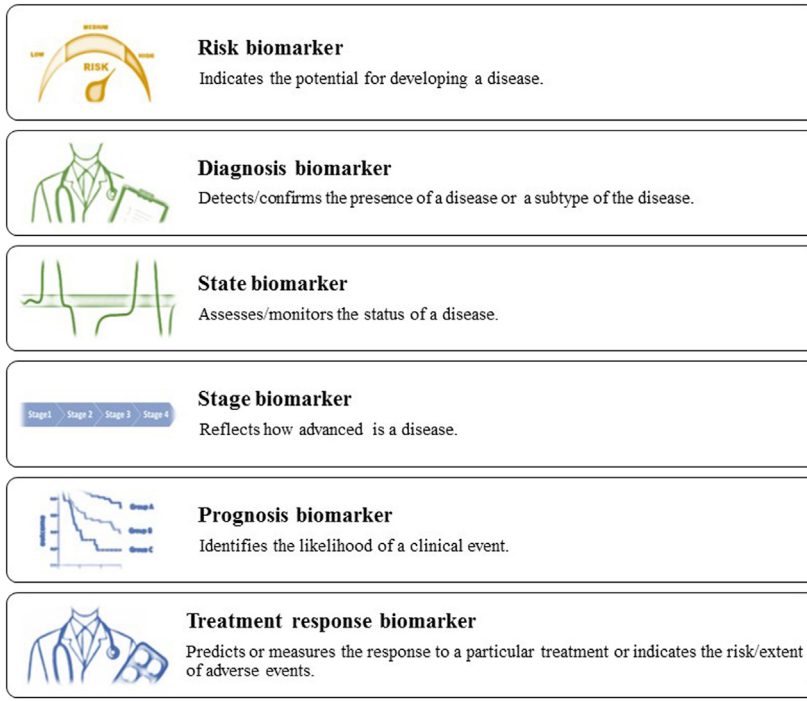

FIGURE 1.3 **Biomarker categories in neuropsychiatric diseases, as proposed by Davis et al**. *Data from Davis, J., Maes, M., Andreazza, A., McGrath, J. J., Tye, S. J., & Berk, M. (2015). Towards a classification of biomarkers of neuropsychiatric disease: From encompass to compass. Molecular Psychiatry, 20(2), 152–153.*

of several diseases, including BD, which make them a promising study target as risk biomarkers (Fries et al., 2018).

1.3.2 Diagnosis/trait biomarkers

Diagnosis/trait biomarkers are measurable characteristics used to detect or confirm the presence of a disease of interest or to identify individuals with a subtype of the disease which might have a different prognosis or might be more likely to respond to a specific treatment approach (FDA-NIH Biomarker Working Group, 2020). Identifying diagnosis biomarkers for BD would improve the diagnostic accuracy of this disorder, which is often underdiagnosed or misdiagnosed, mainly as unipolar depressive disorder or psychotic disorders (Carvalho, Firth, et al., 2020; Vieta, Salagre, et al., 2018). Altered white matter connectivity within the corpus callosum and the cingulum, for instance, has been found to be strongly associated with BD in collaborative international studies within the ENIGMA consortium, and thus

has been suggested as putative trait biomarkers for BD (Favre, Pauling, & Stout, 2019). Other proposed diagnosis or trait biomarkers are the proinflammatory cytokines soluble interleukin-2 receptor (sIL-2R), sIL-6R, and tumor necrosis factor-alpha (TNF-α), the antiinflammatory cytokine IL-4, and morning cortisol, which have been found consistently elevated in BD compared to healthy controls (Carvalho, Solmi, et al., 2020; Yuan et al., 2019).

1.3.3 State or acuity biomarkers

A state or acuity biomarker is a characteristic measured serially for assessing or monitoring the status of a disease. When focusing specifically in BD, state biomarkers are those biological markers associated with one or various mood states, meaning mania, depression, and/or euthymia (Frey et al., 2013). Hence, this biomarkers can be used to monitor or detect disease activity (i.e., mood relapse). Examples of state biomarkers would be the brain-derived neurotrophic factor (BDNF), which has been found to be elevated in mania and depression (Fernandes, Molendijk, & Kohler, 2015; Munkholm, Vinberg, & Kessing, 2016), C-reactive protein (CRP) (Dargél, Godin, Kapczinski, Kupfer, & Leboyer, 2015; Fernandes, Steiner, & Molendijk, 2016), or homocysteine (Salagre, Vizuete, & Leite, 2017). The latter two might be especially useful to detect manic relapses (Dargél et al., 2015; Fernandes et al., 2016; Salagre, Vizuete, et al., 2017).

1.3.4 Stage biomakers

A stage biomarker is a measurable characteristic reflecting how advanced is a disease, that is, describing where a patient is within the temporal spectrum of progression of the disorder. This kind of biomarkers allow to adapt treatment selection according to illness stage. In BD, the concept of staging relies on the notion that BD is a neuroprogressive illness that moves from at-risk and prodromal stages, to more severe and chronic stages, often characterized by functional and cognitive impairment, and/or treatment resistance (Berk, Post, & Ratheesh, 2017; Kapczinski, Magalhaes, & Balanza-Martinez, 2014; Salagre, Dodd, & Aedo, 2018). Following the hypothesis of neuroinflammation and neuroprogression in BD (Kapczinski, Mwangi, & Cassidy, 2017), most studies to date investigating stage biomarkers have focused on neurotrophins (Bond, Torres, Lam, & Yatham, 2020; Kauer-Sant'Anna et al., 2009) and inflammatory markers (Grande et al., 2010; Smedler, Bergen, Song, & Landén, 2019; Tatay-Manteiga et al., 2017), with conflicting results. Although some studies describe increased IL-6, TNF-α, and IL-10 in patients in later stages of BD compared to those in early stages, others studies report opposite findings (Grande et al., 2010; Smedler et al., 2019; Tatay-Manteiga et al., 2017). The lack of a clear and universal definition of early and late stages might account for the disparities in the results. Regarding

neurotrophins, one study reported that patients in later stages of BD showed lower levels of BDNF than those in earlier stages (Kauer-Sant'Anna et al., 2009).

1.3.5 Prognostic biomarker

Prognostic biomarkers indicate an increased or decreased likelihood of a future clinical event, disease recurrence, or progression (FDA-NIH Biomarker Working Group, 2020). Considering that the clinical course can be very heterogeneous among patients with BD, prognostic biomarkers could ideally predict the more likely natural outcome of the illness for every patient thus allowing a more personalized treatment approach (Fernandes et al., 2017; Vieta, 2015). Nowadays, there are already some clinical prognostic markers, such as predominant polarity (Popovic, Torrent, & Goikolea, 2014; Rosa, Andreazza, & Kunz, 2008) and some preliminary data on biological prognostic markers is starting to appear. As an example, a single nucleotide polymorphism (SNP) in the calcium channel subunit gene CACNA2D3 has been associated with sensitization, that is, with a tendency to show progressively shorter times to recurrence as the disease progresses (Smedler et al., 2019). Prognostic biomarkers would also be useful to identify patients at higher risk for suicide attempts. The Psychiatric Genomics Consortium has shown the potential of GWAS to identify genetic loci related to suicide attempts in BD, yet the results could not be replicated in independent samples (Mullins, Bigdeli, & Børglum, 2019). Cognitive impairment is another important outcome in BD, as it is related to difficulties in daily functioning (Bonnín, Jiménez, & Solé, 2019; Miskowiak, Burdick, & Martinez-Aran, 2018). Higher levels of CRP levels have been suggested as predictors of cognitive decline, although the interpretability of these results is limited by the cross-sectional nature of the study reporting this finding (Millett, Perez-Rodriguez, & Shanahan, 2019).

1.3.6 Treatment response biomarker

A treatment response biomarker can indicate the likelihood of responding to a particular treatment (predictive biomarker), measure if a biological response to treatment has taken place (pharmacodynamic biomarker) or indicate the risk of adverse events or the extent of toxicity as an adverse effect (safety biomarker) (FDA-NIH Biomarker Working Group, 2020). Up to a third of individuals with BD do not achieve an optimal response to available treatments, probably due to individual differences in the biological factors underlying psychopathology (Quinlan, Banaschewski, & Barker, 2020). Treatment response biomarkers could help to guide treatment selection by indicating the individual probability of responding to a particular treatment or developing adverse events. They could also be used to monitor treatment

response (Quinlan et al., 2020). So far, genetic (Anghelescu & Dettling, 2014; Hou, Heilbronner, & Degenhardt, 2016), neuroimaging (Selek, Nicoletti, & Zunta-Soares, 2013) and epigenetic (Marie-Claire, Lejeune, & Mundwiller, 2020) biomarkers of response to lithium have been proposed. Polygenic risk scores are arising as a useful complementary tool to identify potential biotypes of treatment response (Murray et al., 2020). Different works from the International Consortium on Lithium Genetics (ConLi + Gen) have reported that individuals with BD with a low polygenic load for major depressive disorder or schizophrenia are more likely to show a favorable response to lithium compared to those patients with high polygenic loads (Amare, Schubert, & Hou, 2020; Amare, Schubert, & Hou, 2018). The field of pharmacogenomics, which studies the individual genetic variation associated with drug response and tolerance, is expected to help advancing in the identification of safety biomarkers (Cuéllar-Barboza, McElroy, & Veldic, 2020). In the meantime, serum creatinine, thyroid-stimulating hormone (TSH), plasma calcium or prolactin levels are safety biomarkers related to lithium or antipsychotic treatment already used in clinical practice (Yatham, Kennedy, & Parikh, 2018).

1.4 Biomarkers in bipolar disorder: current limitations

Despite the efforts to find biomarkers for BD, current candidates still face several limitations that prevent them from being incorporated in clinical practice (Box 1) (Teixeira et al., 2016).

The limited reproducibility of the results is one of the main limitations. It might be explained by substantial shortcomings in the design and statistical power of the available studies (Carvalho, Köhler, & Fernandes, 2016). Small sample sizes, heterogeneous samples (i.e., patients with diverse subtypes of BDs or in different mood states or clinical stages), or disparities in sample acquisition, processing or storage are examples of those methodological flaws (Carvalho et al., 2016; Pan, Ryu, & Geske, 2020; Schnack & Kahn, 2016; Teixeira et al., 2016). Not controlling for potential confounders (e.g., gender, BMI, pharmacological treatments, substance use, comorbidities, chronic stress) or not taking into account multiple comparisons and/or overfitting statistical models can also lead to false findings (Yuan et al., 2019). Furthermore, only few studies report measures of predictive accuracy, such as sensitivity (i.e., the fraction of people with disease who test positive), specificity (i.e., the fraction of people without the disease who test negative), and AUC-ROC curves, which are needed to evaluate the real clinical utility of the biomarkers (Teixeira et al., 2016). Importantly, two *meta*-analyses have illustrated that publication bias and reporting bias for the positive results are likely to occur in the field of biomarkers (Carvalho et al., 2016; Yuan et al., 2019). According to Yuan et al. (2019) the studies measuring state-related

biomarkers are the ones with more inconsistencies, especially among those studies performing pretreatment and posttreatment comparisons.

A second major drawback is the lack of specificity of the candidate biomarkers for BD. Current evidence suggests that most of the identified molecular/peripheral markers are common across different neuropsychiatric disorders and even across nonpsychiatric diseases (Wiener, Moreira, & Portela, 2019; Goldsmith, Rapaport, & Miller, 2016; Lawes, Demakakos, Steptoe, Lewis, & Carvalho, 2019). Altered inflammatory biomarkers, for instance, have also been reported in cardiovascular or neoplastic diseases (Lawes et al., 2019). Even so, it may be that combining different biomarkers would allow to differentiate BD from other psychiatric conditions, specially major depressive disorder and schizophrenia (Wise, Radua, & Via, 2017; Brunoni, Supasitthumrong, & Teixeira, 2020). Moreover, collaborative GWAS have found specific loci responsible for some of the differences between BD and schizophrenia, (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium., 2018) and it is expected that future work from international consortia in genetics will help to gain further insight in the biological components underlying differences and similarities between these two diagnostic groups and also between subtypes of BDs (Almeida et al., 2020).

Another question that remains unsolved is whether current evidence regarding putative biomarkers can be generalized to individuals from those cultural and ethnic backgrounds that are not represented in the available studies, and who might present differences in lifestyle, genetic background, and environmental exposure (Budach & Tinhofer, 2019; Komatsu, Takeuchi, & Kikuchi, 2020). This point is specially crucial when considering the translation of a biomarker into clinical practice (Budach & Tinhofer, 2019). Current international collaborative studies are taking this aspect into account and working on protocol harmonization across the different participating centers in order to be able to validate their findings in diverse cultural and environmental contexts (Quinlan et al., 2020).

Finally, while the use of peripheral biomarkers as surrogates for pathophysiological processes in the brain has the advantage of the ease of access and the low cost, it needs to be clarified whether this practice is accurate, as changes in the periphery may not necessarily reflect changes in the brain (Carvalho et al., 2016; Fernandes, Steiner, & Berk, 2015). Also, longitudinal studies with multiple-time-point measures are still scarce in the field. However, they are needed to test the real potential of most of the proposed biomarkers, given that they might fluctuate over time depending on factors such as environmental changes (Yuan et al., 2019). In consequence, there is a risk that results from cross-sectional studies with single-point measures might be misleading (Yuan et al., 2019).

1.5 Future directions in the field of biomarkers in bipolar disorder

While a specific biomarker for BD has not yet been identified, rapid technological progresses and improvements in artificial intelligence techniques, such as machine learning, could bring encouraging results in the future. In fact, only a limited number of genetic and molecular biomarkers that could potentially play a role in BD have been studied, in some cases due to methodological constraints, but new advances in technology might help to overcome this limitation. High-throughput approaches, such as new generation proteomics, are among these promising tools (Ren, Zhao, & Sun, 2017).

Furthermore, given the multifactorial nature of BD and the apparently lack of specificity and limited prognostic accuracy of single biomarkers, an increasing number of studies are moving the focus from single biomarkers to panels of biomarkers. Recent technological advances are offering the opportunity for the simultaneous analysis of a large number of different biomarkers in a single experiment (Fernandes et al., 2017). So far, it has been shown that combining several peripheral biomarkers might improve diagnosis accuracy and allow to create a more specific mood-phase signature (Chen, Jiang, & Liu, 2017; Rowland, Perry, & Upthegrove, 2018). Some studies have combined potential biomarkers measurements and machine learning techniques to try to find a panel of inflammatory, oxidative and cognitive markers that could differentiate patients with BD from patients with schizophrenia (Wollenhaupt-Aguiar, Librenza-Garcia, & Bristot, 2020; Fernandes, Karmakar, & Tamouza, 2020). Although machine learning is a promising tool, as it facilitates the integration of multiple measurements (e.g., patient clinical records, laboratory testing, brain imaging data, -omics data or environmental information) (Librenza-Garcia, Kotzian, & Yang, 2017) models so far have only shown low-to-moderate performance for the differential diagnosis of BD and major depressive disorder or schizophrenia, preventing from their use in clinical settings. Ongoing studies combining clinical and objective markers will provide more information on the utility of multimodal biomarker panels (Kishimoto, Takamiya, & Liang, 2020). One example is the R-LiNK initiative, a prospective cohort study that aims to identify early biosignatures of response to lithium in BD-I by combining clinical information with multimodal biomarkers, including -omics, neuroimaging or information about rest/activity cycles monitored with an actigraph (Scott, Hidalgo-Mazzei, & Strawbridge, 2019).

Incorporating objective markers into research and clinical management of BD would have several advantages. Classifying individuals in different levels of risk for BD based on specific genetic markers associated with the disease would presumably be more accurate than relying on the reported information about the family history of the illness (Mayeux, 2004). Having an objective diagnostic test would likewise increase validity and precision of

psychiatric diagnoses. As so, they could be useful in reducing disease heterogeneity in clinical trials or epidemiologic studies (Mayeux, 2004). Likewise, treatment response biomarkers could become targets for clinical trials, for instance, to assess the effectiveness of new pharmacological treatments or of early interventions aimed to reduce the risk of onset of BD (Mayeux, 2004). To advance in the biomarker field in BD, though, designing adequately powered studies and establishing standardized common practices to ensure high-quality data that will lead to reproducible and comparable biomarkers is paramount (Radua, Vieta, & Shinohara, 2020; Yuan et al., 2019). Large-scale, coordinated actions for research in BD could be the way to go to create such consensus, while enabling for the integration of international large-scale data from multiple levels of analysis, including biological data and clinical information information (Manchia, Vieta, & Smeland, 2020).

1.6 Conclusion

Major technical advances have helped to gain knowledge on the mechanisms associated with susceptibility to BD, disease expression, and treatment response. These advances are also resulting in an exponential increase in the number of candidate biomarkers for BD. With the increasing emphasis on precision psychiatry, though, biomarkers will have an increasingly important role in healthcare delivery. A biomarker-driven psychiatry is expected to be more efficient, enhancing the cost-effectiveness of interventions, and, most importantly, more effective, reducing the morbidity of the patients and hence improving their quality of life.

References

Almeida, H. S., Mitjans, M., Arias, B., Vieta, E., Ríos, J., & Benabarre, A. (2020). Genetic differences between bipolar disorder subtypes: A systematic review focused in bipolar disorder type II. *Neuroscience and Biobehavioral Reviews*, *118*, 623−630.

Amare, A. T., Schubert, K. O., Hou, L., Clark, S. R., Papiol, S., Heilbronner, U., … Baune, B. T. International Consortium on Lithium Genetics (ConLi + Gen). (2018). Association of polygenic score for schizophrenia and HLA antigen and inflammation genes with response to lithium in bipolar affective disorder: A genome-Wwde association study. *JAMA Psychiatry*, *75*(1), 65−74.

Amare, A. T., Schubert, K. O., Hou, L., Clark, S. R., Papiol, S., Cearns, M., … Baune, B. T. (2020). Association of polygenic score for major depression with response to lithium in patients with bipolar disorder. *Molecular Psychiatry*.

Andlauer, T. F. M., Guzman-Parra, J., Streit, F., Strohmaier, J., González, M. J., Gil Flores, S., … Rietschel, M. (2019). Bipolar multiplex families have an increased burden of common risk variants for psychiatric disorders. *Molecular Psychiatry*, *26*(4), 1286−1298.

Anghelescu, I., & Dettling, M. (2014). Variant GADL1 and response to lithium in bipolar I disorder. *The New England Journal of Medicine*, *370*(19), 1859.

Berk, M., Post, R., Ratheesh, A., Gliddon, E., Singh, A., Vieta, E., … Dodd, S. (2017). Staging in bipolar disorder: From theoretical framework to clinical utility. *World Psychiatry: Official Journal of the World Psychiatric Association (WPA)*, *16*(3), 236−244.

Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2018). Genomic dissection of bipolar disorder and schizophrenia, including 28 subphenotypes. *Cell*, *173*(7), 1705–1715.e1716.

Bond, D. J., Torres, I. J., Lam, R. W., & Yatham, L. N. (2020). Serum epidermal growth factor, clinical illness course, and limbic brain volumes in early-stage bipolar disorder. *Journal of Affective Disorders*, *270*, 30–35.

Bonnín, C. M., Jiménez, E., Solé, B., Torrent, C., Radua, J., Reinares, M., … Vieta, E. (2019). Lifetime psychotic symptoms, subthreshold depression and cognitive impairment as barriers to functional recovery in patients with bipolar disorder. *Journal of Clinical Medicine*, *8*(7).

Brunoni, A. R., Supasitthumrong, T., Teixeira, A. L., Vieira, E. L., Gattaz, W. F., Benseñor, I. M., … Maes, M. (2020). Differences in the immune-inflammatory profiles of unipolar and bipolar depression. *Journal of Affective Disorders*, *262*, 8–15.

Budach, V., & Tinhofer, I. (2019). Novel prognostic clinical factors and biomarkers for outcome prediction in head and neck cancer: A systematic review. *The Lancet Oncology*, *20*(6), e313–e326.

Carvalho, A. F., Firth, J., & Vieta, E. (2020). Bipolar disorder. *The New England Journal of Medicine*, *383*(1), 58–66.

Carvalho, A. F., Köhler, C. A., Fernandes, B. S., Quevedo, J., Miskowiak, K. W., Brunoni, A. R., … Berk, M. (2016). Bias in emerging biomarkers for bipolar disorder. *Psychological Medicine*, *46*(11), 2287–2297.

Carvalho, A. F., Solmi, M., Sanches, M., Machado, M. O., Stubbs, B., Ajnakina, O., … Herrmann, N. (2020). Evidence-based umbrella review of 162 peripheral biomarkers for major mental disorders. *Translational Psychiatry*, *10*(1), 152.

Chen, S., Jiang, H., Liu, Y., Hou, Z., Yue, Y., Zhang, Y., … Yuan, Y. (2017). Combined serum levels of multiple proteins in tPA-BDNF pathway may aid the diagnosis of five mental disorders. *Scientific Reports*, *7*(1), 6871.

Ching, C. R. K., Hibar, D. P., Gurholt, T. P., Nunes, A., Thomopoulos, S. I., Abé, C., … ENIGMA Bipolar Disorder Working Group. (2020). What we learn about bipolar disorder from large-scale neuroimaging: Findings and future directions from the ENIGMA Bipolar Disorder Working Group. *Human Brain Mapping*.

Courtois, E., Schmid, M., Wajsbrot, O., Barau, C., Le Corvoisier, P., Aouizerate, B., … FondaMental Advanced Centers of Expertise in Bipolar Disorders (FACE-BD). (2020). Contribution of common and rare damaging variants in familial forms of bipolar disorder and phenotypic outcome. *Translational Psychiatry*, *10*(1), 124.

Cuéllar-Barboza, A. B., McElroy, S. L., Veldic, M., Singh, B., Kung, S., Romo-Nava, F., … Frye, M. A. (2020). Potential pharmacogenomic targets in bipolar disorder: Considerations for current testing and the development of decision support tools to individualize treatment selection. *International Journal of Bipolar Disorders*, *8*(1), 23.

Dargél, A. A., Godin, O., Kapczinski, F., Kupfer, D. J., & Leboyer, M. (2015). C-reactive protein alterations in bipolar disorder: A *meta*-analysis. *The Journal of Clinical Psychiatry*, *76*(2), 142–150.

Davis, J., Maes, M., Andreazza, A., McGrath, J. J., Tye, S. J., & Berk, M. (2015). Towards a classification of biomarkers of neuropsychiatric disease: From encompass to compass. *Molecular Psychiatry*, *20*(2), 152–153.

Davis, K. D., Aghaeepour, N., Ahn, A. H., Angst, M. S., Borsook, D., Brenton, A., … Pelleymounter, M. A. (2020). Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: Challenges and opportunities. *Nature Reviews Neurology*, *16*(7), 381–400.

Favre, P., Pauling, M., Stout, J., Hozer, F., Sarrazin, S., Abé, C., … ENIGMA Bipolar Disorder Working Group. (2019). Widespread white matter microstructural abnormalities in bipolar disorder: Evidence from mega- and *meta*-analyses across 3033 individuals. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *44*(13), 2285–2293.

Fernandes, B. S., Karmakar, C., Tamouza, R., Tran, T., Yearwood, J., Hamdani, N., … Leboyer, M. (2020). Precision psychiatry with immunological and cognitive biomarkers: A multi-domain prediction for the diagnosis of bipolar disorder or schizophrenia using machine learning. *Translational Psychiatry*, *10*(1), 162.

Fernandes, B. S., Molendijk, M. L., Kohler, C. A., Soares, J. C., Leite, C. M., Machado-Vieira, R., … Carvalho, A. F. (2015). Peripheral brain-derived neurotrophic factor (BDNF) as a biomarker in bipolar disorder: A *meta*-analysis of 52 studies. *BMC Medicine*, *13*, 289.

Fernandes, B. S., Steiner, J., Berk, M., Molendijk, M. L., Gonzalez-Pinto, A., Turck, C. W., … Gonçalves, C. A. (2015). Peripheral brain-derived neurotrophic factor in schizophrenia and the role of antipsychotics: *Meta*-analysis and implications. *Molecular Psychiatry*, *20*(9), 1108–1119.

Fernandes, B. S., Steiner, J., Molendijk, M. L., Dodd, S., Nardin, P., Gonçalves, C. A., … Berk, M. (2016). C-reactive protein concentrations across the mood spectrum in bipolar disorder: A systematic review and *meta*-analysis. *The Lancet Psychiatry.*, *3*(12), 1147–1156.

Fernandes, B. S., Williams, L. M., Steiner, J., Leboyer, M., Carvalho, A. F., & Berk, M. (2017). The new field of 'precision psychiatry'. *BMC Medicine*, *15*(1), 80.

FDA-NIH Biomarker Working Group. BEST (Biomarkers, EndpointS, and other Tools) Resource [Internet]. Silver Spring (MD): Food and Drug Administration (US); 2020. Diagnostic Biomarker. 2016 Dec 22 [Updated 2020 Nov 16]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK402285/ Co-published by National Institutes of Health (US), Bethesda (MD). Accessed 20.09.20.

Frey, B. N., Andreazza, A. C., Houenou, J., Jamain, S., Goldstein, B. I., Frye, M. A., … Young, L. T. (2013). Biomarkers in bipolar disorder: A positional paper from the International Society for Bipolar Disorders Biomarkers Task Force. *The Australian and New Zealand Journal of Psychiatry*, *47*(4), 321–332.

Fries, G. R., Carvalho, A. F., & Quevedo, J. (2018). The miRNome of bipolar disorder. *Journal of Affective Disorders*, *233*, 110–116.

Fries, G. R., Walss-Bass, C., Soares, J. C., & Quevedo, J. (2016). Non-genetic transgenerational transmission of bipolar disorder: Targeting DNA methyltransferases. *Molecular Psychiatry*, *21*(12), 1653–1654.

Goldsmith, D. R., Rapaport, M. H., & Miller, B. J. (2016). A *meta*-analysis of blood cytokine network alterations in psychiatric patients: Comparisons between schizophrenia, bipolar disorder and depression. *Molecular Psychiatry*, *21*(12), 1696–1709.

Gordovez, F. J. A., & McMahon, F. J. (2020). The genetics of bipolar disorder. *Molecular Psychiatry*, *25*(3), 544–559.

Grande, I., Fries, G. R., Kunz, M., & Kapczinski, F. (2010). The role of BDNF as a mediator of neuroplasticity in bipolar disorder. *Psychiatry investigation*, *7*(4), 243–250.

Hou, L., Bergen, S. E., Akula, N., Song, J., Hultman, C. M., Landén, M., … McMahon, F. J. (2016). Genome-wide association study of 40,000 individuals identifies two novel loci associated with bipolar disorder. *Human Molecular Genetics*, *25*(15), 3383–3394.

Hou, L., Heilbronner, U., Degenhardt, F., Adli, M., Akiyama, K., Akula, N., … Schulze, T. G. (2016). Genetic variants associated with response to lithium treatment in bipolar disorder: A genome-wide association study. *Lancet (London, England)*, *387*(10023), 1085–1093.

Jansen, K., Magalhães, P. V., Tavares Pinheiro, R., Kapczinski, F., & Silva, R. A. (2012). Early functional impairment in bipolar youth: A nested population-based case-control study. *Journal of Affective Disorders*, *142*(1–3), 208–212.

Jeong, H., Dimick, M. K., Sultan, A., Duong, A., Park, S. S., El Soufi El Sabbagh, D., … Andreazza, A. C. (2020). Peripheral biomarkers of mitochondrial dysfunction in adolescents with bipolar disorder. *Journal of Psychiatric Research*, *123*, 187–193.

Jiménez-Fernández, S., Gurpegui, M., Garrote-Rojas, D. A., Gutiérrez-Rojas, L., Carretero, M. D., & Correll, C. U. (2020). Oxidative stress parameters and antioxidants in patients with bipolar disorder: Results from a *meta*-analysis comparing patients, including stratification by polarity and euthymic status, with healthy controls. *Bipolar Disorders*.

Kapczinski, F., Magalhaes, P. V., Balanza-Martinez, V., Dias, V. V., Frangou, S., Gama, C. S., … Berk, M. (2014). Staging systems in bipolar disorder: An International Society for Bipolar Disorders Task Force Report. *Acta Psychiatrica Scandinavica*, *130*(5), 354–363.

Kapczinski, N. S., Mwangi, B., Cassidy, R. M., Librenza-Garcia, D., Bermudez, M. B., Kauer-Sant'anna, M., … Passos, I. C. (2017). Neuroprogression and illness trajectories in bipolar disorder. *Expert Review of Neurotherapeutics*, *17*(3), 277–285.

Kauer-Sant'Anna, M., Kapczinski, F., Andreazza, A. C., Bond, D. J., Lam, R. W., Young, L. T., & Yatham, L. N. (2009). Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. *The International Journal of Neuropsychopharmacology*, *12*(4), 447–458.

Kishimoto, T., Takamiya, A., Liang, K. C., Funaki, K., Fujita, T., Kitazawa, M., … PROMPT collaborators. (2020). The project for objective measures using computational psychiatry technology (PROMPT): Rationale, design, and methodology. *Contemporary Clinical Trials Communications*, *19,* 100649.

Knorr, U., Simonsen, A. H., Roos, P., Weimann, A., Henriksen, T., Christensen, E. M., … Kessing, L. V. (2019). Cerebrospinal fluid oxidative stress metabolites in patients with bipolar disorder and healthy controls: A longitudinal case-control study. *Translational Psychiatry*, *9*(1), 325.

Komatsu, H., Takeuchi, H., Kikuchi, Y., Ono, C., Yu, Z., Iizuka, K., … Tomita, H. (2020). Ethnicity-dependent effects of schizophrenia risk variants of the OLIG2 gene on OLIG2 transcription and white matter integrity. *Schizophrenia Bulletin*.

Lawes, S., Demakakos, P., Steptoe, A., Lewis, G., & Carvalho, L. A. (2019). Combined influence of depressive symptoms and systemic inflammation on all-cause and cardiovascular mortality: Evidence for differential effects by gender in the English Longitudinal Study of Ageing. *Psychological Medicine*, *49*(9), 1521–1531.

Librenza-Garcia, D., Kotzian, B. J., Yang, J., Mwangi, B., Cao, B., Pereira Lima, L. N., … Passos, I. C. (2017). The impact of machine learning techniques in the study of bipolar disorder: A systematic review. *Neuroscience and Biobehavioral Reviews*, *80*, 538–554.

Manchia, M., Vieta, E., Smeland, O. B., Altimus, C., Bechdolf, A., Bellivier, F., … European College of Neuropsychopharmacology (ECNP) Bipolar Disorders Network. (2020). Translating big data to better treatment in bipolar disorder - A manifesto for coordinated action. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *36*, 121–136.

Marie-Claire, C., Lejeune, F. X., Mundwiller, E., Ulveling, D., Moszer, I., Bellivier, F., & Etain, B. (2020). A DNA methylation signature discriminates between excellent and non-response to lithium in patients with bipolar disorder type 1. *Scientific Reports*, *10*(1), 12239.

Mayeux, R. (2004). Biomarkers: Potential uses and limitations. *NeuroRx: The journal of the American Society for Experimental NeuroTherapeutics*, *1*(2), 182–188.

Millett, C. E., Perez-Rodriguez, M., Shanahan, M., Larsen, E., Yamamoto, H. S., Bukowski, C., … Burdick, K. E. (2019). C-reactive protein is associated with cognitive performance in a large cohort of euthymic patients with bipolar disorder. *Molecular Psychiatry*. doi:10.1038/s41380-019-0591-1.

Miskowiak, K. W., Burdick, K. E., Martinez-Aran, A., Bonnin, C. M., Bowie, C. R., Carvalho, A. F., … Vieta, E. (2018). Assessing and addressing cognitive impairment in bipolar disorder: The International Society for Bipolar Disorders Targeting Cognition Task Force recommendations for clinicians. *Bipolar Disorders*, *20*(3), 184−194.

Mora, E., Portella, M. J., Piñol-Ripoll, G., López, R., Cuadras, D., Forcada, I., … Mur, M. (2019). High BDNF serum levels are associated to good cognitive functioning in bipolar disorder. *European Psychiatry: The Journal of the Association of European Psychiatrists*, *60*, 97−107.

Mullins, N., Bigdeli, T. B., Børglum, A. D., Coleman, J., Demontis, D., Mehta, D., … Lewis, C. M. (2019). GWAS of suicide attempt in psychiatric disorders and association with major depression polygenic risk scores. *The American Journal of Psychiatry*, *176*(8), 651−660.

Munkholm, K., Vinberg, M., & Kessing, L. V. (2016). Peripheral blood brain-derived neurotrophic factor in bipolar disorder: A comprehensive systematic review and *meta*-analysis. *Molecular Psychiatry*, *21*(2), 216−228.

Murray, G. K., Lin, T., Austin, J., McGrath, J. J., Hickie, I. B., & Wray, N. R. (2020). Could polygenic risk scores be useful in psychiatry?: A review. *JAMA Psychiatry*, Published online October 14, 2020.

Navarrete, F., García-Gutiérrez, M. S., Jurado-Barba, R., Rubio, G., Gasparyan, A., Austrich-Olivares, A., & Manzanares, J. (2020). Endocannabinoid system components as potential biomarkers in psychiatry. *Frontiers in Psychiatry*, *11*, 315.

Pan, A. Y., Ryu, E., Geske, J. R., Zhou, X. Y., McElroy, S. L., Cicek, M. S., … Andreazza, A. C. (2020). The impact of sample processing on inflammatory markers in serum: Lessons learned. *The World Journal of Biological Psychiatry: The Official Journal of the World Federation of Societies of Biological Psychiatry*, *21*(3), 230−237.

Popovic, D., Torrent, C., Goikolea, J. M., Cruz, N., Sánchez-Moreno, J., González-Pinto, A., & Vieta, E. (2014). Clinical implications of predominant polarity and the polarity index in bipolar disorder: A naturalistic study. *Acta Psychiatrica Scandinavica*, *129*(5), 366−374.

Powell, T. R., Dima, D., Frangou, S., & Breen, G. (2018). Telomere length and bipolar disorder. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *43*(2), 445−453.

Quinlan, E. B., Banaschewski, T., Barker, G. J., Bokde, A., Bromberg, U., Büchel, C., … IMAGEN Consortium. (2020). Identifying biological markers for improved precision medicine in psychiatry. *Molecular Psychiatry*, *25*(2), 243−253.

Radua, J., Vieta, E., Shinohara, R., Kochunov, P., Quidé, Y., Green, M. J., … ENIGMA Consortium collaborators. (2020). Increased power by harmonizing structural MRI site differences with the ComBat batch adjustment method in ENIGMA. *Neuroimage*, *218,* 116956.

Ren, J., Zhao, G., Sun, X., Liu, H., Jiang, P., Chen, J., … Zhang, C. (2017). Identification of plasma biomarkers for distinguishing bipolar depression from major depressive disorder by iTRAQ-coupled LC-MS/MS and bioinformatics analysis. *Psychoneuroendocrinology*, *86*, 17−24.

Rosa, A. R., Andreazza, A. C., Kunz, M., Gomes, F., Santin, A., Sanchez-Moreno, J., … Kapczinski, F. (2008). Predominant polarity in bipolar disorder: Diagnostic implications. *Journal of Affective Disorders*, *107*(1−3), 45−51.

Rowland, T., Perry, B. I., Upthegrove, R., Barnes, N., Chatterjee, J., Gallacher, D., & Marwaha, S. (2018). Neurotrophins, cytokines, oxidative stress mediators and mood state in bipolar

disorder: Systematic review and *meta*-analyses. *The British Journal of Psychiatry: The Journal of Mental Science*, *213*(3), 514–525.

Salagre, E., Dodd, S., Aedo, A., Rosa, A., Amoretti, S., Pinzon, J., … Grande, I. (2018). Toward precision psychiatry in bipolar disorder: Staging 2.0. *Frontiers in Psychiatry*, *9*, 641.

Salagre, E., Vieta, E., & Grande, I. (2017). The visceral brain: Bipolar disorder and microbiota. *Revista de psiquiatria y salud mental*, *10*(2), 67–69.

Salagre, E., Vizuete, A. F., Leite, M., Brownstein, D. J., McGuinness, A., Jacka, F., … Fernandes, B. S. (2017). Homocysteine as a peripheral biomarker in bipolar disorder: A *meta*-analysis. *European Psychiatry: The Journal of the Association of European Psychiatrists*, *43*, 81–91.

Schnack, H. G., & Kahn, R. S. (2016). Detecting neuroimaging biomarkers for psychiatric disorders: Sample size matters. *Frontiers in Psychiatry*, *7*, 50.

Scott, J., Hidalgo-Mazzei, D., Strawbridge, R., Young, A., Resche-Rigon, M., Etain, B., … Bellivier, F. (2019). Prospective cohort study of early biosignatures of response to lithium in bipolar-I-disorders: Overview of the H2020-funded R-LiNK initiative. *International Journal of Bipolar Disorders*, *7*(1), 20.

Selek, S., Nicoletti, M., Zunta-Soares, G. B., Hatch, J. P., Nery, F. G., Matsuo, K., … Soares, J. C. (2013). A longitudinal study of fronto-limbic brain structures in patients with bipolar I disorder during lithium treatment. *Journal of Affective Disorders*, *150*(2), 629–633.

Singh, I., & Rose, N. (2009). Biomarkers in psychiatry. *Nature*, *460*(7252), 202–207.

Smedler, E., Bergen, S. E., Song, J., & Landén, M. (2019). Genes, biomarkers, and clinical features associated with the course of bipolar disorder. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *29*(10), 1152–1160.

Squassina, A., Pisanu, C., Congiu, D., Caria, P., Frau, D., Niola, P., … Del Zompo, M. (2016). Leukocyte telomere length positively correlates with duration of lithium treatment in bipolar disorder patients. *European Neuropsychopharmacology: The Journal of the European College of Neuropsychopharmacology*, *26*(7), 1241–1247.

Stahl, E. A., Breen, G., Forstner, A. J., McQuillin, A., Ripke, S., Trubetskoy, V., … Sklar, P. Bipolar Disorder Working Group of the Psychiatric Genomics Consortium. (2019). Genome-wide association study identifies 30 loci associated with bipolar disorder. *Nature Genetics*, *51*(5), 793–803.

Tatay-Manteiga, A., Balanza-Martinez, V., Bristot, G., Tabares-Seisdedos, R., Kapczinski, F., & Cauli, O. (2017). Clinical staging and serum cytokines in bipolar patients during euthymia. *Progress in Neuro-psychopharmacology & Biological Psychiatry*, *77*, 194–201.

Teixeira, A. L., Salem, H., Frey, B. N., Barbosa, I. G., & Machado-Vieira, R. (2016). Update on bipolar disorder biomarker candidates. *Expert Review of Molecular Diagnostics*, *16*(11), 1209–1220.

Vai, B., Bertocchi, C., & Benedetti, F. (2019). Cortico-limbic connectivity as a possible biomarker for bipolar disorder: Where are we now? *Expert Review of Neurotherapeutics*, *19*(2), 159–172.

Vieta, E. (2015). [Personalised medicine applied to mental health: Precision psychiatry]. *Revista de psiquiatria y salud mental*, *8*(3), 117–118.

Vieta, E., Berk, M., Schulze, T. G., Carvalho, A. F., Suppes, T., Calabrese, J. R., … Grande, I. (2018). Bipolar disorders. *Nature reviews Disease Primers*, *4*, 18008.

Vieta, E., Salagre, E., Grande, I., Carvalho, A. F., Fernandes, B. S., Berk, M., … Suppes, T. (2018). Early intervention in bipolar disorder. *The American Journal of Psychiatry*, *175*(5), 411–426.

Vindegaard, N., Speyer, H., Nordentoft, M., Rasmussen, S., & Benros, M. E. (2020). Gut microbial changes of patients with psychotic and affective disorders: A systematic review. *Schizophrenia Research*.

Wiener, C. D., Moreira, F. P., Portela, L. V., Strogulski, N. R., Lara, D. R., da Silva, R. A., … Oses, J. P. (2019). Interleukin-6 and interleukin-10 in mood disorders: A population-based study. *Psychiatry Research*, *273*, 685−689.

Wise, T., Radua, J., Via, E., Cardoner, N., Abe, O., Adams, T. M., … Arnone, D. (2017). Common and distinct patterns of grey-matter volume alteration in major depression and bipolar disorder: Evidence from voxel-based *meta*-analysis. *Molecular Psychiatry*, *22*(10), 1455−1463.

Wollenhaupt-Aguiar, B., Librenza-Garcia, D., Bristot, G., Przybylski, L., Stertz, L., Kubiachi Burque, R., … Kapczinski, F. (2020). Differential biomarker signatures in unipolar and bipolar depression: A machine learning approach. *The Australian and New Zealand Journal of Psychiatry*, *54*(4), 393−401.

Yatham, L. N., Kennedy, S. H., Parikh, S. V., Schaffer, A., Bond, D. J., Frey, B. N., … Berk, M. (2018). Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disorders*, *20*(2), 97−170.

Yuan, N., Chen, Y., Xia, Y., Dai, J., & Liu, C. (2019). Inflammation-related biomarkers in major psychiatric disorders: A cross-disorder assessment of reproducibility and specificity in 43 *meta*-analyses. *Translational Psychiatry*, *9*(1), 233.