Biomarker-Guided Tailored Therapy

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Abstract

Personalized medicine aims to integrate a number of characteristics such as genetic and epigenetic variations, other biomarkers, clinical symptoms, and environmental factors in order to predict susceptibility to disease, aid in diagnosis, and identify efficacious treatments with maximum likelihood of favorable response and minimal chance of adverse effects. The use of personalized medicine approaches in psychiatry is underdeveloped, but has a profound potential for improving prevention and treatment. There are a number of studies that have found promising associations between a variety of biomarkers and clinical response to psychopharmacological treatment in various psychiatric disorders. These biomarkers include neuroimaging, electrophysiology, peripheral serum, and plasma biomarkers, and variations in genomics, epigenetics, proteomics, and metabolomics. Ultimately, the best model for precision medicine in complex, multifactorial diseases such as psychiatric illnesses will likely involve integrated methodology that combines information from multiple sources including biologic, clinical, and environmental data. While much progress has been made in the development of valid biomarkers

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in psychiatric disorders, there is much work to be done in determining their clinical utility.

Keywords
Major depressive disorder · Bipolar disorder · Schizophrenia · Personalized medicine · Precision medicine · Epigenetics · Pharmacogenomics · Neuroimaging

Introduction

Personalized medicine aims to tailor individualized treatment for each patient based on a number of characteristics such as genetic and epigenetic variations, other biomarkers, clinical symptoms, and environmental factors. The ultimate goal is to predict susceptibility to disease, aid in diagnosis, and identify efficacious treatments with maximum likelihood of favorable response and minimal chance of adverse effects [1]. Over the past decade, the Food and Drug Administration has approved a number of genetically prescreened drugs, labeled as pharmacogenomics, leading to significant advances in patient care in fields such as oncology, rheumatology, pulmonary medicine, and gastroenterology [2, 3].

Psychiatric illness is a huge burden to global society and the leading cause of years lost to disability [4]. The use of personalized medicine approaches in psychiatry is underdeveloped, but has a profound potential for improving prevention and treatment. The number and diversity of available treatments for psychiatric disorders alone illustrate the difficulty of matching the best treatment for the individual patient. The mechanisms by which psychotropic drugs act are incompletely understood and each drug has side effects. When an ineffective drug is prescribed, time is wasted for the patient with persistent symptoms and often bothersome side effects. Traditionally, psychiatric diagnosis has been based on the mental health professional's interpretation of patient (and family members) reports of behavioral signs and symptoms, and objective clinical measures such as biomarkers have not yet been incorporated into diagnostic criteria or monitoring of treatment response [4]. The development of personalized medicine approaches in psychiatry will be realized by the identification of relevant disease biomarkers, which can provide an objective measure of biologic function (or dysfunction), response to treatment, and disease severity. Biomarkers under investigation for psychiatric disorders include peripheral serum or plasma markers, neuroimaging findings, electrophysiology, and variations in genomics, epigenetics, proteomics, and metabolomics.

In this chapter, evidence to support the use of biomarkers to guide treatment and prevention in psychiatric disorders will be reviewed. The evidence is most robust in the area of predicting response to treatment for mood disorders, so much of the chapter will focus on this topic. Schizophrenia and psychotic disorders will only be briefly discussed as well as future directions, including biomarker-guided prevention efforts.

Major Depressive Disorder

Overview of Treatment of Major Depressive Disorder

Major depressive disorder (MDD) is the most prevalent psychiatric disorder, estimated to affect more than 100 million people worldwide. Up to 40% of individuals suffering from MDD never seek treatment, and approximately half of suicide victims visited a primary care provider in the month prior to their death [5]. This devastating disease exhibits considerable genetic heritability [6]. There are currently approximately 30 FDA-approved medications for the treatment of MDD that are believed to modulate the availability or activity of different neurotransmitter systems in the brain. These include serotonin, norepinephrine, and dopamine [7]. There is no established paradigm for choosing psychotropic medications and treatment is largely chosen based on physician preference and factors such as family or personal history of good treatment response, affordability, and side effect profile. Remission rates after treatment with a single antidepressant are modest, estimated to be roughly 30–50% after 12 weeks. An additional 30–40% of patients fail to achieve adequate response after multiple medication trials over 1 year of treatment [8]. Another commonly used treatment modality for MDD is evidence-based psychotherapies (i.e., cognitive behavioral therapy (CBT) and interpersonal psychotherapy (IPT)), which have demonstrated clinical efficacy in multiple randomized controlled clinical trials [7]. There are also three FDA-approved somatic nonpharmacological treatments for MDD: electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and vagus nerve stimulation (VNS) [7]. However, these modalities are not as commonly used and biomarker-based prediction of response has not been well studied.

Peripheral Serum Markers

Hypothalamic–Pituitary–Adrenal (HPA) Axis

HPA axis hyperactivity is a well-established finding in a significant portion of individuals suffering from MDD and has been replicated in dozens of studies over the last several decades. Patients with MDD have been found to have increased cerebrospinal fluid (CSF) concentrations of corticotropin-releasing hormone (CRH), as well as increased levels of cortisol in blood, urine, and CSF [9]. Elevated levels of cortisol are observed in up to 70% of patients with MDD after a dexamethasone suppression test (DST) [10], evidence of HPA axis hyperactivity. Several studies have shown that treatment with selective serotonin reuptake inhibitors (SSRIs) and clinical recovery leads to normalization of HPA axis hyperactivity [11]. The DST or combined CRH/DST challenge test may have clinical utility as a laboratory marker for treatment outcome. MDD patients who were initially

non-suppressors who exhibit normalization of the DST response show clinical improvement after antidepressant treatment [12]. In multiple studies, persistent non-suppression in response to DST after antidepressant treatment predicts poorer treatment response [11, 12]. The major confound in these studies is the finding that early life trauma in the form of child abuse or neglect is associated with alterations in HPA axis activity [13].

Hypothalamic–Pituitary–Thyroid (HPT) Axis

There is a well-documented relationship between MDD and abnormalities in the hypothalamic–pituitary–thyroid (HPT) axis. This has been consistently replicated in clinical trials over the last 40 years [14, 15]. Patients with thyroid dysfunction are more likely to develop depressive symptoms, and abnormalities in thyroid function are observed in a subset of patients with MDD [15]. Plasma concentrations of thyroid hormones (T3, T4) are typically normal in depressed patients, however other abnormalities have been observed. Patients with MDD have been found to have elevated TRH concentrations in the CSF [15, 16]. Another well-replicated finding is the presence of higher levels of circulating antithyroid antibodies in the plasma of depressed patients compared to nondepressed controls [15–17]. Plasma thyroid-stimulating hormone (TSH) responses after intravenous administration of thyrotropin-releasing hormone (TRH) as part of the TRH stimulation test are blunted in approximately 25% and abnormally elevated in approximately 15% of patients with MDD [14]. Research studies examining the prognostic utility of the TRH stimulation test in clinical trials have yielded mixed findings [18, 19]. In a study of 95 depressed patients treated with either nortriptyline ($N=46$) or fluoxetine ($N=49$) for 6 weeks, significant differences were seen in the maximum TSH response (ΔmaxTSH) to a TRH stimulation test between patients treated with each medication; ΔmaxTSH concentrations decreased significantly in fluoxetine responders after treatment and increased significantly in nortriptyline responders. Additionally, a significant decrease in plasma concentrations of thyroxine (T4) and free thyroxine (FT4) was observed after treatment with both medications in responders, but not nonresponders [20]. Several other studies have shown a significant decrease in plasma T4 and/or FT4 concentrations after at least 4 weeks of antidepressant treatment with SSRIs or TCAs in treatment responders, but not in nonresponders [21–23] Although the majority of patients with MDD do not have clinically significant thyroid disease, existing literature indicates a relationship between MDD and subclinical thyroid dysfunction. Triiodothyronine (T3) has been definitively shown to augment the efficacy of several antidepressants and is commonly used as adjunctive therapy in clinical practice for treatment-resistant patients, many of whom have thyroid indices within normal range [15, 16, 24]. While the mechanisms of thyroid supplementation in initially nonresponsive patients receiving antidepressant treatment remains unclear, assessment of thyroid function in depressed patients may serve as a useful personalized medicine approach to treatment of MDD.

Inflammatory Biomarkers

The association between MDD and inflammation has been consistently replicated in a multitude of clinical studies. One meta-analysis revealed that elevated

C-reactive protein (CRP) levels are associated with increased risk of future MDD [25]. Another meta-analysis found that treatment with antidepressants resulted in a marginally significant decrease in CRP levels, and moreover higher baseline CRP concentrations were associated with a greater reduction in depressive symptoms [26]. In contrast, Chang et al. found higher baseline CRP levels predicted poorer response to 2 weeks of treatment with either venlafaxine or fluoxetine [27]. Several recent trials [28, 29] suggest that lower pretreatment levels of CRP (<0.1 mg/L) are associated with a good response to SSRIs while individuals with higher pretreatment CRP levels (≥0.1 mg/L) may require combination therapy or the use of agents that act on additional neurotransmitter systems. In a clinical trial designed to determine if tumor necrosis factor (TNF) antagonism would reduce depressive symptoms (measured by HAM-D scores) in patients with treatment-resistant depression and if higher baseline levels of inflammatory biomarkers would predict treatment response, subjects with moderate treatment-resistant depression (as determined by the Massachusetts General Hospital Staging method) were randomized to receive three infusions of infliximab (baseline, 2 and 6 weeks), a TNF antagonist, or placebo in a 12-week study. There was no significant difference in HAM-D change scores between the two treatment groups over the 12-week period. However, subjects with baseline CRP >5 mg/L treated with infliximab showed significantly greater treatment response (≥50% reduction in HAM-D score at any point during treatment) as compared to the placebo group. This suggests that although TNF antagonism did not have a significant effect in treatment-resistant depression overall, it may have efficacy in a subset of patients with elevated baseline inflammatory biomarkers [30].

Multiple studies have demonstrated elevated levels of pro-inflammatory cytokines in depressed patients compared to controls [31]. In a meta-analysis of studies investigating the effect of antidepressant treatment on inflammatory cytokines IL-1β, IL-6, and TNF-α, antidepressant treatment lowered levels of IL-1β and possibly IL-6, but had no significant effect on TNF-α. Further analysis of antidepressant classes revealed that treatment with SSRIs, in particular, significantly lowered levels of IL-6 and TNFα [32]. A separate meta-analysis confirmed that antidepressant drugs decreased levels of IL-6, and higher baseline IL-6 levels were associated with larger decreases in depressive symptoms [26]. Dahl et al. measured plasma levels of cytokines in depressed patients and healthy controls at baseline and after 12 weeks of antidepressant treatment. At baseline, MDD patients had significantly higher levels of IL-1β, IL-1 receptor antagonist (IL-1Ra), IL-5, IL-6, IL-7, IL-8, IL-10, granulocyte colony-stimulating factor (G-CSF), and interferon gamma (IFNγ) compared to healthy controls ($p = 0.01$–0.047). After 12 weeks of treatment with antidepressant medications and/or psychotherapy, plasma levels of seven cytokines (IL-1Ra, IL-6, IL-7, IL-8, IL-10, G-CSF, and IFNγ) had decreased significantly in patients meeting criteria for recovery and did not differ significantly from levels in healthy controls. Depressive symptoms were simultaneously significantly reduced, and cytokine levels did not normalize in MDD patients who did not meet criteria for recovery [31].

One study by Danese et al. in 1,000 subjects revealed that maltreated children exhibit a significant and graded increase in CRP 20 years later, independent of

adult behavior, health, or recent life stressors; this effect was especially robust in depressed adults with a history of childhood maltreatment. In a separate study, the same group found significant elevations in CRP in 12-year-olds with depression and a history of maltreatment compared to depressed only, maltreated only, or age-matched controls. A study of 7,642 individuals in the UK reported that separation from parents in childhood was associated with a significant increase in CRP levels at age 44. Slopen et al. found that adverse events prior to age 8 predicted increased inflammatory markers, including IL-6 and CRP, at age 10 [13].

In summary, inflammatory markers are more likely to be elevated in depressed patients with a history of early life stressors (ELS) such as childhood abuse and/or neglect. Multiple studies have revealed an increase in inflammatory markers including CRP and IL-6 in patients who are depressed and have a history of exposure to ELS, especially in patients exposed to childhood abuse or maltreatment before age 8. Several studies have revealed persistently elevated levels up to 20 years later [13].

Protein S100B

Protein S100B is a neurotrophic protein that is used as a biomarker for glial alterations and neuroplasticity. Loss of neuroplasticity has been hypothesized to contribute to the pathogenesis of mood disorders [33] and several studies have found elevated serum levels of S100B in mood disorders, with higher levels seen in patients with MDD compared to bipolar disorder [34]. In a combined analysis of three studies in 46 MDD patients, Shroeter et al. found a positive correlation between clinical treatment response (measured by the HAM-D) and increases in serum S100B, suggesting that S100B could be a reliable indicator of treatment efficacy [34]. A separate study by Shroeter et al. [33] in 20 patients with a mood disorder and 12 age-matched healthy controls found that antidepressant treatment reduced serum S100B; the magnitude of the decrease was correlated with decreased severity of depressive symptoms (measured by HAM-D) ($\text{rho} < 0.01$); depression severity was positively correlated with serum S100B ($r(s) = 0.51$, $\text{rho} < 0.005$) [33]. Higher levels of serum S100B have been found to predict a better response to MDD treatment with various classes of antidepressants chosen by clinician based on symptomatology and anticipated side effects, after 4 or 6 weeks [35].

Neuroimaging

Neuroimaging studies show promise in identifying potential biomarkers to aid in the prediction of treatment outcomes for MDD. A 2013 systematic review of neural predictors of response to pharmacotherapy and psychotherapy in subjects with MDD who underwent neuroimaging (PET or structural MRI) prior to treatment initiation revealed a number of interesting findings [36]. The functional imaging meta-analysis included 20 studies from 15 independent samples. Across studies, increased baseline activity in the anterior cingulate and medial prefrontal cortices was predictive of a higher likelihood of symptom improvement and increased

baseline activation in the insula and striatum was associated with a poor clinical response. For the amygdala, there was inconsistency with some reports of increased activity and some of decreased activity associated with a positive therapeutic outcome [36]. The structural imaging (MRI) meta-analysis included nine studies from six independent samples and found that a decrease in right hippocampal volume was a statistically significant predictor of lower likelihood of good treatment response [36]. Again a potential confound here is early life trauma, which is associated with reduced hippocampal volume [13].

Using PET, McGrath et al. investigated predictors of response to escitalopram or CBT in 38 subjects with MDD. Right anterior insula hypometabolism was associated with remission of symptoms after CBT and poor response to escitalopram, whereas insula hypermetabolism was associated with remission of symptoms after escitalopram and poor response to CBT [37]. In another PET study, McGrath investigated predictors of response to citalopram and/or CBT in a two-phase study. Nonresponders to both therapies had significantly higher subcallosal cingulate (SCC) metabolism compared to the remitters [38]. A study by Dunlop et al. [39] evaluated functional MRI resting-state functional connectivity in 122 treatment-naive patients with MDD who completed 12 weeks of treatment with either CBT or antidepressant medication (escitalopram or venlafaxine). The resting-state functional connectivity of the SCC with three brain regions (left anterior ventrolateral prefrontal cortex/insula, the dorsal midbrain, and the left ventromedial prefrontal cortex) was differentially associated with outcomes of remission and treatment failure to psychotherapeutic and psychopharmacological interventions. Greater positive summed functional connectivity with the SCC was associated with remission to CBT and treatment failure with medication. Negative or absent summed functional connectivity with the SCC was associated with remission to medication and treatment failure with CBT; resting-state functional connectivity patterns differentiating CBT and medication outcomes were consistent for both escitalopram and venlafaxine [39].

In a systematic review of 21 studies investigating the use of resting-state fMRI to predict antidepressant treatment response, increased functional connectivity between the frontal lobe and limbic system was associated with response to antidepressant treatment, potentially suggesting greater inhibitory control over neural circuitry involved in emotional processing. Connectivity in visual recognition circuits (including the lingual gyrus, middle occipital gyrus, fusiform gyrus, and cuneus) showed potential utility in several studies in distinguishing treatment-responsive from treatment-resistant MDD patients. Finally, subcallosal cingulate gyrus connectivity consistently predicted treatment response to rTMS and was also implicated in treatment response to antidepressants [40].

Electrophysiologic Biomarkers

A 2018 meta-analysis by Widge et al. including 76 articles reporting 81 biomarkers sought to quantify the reliability of quantitative EEG (QEEG) for response

prediction in MDD. The analysis found that no specific QEEG biomarker or specific treatment showed greater predictive value than the all-studies estimate in a meta-regression, suggesting that QEEG is not a reliable clinical measure for predicting treatment response. However, funnel plot analysis suggested substantial publication bias such as lack of out-of-sample validation, underreporting of negative results, and insufficient direct replication of previous findings [41].

Genetic Predictors

Genetic heritability is thought to account for approximately 40–70% of the risk of developing MDD and also appears to play a role in treatment response [6]. A genome-wide association study (GWAS) evaluating the role of genetic variation in antidepressant treatment response found that common genetic variants accounted for 42% of individual differences in antidepressant treatment response [42]. Another GWAS study including a total of over 1500 subjects with MDD found associations with a few single nucleotide polymorphisms (SNPs) and antidepressant treatment response; however, no effect withstood correction for multiple testing. Of interest, 46 SNPs were in the same direction and significant before correction and they found a significant association of the number of response alleles (high versus low) to treatment response. The least favorable outcome was observed in patients with comorbid anxiety disorder in combination with a low number of response alleles [43].

Studies targeting specific SNPs involved in biologic pathways known to be involved in MDD have generally proven more promising. For example, genes involved in modulation of the HPA axis theoretically could impact the risk for developing MDD and treatment response [44]. O'Connell et al. found that a specific SNP of the corticotropin-releasing hormone-binding protein (rs28365143) was a positive predictor for treatment response to antidepressants, confirming a previous report from the Star D sample. Patients homozygous for the G allele of rs28365143 had greater remission, response rates, and symptom reduction in response to escitalopram and sertraline (SSRIs) compared to A allele carriers. There was no association observed between this genotype and treatment response to venlafaxine, an SNRI [44]. In a separate study that evaluated genetic variants in the corticotropin-releasing hormone-binding protein, African American and Hispanic carriers of the T allele of a specific SNP (rs10473984) had significantly poorer treatment response to citalopram (SSRI) [45]. Binder et al. identified SNPs in the FK506-binding protein 5 (FKBP5), a key component of the glucocorticoid receptor complex, that were associated with both a more rapid therapeutic response to antidepressant therapy and an increased recurrence of depressive episodes [46]. These SNPs were associated with increased intracellular FKBP5 protein and less HPA axis hyperactivity during depressive episodes [46].

Genes encoding for components of the serotonin (5-HT) system have also been studied. Serotonin reuptake, regulated by the serotonin transporter (5-HTT), is involved in the regulation of serotonergic activity and is thought to be a major site

of action for many antidepressant medications. A polymorphism in 5-HTTLPR, the promoter region of 5-HTT, influences both risk for developing MDD and response to antidepressant therapy. A number of studies, primarily in Caucasians, have linked the 5-HTTLPR long allele (l/l) with greater therapeutic response and the short allele (s/s) with slower or poorer response to SSRIs [47–50]. However, conflicting studies show no significant relationship between these genotypes and antidepressant response [6, 51]. The short allele has also been associated with greater therapeutic response in several studies in Asian populations, elderly patients, and patients being simultaneously treated with lithium or pindolol [48, 52]. Several clinical trials investigating the role of genetic polymorphisms in serotonin receptors, 5HTR1A and 5HTR2A, have yielded inconsistent results [6, 51, 53, 54]. Genetic variation in the expression of the cytochrome P450 (CYP450) isoenzymes impacts the metabolism of many antidepressants and psychotropic medications, as well as other commonly prescribed medications. There are several commercially available combinatorial pharmacogenetic tests that classify phenotypes of hepatic CYP450 metabolism as poor, intermediate, extensive/normal, or ultrarapid metabolizers [55]. These could plausibly have clinical utility in guiding medication choice and improving treatment course. For example, when determining the appropriate starting dose for a medication, higher doses would be needed for ultrarapid metabolizers, whereas poor metabolizers would be more susceptible to adverse effects which would prompt a prescriber to start at a low dose or refrain from prescribing that medication [55]. They also claim to predict treatment efficacy, but the database is insufficient at this time to recommend their use. Indeed, there are few well-designed clinical trials investigating the efficacy and clinical applicability of these pharmacogenetic tests, and further research is clearly needed before this testing is integrated into routine clinical practice [55, 56].

Bipolar Affective Disorder

Overview of Treatment of Bipolar Disorder

Bipolar disorder (BD) is a heterogeneous disease with significant variability in clinical presentation. Lithium is currently the first-line treatment for BD and, based on current evidence, is the treatment most likely to achieve long-term relapse prevention [2]. However, lithium is associated with remission in only approximately 30% of patients. Additionally, it has a low therapeutic index, and many patients are non-adherent due to side effects such as tremor, weight gain, nausea, and sedation which likely contributes to suboptimal dosing and lower remission rates [57]. Other FDA-approved treatments for mania or bipolar depression include lamotrigine, olanzapine, valproate, quetiapine, aripiprazole, and risperidone; however, it remains difficult to predict which drug will produce the best response in an individual patient [2]. In general, it is estimated that only 50% of patients with BD respond to monotherapy with a mood stabilizer, with an additional benefit of approximately 20% with addition of a second mood stabilizer

[58]. Because early intervention and providing an effective treatment early in the progression of the disease is important to long-term outcomes, better information about tailoring treatment for BD is critical [59, 60]. It is of paramount importance to identify biomarkers with predictive value for treatment response to enable early and efficacious intervention.

Peripheral Biomarkers

Inflammatory Biomarkers

Several studies have investigated the impact of treatment response on inflammatory biomarkers in BD during manic, depressive, and euthymic states. Kim et al. found that IL-6 levels were increased in acute mania and decreased after 6 weeks of treatment with lithium, valproate or a combination of both [61]. In a separate study, this group also found that levels of IL-12 decreased significantly in bipolar patients after 8 weeks of treatment with lithium or valproate [62]. Su et al. evaluated the relationship between lithium response and levels of interferon gamma (IFN-ɣ) and IL-10 and found no differences in patients medicated with lithium compared to unmedicated patients [63]. Guloksuz et al. found increased levels of TNF-a and IL-4 in euthymic bipolar patients treated with lithium ($N = 15$) compared to unmedicated euthymic bipolar patients ($N = 16$) and healthy controls ($N = 16$); however, no significant differences were found in unmedicated euthymic bipolar patients compared to healthy controls [64]. Two studies evaluated the relationship between treatment response and soluble IL-2 (sIL-2R) and IL-6 (sIL-6R) receptors with inconsistent results. One study found that patients with rapid cycling bipolar disorder exhibited normalization of the sIL-2R and sIL-6R levels after 30 days of treatment with lithium [65] while another study found no significant change following treatment with valproate for 30 days [66]. Boufidou et al. investigated cytokine production in isolated lymphocytes in 40 euthymic BD patients on chronic lithium therapy and found a significant reduction in cells secreting IL-2, IL-6, IL-10, and IFN-ɣ in patients on lithium compared to healthy controls [67].

HPA Axis

A recent meta-analysis [68] of 41 case–control studies investigating HPA axis activity in 1069 BD patients and 1836 healthy controls showed that BD patients had higher basal cortisol than controls at all time points assessed, and cortisol levels measured over 12 or 24 hours were also significantly higher in bipolar patients compared to controls. Another meta-analysis comparing 19 case–control studies investigating morning cortisol levels revealed increased morning cortisol levels in BD patients compared to controls, with greater morning cortisol levels observed in non-manic BD outpatients [69]. As seen in MDD, patients with BD have frequently been found to be non-suppressors in the dexamethasone suppression test (DST) or DST/CRH combination test, particularly in the depressed or mixed

state [68, 70]. These tests have been proposed as biomarkers to assess HPA axis response to treatment in mood disorders.

Thyroid

Thyroid dysfunction has been frequently observed in patients with BD, with one study indicating that BD patients are 2.55 times more likely to experience thyroid dysfunction compared to healthy controls [71]. Cole et al. studied thyroid function in a group of 65 BD patients treated with mood stabilizers (lithium ($N = 57$, 88%), divalproex, combination, or carbamazepine). Lower free thyroxine index (FTI) values and higher thyroid-stimulating hormone (TSH) levels were significantly associated with a poorer lithium response. Lower TSH combined with higher FTI was associated with a substantially more rapid remission of depression [72]. A 2017 systematic review of 11 studies investigating the relationship between BD and thyroid autoimmunity found an increased prevalence of circulating thyroid autoantibodies in depressed and mixed BD patients; however, no evidence was found to support a relationship between specific autoimmune thyroid diseases and BD. Findings from a study in twins with BD suggested that autoimmune thyroiditis is related to the genetic vulnerability to develop BD rather than the pathogenesis of the disease itself. These findings suggest that thyroid autoantibodies could have potential utility as a biomarker of vulnerability for BD [73].

Brain-Derived Neurotrophic Factor (BDNF)

Lithium may exert its therapeutic action, in part, by upregulating BDNF expression to achieve mood stabilization, suggested by the finding that serum BDNF levels positively correlate with lithium levels [74]. Lithium increases BDNF expression in cultured rodent neurons [75], and platelet BDNF mRNA increases after 8 weeks of medication treatment for BD (lithium, valproate, or atypical antipsychotic) [76]. In one study, chronic administration of mood stabilizers (carbamazepine and lamotrigine) in rats increased BDNF mRNA expression and protein concentrations in the frontal cortex [77]. Increased blood concentrations of BDNF have been reported following treatment with antidepressants or mood stabilizers in BD and other mood disorders [78]. A 16-week open trial of quetiapine XR for BD indicated that independent of clinical response to treatment, serum BDNF concentrations increased in patients with bipolar depression but decreased in manic and mixed patients [79]. There is conflicting data concerning changes in levels of BDNF associated with different medication treatments for BD with some investigators finding changes associated with specific medication treatments [80] and others with discordant findings [81–83]. Suwalska et al. reported that lithium-treated patients as a group had lower BDNF levels compared to healthy controls, and moreover patients that did not respond to lithium had significantly lower BDNF levels compared with healthy control subjects [84]. Several studies have attempted to correlate peripheral BDNF levels to treatment response in acute mania. In one study, a significant increase in plasma BDNF levels was observed after 28 days of lithium monotherapy for acute mania, with 87% of responders showing an increase in BDNF levels after treatment compared to baseline [85].

Tramontina et al. found that BDNF levels were significantly decreased in acutely manic patients when compared to controls; after treatment, however, there was no longer a significant difference observed between the two groups. In the BD patients, a sharp increase in BDNF was observed after effective treatment of acute mania [86]. A systematic review and meta-regression analysis of 3 studies found that BDNF levels increase after treatment for acute mania [87].

Overall, the data suggest that BDNF may play an important role in the pathophysiology of BD and lithium responders may upregulate BDNF in response to treatment. BDNF also appears to be a potential marker for mood state, as it is generally lower during mood episodes in BD and often normalizes in euthymia. There have been conflicting findings, however, and future research should focus on BDNF levels over time, individual patient mood state, and treatment response. Whether peripheral BDNF concentrations represent an index of CNS BDNF activity remains unclear.

Neuroimaging

Although the investigation of imaging techniques to predict treatment response in BD is in its infancy, there are several promising findings. Using (15)O water PET to measure changes in regional cerebral blood flow during an induced sadness task, different activity patterns were demonstrated in BD lithium ($n=9$) and valproate ($N=9$) responders with both groups showing changes in premotor cortex, dorsal anterior cingulate, and anterior insula, and valproate responders showing a larger magnitude of change in most regions. Comparison of the change patterns revealed differences in the rostral anterior cingulate and the dorsolateral prefrontal cortex between lithium and valproate responders [83]. In a small study ($n=20$) using fMRI and proton magnetic resonance spectroscopy (H-MRS) to predict lithium treatment outcome in BD subjects, investigators applied a data algorithm that showed excellent predictive power in determining a good lithium response [88].

A recent systematic review of 60 studies investigating neuroimaging and behavioral predictors of treatment efficacy in unipolar and bipolar patients found that good response to pharmacotherapy for depression was predicted by lower baseline responsivity in limbic regions coupled with heightened medial and dorsal prefrontal responses to emotional stimuli. Alternatively, good treatment response to psychotherapy was predicted by heightened baseline limbic and ventral prefrontal reactivity to emotional stimuli [89].

Genetic Predictors

GWAS findings suggest a genetic component in the response to specific drugs in BD patients. Specifically, several studies suggest that those who respond well to lithium are a genetically unique subset of patients. One prospective GWAS (average follow-up of 12 years) in 247 individuals from 31 families (106 diagnosed

with BD) with a history of good lithium response revealed strong evidence for linkage with a locus on chromosome 15q14 (ACTC, lod score = 3.46, locus-specific p-value = 0.000014). Further analyses of these results suggested that this locus may be associated with the underlying etiology of BD. A possible linkage was also observed for a marker on chromosome 7q11.2 (D7S1816, lod score = 2.68, locus-specific p-value = 0.00011), with further analyses suggesting that this locus could potentially be useful in predicting response to lithium treatment. [90]. Another study by the same group comparing 136 bipolar patients with good lithium response and 163 healthy controls revealed that one polymorphism in the PLCG1 gene was observed at a significantly higher frequency in the lithium-responder bipolar group compared to controls ($p = 0.033$). A follow-up study with a Norwegian population confirmed these findings [91]. PLCG1 gene codes for a gamma-1 isozyme of phospholipase C, an enzyme that plays an important role in the phosphoinositide cycle. This second messenger system is believed to be involved in the mechanism of action of lithium in mood stabilization [92].

A GWAS in 294 BD Type 1 patients of Han Chinese descent revealed a strong association between good treatment response to lithium and two SNPs located in the introns of glutamic acid decarboxylase–like protein 1 (GADL1): rs17026688 ($p = 5.50 \times 10^{-37}$) and rs17026651 ($i = 2.52 \times 10^{-37}$). These two SNPs had 93% sensitivity for predicting lithium response and differentiated between patients with a good and poor response [93]. These findings were not replicated in a follow-up study in an Indian population [94].

In a recent GWAS on 2586 BD patients, the International Consortium on Lithium Genetics [95] assessed response to lithium treatment. A polygenic score for schizophrenia (PGS) was constructed using estimates from 36, 989 schizophrenia patients and cross-trait analysis was performed. A high polygenic score for schizophrenia was inversely associated ($p < 0.05$) with a good lithium response [96]. This finding concurs with evidence that patients with BD with a family history of schizophrenia have a poor response to lithium [95].

Circadian rhythm dysfunction has been posited to be involved in the pathogenesis of BD. A recent prospective study following 170 BPD patients over a 27-year period investigated the influence of polymorphisms in the Rev-erb-alpha gene, an important component of the mammalian circadian rhythm cycle, on response to lithium treatment. Patients carrying the T allele for the rs2314339 SNP were 3.5 times more likely to show no improvement from lithium prophylaxis or to experience worsened symptoms with treatment [97].

Multiple studies have found associations between lithium response and polymorphisms in the serotonin transporter gene 5-HTTLPR. Serretti et al. found that individuals with the s/s variant of the gene showed a poorer lithium response compared to those with l/s or l/l variant [98]. A follow-up study replicated the finding of better response in the l/s variant but did not reveal a significantly poorer response in individuals with the s/s variant [2]. Another study found that the s/s genotype variant and s allele were significantly more frequent in patients who did not respond to lithium compared to patients with a partial or excellent response to lithium [99].

The Val158Met polymorphism in the COMT gene may have predictive value for treatment response to mood stabilizers. Lee et al. conducted a study in a Korean population with 144 manic BDI patients and 157 controls and found that the Met/Met genotype was more frequent in nonresponders to mood stabilizers (lithium, valproate, or carbamazepine) than in treatment responders. There were no significant differences between BD patients and controls [100].

There has been an association reported between treatment response to valproate and the 116C/G polymorphism in the promoter region of the X-box-binding protein 1 (XBP1). In a sample of 51 BD patients, the G allele was associated with a better response to valproate compared to the C allele. An association has also been observed between the 116C/G polymorphism and clinical response to lithium [58].

Schizophrenia and Schizoaffective Disorders

Overview of Treatment

Schizophrenia is a devastating disease with enormous variability in presentation and treatment response. It is widely believed to be a neurodevelopmental disorder with early alterations in neuronal migration leading to absent and aberrant connections that alter development of surrounding cerebral regions. Many of the causative factors involved in the etiology of schizophrenia likely exist at birth, but do not become apparent until late adolescence/early adulthood as a result of environmental and genetic factors. This makes identification of biomarkers in schizophrenia challenging, as some abnormalities may occur years before disease presentation and may no longer be detectable at the time of disease presentation [101]. Treatment of schizophrenia largely involves the use of antipsychotic medications. A meta-analysis of 65 trials involving 6493 patients showed that treatment response to antipsychotics was superior compared with placebo, evidenced by relapse and readmission rates less than half in the medication groups compared to placebo groups. With maintained medication adherence, relapse rates did not change after several years of treatment [102]. There are a number of antipsychotic drugs, but all block dopamine D2 receptors which are considered to be key to antipsychotic efficacy. Various antipsychotics have differing actions on other neurotransmitter receptors/systems and their side effect profiles differ accordingly. As with the other treatments discussed in this chapter, there is not an abundance of evidence to guide antipsychotic drug choice, and side effect profile and clinician preference weigh heavily in decision-making. As with other medications discussed, side effects can be troubling and, in some cases, long-lasting. Positive treatment response is associated with long-term functional improvement, and being able to efficiently choose the right drug for the right patient can have profound implications. With the exception of clozapine which is clearly effective in many patients who have failed treatment with other antipsychotics, all of the other agents have equal efficacy [2].

Peripheral Biomarkers

Inflammatory Markers

Inflammation has long been posited to play a role in the pathophysiology of schizophrenia, and several studies have revealed elevated inflammatory markers in schizophrenic patients. Multiple studies revealed that CRP concentrations were higher in schizophrenic patients when compared to healthy controls, with some studies demonstrating higher CRP levels associated with more severe symptoms as determined by the Positive and Negative Syndrome Scale (PANSS) [103].

A meta-analysis by Miller et al. included 40 studies investigating levels of various cytokines in acutely relapsed schizophrenic (AR) patients and/or patients with first episode psychosis (FEP). In AR patients, blood IL-10 levels were significantly decreased ($p \leq 0.006$) and IL-6, IL-8, TNF-α, IFN-γ, transforming growth factor-β (TGF-β), and IL-1RA levels were significantly increased when compared with control subjects ($p \leq 0.02$ for all). There were no significant differences in blood levels of IL-2 or soluble IL-2 receptor (sIL-2R) between AR and control subjects. The most replicated finding (5/6 studies) was significantly increased IL-6 in AR compared to control subjects. In first episode psychosis patients, blood IL-1β, IL-6, IL-12, IFN-γ, TNF-α, TGF-β, and sIL-2R levels were significantly increased compared to control subjects ($p \leq 0.003$ for all). There was no significant difference observed in blood IL-2 levels between FEP and control subjects. The most replicated finding was for TNF-α, which was increased in FEP subjects in all four studies analyzed [104]. The same group also investigated the effect of antipsychotic treatment on cytokine levels in 488 patients after an acute exacerbation of schizophrenia. After a mean of 53 days of treatment with antipsychotics (which were not standardized in seven (58%) of the studies included in the analysis), there was a significant decrease in IL-1β, IL-6, and TGF-β ($p \leq 0.005$ for all) and a significant increase in sIL-2R ($p = 0.04$) and IL-12 ($p = 0.02$) levels [104]. Another meta-analysis by Tourjman et al. that included 23 follow-up studies in 762 subjects found an increase of sIL-2 and decrease of IL-1β and IFN-γ levels after treatment with antipsychotics [105]. A longitudinal study in 68 FEP patients found that those who did not respond to 12 weeks of antipsychotic treatment had higher pretreatment IL-6 and IFN-γ levels compared to patients who did respond [106].

HPA Axis

HPA axis dysfunction may potentially play a role in the pathophysiology of schizophrenia, but studies have yielded conflicting results. Patients with schizophrenia have been found to exhibit elevated basal levels of cortisol [69] and non-suppression of cortisol in response to a DST compared to controls [103]. However, findings have been inconsistent, with studies showing both hyper- and hypoactivity of the HPA axis [107]. Some studies have shown decreases in cortisol after treatment with atypical antipsychotics (olanzapine, clozapine, quetiapine) and increases after treatment with typical antipsychotics (fluphenazine) [107].

BDNF

Peripheral BDNF levels could also have potential clinical utility in monitoring therapeutic response to antipsychotics in patients with schizophrenia and/or first-onset psychosis. Significantly decreased CSF BDNF concentrations have been reported, as well as in the hippocampus and prefrontal cortex of schizophrenic patients compared to controls [103]. A meta-analysis of 16 studies comparing plasma BDNF levels in schizophrenic patients versus healthy controls found a moderate reduction in schizophrenic patients [108]. Studies investigating the effect of antipsychotic treatment on peripheral BDNF levels in schizophrenia have yielded inconsistent results. In the previously mentioned meta-analysis, no significant difference in BDNF levels was observed between medicated and medication-naive schizophrenic patients. One study found a significant correlation between clozapine and BDNF levels, with the implication that clozapine may promote cognitive enhancement in schizophrenic patients [103]. Laboratory animal studies revealed that haloperidol and risperidone decreased BDNF mRNA expression and protein levels in multiple areas of the brain, including the hippocampus and prefrontal cortex. BDNF levels in the rat hippocampus normalized after switching from haloperidol treatment to olanzapine [103].

Neuroimaging

There have been relatively few studies of neuroimaging biomarkers in schizophrenia. Kapur et al. [109] studied the response to haloperidol in 21 patients with schizophrenia. The responders had significantly higher dopamine D2 receptor occupancy, as determined with raclopride and PET, after two weeks of treatment ($p<0.009$). Using it as a predictor with a 65% cutoff, D2 occupancy provided optimal separation: 80% of the responders were above it and 67% of nonresponders were below ($p=0.04$, Fisher's exact test). A study done in 51 adolescents and young adults at clinical high risk (CHR) for psychosis and 47 matched healthy controls used resting-state fMRI to systematically characterize functional connectivity (FC) and determine if abnormalities in FC during this period are associated with psychosis risk and severity of psychosis. The findings revealed between-group differences in whole-brain connectivity patterns of bilateral temporal regions, primarily affecting functional connections to the thalamus, which is consistent with well-established FC abnormalities observed in the thalamus and temporal regions of schizophrenic patients. In those individuals who went on to develop psychosis over the next 3.9 years ($N=12$), more severe positive symptoms were associated with greater FC abnormalities in the anterior cingulate and frontal cortex [110].

Genetic Predictors

Schizophrenia is thought to be one of the most heritable of the psychiatric disorders, with genetics contributing to 50–80% of risk. However, studies to date have

demonstrated that schizophrenia is genetically complex with a large polygenic component [6]. In a GWAS study of 117 Chinese Han patients with schizophrenia, Reynolds et al. [111] investigated the dopamine 3 (D3), D2 and the 5-HT2C receptor promoter polymorphisms following 10 weeks of antipsychotic treatment with risperidone or chlorpromazine. The D3 receptor polymorphism was significantly associated with both improved symptoms and behavioral symptomatology on admission. The 5-HT2C receptor polymorphism was associated with treatment improvement but not baseline behavioral symptoms. Another study [112] of genetic variation underlying individual differences in response to a variety of antipsychotic medications in 738 subjects with schizophrenia found that two SNPs mediated the effect of ziprasidone on positive symptoms: rs17390445 on chromosome 4p15, with a q-value of slightly less than 0.05 ($p = 9.8$ Å ~ 10), and rs11722719 with a q-value of less than 0.15 ($p = 5.4$ Å ~ 10). SNP rs7968606 in the ANKS1B gene showed a q-value of 0.16 ($p = 3.2$ Å ~ 10) for mediating the effect of olanzapine on negative symptoms. Two SNPs were found to mediate the effect of risperidone on negative symptoms: rs17727261 in the CNTNAP5 gene with a q-value of 0.13 ($p = 5.4$ Å ~ 10) and rs17815774 in the TRPM1 gene, with a q-value of 0.4 ($p = 3.3$ Å ~ 10) [112].

Zhang et al. [113] scrutinized a dopamine D2 receptor (DRD2) locus in a large-scale GWAS from the Psychiatric Genomics Consortium [114] to investigate whether the rs2514218 SNP could predict antipsychotic response in a cohort of 100 FEP patients, half treated with risperidone and half with aripiprazole for 12 weeks. Linear mixed model analysis showed that homozygotes for the risk (C) allele had a significantly greater reduction in positive symptoms during 12 weeks of treatment compared with the T allele carriers ($p = 0.044$). Ikeda et al. [115] also showed that an SNP in DRD2 was a significant predictor of the response to risperidone along with an SNP in TaqIA and two SNPs in AKT1.

Multiple studies have found a significant association between the BDNF Val66Met polymorphism and antipsychotic treatment response, showing a higher frequency of the Val/Val homozygous genotype in patients with good clinical response to antipsychotic treatment (clozapine or olanzapine) compared to nonresponders. However, subsequent studies failed to confirm the association between the BDNF Val66Met polymorphism and treatment response to clozapine [103].

Electrophysiologic Biomarkers

Mismatch negativity (MMN) is an event-related potential response, passively evoked when a sequence of repetitive standard auditory stimuli are interrupted by deviations in pitch or duration and represents an automatic, preconscious process of detecting a mismatch between auditory sensory memory and deviant stimuli. In dozens of trials over the last 20 years, reduced MMN amplitude has consistently been found in schizophrenic patients compared to healthy controls [116–119]. A meta-analysis of 32 studies found that the effect sizes of MMN reduction were significantly correlated with duration of illness, suggesting that this may be a useful index of progression of neuropathologic changes in schizophrenia. In a study

by Lee et al. of 25 patients with schizophrenia, 21 first-degree relatives and 29 healthy controls, MMN was a stronger predictor of functional outcomes in schizophrenia than neurocognition or theory of mind [117]. A similar study found that higher MMN activity in frontocentral regions of schizophrenic patients was correlated with better social perception, work, and independent living. [116]. While MMN is one of the most promising biomarkers for tracking response to therapeutic interventions in schizophrenia, it has yet to be used to study response to specific medication. [118]. Targeting early auditory perceptual processing in schizophrenic patients with MMN deficits in an effort to decrease the deficit has been hypothesized to improve cognitive and psychosocial functioning. Targeted cognitive training (TCT) uses neuroplasticity-based computerized cognitive tasks with the ultimate goal of inducing plastic changes within the neural substrates of low-level information processing, which in turn leads to improvement in higher order cognitive operations [120]. One study of 55 clinically stable schizophrenic patients found that subjects randomly assigned to 50 hours of TCT showed significant improvements in verbal working memory ($p<0.05$), verbal learning, verbal memory, and global cognition ($p<0.01$). [121]. Multiple clinical trials have demonstrated that changes in MMN are detectable in early stages of cognitive training, predict generalized improvements in higher order cognitive domains, and correspond to objective changes of cortical plasticity [118]. While these trials have shown promise at a group level, individual responses to TCT are variable and it is important to identify which patients are most likely to benefit as it is very resource and time-consuming [120]. Several trials have demonstrated that a larger baseline MMN predicted greater response to TCT, [101, 122] and in one smaller trial with 13 schizophrenic patients, it predicted greater response to a 3-month social skills training program [123]. This suggests that higher baseline MMN could be used to identify patients who are more likely to respond to TCT and social skills training.

Conclusions/Future Directions

Although the field of precision medicine for psychiatry is in its infancy, there are a number of studies that have found promising associations between a variety of biomarkers and clinical response to psychopharmacological treatment. These biomarkers include neuroimaging, electrophysiology, peripheral serum measures of HPA activity and inflammation, single nucleotide polymorphisms, and others.

Although some neuroimaging studies have shown promise in response prediction, the findings have not been overwhelmingly consistent. This fact, combined with the expense and limited accessibility to neuroimaging (especially of PET) in many front-line settings has limited the clinical utility of neuroimaging as a biomarker.

In recent years, DNA sequencing has become substantially more efficient and affordable, with the cost of DNA sequencing of a single human subject reduced from $300 million in 2001 to $1000 in 2014 [124]. Extensive GWAS investigation has revealed genetic variants linked with the risk for a number of psychiatric

disorders. However, the contribution of individual gene variants appears to be small, and in many cases, follow-up studies have failed to consistently replicate the initial findings. One potential area for improvement is the expansion to include transcriptomics (the study of all expressed messenger RNA (mRNA)) and proteomics (study of expressed proteins). It is estimated that 98% of the human genome is not translated into protein, and multiple epigenetic changes (DNA methylation, histone modification, alternative splicing, RNA editing, and nontranscriptional gene silencing via microRNAs) occur as DNA is transcribed into RNA, which is subsequently translated into proteins. The ability to analyze all of these processes would immensely improve the knowledge base and could enhance the ability to make informed treatment decisions [6].

Another promising area is combinatorial pharmacogenetic testing, which has been attracting more attention in recent years with over 30 tools commercially available [55]. However, the clinical applicability of these tests is questionable as the companies that market them often do not report the specific genetic variants that are included in the tests and fail to disclose how the pharmacogenetic algorithms integrate and weigh important genetic variants [55]. In addition, the literature investigating the clinical efficacy is limited by small sample size and lack of scientific rigor with the majority of studies sponsored by the companies that market the tests or institutions with a commercial stake in the tests used [56]. As such, there is currently insufficient evidence to justify the widespread clinical use of these tests and further investigation is warranted with blinded, randomized controlled trials in larger samples.

Although biomarkers have promise in guiding future treatment of psychiatric disorders, one single biomarker is unlikely to definitively determine the most ideal treatment option but rather a combination of different biomarkers should be considered. The International Study to Predict Optimized Treatment in Depression (iSPOT-D) [125] is a large ongoing trial that aims to identify genetic, behavioral, and biological predictors of treatment response to commonly used antidepressants (escitalopram, venlafaxine-XR, sertraline) in order to ultimately develop a treatment model that incorporates a variety of predictors and moderators. These data are still being analyzed but have already provided an abundance of valuable data.

Biomarkers can have some predictive value with regard to treatment response, but it is important to consider the role of these biomarkers combined with behavioral and physiologic data captured in a naturalistic setting. Mobile health (mHealth) is a growing field that utilizes multiple tools and resources such as mobile and wireless communication devices to deliver and improve healthcare services, outcomes, and research. This technology aims to incorporate remotely acquired patient data (self-report mood scales, exposure to stressful environmental triggers, etc.) with biomarker data to enhance clinical outcomes. This field is rapidly expanding to also collect physiologic data using mobile biosensor devices to assess measures such as autonomic nervous system functioning, electrodermal activity, ECG, and breath alcohol or carbon monoxide levels [126].

Ultimately, the best model for precision medicine in complex, multifactorial diseases such as psychiatric illnesses will likely involve integrated methodology

that combines information from multiple sources including biologic, clinical, and environmental data. While much progress has been made in the development of valid biomarkers in psychiatric disorders, there is much work to be done in determining their clinical utility.

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References

1. Gadad BS, Jha MK, Czysz A, et al. Peripheral biomarkers of major depression and antidepressant treatment response: current knowledge and future outlooks. J Affect Disord. 2018;233:3–14.
2. Stern S, Linker S, Vadodaria KC, Marchetto MC, Gage FH. Prediction of response to drug therapy in psychiatric disorders. Open Biol. 2018;8(5).
3. Garraway LA, Verweij J, Ballman KV. Precision oncology: an overview. J Clin Oncol. 2013;31(15):1803–5.
4. Biologically-inspired biomarkers for mental disorders. EBioMedicine. 2017;17:1–2.
5. Miller DB, O'Callaghan JP. Personalized medicine in major depressive disorder—opportunities and pitfalls. Metabolism. 2013;62(Suppl 1):S34–9.
6. Ozomaro U, Wahlestedt C, Nemeroff CB. Personalized medicine in psychiatry: problems and promises. BMC Med. 2013;11:132.
7. Nemeroff CB. The holy grail of psychiatry. Cerebrum. 2015;2015.
8. Petkova E, Ogden RT, Tarpey T, et al. Statistical analysis plan for stage 1 EMBARC (establishing moderators and biosignatures of antidepressant response for clinical care) study. Contemp Clin Trials Commun. 2017;6:22–30.
9. Nemeroff CB, Widerlov E, Bissette G, et al. Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. Science. 1984;226(4680):1342–4.
10. Perna GBR, Nemeroff CB. Precision psychiatry: personalized clinical approach to depression. In: Kim YK, editor. Understanding depression, vol. 1. Singapore: Springer; 2018. p. 245–62.
11. Binder EB, Kunzel HE, Nickel T, et al. HPA-axis regulation at in-patient admission is associated with antidepressant therapy outcome in male but not in female depressed patients. Psychoneuroendocrinology. 2009;34(1):99–109.
12. Greden JF, Gardner R, King D, Grunhaus L, Carroll BJ, Kronfol Z. Dexamethasone suppression tests in antidepressant treatment of melancholia. The process of normalization and test-retest reproducibility. Arch Gen Psychiatry. 1983;40(5):493–500.

13. Nemeroff CB. Paradise lost: the neurobiological and clinical consequences of child abuse and neglect. Neuron. 2016;89(5):892–909.
14. Nemeroff CB. Clinical significance of psychoneuroendocrinology in psychiatry: focus on the thyroid and adrenal. J Clin Psychiatry. 1989;50 Suppl:13–20; discussion 21–12.
15. Hage MP, Azar ST. The link between thyroid function and depression. J Thyroid Res. 2012;2012:590648.
16. Musselman DL, Nemeroff CB. Depression and endocrine disorders: focus on the thyroid and adrenal system. Br J Psychiatry Suppl. 1996;30:123–8.
17. Eller T, Metskula K, Talja I, Maron E, Uibo R, Vasar V. Thyroid autoimmunity and treatment response to escitalopram in major depression. Nord J Psychiatry. 2010;64(4):253–7.
18. Kirkegaard C, Norlem N, Lauridsen UB, Bjorum N. Prognostic value of thyrotropin-releasing hormone stimulation test in endogenous depression. Acta Psychiatr Scand. 1975;52(3):170–7.
19. Amsterdam JD, Fava M, Maislin G, Rosenbaum J, Hornig-Rohan M. TRH stimulation test as a predictor of acute and long-term antidepressant response in major depression. J Affect Disord. 1996;38(2–3):165–72.
20. Gendall KA, Joyce PR, Mulder RT, Luty SE. Thyroid indices and response to fluoxetine and nortriptyline in major depression. J Psychopharmacol. 2003;17(4):431–7.
21. Joffe RT, Singer W. The effect of tricyclic antidepressants on basal thyroid hormone levels in depressed patients. Pharmacopsychiatry. 1990;23(2):67–9.
22. Kusalic M, Engelsmann F, Bradwejn J. Thyroid functioning during treatment for depression. J Psychiatry Neurosci. 1993;18(5):260–3.
23. Brady KT, Anton RF. The thyroid axis and desipramine treatment in depression. Biol Psychiatry. 1989;25(6):703–9.
24. Iosifescu DV, Nierenberg AA, Mischoulon D, et al. An open study of triiodothyronine augmentation of selective serotonin reuptake inhibitors in treatment-resistant major depressive disorder. J Clin Psychiatry. 2005;66(8):1038–42.
25. Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. J Affect Disord. 2013;150(3):736–44.
26. Hiles SA, Baker AL, de Malmanche T, Attia J. Interleukin-6, C-reactive protein and interleukin-10 after antidepressant treatment in people with depression: a meta-analysis. Psychol Med. 2012;42(10):2015–26.
27. Chang HH, Lee IH, Gean PW, et al. Treatment response and cognitive impairment in major depression: association with C-reactive protein. Brain Behav Immun. 2012;26(1):90–5.
28. Jha MK, Minhajuddin A, Gadad BS, et al. Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial. Psychoneuroendocrinology. 2017;78:105–13.
29. Miller AH, Trivedi MH, Jha MK. Is C-reactive protein ready for prime time in the selection of antidepressant medications? Psychoneuroendocrinology. 2017;84:206.
30. Raison CL, Rutherford RE, Woolwine BJ, et al. A randomized controlled trial of the tumor necrosis factor antagonist infliximab for treatment-resistant depression: the role of baseline inflammatory biomarkers. JAMA Psychiatry. 2013;70(1):31–41.
31. Dahl J, Ormstad H, Aass HC, et al. The plasma levels of various cytokines are increased during ongoing depression and are reduced to normal levels after recovery. Psychoneuroendocrinology. 2014;45:77–86.
32. Hannestad J, DellaGioia N, Bloch M. The effect of antidepressant medication treatment on serum levels of inflammatory cytokines: a meta-analysis. Neuropsychopharmacology. 2011;36(12):2452–9.
33. Schroeter ML, Abdul-Khaliq H, Diefenbacher A, Blasig IE. S100B is increased in mood disorders and may be reduced by antidepressive treatment. NeuroReport. 2002;13(13):1675–8.
34. Schroeter ML, Sacher J, Steiner J, Schoenknecht P, Mueller K. Serum S100B represents a new biomarker for mood disorders. Curr Drug Targets. 2013;14(11):1237–48.

35. Jang BS, Kim H, Lim SW, Jang KW, Kim DK. Serum S100B levels and major depressive disorder: its characteristics and role in antidepressant response. Psychiatry Investig. 2008;5(3):193–8.
36. Fu CH, Steiner H, Costafreda SG. Predictive neural biomarkers of clinical response in depression: a meta-analysis of functional and structural neuroimaging studies of pharmacological and psychological therapies. Neurobiol Dis. 2013;52:75–83.
37. McGrath CL, Kelley ME, Holtzheimer PE, et al. Toward a neuroimaging treatment selection biomarker for major depressive disorder. JAMA Psychiatry. 2013;70(8):821–9.
38. McGrath CL, Kelley ME, Dunlop BW, Holtzheimer PE 3rd, Craighead WE, Mayberg HS. Pretreatment brain states identify likely nonresponse to standard treatments for depression. Biol Psychiatry. 2014;76(7):527–35.
39. Dunlop BW, Rajendra JK, Craighead WE, et al. Functional connectivity of the subcallosal cingulate cortex and differential outcomes to treatment with cognitive-behavioral therapy or antidepressant medication for major depressive disorder. Am J Psychiatry. 2017;174(6):533–45.
40. Dichter GS, Gibbs D, Smoski MJ. A systematic review of relations between resting-state functional-MRI and treatment response in major depressive disorder. J Affect Disord. 2015;172:8–17.
41. Widge AS, Bilge MT, Montana R, Chang W, Rodriguez CI, Deckersbach T, Carpenter LL, Kalin NH, Nemeroff CB. Electroencephalographic biomarkers for treatment response prediction in major depressive illness: a meta-analysis. Am J Psychiatry. 2018 (In Press).
42. Tansey KE, Guipponi M, Hu X, et al. Contribution of common genetic variants to antidepressant response. Biol Psychiatry. 2013;73(7):679–82.
43. Ising M, Lucae S, Binder EB, et al. A genomewide association study points to multiple loci that predict antidepressant drug treatment outcome in depression. Arch Gen Psychiatry. 2009;66(9):966–75.
44. O'Connell CP, Goldstein-Piekarski AN, Nemeroff CB, et al. Antidepressant outcomes predicted by genetic variation in corticotropin-releasing hormone binding protein. Am J Psychiatry. 2017:appiajp201717020172.
45. Binder EB, Owens MJ, Liu W, et al. Association of polymorphisms in genes regulating the corticotropin-releasing factor system with antidepressant treatment response. Arch Gen Psychiatry. 2010;67(4):369–79.
46. Binder EB, Salyakina D, Lichtner P, et al. Polymorphisms in FKBP5 are associated with increased recurrence of depressive episodes and rapid response to antidepressant treatment. Nat Genet. 2004;36(12):1319–25.
47. Smits KM, Smits LJ, Peeters FP, et al. The influence of 5-HTTLPR and STin2 polymorphisms in the serotonin transporter gene on treatment effect of selective serotonin reuptake inhibitors in depressive patients. Psychiatr Genet. 2008;18(4):184–90.
48. Porcelli S, Drago A, Fabbri C, Gibiino S, Calati R, Serretti A. Pharmacogenetics of antidepressant response. J Psychiatry Neurosci. 2011;36(2):87–113.
49. Durham LK, Webb SM, Milos PM, Clary CM, Seymour AB. The serotonin transporter polymorphism, 5HTTLPR, is associated with a faster response time to sertraline in an elderly population with major depressive disorder. Psychopharmacology. 2004;174(4):525–9.
50. Arias B, Catalan R, Gasto C, Gutierrez B, Fananas L. 5-HTTLPR polymorphism of the serotonin transporter gene predicts non-remission in major depression patients treated with citalopram in a 12-weeks follow up study. J Clin Psychopharmacol. 2003;23(6):563–7.
51. Peters EJ, Slager SL, McGrath PJ, Knowles JA, Hamilton SP. Investigation of serotonin-related genes in antidepressant response. Mol Psychiatry. 2004;9(9):879–89.
52. Pollock BG, Ferrell RE, Mulsant BH, et al. Allelic variation in the serotonin transporter promoter affects onset of paroxetine treatment response in late-life depression. Neuropsychopharmacology. 2000;23(5):587–90.
53. Kato M, Fukuda T, Wakeno M, et al. Effect of 5-HT1A gene polymorphisms on antidepressant response in major depressive disorder. Am J Med Genet B Neuropsychiatr Genet. 2009;150B(1):115–23.

54. Illi A, Setala-Soikkeli E, Viikki M, et al. 5-HTR1A, 5-HTR2A, 5-HTR6, TPH1 and TPH2 polymorphisms and major depression. NeuroReport. 2009;20(12):1125–8.
55. Zeier Z, Carpenter LL, Kalin NH, et al. Clinical implementation of pharmacogenetic decision support tools for antidepressant drug prescribing. Am J Psychiatry. 2018:appiajp201817111282.
56. Zubenko GS, Sommer BR, Cohen BM. On the marketing and use of pharmacogenetic tests for psychiatric treatment. JAMA Psychiatry. 2018.
57. Oedegaard KJ, Alda M, Anand A, et al. The pharmacogenomics of bipolar disorder study (PGBD): identification of genes for lithium response in a prospective sample. BMC Psychiatry. 2016;16:129.
58. Geoffroy PA, Bellivier F, Leboyer M, Etain B. Can the response to mood stabilizers be predicted in bipolar disorder? Front Biosci (Elite Ed). 2014;6:120–38.
59. Berk M, Hallam KT, McGorry PD. The potential utility of a staging model as a course specifier: a bipolar disorder perspective. J Affect Disord. 2007;100(1–3):279–81.
60. Perry A, Tarrier N, Morriss R, McCarthy E, Limb K. Randomised controlled trial of efficacy of teaching patients with bipolar disorder to identify early symptoms of relapse and obtain treatment. BMJ. 1999;318(7177):149–53.
61. Kim YK, Jung HG, Myint AM, Kim H, Park SH. Imbalance between pro-inflammatory and anti-inflammatory cytokines in bipolar disorder. J Affect Disord. 2007;104(1–3):91–5.
62. Kim YK, Suh IB, Kim H, et al. The plasma levels of interleukin-12 in schizophrenia, major depression, and bipolar mania: effects of psychotropic drugs. Mol Psychiatry. 2002;7(10):1107–14.
63. Su KP, Leu SJ, Yang YY, Shen WW, Chou YM, Tsai SY. Reduced production of interferon-gamma but not interleukin-10 in bipolar mania and subsequent remission. J Affect Disord. 2002;71(1–3):205–9.
64. Guloksuz S, Cetin EA, Cetin T, Deniz G, Oral ET, Nutt DJ. Cytokine levels in euthymic bipolar patients. J Affect Disord. 2010;126(3):458–62.
65. Rapaport MH, Guylai L, Whybrow P. Immune parameters in rapid cycling bipolar patients before and after lithium treatment. J Psychiatr Res. 1999;33(4):335–40.
66. Maes M, Bosmans E, Calabrese J, Smith R, Meltzer HY. Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. J Psychiatr Res. 1995;29(2):141–52.
67. Boufidou F, Nikolaou C, Alevizos B, Liappas IA, Christodoulou GN. Cytokine production in bipolar affective disorder patients under lithium treatment. J Affect Disord. 2004;82(2):309–13.
68. Belvederi Murri M, Prestia D, Mondelli V, et al. The HPA axis in bipolar disorder: systematic review and meta-analysis. Psychoneuroendocrinology. 2016;63:327–42.
69. Girshkin L, Matheson SL, Shepherd AM, Green MJ. Morning cortisol levels in schizophrenia and bipolar disorder: a meta-analysis. Psychoneuroendocrinology. 2014;49:187–206.
70. Gonzalez SD, Williams AJ, Blacker CJ, et al. Putative biological predictors of treatment response in bipolar disorders. Personalized Medicine in Psychiatry. 2017;1–2:39–58.
71. Krishna VN, Thunga R, Unnikrishnan B, et al. Association between bipolar affective disorder and thyroid dysfunction. Asian J Psychiatr. 2013;6(1):42–5.
72. Cole DP, Thase ME, Mallinger AG, et al. Slower treatment response in bipolar depression predicted by lower pretreatment thyroid function. Am J Psychiatry. 2002;159(1):116–21.
73. Barbuti M, Carvalho AF, Kohler CA, et al. Thyroid autoimmunity in bipolar disorder: a systematic review. J Affect Disord. 2017;221:97–106.
74. Tunca Z, Ozerdem A, Ceylan D, et al. Alterations in BDNF (brain derived neurotrophic factor) and GDNF (glial cell line-derived neurotrophic factor) serum levels in bipolar disorder: the role of lithium. J Affect Disord. 2014;166:193–200.
75. Hashimoto R, Takei N, Shimazu K, Christ L, Lu B, Chuang DM. Lithium induces brain-derived neurotrophic factor and activates TrkB in rodent cortical neurons: an essential step for neuroprotection against glutamate excitotoxicity. Neuropharmacology. 2002;43(7):1173–9.

76. Pandey GN, Rizavi HS, Dwivedi Y, Pavuluri MN. Brain-derived neurotrophic factor gene expression in pediatric bipolar disorder: effects of treatment and clinical response. J Am Acad Child Adolesc Psychiatry. 2008;47(9):1077–85.
77. Chang YC, Rapoport SI, Rao JS. Chronic administration of mood stabilizers upregulates BDNF and bcl-2 expression levels in rat frontal cortex. Neurochem Res. 2009;34(3):536–41.
78. Gonzalez SD, Williams AJ, Blacker CJ, Voort JLV, Schak KM, Nemeroff CB, Widge AS, Tohen M. Putative biological predictors of treatment response in bipolar disorders. Pers Med Psychiatry. 2017;1–2:39–58.
79. Grande I, Kapczinski F, Stertz L, et al. Peripheral brain-derived neurotrophic factor changes along treatment with extended release quetiapine during acute mood episodes: an open-label trial in drug-free patients with bipolar disorder. J Psychiatr Res. 2012;46(11):1511–4.
80. Dias VV, Brissos S, Frey BN, Andreazza AC, Cardoso C, Kapczinski F. Cognitive function and serum levels of brain-derived neurotrophic factor in patients with bipolar disorder. Bipolar Disord. 2009;11(6):663–71.
81. Barbosa IG, Huguet RB, Mendonca VA, et al. Increased plasma levels of brain-derived neurotrophic factor in patients with long-term bipolar disorder. Neurosci Lett. 2010;475(2):95–8.
82. Fernandes BS, Gama CS, Kauer-Sant'Anna M, Lobato MI, Belmonte-de-Abreu P, Kapczinski F. Serum brain-derived neurotrophic factor in bipolar and unipolar depression: a potential adjunctive tool for differential diagnosis. J Psychiatr Res. 2009;43(15):1200–4.
83. Kruger S, Alda M, Young LT, Goldapple K, Parikh S, Mayberg HS. Risk and resilience markers in bipolar disorder: brain responses to emotional challenge in bipolar patients and their healthy siblings. Am J Psychiatry. 2006;163(2):257–64.
84. Suwalska A, Sobieska M, Rybakowski JK. Serum brain-derived neurotrophic factor in euthymic bipolar patients on prophylactic lithium therapy. Neuropsychobiology. 2010;62(4):229–34.
85. de Sousa RT, van de Bilt MT, Diniz BS, et al. Lithium increases plasma brain-derived neurotrophic factor in acute bipolar mania: a preliminary 4-week study. Neurosci Lett. 2011;494(1):54–6.
86. Tramontina JF, Andreazza AC, Kauer-Sant'anna M, et al. Brain-derived neurotrophic factor serum levels before and after treatment for acute mania. Neurosci Lett. 2009;452(2):111–3.
87. Fernandes BS, Gama CS, Cereser KM, et al. Brain-derived neurotrophic factor as a state-marker of mood episodes in bipolar disorders: a systematic review and meta-regression analysis. J Psychiatr Res. 2011;45(8):995–1004.
88. Fleck DE, Ernest N, Adler CM, et al. Prediction of lithium response in first-episode mania using the LITHium Intelligent Agent (LITHIA): pilot data and proof-of-concept. Bipolar Disord. 2017;19(4):259–72.
89. Seeberg I, Kjaerstad HL, Miskowiak KW. Neural and behavioral predictors of treatment efficacy on mood symptoms and cognition in mood disorders: a systematic review. Front Psychiatry. 2018;9(337).
90. Turecki G, Grof P, Grof E, et al. Mapping susceptibility genes for bipolar disorder: a pharmacogenetic approach based on excellent response to lithium. Mol Psychiatry. 2001;6(5):570–8.
91. Lovlie R, Berle JO, Stordal E, Steen VM. The phospholipase C-gamma1 gene (PLCG1) and lithium-responsive bipolar disorder: re-examination of an intronic dinucleotide repeat polymorphism. Psychiatr Genet. 2001;11(1):41–3.
92. Turecki G, Grof P, Cavazzoni P, et al. Evidence for a role of phospholipase C-gamma1 in the pathogenesis of bipolar disorder. Mol Psychiatry. 1998;3(6):534–8.
93. Chen CH, Lee CS, Lee MT, et al. Variant GADL1 and response to lithium therapy in bipolar I disorder. N Engl J Med. 2014;370(2):119–28.
94. Kotambail A, Mathur A, Bhat SM, Rai PS, Sharma PS, Satyamoorthy K. GADL1 gene polymorphisms and lithium response in bipolar I disorder: lack of association from an Indian population. Psychiatr Genet. 2015;25(1):39–40.

95. International Consortium on Lithium G, Amare AT, Schubert KO, et al. Association of polygenic score for schizophrenia and HLA antigen and inflammation genes with response to lithium in bipolar affective disorder: a genome-wide association study. JAMA Psychiatry. 2018;75(1):65–74.
96. Duffy A, Alda M, Milin R, Grof P. A consecutive series of treated affected offspring of parents with bipolar disorder: is response associated with the clinical profile? Can J Psychiatry. 2007;52(6):369–76.
97. Campos-de-Sousa S, Guindalini C, Tondo L, et al. Nuclear receptor rev-erb-{alpha} circadian gene variants and lithium carbonate prophylaxis in bipolar affective disorder. J Biol Rhythms. 2010;25(2):132–7.
98. Serretti A, Lilli R, Mandelli L, Lorenzi C, Smeraldi E. Serotonin transporter gene associated with lithium prophylaxis in mood disorders. Pharmacogenomics J. 2001;1(1):71–7.
99. Rybakowski JK, Suwalska A, Czerski PM, Dmitrzak-Weglarz M, Leszczynska-Rodziewicz A, Hauser J. Prophylactic effect of lithium in bipolar affective illness may be related to serotonin transporter genotype. Pharmacol Rep. 2005;57(1):124–7.
100. Lee HY, Kim YK. Catechol-O-methyltransferase Val158Met polymorphism affects therapeutic response to mood stabilizer in symptomatic manic patients. Psychiatry Res. 2010;175(1–2):63–6.
101. Light GA, Swerdlow NR. Neurophysiological biomarkers informing the clinical neuroscience of schizophrenia: mismatch negativity and prepulse inhibition of startle. Curr Top Behav Neurosci. 2014;21:293–314.
102. Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. Lancet. 2012;379(9831):2063–71.
103. Perkovic MN, Erjavec GN, Strac DS, Uzun S, Kozumplik O, Pivac N. Theranostic biomarkers for schizophrenia. Int J Mol Sci. 2017;18(4).
104. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry. 2011;70(7):663–71.
105. Tourjman V, Kouassi E, Koue ME, et al. Antipsychotics' effects on blood levels of cytokines in schizophrenia: a meta-analysis. Schizophr Res. 2013;151(1–3):43–7.
106. Mondelli V, Ciufolini S, Belvederi Murri M, et al. Cortisol and inflammatory biomarkers predict poor treatment response in first episode psychosis. Schizophr Bull. 2015;41(5):1162–70.
107. Bradley AJ, Dinan TG. A systematic review of hypothalamic-pituitary-adrenal axis function in schizophrenia: implications for mortality. J Psychopharmacol. 2010;24(4 Suppl):91–118.
108. Green MJ, Matheson SL, Shepherd A, Weickert CS, Carr VJ. Brain-derived neurotrophic factor levels in schizophrenia: a systematic review with meta-analysis. Mol Psychiatry. 2011;16(9):960–72.
109. Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry. 2000;157(4):514–20.
110. Colibazzi T, Yang Z, Horga G, et al. Aberrant temporal connectivity in persons at clinical high risk for psychosis. Biol Psychiatry Cogn Neurosci Neuroimaging. 2017;2(8):696–705.
111. Reynolds GP, Yao Z, Zhang X, Sun J, Zhang Z. Pharmacogenetics of treatment in first-episode schizophrenia: D3 and 5-HT2C receptor polymorphisms separately associate with positive and negative symptom response. Eur Neuropsychopharmacol. 2005;15(2):143–51.
112. McClay JL, Adkins DE, Aberg K, et al. Genome-wide pharmacogenomic analysis of response to treatment with antipsychotics. Mol Psychiatry. 2011;16(1):76–85.
113. Zhang JP, Robinson DG, Gallego JA, et al. Association of a schizophrenia risk variant at the DRD2 locus with antipsychotic treatment response in first-episode psychosis. Schizophr Bull. 2015;41(6):1248–55.
114. Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014;511(7510):421–427.

115. Ikeda M, Yamanouchi Y, Kinoshita Y, et al. Variants of dopamine and serotonin candidate genes as predictors of response to risperidone treatment in first-episode schizophrenia. Pharmacogenomics. 2008;9(10):1437–43.
116. Wynn JK, Sugar C, Horan WP, Kern R, Green MF. Mismatch negativity, social cognition, and functioning in schizophrenia patients. Biol Psychiatry. 2010;67(10):940–7.
117. Lee SH, Sung K, Lee KS, Moon E, Kim CG. Mismatch negativity is a stronger indicator of functional outcomes than neurocognition or theory of mind in patients with schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2014;48:213–9.
118. Light GA, Swerdlow NR. Future clinical uses of neurophysiological biomarkers to predict and monitor treatment response for schizophrenia. Ann N Y Acad Sci. 2015;1344:105–19.
119. Umbricht D, Krljes S. Mismatch negativity in schizophrenia: a meta-analysis. Schizophr Res. 2005;76(1):1–23.
120. Vinogradov S, Fisher M, de Villers-Sidani E. Cognitive training for impaired neural systems in neuropsychiatric illness. Neuropsychopharmacology. 2012;37(1):43–76.
121. Fisher M, Holland C, Merzenich MM, Vinogradov S. Using neuroplasticity-based auditory training to improve verbal memory in schizophrenia. Am J Psychiatry. 2009;166(7):805–11.
122. Menning H, Roberts LE, Pantev C. Plastic changes in the auditory cortex induced by intensive frequency discrimination training. NeuroReport. 2000;11(4):817–22.
123. Kawakubo Y, Kamio S, Nose T, et al. Phonetic mismatch negativity predicts social skills acquisition in schizophrenia. Psychiatry Res. 2007;152(2–3):261–5.
124. Perna G, Grassi M, Caldirola D, Nemeroff CB. The revolution of personalized psychiatry: will technology make it happen sooner? Psychol Med. 2018;48(5):705–13.
125. Williams LM, Rush AJ, Koslow SH, et al. International study to predict optimized treatment for depression (iSPOT-D), a randomized clinical trial: rationale and protocol. Trials. 2011;12:4.
126. Adams Z, McClure EA, Gray KM, Danielson CK, Treiber FA, Ruggiero KJ. Mobile devices for the remote acquisition of physiological and behavioral biomarkers in psychiatric clinical research. J Psychiatr Res. 2017;85:1–14.