

Biomarker-Guided Tailored Therapy in Major Depression

19

Giampaolo Perna, Alessandro Spiti, Tatiana Torti,
Silvia Daccò, and Daniela Caldirola

Abstract

This chapter provides a comprehensive examination of a broad range of biomarkers used for the diagnosis and prediction of treatment outcomes in major depressive disorder (MDD). Genetic, epigenetic, serum, cerebrospinal fluid (CSF), and neuroimaging bio-

markers are analyzed in depth, as well as the integration of new technologies such as digital phenotyping and machine learning. The intricate interplay between biological and psychological elements is emphasized as essential for tailoring MDD management strategies. In addition, the evolving link between psychotherapy and biomarkers is explored to uncover potential associations that shed light on treatment response. This analysis underscores the importance of individualized approaches in the treatment of MDD that integrate advanced biological insights into clinical practice to improve patient outcomes.

G. Perna (✉) · D. Caldirola

Department of Biomedical Sciences, Humanitas University, Milan, Italy

Department of Clinical Neurosciences, Hermanas Hospitalarias, Villa San Benedetto Menni Hospital, Como, Italy

Humanitas SanpioX, Milan, Italy

e-mail: giampaolo.perna@hunimed.eu; daniela.caldirola@hunimed.eu

A. Spiti

IRCCS Humanitas Research Hospital, Milan, Italy

Psicocare, Humanitas Medical Care, Monza, Italy

e-mail: alessandro.spiti@mc.humanitas.it

T. Torti

ASIPSE School of Cognitive-Behavioral-Therapy, Milan, Italy

e-mail: tatiana.torti@asipse.it

S. Daccò

Department of Biomedical Sciences, Humanitas University, Milan, Italy

Humanitas SanpioX, Milan, Italy

Psicocare, Humanitas Medical Care, Monza, Italy

e-mail: silvia.dacco@hunimed.eu

Keywords

Major depressive disorder · Precision medicine · Biomarkers · Genetics · Neuroimaging · Machine learning · Personalized medicine

19.1 Introduction

In the field of clinical medicine, doctors have traditionally relied on their accumulated experience rather than on systematic scientific parameters when making diagnostic and therapeutic decisions. The advent of evidence-based medicine (EBM), a branch of clinical epidemiology, has

revolutionized patient care by emphasizing the application of specific scientific criteria (Djulgovic and Guyatt 2017). For example, psychiatrists now typically use clinical practice guidelines developed by expert committees and supported by numerous scientific studies to assess the mental health of individual patients (Paulus 2017). While this evidence-based approach offers advantages, such as reducing subjective bias, it can also lead to the unique characteristics of individual patients being overlooked (Gupta 2007).

Given this limitation, there has been a call for a new medical model that takes greater account of the individual's unique characteristics, complexities, and variations (Chan and Ginsburg 2011). This model, often referred to as "personalized medicine" (PM), gained prominence with the Human Genome Project at the end of the twentieth century (Carrasco-Ramiro et al. 2017). PM assumes that understanding both genomic influences and individual characteristics can improve the prediction, diagnosis, and treatment of disease. The concept has evolved over time, with organizations such as the Personalized Medicine Coalition (PMC) attempting to define and promote it (Abrahams et al. 2005). However, because personalized medicine encompasses a variety of factors beyond genetics, such as psychological traits, social contexts, and cultural backgrounds, it has encountered challenges in its precise definition and implementation. In response to these challenges, the term "precision medicine" (PRM) emerged as an alternative, emphasizing the use of molecular diagnostics to more accurately categorize and treat disease (Kosorok and Laber 2019). This approach gained prominence following publications such as the US National Research Council's report, "Toward Precision Medicine" (National Research Council 2011). While both terms aim to tailor medical interventions to the individual patient, the debate over their semantics emphasizes the complexity of integrating biological, genetic, environmental, and psychosocial factors into medical practice (Perna et al. 2020).

This evolving landscape of personalized and precision medicine has attracted global attention,

with both American and European institutions outlining strategies for its implementation, including in clinical psychiatric practice (Fernandes et al. 2017). In a closer examination of the existing psychiatric literature, the term "personalized psychiatry" was used to refer to a broader range of topics, including clinical features, treatment, biomarkers, and genetic/epigenetic factors, without clear distinctions (Ozomaro et al. 2013), whereas "precision psychiatry" was predominantly associated with molecular biology, genetics, genomics, and brain imaging studies (Gandal et al. 2016).

Leaving aside the semantic debate around these two concepts, which ultimately have more overlap than difference (Perna et al. 2020), one of the most exciting challenges in psychiatric practice today is to combine the subjective factors in the diagnostic and therapeutic assessment of the patient with the use of biomarkers to improve the accuracy of clinical interventions (Quinlan et al. 2019). Today, the diagnostic process relies primarily on observations and descriptions of patient behavior, while treatment decisions are often guided by practice guidelines that recommend scientifically proven interventions that are most effective for the "average" patient with a particular disorder. However, the limited effectiveness of certain therapeutic interventions for complex mental disorders underscores the urgent need for a precision medicine approach to psychiatry (Maj 2018). To implement precision psychiatry, it is essential to recognize the biological signature of each patient's psychiatric illness and link it to environmental and lifestyle factors (Trivedi 2016). Neuroscientists are actively seeking to dissect the major mental disorders into distinct biotypes with specific and individualized biological signatures, with biomarkers playing a central role (Maj 2018; Trivedi 2016).

This chapter focuses on the potential of biomarkers to provide accurate and tailored assessments in patients with major depressive disorder (MDD) at all stages of the illness, from assessing the risk of developing the disorder to evaluating the efficacy of treatment.

19.1.1 Personalized Psychiatry in Major Depressive Disorder

Major depressive disorder (MDD) stands as a leading cause of disability, impacting approximately 280 million individuals globally (Marx et al. 2023). The impact of this condition on an individual's ability to function was particularly high even before the Coronavirus Disease-2019 (COVID-19) pandemic, which inevitably further complicated the situation (Leightley et al. 2021; Brasso et al. 2023). According to the World Health Organization (WHO), the global depression rate rose by 25% in the years of the COVID-19 pandemic (World Health Organization 2022). The impact of the pandemic on mental health was significant, with factors such as social isolation, work restrictions, and bereavement contributing to increased stress (World Health Organization 2022; Usher et al. 2020). Young people, women, and people with pre-existing physical conditions were particularly affected: The disruption to mental health services has led to significant gaps in care and exacerbated the problem (Wiedemann et al. 2022). The impact of the pandemic has further highlighted the importance of diagnostic and therapeutic tools that could represent a breakthrough in the individualized care of depressed patients.

The course of major depression is pleiomorphic and exhibits considerable variability in terms of recovery and persistence (Marx et al. 2023; Monroe and Harkness 2022). Factors such as the severity of symptoms, the presence of other mental illnesses, and childhood trauma are all indicators of a less positive course (Ju et al. 2020). In studies based on the general population, the average duration of an episode is between 13 and 30 weeks, with around 70% of sufferers recovering within a year (Spijker et al. 2002). In the outpatient setting, however, the prognosis is less optimistic: only a quarter of those affected achieve remission within 6 months, and more than half are still struggling with MDD after 2 years (Boschloo et al. 2014). Following successful remission, individuals with major depressive disorder often experience persistent symptoms and functional impairments. Moreover,

the risk of MDD recurrence is substantial, with approximately 80% of individuals encountering at least one relapse post-remission in their lifetime (Lye et al. 2020; Vos et al. 2004).

Currently, personalized treatment of MDD is based on the recognition of the predominant symptoms within a specific clinical setting, distinguishing the subtypes of diagnosis described in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The symptoms described in the DSM-5 manual, particularly those related to appetite/body weight, sleep behavior, and psychomotor activity, vary between the different subtypes of MDD. For example, individuals with melancholic traits typically show decreased appetite, weight loss, insomnia, and increased psychomotor agitation. Conversely, atypical depression is characterized by increased appetite or weight gain, fatigue, excessive sleepiness, and psychomotor slowness. **The diagnosis of a major depressive episode can potentially lead to up to 700 distinct subtypes, considering all conceivable combinations of the DSM-5 criteria.** Since there are no objective parameters to support the clinical diagnosis, psychiatrists can only provide specific treatment via a dimensional approach based on the predominant symptomatology. For example, if a depressive episode is characterized by psychomotor retardation and hypersomnia, medications that enhance excitatory monoamines, such as SNRIs or bupropion, may be the first choice. However, depression is a complex condition that affects various biological functions, including inflammation, neuroendocrine activity, platelet function, autonomic nervous system responses, and cardiovascular and bone health. For instance, studies indicate that amelioration in clinical depression frequently aligns with the normalization of inflammatory markers. Conversely, sustained elevation of pro-inflammatory cytokines is linked with resistance to treatment, which may exacerbate disease advancement and result in less favorable clinical outcomes (Berk et al. 2013). In addition, childhood maltreatment experiences, a recognized risk factor for depression in adulthood, have been associated with elevated levels of C-reactive pro-

tein (CRP), which is indicative of systemic inflammation (Metcalf et al. 2023).

These scientific findings, which underlie the conceptualization of depression as a systemic disease, show that there are biomarkers that can provide a valuable tool for clinicians to make diagnostic and therapeutic decisions and prevent new relapses in the maintenance phase.

19.2 The Concept of “Biomarker”

In early 2015, the Food and Drug Administration (FDA) and the National Institute of Health (NIH) Joint Leadership Council recognized the importance of aligning terminology used in translational science and medical product development, particularly with regard to terms related to study endpoints and biomarkers. To improve communication, synchronize expectations, and promote scientific understanding, the two organizations created the BEST (Biomarkers, EndpointS, and other Tools) resource (FDA-NIH Biomarker Working Group 2016). According to the BEST glossary, a biomarker is “a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention.”

In this context, a classification has been created to distinguish the different types of biomarkers based on their function:

1. **Diagnostic biomarker:** It is instrumental in identifying or verifying the presence of a targeted disease or condition, as well as in distinguishing individuals with a particular subtype of the disease.
2. **Surveillance biomarker:** It can be measured serially to assess the status of a disease or medical condition, to provide evidence of exposure to a medical product or environmental agent, or to detect an effect of a medical product or biological agent.
3. **Pharmacodynamic response biomarker:** It changes in response to exposure to a medical product or an environmental agent.
4. **Predictive biomarker:** It is defined by the finding that the presence or change in the biomarker predicts an individual or group of individuals who are more likely to experience a favorable or unfavorable effect of exposure to a medical device or environmental agent.
5. **Prognostic biomarker:** It is employed to ascertain the probability of a clinical event, disease relapse, or disease progression in individuals with a specific disease or medical condition.
6. **Safety biomarker:** It is quantified either before or after exposure to a medical intervention or environmental factor to signify the probability, presence, or degree of toxicity as an adverse event.

It is important to emphasize that a single biomarker can fulfill different criteria for different functions.

The application of biomarkers in the diagnosis and treatment of cardiovascular diseases (Kott et al. 2022), infections (Hwang et al. 2018), immunological (Gehring et al. 2022) and genetic disorders (Jain 2017), and cancer is well known (Ohnmacht et al. 2023). Significant attention has been directed toward assessing biomarkers as potential assets for enhancing prevention, diagnosis, drug response, and drug development in psychiatric disorders (Lozupone et al. 2019). Unlike many other diseases, mental illnesses are characterized by diagnostic categories that encompass a broad spectrum of symptoms. Consequently, individuals diagnosed with the same psychiatric disorder exhibit considerable heterogeneity in their clinical manifestations (Nunes et al. 2020). This results in notable variability in the clinical profiles of individuals diagnosed with the same psychiatric disorder (Howes et al. 2021). Therefore, the identification of biomarkers in psychiatry is increasingly crucial for the stratification of subgroups within the syndrome in order to develop more targeted treatment approaches (Kessler and Luedtke 2021).

19.2.1 Biomarkers in Major Depressive Disorder (MDD)

Biomarkers for depression can be divided into three main groups:

1. **Trait biomarkers:** These markers include stable indicators that persist over time. A classic example of such indicators are endophenotypes, quantitatively measurable variables that act as intermediaries between the genetic variability associated with depression and the clinical manifestations of the disease (Iacono 2018). They therefore represent heritable traits associated with the disease. **The existing data do not offer a definitive endophenotype that reliably forecasts the onset of MDD in at-risk groups or predicts responses to antidepressant therapy (Goldstein and Klein 2014).** Examples of potential endophenotypes include baseline activity and neuronal response patterns in depression (van der Wijk et al. 2022), cortical thinning in depression (Peterson and Weissman 2011), and neurotrophic signal transduction pathways (Xiaomin 2024) in mood disorders. It is easy to see how a measure of cortical thinning—a possible endophenotype for major depression—could be helpful in determining risk for major depression or the diagnosis of major depression. A biological trait like this would be very helpful as a diagnostic tool.
2. **State biomarkers:** These markers reflect the person's current clinical state and can fluctuate over time. They only exist during an exacerbation of symptoms and are called episode markers (Perna et al. 2017). Episode markers can be useful for identifying disorders and for monitoring the course and effectiveness of treatment. Typical examples of this type of markers are inflammatory molecules such as cytokines, which may be present at higher levels in patients with treatment-resistant depression (TRD) (Strawbridge et al. 2019).
3. **Temporally stable biomarkers:** These are markers of susceptibility caused by environmental factors that identify individuals who have become susceptible to a disorder due to environmental exposure. This category includes, for example, acquired characteristics as a result of trauma, perinatal complications, or substance abuse.

Research on post-traumatic stress disorder (PTSD) has shown that exposure to trauma can

lead to the emergence of vulnerability indicators. In a study examining identical twins who differed in exposure to combat, Orr et al. found that an increased heart rate to startling sounds was only seen in the exposed twin (Orr 2003). This suggests that the cardiac response is an acquired marker of PTSD rather than an indication of pre-existing genetic susceptibility. Similar changes attributable to traumatic events, particularly in early childhood, and complicated by dysfunctional attachment patterns also appear to be present in patients with MDD (McQuaid 2021).

Artificial intelligence (AI) is emerging as a promising tool in the field of depression research, particularly in the identification and analysis of biomarkers. By applying machine learning techniques, AI algorithms can learn from these datasets to recognize complex patterns and relationships that may not be obvious to human researchers (Ma et al. 2023). This can help identify new biomarkers for depression, improve diagnostic accuracy, and tailor treatment approaches to individual patients (Eder et al. 2023). For example, AI algorithms have been used to analyze neuroimaging data to detect patterns of brain activity or structural changes associated with depression (Fu et al. 2023).

19.3 Biomarkers and Disease Vulnerability

19.3.1 Genetics

“Candidate gene” studies on MDD centered around single genes believed to be involved in the pathophysiology and underlying mechanisms of the disorder (Beckman et al. 1978). Several studies have examined variants in a wide range of candidate genes, often with conflicting results (Flint and Kendler 2014). The serotonin transporter (SERT) regulates serotonin signaling by regulating the concentration of serotonin in the synaptic cleft. Variation in the promoter region of the SERT gene (5-HTTLPR; serotonin transporter-linked polymorphic region) affects the transcription rate of the gene, with the short (S) allele being less efficient than the long (LL)

allele (Luddington et al. 2009). Studies have linked the S-allele to an increased risk of depression following stressful events in early childhood, but some results are contradictory (Duman and Canli 2015). Tryptophan hydroxylase (TPH), which is crucial for serotonin synthesis, has been observed to be differentially associated with susceptibility to MDD (Tsai et al. 2009; Jenkins et al. 2016). Genetic variations in the FKBP5 and CRHR1 genes, which regulate the stress response system, have been associated with susceptibility to depression, recurrence of depression (Lavebratt et al. 2010), response to antidepressants (Ising et al. 2019), and suicidality (De la Cruz-Cano 2017). Studies suggest that these genes may mitigate the effects of childhood trauma on depression and suicide risk (Roy et al. 2012). These studies frequently had insufficient statistical power and did not yield significance levels beyond what could be attributed to chance (Flint and Kendler 2014; McIntosh et al. 2019): due to the lack of robust associations, there is now a strong consensus against the continuation of candidate gene studies (Border et al. 2019).

Genome-wide association studies (GWAS) are comprehensive investigations that assess the entire genome to identify genetic variations associated with particular traits or diseases. This technique had found many genes potentially associated with MDD, but with poor replication (Uffelmann et al. 2021). To obtain additional results, a different method was used: targeting larger population samples with more flexible and easier to measure depressive phenotypes, termed “minimal phenotyping” (Kasyanov et al. 2022). This transition yielded interesting findings, as evidenced by several studies (Howard et al. 2018, 2019; Wray et al. 2018). The neuronal growth regulator 1 (NEGR1) and olfactomedin 4 (OLFM4) genes show the strongest support for association with susceptibility to MDD, with an odds ratio (OR) of 1.04 (Wray et al. 2018; Howard et al. 2019). The cell adhesion molecule neuronal growth regulator 1 (NEGR1) regulates neurite outgrowth, synapse development, and synaptic activity. Olfactomedin 4 (OLFM4), a glycoprotein released by the body, has been

linked to inflammation, innate immune responses, and cancer. Several other linked loci play a role in neurite outgrowth, synaptic function and plasticity, immunology, and inflammation (Fries et al. 2022). Association studies at the gene level have pointed to genes responsible for pre- and post-synaptic functions, in particular receptor components such as glutamate receptors, dopamine receptors, and voltage-gated calcium channels (VGCC) (Wray et al. 2018). RBFOX1, identified by analysis at both single nucleotide polymorphism (SNP) and gene levels, may be important in the development of major depression (Turley et al. 2018). Genes associated with neuronal development pathways, including VGCC and synaptic RNA-binding proteins such as FMRP and CELF4, have been found to be linked with MDD (Kendall et al. 2021). The sample sizes utilized in these studies are substantial; in one of the latest genome-wide association studies (GWAS), data from over one million participants were analyzed, uncovering 178 genetic risk loci and 223 individually significant single nucleotide polymorphisms (SNPs) (Levey et al. 2021). While numerous genome-wide significant loci were indeed identified, the drawback of employing minimal phenotyping lies in the fact that a significant proportion of individuals diagnosed with major depressive disorder (MDD) may not actually have the condition (Cai et al. 2020). The main problem with minimal phenotyping is the use of diagnostic questionnaires with an insufficient number of items. Indeed, most of these questionnaires use questionnaires or self-reports with a single item, via a direct question asking the patient if they have ever consulted a mental health professional for depressive mood. Examination of findings from the literature on single-item screening tests for MDD shows that more than half of the cases identified by this type of screening test yield false-positive results (Mitchell and Coyne 2007). Therefore, it is plausible that most cases recruited to GWAS studies of MDD by these simplistic one- or two-item tests do not actually have MDD. An effective approach to pinpoint MDD variants with strong associations involves finding a balance between

maximizing sample size and emphasizing precise and stringent diagnostic definition (Byrne et al. 2020).

19.3.2 Epigenetics

Alterations in DNA methylation (DNAm) are shaped by a combination of genetic and environmental factors that interact to increase susceptibility to the onset of the disease (Hannon et al. 2018). In recent years, DNAm has attracted attention in the context of major depressive disorder (MDD) (Zhu et al. 2023). A recent epigenome-wide association study (EWAS) discovered three CpG sites that showed differential methylation associated with depressive symptoms (Wahl et al. 2017). In a similar study, 760 differentially methylated CpG sites were found that were predominantly associated with genes involved in neuronal circuitry and plasticity (Roberson-Nay et al. 2020).

In another study that focused on DNA methylation, the authors examined the methylation levels of the promoter of the parvalbumin gene (PVALB) in MDD patients with and without suicide attempts and in healthy controls (Thaweethee-Sukjai et al. 2019). They found a significant increase in PVALB methylation at CpG2 and a decrease at CpG4 in the MDD group compared to controls.

Exposure to stress, toxins, or viruses during fetal development or infancy may increase disease susceptibility later in life, which is mediated by epigenetic mechanisms (Kundakovic and Jaric 2017; Yuan et al. 2023). In addition, studies on postmortem human tissue have shown that early life circumstances are associated with epigenetic regulation of glucocorticoid receptor (GR) expression in the hippocampus (McGowan et al. 2009). Deceased suicides with a history of childhood abuse show lower GR expression and higher cytosine methylation of the GR promoter exon 1-F compared to controls (Labonte et al. 2012). Depressed suicides who were abused in childhood show cell type-specific DNA methylation changes in oligodendrocyte genes and impaired

myelin-related transcriptional programs (Zhou et al. 2020). Moreover, the timing of childhood, especially before the age of three, accounts for greater DNA methylation variability (Dunn et al. 2019), emphasizing the critical role of early childhood in predicting altered DNA methylation patterns due to life stress events. These findings suggest that childhood stress affects glucocorticoid methylation and may be a risk factor for the development of psychopathology.

19.3.3 Serum and Cerebrospinal Fluid (CSF) Biomarkers of Depression

Recent research has pointed toward the involvement of abnormal inflammatory processes in MDD. In the brain, peripheral immune responses are amplified through local inflammatory networks and cytokine production, influencing the balance of neurotransmitters and signaling pathways. Dysregulated inflammation contributes to serotonin synthesis disruption, hypothalamic-pituitary-adrenal (HPA) axis activation, and reduced neuroplasticity, culminating in depressive symptomatology. Patients with MDD often exhibit elevated pro-inflammatory cytokines (IL1, IL6, CRP) and reduced levels of anti-inflammatory cytokines (IL 4, IL10) (Al-Hakeim et al. 2020; Felger and Lotrich 2013; Gasparini et al. 2022).

Cortisol, which belongs to the glucocorticoid class of steroid hormones, plays an important role in controlling human behavior. The hypothalamic-pituitary-adrenal (HPA) axis is the most extensively studied of all endocrine axes in the field of psychiatry. Cortisol can be determined by blood, saliva, or urine measurements. Knorr et al. conducted a systematic review and meta-analysis of salivary cortisol levels in depressed individuals compared to controls and concluded that salivary cortisol is unable to differentiate between individuals with and without depression (Knorr et al. 2010). Previous research has examined serum or plasma cortisol levels in depressed patients with conflicting results regard-

ing the relationship between cortisol and depression. According to a recent systematic review, there is a statistically significant difference in morning serum or plasma cortisol levels between individuals with depression and controls. Depressed patients were found to have higher serum or plasma cortisol levels compared to controls, indicating the potential of this biomarker in discriminating between depressed and non-depressed individuals (Kumar et al. 2022). These findings are consistent with previous research indicating a link between depression and HPA axis activity.

In the last 10 years, research has increasingly focused on the role of vitamin D in depression. There is evidence of increased expression of vitamin D receptors in brain regions involved in mood regulation, as well as a possible modulation of the link between depression and inflammation through immunomodulatory mechanisms (Grudet et al. 2020). In addition, new findings point to the neuroprotective potential of vitamin D, which is attributed to its anti-inflammatory effect (Kouba et al. 2022). Depressive symptoms can also lead to a decrease in physical activity and sun exposure, which in turn results in vitamin D deficiency—a phenomenon known as reverse causality. Current observational data suggest that serum vitamin D levels may be a risk factor for the development of major depressive disorder (MDD). Numerous meta-analyses of longitudinal studies have demonstrated a prospective association between vitamin D status and depression in older adults. In addition, a recent study with a significant sample size ($N = 139,128$) has shown that both vitamin D deficiency and vitamin D insufficiency are associated with the occurrence of depression in adults (Grudet et al. 2020). An inverse correlation between plasma 25(OH)D3 levels and symptoms of depression, including major depressive disorder, has been consistently observed in numerous epidemiologic and clinical studies (Kouba et al. 2022). These studies show heterogeneity in terms of the defined thresholds for vitamin D sufficiency, insufficiency, and deficiency, as well as the demographic characteristics of the study populations and the rating scales used to measure depressive symptoms. However,

a consistent finding across all studies is that individuals with higher vitamin D levels have a lower risk of suffering from depressive symptoms or developing depression. In a longitudinal cohort study that spanned 4 years and included a substantial sample size, it was found that individuals with a vitamin D deficiency had a 75% higher risk of developing depression than those with adequate vitamin D levels (Libuda et al. 2019).

Lipids play a critical role in supporting and regulating various aspects of neuronal function, including synaptic transmission, membrane integrity, and overall neural signaling processes. They fulfil various functions such as modulating membrane fluidity and permeability, facilitating vesicle formation and transport, regulating the release of neurotransmitters, and maintaining cell integrity and plasticity. Cholesterol and cholesterol-containing molecules are not only associated with cardiovascular disease, but also with major depressive disorder. Depressed individuals often have reduced serum total cholesterol compared to healthy controls, as well as changes in high-density lipoprotein (HDL), low-density lipoprotein (LDL), and the LDL/HDL ratio (Han 2022). However, these results are challenged by conflicting studies, particularly in older people. While some studies report increased levels of very low-density lipoproteins (VLDL), others find increased total cholesterol levels or no significant changes (Parekh et al. 2017). Recent meta-analyses suggest an inverse association between circulating LDL levels and depression (Shin et al. 2008). Nevertheless, discrepancies persist and more comprehensive studies in different cohorts are needed to clarify the association between cholesterol and depression and its diagnostic utility.

Studies on monoaminergic biomarkers, including peripheral and CSF levels of serotonin, dopamine, and noradrenaline and their metabolites, have yielded unreliable results (Kunugi et al. 2015). However, there is consensus that reduced levels of 5-hydroxyindoleacetic acid (5-HIAA) in the CSF are associated with increased suicidality (Asberg and Träskman 1981).

19.3.4 Neuroimaging Biomarker of Depression

Investigating the pathophysiology of MDD, particularly brain function, is essential for understanding the relationship between brain biomarker regions and functional impairment.

The use of magnetic resonance spectroscopy (MRS) has revealed potential biomarkers for major depressive disorder (MDD) through the detection and quantification of neuronal metabolites in specific brain regions. Studies have shown an increased choline/creatine ratio in the anterior cingulate cortex (ACC) of MDD patients, indicating a possible biomarker for MDD diagnosis (Shi et al. 2014). In addition, higher choline levels in the frontal lobe have been specifically linked to the pathophysiology of MDD (Riley and Renshaw 2018). In melancholic adolescent patients with MDD, a study has identified increased neurotoxic metabolites in limbic areas, particularly in the striatum (Gabbay et al. 2010). Decreased glutamate levels in the ventromedial prefrontal cortex (PFC) have also been suggested as a potential biomarker for MDD (Draganov et al. 2020). However, further research is needed to fully understand the complex relationship between altered metabolites and structural changes in fronto-limbic regions associated with MDD.

In terms of magnetic resonance imaging (MRI), both structural and functional MRI (fMRI) have provided insights into biomarkers for MDD. Structural MRI studies have revealed changes in gray matter volume (GMV), cortical thickness, and microintegrity of white matter tracts, particularly in the ACC, suggesting its potential as a biomarker for MDD (Lai and Wu 2014). Resting-state fMRI (Rs-fMRI) studies have shown abnormal patterns of functional connectivity in fronto-limbic networks, including the ACC, amygdala, and hippocampus, which are correlated with the severity of MDD (Bijsterbosch et al. 2018). Task-related fMRI studies have found hyperactivity and hyperconnectivity within and between brain networks associated with emotional processing, reward processing, and executive functions in MDD patients (Kumar

et al. 2018). The convergence of findings across different MRI modalities supports the importance of the fronto-limbic system in the pathophysiology of MDD and highlights potential biomarker regions for further investigation, including the ACC, amygdala, hippocampus, and frontal regions.

Nuclear medicine methods include positron emission tomography (PET) and single photon emission computed tomography (SPECT). A PET study suggests that susceptibility to MDD may be related to serotonergic dysregulation in the fronto-limbic regions, where alteration of serotonergic receptors has been found (Frokjaer et al. 2008). In addition, MDD patients with suicide attempts show reduced serotonin transporter binding potential in several brain regions (Underwood et al. 2018). SPECT studies show decreased distribution of serotonin transporters in the basal ganglia and midbrain, decreased blood flow in key regions such as the ACC, dorsolateral prefrontal cortex (DLPFC), and orbito-frontal cortex (OFC), and altered occupancy of serotonin transporters in the midbrain (Pu et al. 2015).

Near-infrared spectroscopy (NIRS) enables the measurement of blood oxygenation, blood flow, and brain activity. MDD patients with suicidal ideation showed reduced hemodynamic changes in the DLPFC and OFC in verbal fluency tests that correlated with the severity of suicidal ideation, suggesting neural correlates for suicidal ideation (Pu et al. 2015). Emotional face recognition tasks revealed altered hemodynamic oscillations in the left prefrontal cortex in MDD (Gao et al. 2019), with an inverse relationship between evoked waves in the left superior frontal cortex and the severity of depression during the emotional Stroop task (Nishizawa et al. 2019). NIRS values can predict MDD in all regions of the prefrontal cortex, with significantly lower hemodynamic responses in the right frontal cortex during verbal testing (Husain et al. 2020).

The EEG serves as a conventional tool to study the physiological activities of the brain. Changes in the rostral ACC during error-response tasks have been identified as biomarkers for MDD (Pizzagalli et al. 2006). Vigilance regula-

tion patterns and alpha asymmetry with increased right lateralized activity are also promising biomarkers (Olbrich and Arns 2013). A recent meta-analysis points to changes in REM density and slow waves during sleep as potential sleep EEG biomarkers for MDD (Pillai et al. 2011). A recent study shows that increased slow wave activity in the frontal regions during sleep correlates positively with the diagnosis of MDD in adolescents (Tesler et al. 2016).

19.4 Biomarkers and Treatment Response

19.4.1 Genetics

The literature suggests that genetic factors play a significant role in the variability in drug response and side effects across all the classes of antidepressants (Cacabelos 2015). Consequently, when making decisions about the selection and dosage of antidepressants, it is essential to consider the genetic profile of the individual. The cytochrome P450 (CYP450) family comprises a group of enzymes that are crucial for the metabolism of various drugs, including antidepressants. Key enzymes such as CYP2D6, CYP2C19, and others play an important role in the metabolism of antidepressants. Genetic variations in these enzymes lead to individual differences in drug metabolism and response: specific tools are available to study genetic polymorphisms in the genes encoding these liver enzymes, which could provide valuable insights for the clinical field. The different phenotypes, including poor metabolizers (PMs), intermediate metabolizers (IMs), extensive metabolizers (EMs), and ultra-rapid metabolizers (UMs), are based on enzyme activity influenced by genetic variants. PMs and IMs have a slower metabolism and require lower doses of antidepressants to avoid side effects, while UMs require higher doses to achieve therapeutic effects.

The P-glycoprotein (P-gp), which belongs to the ATP-binding transporter family and is encoded by the ABCB1 or MDR1 gene, regulates the absorption, distribution, and excretion of drugs. It is present in various tissues, including

the blood-brain barrier, and influences the efficacy of drugs. Genetic variations in ABCB1 affect the expression and activity of P-gp and alter the pharmacokinetics and efficacy of drugs. Common variants such as C3435T, C1236T, and G2677T reduce the response to antidepressants (Radosavljevic et al. 2023). The 2677G > T polymorphism can enhance the penetration of P-gp substrates into the brain, which predicts significant efficacy of antidepressant treatment (O'Brien et al. 2012). Polymorphisms such as rs2235040 and rs4148739 determine a faster onset of antidepressant response (Radosavljevic et al. 2023).

Enzymes of monoamine metabolism, including tryptophan hydroxylase (TPH), monoamine oxidases (MAOs), and catechol-*O*-methyltransferase (COMT), are crucial for the regulation of neurotransmitters and influence the response to antidepressants. Certain genetic variants in these enzymes are associated with treatment outcomes.

In TPH, variants affecting serotonin synthesis, such as rs1800532, have been associated with prediction of antidepressant response. TPH A/A was associated with slower response to fluvoxamine; TPH A/A and A/C variants were associated with poorer response to treatment with paroxetine; and TPH1 A/A and A/C variants were associated with poorer remission to citalopram (Serretti et al. 2001).

MAO-A, responsible for monoamine metabolism, has variants such as rs6323 that influence enzyme activity and the efficacy of antidepressants. The COMT Val158Met (rs4680) polymorphism also influences enzyme activity, with the Val/Val genotype being associated with a poorer response to SSRIs such as fluoxetine and paroxetine compared to the Met/Met or Val/Met genotypes (Marshe et al. 2020).

Monoamine transporters such as the serotonin transporter (SERT) have the serotonin transporter-linked polymorphic region (5-HTTLPR), with the S-allele associated with decreased expression and poorer response to SSRIs (Sreeja et al. 2024).

Monoamine receptors, such as the 5-HT1A receptor encoded by the HTR1A gene, have variants such as rs6295, which may determine a better response to citalopram. There are also variants

within the HTR2A gene, which encodes the 5-HT_{2A} receptor, such as rs7997012, which may affect how individuals respond to SSRIs (Badamasi et al. 2021). Among dopamine receptors, particularly DRD2, there are variants such as rs1076562 and rs4245147 that are associated with the timing of the onset of the antidepressant response and the response to certain antidepressants (Radosavljevic et al. 2023).

These variants provide insight into individual differences in response to antidepressants and help predict treatment outcomes. However, further research is needed to fully understand their clinical impact and optimize personalized treatment approaches.

19.4.2 Epigenetics

Epigenetic changes, especially DNA methylation, are promising for predicting response to antidepressants. Research suggests that methylation patterns at specific CpG sites in genes may influence treatment outcomes. For example, methylation at CpG sites associated with the interleukin-11 gene (IL11) predicts response to antidepressants such as escitalopram and nortriptyline (Powell et al. 2013).

The brain-derived neurotrophic factor (BDNF) gene, which is subject to epigenetic regulation, also influences the response to antidepressants: lower methylation levels at the BDNF promoter are associated with a better response to antidepressants and reduced BDNF plasma levels after 1 week of treatment (Zelada et al. 2023).

FK506 Binding Protein 5 (FKBP5), a regulator of glucocorticoid receptor activity, influences BDNF methylation and response to antidepressants. Glucocorticoid signaling pathways involved in stress responses also modulate epigenetic mechanisms and influence treatment efficacy (Wietfeldt 2020).

Non-coding RNAs such as miRNAs are associated with antidepressant responses. miR-1202, miR-124, miR-135a, miR-145, and miR-20b are associated with significant antidepressant activity; others such as miR-146a5p, miR-146b-5p, miR-425-3p, and miR-24-3p show decreased

expression during antidepressant therapy and serve as potential biomarkers for antidepressant response (Shi et al. 2021).

19.4.3 Serum and CSF Biomarkers

Researchers have long sought to identify predictors of different responses to antidepressant treatments based on blood values or other peripheral measurements.

Evidence of hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, characterized by elevated levels of cortisol in the blood, cerebrospinal fluid (CSF), or urine, and elevated levels of corticotropin-releasing hormone (CRH) in the CSF, has been demonstrated in over 70% of patients with major depressive disorder (MDD), particularly in severe or melancholic cases (Schumacher and Santambrogio 2023). Studies have shown that selective serotonin reuptake inhibitors (SSRIs) generally reduce hyperactivity of the HPA axis, although there are conflicting results. Remarkably, these effects appear to occur primarily in MDD patients who respond positively to treatment, suggesting that normalization of HPA axis abnormalities during MDD treatment may indicate a response to SSRIs (Menke and The 2024).

Changes in the response to the dexamethasone suppression test (DST) in MDD patients receiving antidepressants may serve as a laboratory marker of treatment success. Most patients who initially fail to suppress cortisol levels during the DST show progressive normalization of DST responses with concomitant clinical improvement. Conversely, failure to normalize DST responses is often associated with poorer clinical outcome (Scherf-Clavel et al. 2020).

With the availability of CRH for clinical trials, the DST was combined with CRH administration to dexamethasone CRH (DEX/CRH) testing, which proved to be more sensitive in detecting changes in the HPA system compared to the original DST. Increased cortisol secretion following the DEX/CRH test has been consistently observed in patients with acute major depressive episodes, and normalization of this test often precedes or

accompanies a positive response to antidepressant treatment (Schüle et al. 2009). Persistent non-suppression of the HPA axis during DEX/CRH testing in MDD patients predicts a poorer response to treatment and may be associated with depressive relapse (Aubry et al. 2007).

Immunoassays such as Western blots or enzyme-linked immunosorbent assays (ELISA) allow the quantification of single proteins or the multiplex analysis of several proteins simultaneously. They are frequently used in biomarker research, particularly in inflammatory processes. Meta-analyses have consistently identified serum levels of TNF α , IL-6, CRP, BDNF, and IL-1 β as proteomic markers associated with response to treatment for major depressive disorder (MDD). C-reactive protein (CRP), a well-characterized marker of inflammation, has shown promise as a biomarker of treatment response. Studies have shown that low baseline CRP levels (<1 mg/mL) predict a better response to escitalopram compared to nortriptyline, while higher levels are associated with a greater reduction in depression severity with nortriptyline treatment (Halaris et al. 2022). In addition, MDD patients with low baseline CRP levels (<1 mg/L) respond better to SSRI monotherapy, while patients with higher CRP levels respond better to combination therapy of bupropion and SSRIs (Jha et al. 2017). In addition to CRP, ELISAs were used to quantify other potential biomarkers such as the protein p11 in natural killer (NK) cells and monocytes. The reduction in p11 levels following citalopram treatment correlates with a subsequent reduction in the severity of depression (Svenningsson et al. 2014). Recent studies have found changes in inflammatory markers such as eotaxin/CCL11 and IFN γ before and after antidepressant treatment, with an increase in eotaxin being associated with remission and a decrease in IFN γ being associated with non-remission (Gadad et al. 2017). While antibody-based assays provide a viable platform for biomarker research, challenges include the limited availability of protein-specific antibodies, low throughput, and high cost.

Several studies have attempted to investigate the role of brain-derived neurotrophic factor

(BDNF) as a potential biomarker for treatment response in major depressive disorder (MDD). In a 2021 clinical trial involving 121 MDD patients, cognitive function, BDNF levels, and response to treatment with escitalopram and vortioxetine were examined. The results showed that higher baseline BDNF levels correlated with better cognitive outcomes when treated with vortioxetine (Šagud et al. 2021). In a 2011 pilot study of 34 MDD patients treated with venlafaxine, responders showed increased BDNF levels within the first 2 weeks, in contrast to non-responders (Rojas et al. 2011). A 2014 study examined whether changes in serum levels of neurotrophic factor (BDNF) over a 4-week period following initiation of treatment with selective serotonin reuptake inhibitors (SSRIs) could predict response to antidepressant therapy after 8 weeks in individuals diagnosed with major depressive disorder (MDD). Despite previous evidence of an association between elevated BDNF levels and treatment efficacy, the results of the study showed that changes in serum BDNF levels did not reliably predict treatment response at 8 weeks (Yoshimura et al. 2014). Recent studies confirmed these results and showed no significant differences in baseline BDNF levels between responders and controls (Lee et al. 2020).

19.4.4 Neuroimaging

Neuroimaging techniques, particularly magnetic resonance imaging (MRI), could serve as useful tools for predicting treatment response in patients with MDD.

One of the most observed findings in MRI studies is the relationship between hippocampal volume and treatment outcomes in MDD. Smaller hippocampal volumes have been clearly associated with a poorer response to antidepressant therapies, while larger volumes indicate a greater likelihood of achieving remission. This underscores the fundamental role of the hippocampus in MDD and its potential as a predictive biomarker of treatment response (Colle et al. 2016).

In addition to the hippocampus, changes in other brain regions also provide valuable prog-

nostic information. For example, reduced volumes in regions such as the lingual gyrus and middle frontal gyrus are often associated with a poorer response to antidepressants, while larger volumes in these areas may indicate better treatment outcomes (Jung et al. 2014). In addition, changes in cortical thickness have been shown to be promising indicators of treatment response. Increased thickness in regions such as the rostral anterior cingulate cortex has been associated with a positive response to selective serotonin reuptake inhibitors (SSRIs) and offers insights into the neurobiological mechanisms underlying treatment efficacy (Godlewska et al. 2018). Conversely, the presence of subcortical white matter hyperintensities, particularly in the left hemisphere, has been consistently associated with a poorer therapeutic response and lower remission rate to treatment with fluoxetine (Iosifescu et al. 2006). This suggests that white matter integrity plays a critical role in treatment outcomes and underscores the importance of considering both gray and white matter changes in predicting response to antidepressant therapies.

Diffusion tensor imaging (DTI) is an imaging technique that maps the neuronal pathways of white matter by analyzing water diffusion in brain tissue to reveal disturbances in neuronal connectivity. Key measures include fractional anisotropy (FA) and mean diffusivity (MD). Studies show that individuals who do not respond to antidepressant treatment have lower FA in the medial fornix but higher FA in the superior frontal and anterior cingulate cortex. Conversely, responders show increased FA and decreased MD in the left amygdala (Tura and Goya-Maldonado 2023).

EEG changes provide insight into predicting response to antidepressant treatment, with some changes indicating a positive response and others indicating a poor response.

Gamma power (20–70 Hz) at the frontal, central, and temporal electrodes at baseline is significantly associated with response to treatment with paroxetine in MDD patients, suggesting that this change positively predicts treatment response (Arikan et al. 2018). Altered late gamma band

activity has been shown to be a persistent biomarker for risk of recurrent MDD, suggesting that this alteration predicts poor response to antidepressant treatment (Yamamoto et al. 2018). In a previous EEG study using the source localization method, patients with MDD who did not respond had higher theta waves in the resting EEG in the frontal and rostral anterior cingulate cortex, suggesting that higher theta waves predict poor response to antidepressant treatment (Arns et al. 2015). Wu and colleagues developed a specialized machine learning algorithm to analyze resting-state EEG data. This algorithm was then applied to a large antidepressant trial using brain imaging and a placebo control group. The results showed that the improvement in symptoms with sertraline could be accurately predicted. In addition, they found a correlation between the effects of sertraline on resting EEG and prefrontal neuronal activity measured by simultaneous transcranial magnetic stimulation and EEG (Wu et al. 2020).

The assessment of cerebral glucose metabolism using PET scans of the brain before and after treatment yielded contradictory results. For example, in a 2013 study, decreased metabolism in the insula was associated with a favorable response to cognitive behavioral therapy (CBT) but a poorer response to escitalopram, whereas increased metabolism was associated with better therapeutic outcomes with escitalopram compared to CBT (McGrath et al. 2013). In contrast, the authors of a recent study found that FDG-PET imaging in cohorts with major depression did not reveal a clinically significant biomarker of response to treatment with escitalopram or placebo (Hill et al. 2021).

19.5 Biomarkers for Psychotherapy Response Prediction

It is important to emphasize the central role of psychotherapy in the treatment of MDD. It can be particularly effective as a monotherapy for mild depressive symptoms triggered by significant life stresses such as bereavement, relationship diffi-

culties, or career setbacks. In severe cases, where symptoms are more pronounced and distressing, psychotherapy is an important part of a comprehensive treatment plan alongside pharmacological treatment. Existing research points to a synergistic interplay between psychotherapy and pharmacotherapy in the effective alleviation of depressive symptoms and emphasizes the intricate interrelationship between biological and psychological dimensions in the comprehensive treatment of the complex manifestations of major depressive disorder (MDD). In the field of MDD research, the convergence of biomarkers with psychotherapeutic interventions challenges conventional wisdom by suggesting predictive links between biological signatures and these treatment outcomes. In the past, researchers have been reluctant to address the notion that responses to psychotherapy can be predicted from biological markers. However, recent advances in understanding the complex interplay between neurobiological factors and psychological interventions have opened new avenues for exploring the predictive potential of these biomarkers in the development of treatment strategies for MDD.

According to Fonseka and colleagues (Fonseka et al. 2018), several imaging studies in the field of psychotherapy have primarily investigated biomarkers of response to CBT using functional imaging techniques. In particular, scientific investigations revealed improved functional connectivity between the amygdala and specific brain regions such as the left dorsolateral prefrontal cortex (DLPFC) and the left anterior insula, which correlates with symptom improvement (Han et al. 2021). Higher baseline activity in the ventromedial prefrontal cortex (PFC) and specific valence-related neuronal patterns observed in different brain regions were associated with symptom improvement (Pizzagalli 2010), and lower baseline activity in regions such as the anterior cingulate cortex (ACC), middle frontal gyrus, and insula/inferior frontal gyrus was correlated with positive treatment outcomes (Strege et al. 2023).

In a recent study by Yange Wei et al. (Wei et al. 2023), advanced machine learning techniques and imaging transcriptomics were used to

discover a neuroimaging biomarker predictive of CBT success in patients with a first episode of MDD. This research emphasized the importance of an increase in regional homogeneity (ReHo)—an indicator of local synchronization of brain activity—in the bilateral DLPFC following CBT and highlighted that ReHo levels in the left DLPFC prior to treatment could accurately predict the degree of symptomatic improvement. In addition, the study examined gene expression in the left DLPFC, revealing pathways associated with neuroplasticity and cellular resilience, suggesting the increase in DLPFC function as a potential antidepressant effect contributing to the success of CBT. These observations emphasize the essential function of the DLPFC in regulating emotion and highlight the importance of precise neuroimaging markers in deciphering the variability of responses to CBT in patients.

In addition to these findings, an interesting study using positron emission tomography (PET) has further elucidated the neurobiological substrates of CBT in depression (Kennedy et al. 2007). This study showed a correlation between successful CBT treatment and increased activity in the hippocampus and dorsal anterior cingulate (Brodmann area 24c) and decreased activity in the dorsolateral (Brodmann areas 9, 46), ventrolateral (Brodmann areas 47, 11), and medial (Brodmann areas 9, 10, 11) frontal cortex. Evaluation of metabolic changes in CBT participants from baseline to endpoint reveals distinct patterns indicative of the effects of CBT administration and contributes significantly to our understanding of the neurophysiological effects of psychotherapy in the treatment of depression.

Sleep disturbances are increasingly recognized as potential biomarkers for predicting response to psychotherapeutic treatment in people with MDD. In particular, research conducted by the College of Pittsburgh (Thase et al. 1998) has made an important contribution to this area. They focused on specific sleep abnormalities, including shortened REM latency, increased REM density, and decreased sleep continuity. Patients found to have these sleep patterns showed reduced efficacy of interpersonal psychotherapy and CBT, highlighting the impor-

tance of sleep disturbances in predicting the success of psychotherapy for MDD.

Despite the recognized value of genomic markers in predicting response to psychotherapy, there is a dearth of studies focused on identifying genomic-level biomarkers that can reliably predict such response. Several research papers have investigated how genetic variations influence response, including the effects of the S-allele of 5-HTTLPR on resistance to and benefit from psychotherapy (Goldwaser and Miller 2020). These studies have highlighted that responses to treatment vary substantially by genetic profile, underscoring the need for personalized treatment strategies that consider individual genetic predispositions. Recent studies focusing on the transcriptome have instead provided intriguing evidence of potential markers of response to psychotherapy, particularly in the context of CBT. Certain transcriptomic biomarkers such as PSME1, RAPH1, and IGSF4A/CADM1 have been found to correlate with favorable responses to CBT, highlighting the importance of these transcripts in distinguishing between favorable and unfavorable outcomes of CBT. In addition, transcript levels of ASAH1, ATP11C, and KIAA1539 have been shown to be critical indicators for predicting remission after CBT (Redei et al. 2014).

Currently, there is limited evidence on potential biomarkers in peripheral blood that predict response to psychotherapy. The few studies that have been conducted have focused on molecules associated with the inflammatory cascade, particularly C-reactive protein (CRP) and interleukin-6 (IL-6). A trend has emerged in this area of research linking higher levels of pre-treatment inflammation to lower efficacy of CBT (Lopresti 2017; Harley et al. 2009).

To summarize, recent research demonstrates a new link between psychotherapy and biomarkers in the context of depression treatment. Examination of inflammatory markers and neurobiological factors reveals potential predictive correlations with treatment outcomes in psychotherapy. This evolving relationship paves the way for personalized and more targeted treatment approaches and underscores the synergy between

psychological interventions and physiological markers in advancing psychiatric treatment methods.

19.6 Digital Phenotyping and Markers

Digital phenotyping is about the continuous and unobtrusive monitoring of human behavior in everyday life using data from digital devices. It promises to uncover clinically relevant information by quantifying behavioral and mental states over time. Digital phenotyping captures two categories of data: active data, which is based on participant input, such as survey responses and social media activity, and passive data, which is collected without the person's active involvement, such as GPS coordinates. Digital markers are digitally collected disease indicators that can be used to define a digital phenotype. This concept involves the ability to measure certain symptoms or behaviors specific to a psychiatric disorder using computerized instruments. High model performance is essential to understand how digital phenotyping can improve our understanding of behavioral patterns associated with MDD and support precision medicine efforts for earlier detection and intervention for depressive symptoms. In a recent study, it was observed that as the severity of depressive symptoms increased, the total number of interactions with communication apps and the use of WhatsApp decreased (Leaning et al. 2024). Similarly, in a 2020 study, a significant association was found between higher depression scores and lower levels of social interaction, which was reflected in a shorter duration of phone calls and fewer text messages sent (Cao et al. 2020). In terms of general phone use, two studies found a positive association between the duration of being unlocked and depression scores, with depression scores being positively associated with nightly phone use time (Sun et al. 2023; Zou et al. 2023). In addition, studies suggest that patients with more severe depressive states have lower mobility, in terms of steps taken per day, number of places visited, and variability of places visited (Shin and Bae 2023).

Speech changes may serve as another potential biomarker for the diagnosis of depression. Prosodic abnormalities, such as monotone speech or reduced prosody, are common in people with depression. These changes are thought to be due to cognitive and physiological changes that affect speech production, including disturbances in muscle tone and respiratory rate due to changes in the automatic and somatic nervous systems. Speech analysis, which automatically extracts vocal and linguistic features from audio signals, provides an objective method for detecting and measuring these changes and serves as an additional assessment tool for depression. Temporal features, which include the prosodic timing of speech, are proving to be promising indicators of the severity of depression. Studies have found correlations between various temporal features and depression scores, including speech rate, pause time, reaction time, and measures of emotional elements in speech (Mundt et al. 2012). In addition to the assessment of features that can be directly observed in speech analysis, computerized techniques have also been developed in recent years to measure the characteristics of the acoustic signal through specific calculations and algorithms. Among the most commonly analyzed parameters are the zero-crossing rate (ZCR), the harmonics-to-noise ratio (HNR), and the mel-frequency cepstrum coefficients (MFCC). The zero-crossing rate of an audio frame is the rate at which the signal changes sign during the analyzed frame: in other words, it is the number of times the signal changes its value, from positive to negative and vice versa, divided by the length of the frame. The harmonics-to-noise ratio is the parameter that measures the relationship between the periodic and non-periodic components of a vocal sound. The mel-frequency cepstrum coefficients (MFCC) are coefficients used to evaluate the short-term power spectrum of a sound. Variations in these three parameters appear to be correlated with depressive symptomatology and response to certain treatments (Taguchi et al. 2018).

These are just a few examples of new technological tools that can be used for the diagnosis of depression, based on the integration of digital

data with those from electronic health records. In the future, it is essential to continue integrating data from different sources to develop new algorithms for diagnosis and treatment prediction through machine learning. Machine learning, which integrates computer science, engineering, and statistics, enables computers to learn without explicit programming. Supervised machine learning techniques can develop predictive algorithms to make optimal predictions for new cases, such as predicting a patient's individual response to a therapy before it is administered.

Despite the current lack of concrete evidence for the use of such tools in daily clinical practice, the development of artificial intelligence in the field of precision psychiatry could represent a groundbreaking change in the early diagnosis and prediction of response to treatment of patients with MDD in the future.

19.7 Conclusions

This chapter aims to provide a comprehensive overview of potentially useful biomarkers for the diagnosis and prediction of treatment outcomes in patients with major depressive disorder. To date, patient assessment has relied solely on the clinical judgment of the psychiatrist, with therapeutic approaches varying widely among professionals. As long as dimensional psychopathological assessment is helpful in distinguishing between categories of clinical episodes and subsequent therapeutic approaches, biomarkers should not completely replace it. Rather, biomarkers can help clinicians supplement their observations with objective data to make personalized and specific diagnostic and therapeutic decisions for individual patients, considering biological, psychological, familial, genetic, and life-event-related data. Central to this approach is the assumption that depression is a systemic disease that, like most medical conditions, affects multiple organs and systems. While branches of medicine such as endocrinology and infectious diseases have found scientific evidence for the use of objective diagnostic tools, these are still lacking in psychiatry.

However, the results of recent studies, as well as the development of artificial intelligence in the field of psychiatry, represent a crucial first step toward refining early diagnosis and treatment techniques that can lead to an improved prognosis for this condition, which is currently the leading cause of disability worldwide. Disclosures Giampaolo Perna has received funding from Cariplo Foundation. He has served as consultant for Medibio Ltd, Lundbeck, Pfizer, Biogen, and Willmar Schwabe GmbH.

References

- Abrahams E, Ginsburg GS, Silver M (2005) The personalized medicine coalition. *Am J Pharmacogenomics* 5(6):345–355
- Al-Hakeim HK, Twayej AJ, Al-Dujaili AH, Maes M (2020) Plasma Indoleamine-2,3-dioxygenase (IDO) is increased in drug-Naïve major depressed patients and treatment with sertraline and Ketoprofen normalizes IDO in association with pro-inflammatory and immune-regulatory cytokines. *CNS Neurol Disord Drug Targets* 19(1):44–54
- Arikan MK, Metin B, Tarhan N (2018) EEG gamma synchronization is associated with response to paroxetine treatment. *J Affect Disord* 235:114–116
- Arns M, Etkin A, Hegerl U, Williams LM, DeBattista C, Palmer DM et al (2015) Frontal and rostral anterior cingulate (rACC) theta EEG in depression: implications for treatment outcome? *Eur Neuropsychopharmacol* 25(8):1190–1200
- Asberg M, Träskman L (1981) Studies of CSF 5-HIAA in depression and suicidal behaviour. *Adv Exp Med Biol* 133:739–752
- Aubry JM, Gervasoni N, Osiek C, Perret G, Rossier MF, Bertschy G et al (2007) The DEX/CRH neuroendocrine test and the prediction of depressive relapse in remitted depressed outpatients. *J Psychiatr Res* 41(3–4):290–294
- Badamasi IM, Lye MS, Ibrahim N, Abdul Razaq NA, Ling KH, Stanslas J (2021) Serotonergic receptor gene polymorphism and response to selective serotonin reuptake inhibitors in ethnic Malay patients with first episode of major depressive disorder. *Pharmacogenomics J* 21(12):498
- Beckman G, Beckman L, Cedergren B, Perris C, Strandman E (1978) Serum protein and red cell enzyme polymorphisms in affective disorders. *Hum Hered* 28(1):41–47
- Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S et al (2013) So depression is an inflammatory disease, but where does the inflammation come from? *BMC Med* 11(1):200
- Bijstervosch JD, Ansari TL, Smith S, Gauld O, Zika O, Boessenkool S et al (2018) Stratification of MDD and GAD patients by resting state brain connectivity predicts cognitive bias. *NeuroImage Clin* 19:425–433
- Border R, Johnson EC, Evans LM, Smolen A, Berley N, Sullivan PF et al (2019) No support for historical candidate gene or candidate gene-by-interaction hypotheses for major depression across multiple large samples. *Am J Psychiatry* 176(5):376–387
- Boschloo L, Schoevers RA, Beekman ATF, Smit JH, van Hemert AM, Penninx BWJH (2014) The four-year course of major depressive disorder: the role of staging and risk factor determination. *Psychother Psychosom* 83(5):279–288
- Brasso C, Cisotto M, Del Favero E, Giordano B, Villari V, La Rocca P (2023) Impact of COVID-19 pandemic on major depressive disorder in acute psychiatric inpatients. *Front Psychol* 14:1181832
- Byrne EM, Kirk KM, Medland SE, McGrath JJ, Colodro-Conde L, Parker R et al (2020) Cohort profile: the Australian genetics of depression study. *BMJ Open* 10(5):e032580
- Cacabelos R (2015) Pharmacogenomics of antidepressants. *Psychiatr Depress Anxiety* 1(1):1–42
- Cai N, Revez JA, Adams MJ, Andlauer TFM, Breen G, Byrne EM et al (2020) Minimal phenotyping yields genome-wide association signals of low specificity for major depression. *Nat Genet* 52(4):437–447
- Cao J, Truong AL, Banu S, Shah AA, Sabharwal A, Moukaddam N (2020) Tracking and predicting depressive symptoms of adolescents using smartphone-based self-reports, parental evaluations, and passive phone sensor data: development and usability study. *JMIR Mental Health* 7(1):e14045
- Carrasco-Ramiro F, Peiró-Pastor R, Aguado B (2017) Human genomics projects and precision medicine. *Gene Ther* 24(9):551–561
- Chan IS, Ginsburg GS (2011) Personalized medicine: progress and promise. *Annu Rev Genomics Hum Genet* 12:217–244
- Colle R, Dupong I, Colliot O, Deflesselle E, Hardy P, Falissard B et al (2016) Smaller hippocampal volumes predict lower antidepressant response/remission rates in depressed patients: a meta-analysis. *World J Biol Psychiatry* 19(5):360–367
- De la Cruz-Cano E (2017) Association between FKBP5 and CRHR1 genes with suicidal behavior: a systematic review. *Behav Brain Res* 317:46–61
- Djulbegovic B, Guyatt GH (2017) Progress in evidence-based medicine: a quarter century on. *Lancet* 390(10092):415–423
- Draganov M, Vives-Gilbert Y, de Diego-Adeliño J, Vicent-Gil M, Puigdemont D, Portella MJ (2020) Glutamatergic and GABA-ergic abnormalities in first-episode depression. A 1-year follow-up 1H-MR spectroscopic study. *J Affect Disord* 266:572–577
- Duman EA, Canli T (2015) Influence of life stress, 5-HTTLPR genotype, and SLC6A4 methylation on gene expression and stress response in healthy Caucasian males. *Biol Mood Anxiety Disord* 5(1):2
- Dunn EC, Soare TW, Zhu Y, Simpkin AJ, Suderman MJ, Klengel T et al (2019) Sensitive periods for the effect of childhood adversity on DNA methylation: results

- from a prospective, longitudinal study. *Biol Psychiatry* 85(10):838–849
- Eder J, Pfeiffer L, Wichert SP, Keeser B, Simon MS, Popovic D et al (2023) Deconstructing depression by machine learning: the POKAL-PSY study. *Eur Arch Psychiatry Clin Neurosci*
- FDA-NIH Biomarker Working Group (2016) BEST (Biomarkers, EndpointS, and other tools) resource. Food and Drug Administration (US)
- Felger JC, Lotrich FE (2013) Inflammatory cytokines in depression: neurobiological mechanisms and therapeutic implications. *Neuroscience* 246:199–229
- Fernandes BS, Williams LM, Steiner J, Leboyer M, Carvalho AF, Berk M (2017) The new field of “precision psychiatry”. *BMC Med* 15(1):80
- Flint J, Kendler KS (2014) The genetics of major depression. *Neuron* 81(3):484–503
- Fonseka TM, MacQueen GM, Kennedy SH (2018) Neuroimaging biomarkers as predictors of treatment outcome in major depressive disorder. *J Affect Disord* 233:21–35
- Fries GR, Saldana VA, Finnstein J, Rein T (2022) Molecular pathways of major depressive disorder converge on the synapse. *Mol Psychiatry* 28(1):1–14
- Frokjaer VG, Mortensen EL, Nielsen FC, Haugbøl S, Pinborg LH, Adams K et al (2008) Frontolimbic serotonin 2A receptor binding in healthy subjects is associated with personality risk factors for affective disorder. *Biol Psychiatry* 63(6):569–576
- Fu CHY, Erus G, Fan Y, Antoniadis M, Arnone D, Arnott SR et al (2023) AI-based dimensional neuroimaging system for characterizing heterogeneity in brain structure and function in major depressive disorder: COORDINATE-MDD consortium design and rationale. *BMC Psychiatry* 23:59
- Gabbay V, Klein RG, Katz Y, Mendoza S, Guttman LE, Alonso CM et al (2010) The possible role of the kynurenine pathway in adolescent depression with melancholic features. *J Child Psychol Psychiatry* 51(8):935–943
- Gadad BS, Jha MK, Grannemann BD, Mayes TL, Trivedi MH (2017) Proteomics profiling reveals inflammatory biomarkers of antidepressant treatment response: findings from the CO-MED trial. *J Psychiatr Res* 94:1–6
- Gandal MJ, Leppa V, Won H, Parikshak NN, Geschwind DH (2016) The road to precision psychiatry: translating genetics into disease mechanisms. *Nat Neurosci* 19(11):1397–1407
- Gao L, Cai Y, Wang H, Wang G, Zhang Q, Yan X (2019) Probing prefrontal cortex hemodynamic alterations during facial emotion recognition for major depression disorder through functional near-infrared spectroscopy. *J Neural Eng* 16(2):026026–026026
- Gasparini A, Callegari C, Lucca G, Bellini A, Caselli I, Ielmini M (2022) Inflammatory biomarker and response to antidepressant in major depressive disorder: a systematic review and meta-analysis. *Psychopharmacol Bull* 52(1):36–52
- Gehring AJ, Mendez P, Richter K, Ertl H, Donaldson EF, Mishra P et al (2022) Immunological biomarker discovery in cure regimens for chronic hepatitis B virus infection. *J Hepatol* 32(154)
- Godlewska BR, Browning M, Norbury R, Igoumenou A, Cowen PJ, Harmer CJ (2018) Predicting treatment response in depression: the role of anterior cingulate cortex. *Int J Neuropsychopharmacol* 21(11):988–996
- Goldstein BL, Klein DN (2014) A review of selected candidate endophenotypes for depression. *Clin Psychol Rev* 34(5):417–427
- Goldwaser EL, Miller CWT (2020) The genetic and neural circuitry predictors of benefit from manualized or open-ended psychotherapy. *Am J Psychother* 73(3):72–84
- Grudet C, Wolkowitz OM, Mellon SH, Malm J, Reus VI, Brundin L et al (2020) Vitamin D and inflammation in major depressive disorder. *J Affect Disord* 267:33–41
- Gupta M (2007) Does evidence-based medicine apply to psychiatry? *Theor Med Bioeth* 28(2):103–120
- Halaris A, Prochaska D, Stefanski A, Filip M (2022) C-reactive protein in major depressive disorder: promise and challenge. *J Affect Disord Rep* 10:100427
- Han AL (2022) Association between lipid ratio and depression: a cross-sectional study. *Sci Rep* 12(1):6190
- Han KM, Ham BJ, Kim YK (2021) Development of neuroimaging-based biomarkers in major depression. *Adv Exp Med Biol* 1305:85–99
- Hannon E, Knox O, Sugden K, Burrage J, Wong CCY, Belsky DW et al (2018) Characterizing genetic and environmental influences on variable DNA methylation using monozygotic and dizygotic twins. *PLOS Genet*. 14(8):e1007544
- Harley J, Luty S, Carter J, Mulder R, Joyce P (2009) Elevated C-reactive protein in depression: a predictor of good long-term outcome with antidepressants and poor outcome with psychotherapy. *J Psychopharmacol* 24(4):625–626
- Hill KR, Gardus JD, Bartlett EA, Perlman G, Parsey RV, DeLorenzo C (2021) Measuring brain glucose metabolism in order to predict response to antidepressant or placebo: a randomized clinical trial. *NeuroImage Clin* 32:102858
- Howard DM, Adams MJ, Shiri M, Clarke TK, Marioni RE, Davies G et al (2018) Genome-wide association study of depression phenotypes in UK biobank identifies variants in excitatory synaptic pathways. *Nat Commun* 9(1):1470
- Howard DM, Adams MJ, Clarke TK, Hafferty JD, Gibson J, Shiri M et al (2019) Genome-wide meta-analysis of depression identifies 102 independent variants and highlights the importance of the prefrontal brain regions. *Nat Neurosci* 22(3):343–352
- Howes OD, Thase ME, Pillinger T (2021) Treatment resistance in psychiatry: state of the art and new directions. *Mol Psychiatry* 27(1):58–72
- Husain SF, Tang TB, Yu R, Tam WW, Tran B, Quek TT et al (2020) Cortical haemodynamic response measured by functional near infrared spectroscopy during a verbal fluency task in patients with major depression

- and borderline personality disorder. *EBioMedicine* 51:102586
- Hwang H, Hwang BY, Bueno J (2018) Biomarkers in infectious diseases. *Dis Markers* 2018:1–2
- Iacono WG (2018) Endophenotypes in psychiatric disease: prospects and challenges. *Genome Med* 10(1):11
- Iosifescu DV, Renshaw PF, Lyoo IK, Lee HK, Perlis RH, Papakostas GI et al (2006) Brain white-matter hyperintensities and treatment outcome in major depressive disorder. *Br J Psychiatry* 188(02):180–185
- Ising M, Maccarrone G, Brückl T, Scheuer S, Hennings J, Holsboer F et al (2019) FKBP5 gene expression predicts antidepressant treatment outcome in depression. *Int J Mol Sci* 20(3):485
- Jain KK (2017) Biomarkers of genetic disorders. Springer eBooks, pp 239–247
- Jenkins T, Nguyen J, Polglaze K, Bertrand P (2016) Influence of tryptophan and serotonin on mood and cognition with a possible role of the gut-brain axis. *Nutrients* 8(1):56
- Jha MK, Minhajuddin A, Gadad BS, Greer T, Grannemann B, Soyombo A et al (2017) Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial. *Psychoneuroendocrinology* 78:105–113
- Ju Y, Wang M, Lu X, Sun J, Dong Q, Zhang L et al (2020) The effects of childhood trauma on the onset, severity and improvement of depression: the role of dysfunctional attitudes and cortisol levels. *J Affect Disord* 276:402–410
- Jung J, Kang J, Won E, Nam K, Lee MS, Tae WS et al (2014) Impact of lingual gyrus volume on antidepressant response and neurocognitive functions in major depressive disorder: a voxel-based morphometry study. *J Affect Disord* 169:179–187
- Kasyanov ED, Rakitko AS, Rukavishnikov GV, Golimbet VE, Shmukler AB, Iliinsky VV et al (2022) Contemporary genome-wide association studies in depression: the critical role of phenotyping. *Neurosci Behav Physiol* 52(6):826–835
- Kendall KM, Van Assche E, Andlauer TFM, Choi KW, Luyckx JJ, Schulte EC et al (2021) The genetic basis of major depression. *Psychol Med* 51(13):1–14
- Kennedy SH, Konarski JZ, Segal ZV, Lau MA, Bieling PJ, McIntyre RS et al (2007) Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. *Am J Psychiatry* 164(5):778–788
- Kessler RC, Luedtke A (2021) Pragmatic precision psychiatry—a new direction for optimizing treatment selection. *JAMA Psychiatry* 78:1384
- Knorr U, Vinberg M, Kessing LV, Wetterslev J (2010) Salivary cortisol in depressed patients versus control persons: a systematic review and meta-analysis. *Psychoneuroendocrinology* 35(9):1275–1286
- Kosorok MR, Laber EB (2019) Precision Medicine. *Ann Rev Statist Its Appl* 6(1):263–286
- Kott KA, Bishop M, Yang CHJ, Plasto TM, Cheng DC, Kaplan AI et al (2022) Biomarker development in cardiology: reviewing the past to inform the future. *Cells* 11(3):588
- Kouba BR, Camargo A, Gil-Mohapel J, Rodrigues ALS (2022) Molecular Basis Underlying the Therapeutic Potential of Vitamin D for the Treatment of Depression and Anxiety. *Int J Mol Sci* 23(13):7077
- Kumar K, Toews M, Chauvin L, Colliot O, Desrosiers C (2018) Multi-modal brain fingerprinting: a manifold approximation based framework. *NeuroImage* 183:212–226
- Kumar M, Sahu M, Dubey R, Chandrakar A, Kumar M (2022) A systematic review and meta-analysis of serum and plasma cortisol levels in depressed patients versus control. *Indian J Psychiatry* 64(5):440
- Kundakovic M, Jaric I (2017) The epigenetic link between prenatal adverse environments and neurodevelopmental disorders. *Genes* 8(3):104
- Kunugi H, Hori H, Ogawa S (2015) Biochemical markers subtyping major depressive disorder. *Psychiatry Clin Neurosci* 69(10):597–608
- Labonte B, Yerko V, Gross J, Mechawar N, Meaney MJ, Szyf M et al (2012) Differential glucocorticoid receptor exon 1B, 1C, and 1H expression and methylation in suicide completers with a history of childhood abuse. *Biol Psychiatry* 72(1):41–48
- Lai CH, Wu YT (2014) Alterations in white matter micro-integrity of the superior longitudinal fasciculus and anterior thalamic radiation of young adult patients with depression. *Psychol Med* 44(13):2825–2832
- Lavebratt C, Åberg E, Sjöholm LK, Forsell Y (2010) Variations in FKBP5 and BDNF genes are suggestively associated with depression in a Swedish population-based cohort. *J Affect Disord* 125(1–3):249–255
- Leaning IE, Ikani N, Savage HS, Leow A, Beckmann C, Ruhé HG et al (2024) From smartphone data to clinically relevant predictions: a systematic review of digital phenotyping methods in depression. *Neurosci Biobehav Rev* 158:105541–105541
- Lee J, Lee KH, Kim SH, Han JY, Hong SB, Cho SC et al (2020) Early changes of serum BDNF and SSRI response in adolescents with major depressive disorder. *J Affect Disord* 265:325–332
- Leightley D, Lavelle G, White KM, Sun S, Matcham F, Ivan A et al (2021) Investigating the impact of COVID-19 lockdown on adults with a recent history of recurrent major depressive disorder: a multi-Centre study using remote measurement technology. *BMC Psychiatry* 21(1):435
- Levey DF, Stein MB, Wendt FR, Pathak GA, Zhou H, Aslan M et al (2021) Bi-ancestral depression GWAS in the million veteran program and meta-analysis in >1.2 million individuals highlight new therapeutic directions. *Nat Neurosci* 24(7):954–963
- Libuda L, Laabs BH, Ludwig C, Bühlmeier J, Antel J, Hinney A et al (2019) Vitamin D and the risk of depression: a causal relationship? findings from a mendelian randomization study. *Nutrients* 11(5):1085
- Lopresti AL (2017) Cognitive behaviour therapy and inflammation: a systematic review of its relationship

- and the potential implications for the treatment of depression. *Aust NZ J Psychiatry* 51(6):565–582
- Lozupone M, La Montagna M, D’Urso F, Daniele A, Greco A, Seripa D et al (2019) The role of biomarkers in psychiatry. *Adv Exp Med Biol* 1118:135–162
- Luddington NS, Mandadapu A, Husk M, El-Mallakh RS (2009) Clinical implications of genetic variation in the serotonin transporter promoter region. *Prim Care Companion J Clin Psychiatry* 11(3):93–102
- Lye MS, Tey YY, Tor YS, Shahabudin AF, Ibrahim N, Ling KH et al (2020) Predictors of recurrence of major depressive disorder. *PLOS ONE*. 15(3):e0230363
- Ma S, Xie X, Deng Z, Wang W, Xiang D, Yao L et al (2023) A machine learning analysis of “big” metabolomics data for classifying depression: model development and validation. *Biol Psychiatry* 28(16)
- Maj M (2018) Why the clinical utility of diagnostic categories in psychiatry is intrinsically limited and how we can use new approaches to complement them. *World Psychiatry* 17(2):121–122
- Marshé VS, Islam F, Maciukiewicz M, Bousman C, Eyre HA, Lavretsky H et al (2020) Pharmacogenetic implications for antidepressant pharmacotherapy in late-life depression: a systematic review of the literature for response, pharmacokinetics and adverse drug reactions. *Am J Geriatr Psychiatry* 28(6):609–629
- Marx W, Penninx BWJH, Solmi M, Furukawa TA, Firth J, Carvalho AF et al (2023) Major depressive disorder. *Nat Rev Dis Primers* 9(1):44
- McGowan PO, Sasaki A, D’Alessio AC, Dymov S, Labonté B, Szyf M et al (2009) Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 12(3):342–348
- McGrath CL, Kelley ME, Holtzheimer PE, Dunlop BW, Craighead WE, Franco AR et al (2013) Toward a neuroimaging treatment selection biomarker for major depressive disorder. *JAMA Psychiatry* 70(8):821
- McIntosh AM, Sullivan PF, Lewis CM (2019) Uncovering the genetic architecture of major depression. *Neuron* 102(1):91–103
- McQuaid R (2021) Transdiagnostic biomarker approaches to mental health disorders: consideration of symptom complexity, comorbidity and context. *Brain Behav Immun Health* 16:100303
- Menke A, The HPA (2024) Axis as target for depression. *Curr Neuropsychopharmacol* 22(5):904–915
- Metcalfe CA, Johnson RL, Duffy KA, Freeman EW, Sammel MD, Epperson CN (2023) Depressed, stressed, and inflamed: C-reactive protein linked with depression symptoms in midlife women with both childhood and current life stress. *Stress Health* 40:e3313
- Mitchell AJ, Coyne JC (2007) Do ultra-short screening instruments accurately detect depression in primary care? A pooled analysis and meta-analysis of 22 studies. *Br J Gen Pract* 57(535):144–151
- Monroe SM, Harkness KL (2022) Major depression and its recurrences: life course matters. *Annu Rev Clin Psychol* 18(1):329
- Mundt JC, Vogel AP, Feltner DE, Lenderking WR (2012) Vocal acoustic biomarkers of depression severity and treatment response. *Biol Psychiatry* 72(7):580–587
- National Research Council (2011) Toward precision medicine. National Academies Press, Washington, DC
- Nishizawa Y, Kanazawa T, Kawabata Y, Matsubara T, Maruyama S, Kawano M et al (2019) fNIRS assessment during an emotional Stroop task among patients with depression: replication and extension. *Psychiatry Investig* 16(1):80–86
- Nunes A, Trappenberg T, Alda M (2020) The definition and measurement of heterogeneity. *Transl Psychiatry* 10(1):301
- O’Brien FE, Dinan TG, Griffin BT, Cryan JF (2012) Interactions between antidepressants and P-glycoprotein at the blood–brain barrier: clinical significance of in vitro and in vivo findings. *Br J Pharmacol* 165(2):289–312
- Ohnmacht AJ, Stahler A, Stintzing S, Modest DP, Holch JW, Westphalen CB et al (2023) The oncology biomarker discovery framework reveals cetuximab and bevacizumab response patterns in metastatic colorectal cancer. *Nat Commun* 14(1):5391
- Olbrich S, Arns M (2013) EEG biomarkers in major depressive disorder: discriminative power and prediction of treatment response. *Int Rev Psychiatry (Abingdon, England)* 25(5):604–618
- Orr SP (2003) Physiologic responses to sudden, loud tones in monozygotic twins discordant for combat exposure association with posttraumatic stress disorder. *Arch Gen Psychiatry* 60(3):283
- Ozomaro U, Wahlestedt C, Nemeroff CB (2013) Personalized medicine in psychiatry: problems and promises. *BMC Med* 11(1):132
- Parekh A, Smeeth D, Milner Y, Thuret S (2017) The role of lipid biomarkers in major depression. *Healthcare* 5(1):5
- Paulus MP (2017) Evidence-based pragmatic psychiatry—a call to action. *JAMA Psychiatry* 74(12):1185
- Perna G, Balletta R, Nemeroff CB (2017) Precision psychiatry: personalized clinical approach to depression. Springer eBooks, pp 245–261
- Perna G, Cuniberti F, Daccò S, Grassi M, Caldirola D (2020) “Precision” or “personalized” psychiatry: different terms—same content? *Forts Neurol Psychiatr* 88(12):759–766
- Peterson BS, Weissman MM (2011) A brain-based Endophenotype for major depressive disorder. *Annu Rev Med* 62(1):461–474
- Pillai V, Kalmbach DA, Ciesla JA (2011) A meta-analysis of electroencephalographic sleep in depression: evidence for genetic biomarkers. *Biol Psychiatry* 70(10):912–919
- Pizzagalli DA (2010) Frontocingulate dysfunction in depression: toward biomarkers of treatment response. *Neuropsychopharmacology* 36(1):183–206
- Pizzagalli DA, Peccoralo L, Davidson RJ, Cohen JD (2006) Resting anterior cingulate activity and abnormal responses to errors in subjects with elevated

- depressive symptoms: a 128-channel EEG study. *Hum Brain Mapp* 27(3):185–201
- Powell TR, Smith R, Hackinger S, Schalkwyk LC, Uher R, McGuffin P et al (2013) DNA methylation in interleukin-11 predicts clinical response to antidepressants in GENDEP. *Transl Psychiatry* 3(9):e300
- Pu S, Nakagome K, Yamada T, Yokoyama K, Matsumura H, Yamada S et al (2015) Suicidal ideation is associated with reduced prefrontal activation during a verbal fluency task in patients with major depressive disorder. *J Affect Disord* 181(12):9–17
- Quinlan EB, Banaschewski T, Barker GJ, Bokde ALW, Bromberg U, Büchel C et al (2019) Identifying biological markers for improved precision medicine in psychiatry. *Mol Psychiatry* 25(2):243–253
- Radosavljevic M, Svob Strac D, Jancic J, Samardzic J (2023) The role of pharmacogenetics in personalizing the antidepressant and anxiolytic therapy. *Genes* 14(5):1095
- Redei EE, Andrus BM, Kwasny MJ, Seok J, Cai X, Ho J et al (2014) Blood transcriptomic biomarkers in adult primary care patients with major depressive disorder undergoing cognitive behavioral therapy. *Transl Psychiatry* 4(9):e442–e442
- Riley CA, Renshaw PF (2018) Brain choline in major depression: a review of the literature. *Psychiatry Res Neuroimaging* 271(13):142–153
- Roberson-Nay R, Lapato DM, Wolen AR, Lancaster EE, Webb BT, Verhulst B et al (2020) An epigenome-wide association study of early-onset major depression in monozygotic twins. *Transl Psychiatry* 10(1):301
- Rojas PS, Fritsch R, Rojas RA, Jara P, Fiedler JL (2011) Serum brain-derived neurotrophic factor and glucocorticoid receptor levels in lymphocytes as markers of antidepressant response in major depressive patients: a pilot study. *Psychiatry Res* 189(2):239–245
- Roy A, Hodgkinson CA, DeLuca V, Goldman D, Enoch MA (2012) Two HPA axis genes, CRHBP and FKBP5, interact with childhood trauma to increase the risk for suicidal behavior. *J Psychiatr Res* 46(1):72–79
- Šagud M, Perković MN, Dvojkovic A, Jakšić N, Vuksan-Ćusa B, Živković M et al (2021) Distinct association of plasma BDNF concentration and cognitive function in depressed patients treated with vortioxetine or escitalopram. *Psychopharmacology* 238(6):1575–1584
- Scherf-Clavel M, Wurst C, Nitschke F, Stonawski S, Burschka C, Friess L et al (2020) Extent of cortisol suppression at baseline predicts improvement in HPA axis function during antidepressant treatment. *Psychoneuroendocrinology* 114:104590
- Schüle C, Baghai TC, Eser D, Häfner S, Born C, Herrmann S et al (2009) The combined dexamethasone/CRH test (DEX/CRH test) and prediction of acute treatment response in major depression. *Plos ONE*. 4(1):e4324
- Schumacher MM, Santambrogio J (2023) Cortisol and the dexamethasone suppression test as a biomarker for melancholic depression: a narrative review. *J Person Med* 13(5):837
- Serretti A, Zanardi R, Rossini D, Cusin C, Lilli R (2001) Influence of tryptophan hydroxylase and serotonin transporter genes on fluvoxamine antidepressant activity. *Mol Psychiatry* 6(5):586–592
- Shi X, Forrest LN, Kuykendall MD, Prescott AP, Sung YC, Huber RS et al (2014) Anterior cingulate cortex choline levels in female adolescents with unipolar versus bipolar depression: a potential new tool for diagnosis. *J Affect Disord* 167:25–29
- Shi Y, Wang Q, Song R, Kong Y, Zhang Z (2021) Non-coding RNAs in depression: promising diagnostic and therapeutic biomarkers. *EBioMedicine* 71:103569
- Shin J, Bae SM (2023) A systematic review of location data for depression prediction. *Int J Environ Res Public Health* 20(11):5984
- Shin JY, Suls J, Martin R (2008) Are cholesterol and depression inversely related? A meta-analysis of the association between two cardiac risk factors. *Ann Behav Med* 36(1):33–43
- Spijker J, De Graaf R, Bijl RV, Beekman ATF, Ormel J, Nolen WA (2002) Duration of major depressive episodes in the general population: results from The Netherlands mental health survey and incidence study (NEMESIS). *Br J Psychiatry* 181(03):208–213
- Sreeja V, Jose A, Patel S, Menon B, Athira KV, Chakravarty S (2024) Pharmacogenetics of selective serotonin reuptake inhibitors (SSRI): a serotonin reuptake transporter (SERT)-based approach. *Neurochem Int* 173:105672
- Strawbridge R, Hodsoll J, Powell TR, Hotopf M, Hatch SL, Breen G et al (2019) Inflammatory profiles of severe treatment-resistant depression. *J Affect Disord* 246:42–51
- Strege MV, Siegle GJ, Richey JA, Krawczak RA, Young K (2023) Cingulate prediction of response to antidepressant and cognitive behavioral therapies for depression: meta-analysis and empirical application. *Brain Imaging Behav* 17:450
- Sun S, Folarin AA, Zhang Y, Cummins N, Garcia-Dias R, Stewart C et al (2023) Challenges in using mHealth data from smartphones and wearable devices to predict depression symptom severity: retrospective analysis. *J Med Internet Res* 25:e45233–e45233
- Svenningsson P, Berg L, Matthews D, Ionescu DF, Richards EM, Niciu MJ et al (2014) Preliminary evidence that early reduction in p11 levels in natural killer cells and monocytes predicts the likelihood of antidepressant response to chronic citalopram. *Mol Psychiatry* 19(9):962–964
- Taguchi T, Tachikawa H, Nemoto K, Suzuki M, Nagano T, Tachibana R et al (2018) Major depressive disorder discrimination using vocal acoustic features. *J Affect Disord* 225:214–220
- Tesler N, Gerstenberg M, Franscini M, Jenni OG, Walitza S, Huber R (2016) Increased frontal sleep slow wave activity in adolescents with major depression. *NeuroImage Clin* 10:250–256
- Thase ME, Fasiczka AL, Berman SR, Simons AD, Reynolds CF (1998) Electroencephalographic sleep profiles before and after cognitive behavior therapy of depression. *Arch Gen Psychiatry* 55(2):138

- Thaweethee-Sukjai B, Suttajit S, Thanoi S, Dalton CF, Reynolds GP, Nudmamud-Thanoi S (2019) Parvalbumin promoter methylation altered in major depressive disorder. *Int J Med Sci* 16(9):1207–1214
- Trivedi MH (2016) Right patient, right treatment, right time: biosignatures and precision medicine in depression. *World Psychiatry* 15(3):237–238
- Tsai SJ, Hong CJ, Liou YJ, Yu YW-Y, Chen TJ, Hou SJ et al (2009) Tryptophan hydroxylase 2 gene is associated with major depression and antidepressant treatment response. *Prog Neuro-Psychopharmacol Biol Psychiatry* 33(4):637–641
- Tura A, Goya-Maldonado R (2023) Brain connectivity in major depressive disorder: a precision component of treatment modalities? *Transl Psychiatry* 13(1):196
- Turley P, Walters RK, Maghzian O, Okbay A, Lee JJ, Fontana MA et al (2018) Multi-trait analysis of genome-wide association summary statistics using MTAG. *Nat Genet* 50(2):229–237
- Uffelmann E, Huang QQ, Munung NS, de Vries J, Okada Y, Martin AR et al (2021) Genome-wide association studies. *Nat Rev Methods Primers* 1793:37–49
- Underwood MD, Kassir SA, Bakalian MJ, Galfalvy H, Dwork AJ, Mann JJ et al (2018) Serotonin receptors and suicide, major depression, alcohol use disorder and reported early life adversity. *Transl Psychiatry* 8(1):279
- Usher K, Durkin J, Bhullar N (2020) The COVID-19 pandemic and mental health impacts. *Int J Ment Health Nurs* 29(3):315
- van der Wijk G, Harris JK, Hassel S, Davis AD, Zamyadi M, Arnott SR et al (2022) Baseline functional connectivity in resting state networks associated with depression and remission status after 16 weeks of pharmacotherapy: a CAN-BIND report. *Cerebral Cortex (New York, NY: 1991)* 32(6):1223–1243
- Vos T, Haby MM, Barendregt JJ, Kruijschaar M, Corry J, Andrews G (2004) The burden of major depression avoidable by longer-term treatment strategies. *Arch Gen Psychiatry* 61(11):1097
- Wahl S, Drong A, Lehne B, Loh M, Scott WR, Kunze S et al (2017) Epigenome-wide association study of body mass index, and the adverse outcomes of adiposity. *Nature* 541(7635):81–86
- Wei Y, Zhang R, Wang Y, Womer FY, Dong S, Zheng J et al (2023) Towards a neuroimaging biomarker for predicting cognitive behavioural therapy outcomes in treatment-naïve depression: preliminary findings. *Psychiatry Res* 329:115542
- Wiedemann A, Stochl J, Neufeld SAS, Fritz J, Bhatti J, Hook RW et al (2022) The impact of the initial COVID-19 outbreak on young adults' mental health: a longitudinal study of risk and resilience factors. *Sci Rep* 12(1):16659
- Wietfeldt N (2020) FKBP5 gene variants as predictors for antidepressant response in individuals with major depressive disorder who have experienced childhood trauma. A systematic review. *Int J Med Stud* 20(3):485
- World Health Organization (2022) Mental health and COVID-19: early evidence of the pandemic's impact: scientific brief. World Health Organization
- Wray NR, Ripke S, Mattheisen M, Trzaskowski M, Byrne EM, Abdellaoui A et al (2018) Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet* 50(5):668–681
- Wu W, Zhang Y, Jiang J, Lucas MV, Fonzo GA, Rolle CE et al (2020) An electroencephalographic signature predicts antidepressant response in major depression. *Nat Biotechnol* 38:439
- Xiaomin L (2024) Progress in the “brain-derived neurotrophic factor depression hypothesis. Institute of Psychology, Chinese Academy Sciences. Sourcedb Psych Cas Cn 8AD
- Yamamoto T, Sugaya N, Siegle GJ, Kumano H, Shimada H, Machado S et al (2018) Altered gamma-band activity as a potential biomarker for the recurrence of major depressive disorder. *Front Psychiatry* 9:691
- Yoshimura R, Kishi T, Hori H, Katsuki A, Sugita-Ikenouchi A, Umene-Nakano W et al (2014) Serum levels of brain-derived neurotrophic factor at 4 weeks and response to treatment with SSRIs. *Psychiatry Investig* 11(1):84–84
- Yuan M, Yang B, Rothschild G, Mann JJ, Sanford LD, Tang X et al (2023) Epigenetic regulation in major depression and other stress-related disorders: molecular mechanisms, clinical relevance and therapeutic potential. *Signal Transduct Target Ther* 8(1):309
- Zelada MI, Garrido V, Liberona A, Jones N, Zúñiga K, Silva H et al (2023) Brain-derived neurotrophic factor (BDNF) as a predictor of treatment response in major depressive disorder (MDD): a systematic review. *Int J Mol Sci* 24(19):14810
- Zhou B, Zhu Z, Ransom BR, Tong X (2020) Oligodendrocyte lineage cells and depression. *Mol Psychiatry* 26(1):103–117
- Zhu JH, Bo HH, Liu BP, Jia CX (2023) The associations between DNA methylation and depression: a systematic review and meta-analysis. *J Affect Disord* 3(27):439–450
- Zou B, Zhang X, Xiao L, Bai R, Li X, Liang H et al (2023) Sequence modeling of passive sensing data for treatment response prediction in major depressive disorder. *IEEE Trans Neural Syst Rehabil Eng* 31:1786–1795