Chapter 27
Precision Psychiatry: Biomarker-Guided Tailored Therapy for Effective Treatment and Prevention in Major Depression

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Abstract Depression contributes greatly to global disability and is a leading cause of suicide. It has multiple etiologies and therefore response to treatment can vary significantly. By applying the concepts of personalized medicine, precision psychiatry attempts to optimize psychiatric patient care by better predicting which individuals will develop an illness, by giving a more accurate biologically based diagnosis, and by utilizing more effective treatments based on an individual's biological characteristics (biomarkers). In this chapter, we discuss the basic principles underlying the role of biomarkers in psychiatric pathology and then explore multiple biomarkers that are specific to depression. These include endophenotypes, gene variants/polymorphisms, epigenetic factors such as methylation, biochemical measures, circadian rhythm dysregulation, and neuroimaging findings. We also examine the role of early childhood trauma in the development of, and treatment response to, depression. In addition, we review how new developments in technology may play a greater role in the determination of new biomarkers for depression.

Keywords Depression · Biomarkers · Precision psychiatry · Endophenotypes · Genetics · Epigenetics · Neuroimaging

27.1 Introduction

Depression is the leading cause of disability across the globe, affecting over 264 million people worldwide [1–3]. It is a major determining factor of quality of life and survival, with potential to cause significant functional impairment and even

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Y.-K. Kim (ed.), *Major Depressive Disorder*, Advances in Experimental Medicine and Biology 1305, https://doi.org/10.1007/978-981-33-6044-0_27

death in its most severe form [4]. According to the WHO 2020 report on depression, suicide is the second leading cause of death among individuals between ages 15–29 years old [2]. Multiple treatment options exist for patients with symptoms of depression, most commonly being antidepressant medications. However, only about one-third of these patients reach remission with any single antidepressant [5–7]. In a heterogeneous population, response to medical treatment for any given illness can differ significantly. An individual's response to treatment is influenced by multiple factors, including genetic predisposition, heterogeneity of cohorts, ethnicity, metabolic rate, epigenetic variables, and time of illness onset [8]. In addition, a reliable and highly accurate diagnosis optimally requires integrating known biomarkers, symptoms, environmental influences, genetics, epigenetics, and physical exam findings. A biomarker is defined as a biological characteristic that can be measured objectively and used as an indicator of normal biological function, pathology, and treatment response [9, 10].

The goal of precision medicine, also known as personalized medicine, is to predict disease risk, assist in formulating a more accurate and biologically based diagnosis, and help determine the most effective treatment option based on individual biological traits [11]. Precision medicine assumes that the determination of a reliable medical diagnosis and the subsequent treatment plan is unfeasible if based on symptomology alone [8, 12]. This concept is exemplified by Novick and colleagues' 2017 study, in which they followed 1297 subjects over a 6-month period to determine the extent that individual baseline functioning impacts depression recovery. They defined recovery as both clinical and functional remission. The results of this study revealed that depression remission rates are significantly lower when functional status is included in diagnostic criteria, rather than using DSM-V criteria alone. These results imply that a list of symptom-based criteria is an insufficient diagnostic tool for reliably diagnosing depression and predicting outcome. Whether biological, socioeconomic, or psychosocial, there remain missing pieces to our current methods of assessing depression [12]. Current psychiatric research has focused on identifying specific biomarkers of depression with the aim of further developing precision psychiatry and steering away from the practice of empirical medicine [8, 11]. This chapter focuses on how biomarkers can be used as a more reliable and precise measurement of treatment response, as well as aid in predicting vulnerability to the development of depression.

The use of biomarkers has evolved rapidly in some medical specialties such as oncology; however, in psychiatry, biomarkers are only beginning to be researched and incorporated into clinical practice [11]. Their absence contributes to the varying treatment responses that are seen in individuals with major psychiatric illnesses including depression [13]. Depression is not a single illness but rather a syndrome with a heterogeneous presentation comprised of many different etiologies influenced by the many factors noted above. This concept is supported by a study from Takahashi and colleagues in which they assessed antidepressant response in individuals with depression based on their serotonin transporter gene polymorphism. This resulted in identification of a distinct subgroup with significantly less dysphoric-related symptoms than the others, demonstrating a specific example of how

incorporating biomarkers into psychiatric practice can contribute to a more individualized approach of identifying depression subtypes and ultimately improving outcome [14]. In this chapter, we will explore multiple biomarkers, both established and those currently being researched, that are specific to depression. These include gene variants/polymorphisms, endophenotypes, epigenetic factors (methylation), biochemical measures, circadian rhythm dysregulation, neuroimaging findings, and developments in technology [11]. First, however, we will take a broad look at the current tools being used in precision psychiatry as well as the basic principles underlying the role of biomarkers in medical pathology.

27.1.1 The Tools of Precision Psychiatry

The goal of precision psychiatry is to optimize patient care by considering environment, lifestyle, and gene variability at the level of the individual. Biomarkers are an important component of the emerging vision of individualized care in psychiatry [15]. However, in order to identify individual biomarkers, first researchers have to collect and analyze data extracted from a large assortment of cohort studies of psychiatric illness [16]. This is done through tools that are able to evaluate thousands of data entries at once [17]. The most common example of this in psychiatry is genome-wide association studies, or GWASs. These have been helpful in identifying genetic etiology and pleiotropy shared between multiple psychiatric disorders [18].

Genome-wide association studies are observational studies that scrutinize the whole genome in groups of individuals to determine if any particular genetic variant is associated with a specific illness or trait. Advanced computational methods examining large amounts of genetic and biologic data have made these studies possible. As an example, in their review discussing successful GWAS for depression, Ormel et al. [19] note that recent GWASs have found more than 80 genetic loci associated with depression. However, they also caution that these GWASs only identify genomic regions associated with depression without determining the mechanism of underlying biologic function for specific pathophysiology. Genome-wide association studies have been challenging to interpret because gene variants that are directly involved in an upstream biologic process not only affect those upstream processes but indirectly also modulate many processes and traits downstream in biologic and development pathways (which might result in or impact a number of clinical conditions). In the future, researchers hope to determine the biologic mechanisms for depression-related loci and to discover new loci (or groups of loci) associated with affective disorders.

In general, there are currently (and under development) an increasing number of tools to aid the implementation of precision psychiatry. Genetic and epigenetic analyses can help determine disease risk, the course of disease, and perhaps responses to treatment. Neuroimaging can help characterize various syndromes and pathologic mechanisms, identify the neuroanatomical and neurophysiological correlates of illnesses, and be useful in predicting treatment response. Blood plasma

tests (e.g., vitamin D, thyrotropin, testosterone, or C-reactive protein) can serve as indicators of disease risk and can help identify disease subtypes. In addition other tests of blood and body fluids (such as blood or salivary cortisol levels) can assist with the diagnosis of clinical conditions. Electrophysiologic indicators (as examples, EEG patterns or the N1 event-related potential response) can assist the characterization of clinical syndromes and perhaps predict treatment response. In addition, the electronic medical record can serve as a valuable tool when psychiatrically relevant medical history is recorded so that the information is readily available to all healthcare workers (e.g., history of early-life traumatic experiences can impact treatment response in depression). Biotechnology (such as physiologic monitors attached to smart phones) can help to monitor parameters associated with certain conditions (e.g., heart rate in anxiety disorders) and to associate the data collected with symptoms and treatment effects. Overall, the increasing number and diversity of tools becoming available in psychiatry will help implement and shape precision psychiatry through the coming years.

27.2 Biomarkers: The Basics

In biomedical research, a biomarker (occasionally termed "bioindicator") could be any measurable indicator of a disease [20]. The National Institute of Environmental Health Sciences defines biomarkers as "key molecular or cellular events that link a specific environmental exposure to a health outcome." Response to treatment varies across heterogeneity of the population due to variables such as genetic predisposition [10]. Biomarkers are already established as risk and diagnostic tools in some medical specialties such as cardiology, for example, high serum cholesterol as a risk factor for cardiovascular disease. In this example, the biomarker is correlated with an aspect of the disease process but does not fall within the genotype to phenotype pathway and, therefore, may not be specifically embedded in the causal chain for the disease. A biomarker can also reflect a biologically detectable effect of an outside agent upon an organism. For example, blood or urine lead levels are biomarkers of environmental lead exposure. A biomarker may be useful in distinguishing between biological factors that occur secondary to an illness but fall outside the realm of endophenotypes (e.g., state markers are not endophenotypes). Biomarkers may be useful when discussing the biological impact of environmental or exogenous factors on the emergence of psychopathology [20]. However, in comparison, an essential component of the endophenotype concept is that it is inheritable. In short, a biomarker may or may not be subject to genetic influences. In a somewhat outdated terminology, biomarkers can be classified as "trait" markers which connote disease risk and "state" markers which are prominent during the course of disease, for example, an elevated white blood cell count during infection.

Biological factors posited to subtype depression into distinct categories include markers of monoamine systems such as norepinephrine and serotonin and their metabolites, variations in hypothalamic-pituitary-adrenal axis activity,

polymorphisms in various candidate genes, and circadian rhythm changes. In addition, neuroimaging techniques including MRI/fMRI and PET are also being investigated as potential biomarkers for depression and other psychiatric disorders.

27.2.1 State-Dependent vs. State-Independent Biomarkers

Researchers had hoped that individual genetic effects on endophenotypes would be large, but thus far this hope has not been realized. The largest GWASs have identified gene variants associated with one or another psychiatric disorder, but the effect size is quite small. Many reports are of candidate genes with small sample sizes that have often not been verified [9].

State-dependent biomarkers that exist only during exacerbation of symptoms are called episode markers [9]. Episode markers can be useful for monitoring course and treatment effectiveness and for disorder identification. Schizophrenia research has illustrated how psychophysiological measures are associated with the presence of psychotic symptoms. Using a vocalization model adapted from primate research, Ford [21] (and Ford and colleagues [22]) identified an N1 event-related potential response in schizophrenic patients that may index the state of psychosis in this disorder as it appears to evaluate the quality of neural processing associated with hallucinations [21]. Hinkley et al. 2011 [23], by using magnetoencephalography (MEG) to examine functional connectivity across cortical regions, also provided evidence of an electrocortical biomarker for schizophrenia. These investigators reported that psychotic symptoms and impaired cognition were associated with diminished alpha-band connectivity and postulated that this observed neurophysiologic effect might be a treatment target.

An independent state biomarker or trait marker (endophenotype) is heritable [8]. An endophenotype is primarily state-independent meaning that it manifests in an individual whether or not the illness is active. However, a provocative challenge may be needed to reveal the indicator [20].

Temporally stable biomarkers are a third category and are markers of environmentally induced susceptibility that identify those who have become susceptible to a disorder as a consequence of environmental exposure [9]. For example, acquired characteristics, such as those arising subsequent to trauma or secondary to perinatal complications or substance abuse, fall into this category. Studies of posttraumatic stress disorder (PTSD) have shown that traumatic exposure may lead to the development of such susceptibility markers. In research comparing monozygotic twins discordant for combat exposure, Orr et al. 2003 [24] determined that elevated heart rate response to startling sounds was present only in the exposed twins, implying that the cardiac response represents an acquired marker of PTSD rather than a sign of preexisting genetic susceptibility. Environmentally mediated responses, such as respiratory rate, have many of the qualities of an endophenotype, but because they are not usually a result of genetic susceptibility, they would have little use in identifying which genetic mechanisms are involved in an associated clinical disorder [20].

27.2.2 *Reverse Nosology as a Model for Diagnosis of Psychiatric Illness*

Current disease classification in psychiatry is founded on symptom-based criteria (traditional nosology). Despite the common use of biomarkers for genetic-, tissue-, organ-, and system-level measures in other fields of medicine, the application of brain biomarkers in psychiatry is currently lacking. Conventional symptom-based psychiatric diagnoses do not track well with the emerging biomarker-driven constructs [25]. The absence of biologically based disease definitions impedes progress in finding mechanistic targets for the development of novel effective treatments. There is a definite need in psychiatry for developing disease entities built on brain biology and supported by objective, quantitative, clinically relevant disease biomarkers –the approach recently emphasized by the Research Domain Criteria [26, 27]. In a proband sample similar to the one that was used in the Bipolar-Schizophrenia Network on Intermediate Phenotypes (BSNIP), weighted groupings of brain regions or regional brain characteristics are linked to weighted groupings of genetic variables that can then be evaluated for associations [28].

27.3 Endophenotype: A Specific Type of Biomarker

The easiest way to remember the distinction between the two terms "endophenotypes" and "biomarkers" is that all endophenotypes are, by definition, biomarkers, but not all biomarkers are endophenotypes. Whereas an endophenotype must meet all the criteria presented in Table 27.1 [20, 29], a biomarker need only reflect some measurable deviation in the organism, reflective of either internal factors operating in either health/illness or the impact of an external agent. For example, a biomarker that is reflective of an environmental exposure will fail to satisfy those criteria of validity for an endophenotype that concern patterns of familial aggregation (e.g.,

Table 27.1 Criteria for endophenotype

The endophenotype:
[1] Is associated with illness in the population
[2] Is heritable
[3] Is primarily state-independent (manifests in an individual whether or not the illness is active) but may require a challenge to elicit the indicator
[4] Is more prevalent among the ill relatives of ill probands compared with the well relatives of the ill probands (i.e., within families, endophenotype, and illness co-segregate)
[5] Found in affected family members and is found in nonaffected family members at a higher rate than in the general population
[6] Should be a trait that can be measured reliably and ideally is more strongly associated with the disease of interest than with other psychiatric conditions

Adapted from [20, 29]

increased ammonia levels due to some forms of drug abuse do not constitute an endophenotype). Therefore, the term biomarker is not exchangeable with (or equivalent to) endophenotype [20]. Heterogeneity of the cohorts, ethnicity, slow vs. fast metabolizers, epigenetic factors, and early vs. late stage of the disease are all parameters which have an effect on whether a given individual will respond well to a specific treatment. Biomarkers in conjunction with diagnostics can help eliminate the effects of these parameters and enable a shift from empirical medicine (one size fits all) to precision medicine [8].

Historically, the approach to illness/disease has been to classify individuals by their observable characteristics that are often derived from the interactions between genes and the environment. However, this approach to categorization of illness is evolving and leading to research in pathophysiologic mechanisms/processes (molecular/cellular), i.e., endotypes, and their influence on phenotype [30]. Endophenotypes are actually slightly different than a type of biomarker, though some call them biomarkers. They can be distinguished from episode markers and trait markers arising from environmental exposure by their ability to index genetic contributions for a psychiatrically relevant trait. That is, endophenotypes are genetically influenced quantifiable traits that identify those at risk for psychopathology before it manifests and can be used to identify etiologically relevant genetic variants. Assumed to be less genetically complex and closer to the effects of genes, endophenotypes offer a potentially more precise and powerful approach to uncover genetic variants associated with psychopathology [9]. According to Gottesman and Gould, an endophenotype is a measurable component, unseen by the unaided naked eye that lies along the pathway between disease (i.e., observable phenotype) and distal genotype. An endophenotype is not a risk factor; rather it is a manifestation of the underlying disease liability. Thus, an endophenotype is internal and not easily discernable without some technological assistance. An endophenotype may be neurophysiological, endocrinological, neuroanatomical, cognitive, or neuropsychological in nature, and it can include self-report (e.g., inventory) data. The usefulness of an endophenotype is that it represents, in principle, a relatively simpler clue to genetic causes than the disease symptoms [29, 31].

Psychiatric researchers have had a long-term interest in developing reliable biomarkers, i.e., clinically useful biological markers that are associated with mental illness. However, for biomarkers such as neurotransmitter metabolites or measures of inflammatory response in general, there is no consensus regarding which molecules are likely to be the best marker targets. Currently, there is no solid theoretical foundation from which the numerous putative biochemical markers can be reduced to a few plausible ones; therefore, identifying valid biomarkers is an extensive empirical task. The appeal of psychophysiological measures comes from their assessing of the central nervous system function broadly; if the integrity of any element of a brain system is malfunctioning, an electrophysiological measure associated with that system may be altered. As with other types of biomarkers, for psychophysiological measures, the unit of measurement is biological. Like many other types of biomarkers, they depend on a psychological task or circumstance;

understanding the model used to elicit the physiological response is thus essential to the interpretation of the significance of the response [9].The eyeblink startle electromyographic (EMG) response reveals quite different meanings if it is elicited by an intense unexpected event, or the same event when part of a prepulse inhibition sequence, or the same event presented while viewing pleasant or aversive imagery. In only the first two of these examples is the response heritable, and only prepulse inhibition receives strong support as an endophenotype [32, 33]. The endophenotype concept can be summarized as follows: modern psychopathology research supports the inference that most forms of major mental illness (e.g., bipolar illness, schizophrenia, unipolar depression, anxiety disorders) possess an appreciable heritable component. This component contributes, in interaction with other genetic assets and liabilities as well as environmental and epigenetic factors, to the overall predisposition for an illness. It is likely that the underlying predisposition to an illness will manifest itself before the development of its clinical signs and symptoms. For example, in schizophrenia, this translates to the development of detectable pathology before the appearance of psychotic symptoms, even before the prodromal features. In other words, one should be able to detect some internal manifestation of a genetic liability for an illness within the at-risk population that (a) is not visible to common observation, (b) exists in situ (i.e., in place, within (not outside) the person), and (c) predates observable signs or symptoms of illness [20]. One current derivation is from the insect genetics literature, which advocated the term endophenotype to denote a feature *internal* to an organism and visible upon microscopic examination (i.e., *not* an obvious, external feature). Additionally, an endophenotype represents an *unobservable latent entity* (such as a hypothetical latent construct) that cannot be directly observed with the unaided naked eye; rather, an appropriate technology would be needed to "see" the endophenotype. Importantly, the endophenotype is not really "hidden"; rather it can be viewed with the appropriate tools [34].

Advances in psychophysiology, such as improved signal processing and statistical methods, are important. The current level of sophistication used to quantify and process electrophysiological variables is not a significant obstacle to the identification of genetic variants associated with endophenotypes. Electrophysiological variables have psychometric properties that are at least equivalent to, and in many cases are better than, those of phenotypes that have been used successfully in molecular genetic research. However, it is also important to focus on the best practices needed to identify a trait as a suitable endophenotype and to demonstrate its usefulness for uncovering biological pathways to the development of psychiatric disorder [9].

27.3.1 Endophenotypes in Depression

It is worth noting that psychosis-related genes participate in brain development, specifically cell differentiation, adhesion, migration, cell signaling, and myelination. A number of these genes have been associated with risk for schizophrenia, bipolar

disorder, and several neurodevelopmental brain disorders, including epilepsy, mental retardation, and autism. Mokhtari et al. 2016 [35] evaluated the overlap in pathway maps, process networks, and gene ontology processes across three different electrophysiological psychosis-related biomarkers (resting electroencephalography [EEG], auditory oddball, auditory paired stimuli). Neuronal developmental and cellular maintenance processes almost completely accounted for this overlap, including neurogenesis, axon guidance, neuronal development, neuronal differentiation, and neuron projection.

In order to be successful in characterizing mental illnesses such as MDD, a far better understanding of the pathophysiology of these disorders will be required and moreover to determine if there are 5, 10, 50, or 200 distinct endophenotypes of a particular syndrome [11]. Depression involves impairments in a range of cognitive and emotional domains. It was unknown at the time of the Etkin et al. 2015 study [36] whether these impaired functions could aid medication choice when considered as a composite predictive biomarker. Etkin and colleagues tested whether behavioral tests, grounded in the neurobiology of cognitive and emotional functions, could predict outcome with some common antidepressants. They tested several cognitive and emotional capacities to examine whether or not they can be used as biomarkers for response to antidepressants including psychomotor, executive, memory, attention, processing speed, inhibitory, and emotional functions. In this report from the International Study to Predict Optimized Treatment for Depression (iSPOT-D) study, 1008 patients diagnosed with MDD (665 of completed patients were matched to 336 controls) were randomly assigned to escitalopram, sertraline, or venlafaxine. Approximately one-quarter of the cases exhibited cognitive impairment across all domains, and those subjects responded very poorly to treatment. However, within this same subgroup only, task performance was associated with remission on escitalopram with a 72% accuracy using the 16-item Quick Inventory of Depressive Symptomatology [11, 36].

Impaired prepulse inhibition (PPI) is one of the endophenotypes (biological markers) of schizophrenia, autism and other neurodevelopmental disorders. The neural circuit for PPI involves the hippocampus, an area of the brain where neurogenesis occurs postnatally. Researchers hypothesize that a disruption of preadolescent neurogenesis is essential for the onset of sensorimotor gating defects. In order to test this hypothesis, a critical period of neurogenesis that can impact PPI was examined. Osumi et al. 2015 [37] introduced an enriched environment to restore neurogenesis, which resulted in recovering PPI deficits in mice. They found impairments in the maturation of newborn neurons in the hippocampal dentate gyrus (DG) and GABAergic neurons in the hippocampus, which can be described as microphenotypes that are associated with PPI defects. Investigations with more exact genetically controlled neurogenesis models (with precise time points or periods) are needed to support this hypothesis [37].

Potential endophenotypes in depression and other mood disorders include baseline activation and neural response patterns in depression [38], cortical thinning in depression [39], and neurotrophic signal transduction pathways in mood disorders [20, 40]. It is easy to see the potential usefulness that a measure of cortical thinning

(a potential endophenotype of major depression) could have in the diagnosis of major depression or evaluation of major depression risk. Such a biological feature could be quite useful as a diagnostic tool [39].

Research on psychiatric disorders has demonstrated the involvement of numerous genes that are associated with neurogenesis and neural development. Neurogenesis is a biological process that is essential in brain development and continues through life in a select few brain regions. Neurogenesis is a process that involves multiple steps starting from the division of neural stem cells/progenitor cells, leading to self-renewal and at the same time to the production of lineage-committed cells, which include neurons and glial cells. Some relatively minor defects in the neurogenesis process, such as production of fewer new neurons and malformation of neural circuits, could plausibly result in phenotypes of psychiatric disorders at molecular and cellular levels in animal models (here termed as "microphenotypes"). However, because they are difficult to evaluate, microphenotypes are not easily used as biomarkers. Because it is readily measureable, some researchers have focused on sensorimotor gating deficits that can be scored in a prepulse inhibition (PPI) test. It is essential for the field of psychiatry to create methods to define the molecular, cellular, and circuit basis of brain diseases. These definitions could be utilized to develop biologically based disease categories. This would enable a better ability to research disease pathophysiology and etiologies. This is critical for serious mental illnesses [28].

27.4 Biomarkers and Disease Vulnerability

27.4.1 Disease Vulnerability

Although it has been three decades since the human genome project was completed, we still know relatively little about how specific genes influence the development of psychiatric disorders. One significant concern has been that identifying genes is constrained by the inadequacy of the American Psychiatric Association's *Diagnostic and Statistical Manual* (DSM) to categorize biological processes with enough precision to facilitate success. The definition of DSM disorders depends little on biology; instead, disorders remain defined largely by consensus expert opinion, are heterogeneous, and show significant overlap. Therefore, interest in approaches to gene finding that do not depend on the DSM has been high [9].

In addition to genetic influences, researchers have considered other factors as predictors for the development of depression. For example, Wilson et al. 2014 [41] followed 2764 twin children into adulthood and their parents in a prospective study spanning two decades. Risk factors for development of MDD were childhood abuse and having parents with psychiatric disorders. Another risk factor was premorbid dysfunction at age 11 including the following characteristics: lower positive emotionality, higher negative emotionality, higher trait anxiety, substance use/misuse, externalizing symptoms, poorer school functioning, poorer parent-child

relationship quality, and more advanced pubertal development. The risk for a recurrent MDD episode was early onset of MDD [41].

27.4.2 Genetics

27.4.2.1 GWAS: Genome-Wide Association Studies

Genome-wide association studies (GWASs) have identified genetic variants of disease that may contribute to disease vulnerability (especially for bipolar disease and schizophrenia, less promising results in major depression) [11]. The experimental design of genome-wide association studies (GWASs) has only been applied relatively recently (primarily, in the past decade). Visscher et al. 2017 [42] reviewed the range of discoveries it has facilitated in population and complex-trait genetics, the biology of diseases, and translation toward new therapeutics. Data generated from genome-wide SNP surveys have been used to address many scientific questions other than SNP-trait associations. GWAS utilizes an experimental design to detect associations between genetic variants and traits in samples from populations. The primary goal of these studies is to better understand the biology of disease. The path from GWAS to biologic traits is not straightforward because the association between a genetic variant at a genomic locus and a trait is not directly informative with respect to the target gene or the mechanism of how the variant is associated with phenotypic differences. However, as reviewed by Visscher et al., new types of data, new molecular technologies, and new analytical methods have provided opportunities to bridge the knowledge gap from sequence to biologic traits. GWASs have also been utilized to better define the relative roles of genes and the environment in disease risk, supporting risk prediction (enabling preventative and personalized medicine), and in investigating natural selection and population differences [42].

Examining data for 807,557 persons, Howard and colleagues performed a GWAS meta-analysis of depression [43]. The meta-analysis revealed 102 independently segregating genetic variants that were associated with depression in 101 loci. This analysis produced evidence for the role of prefrontal brain regions in depression, and the genes identified contributed to the understanding of biological mechanisms and potential drug targets [43]. Chang and colleagues identified and characterized a novel gene with a potential genetic association with risk for mood disorders [44]. Carriers of mood disorder-risk alleles showed shifts in cognitive performance, emotional stability (neuroticism), amygdala structure, and functions during negative emotion processing similar to mood disorder patients. These risk associations seem to be related to the genetic regulation of *PCDH17* expression, which impacts the morphology and structure of dendritic spines. These results may provide new insights into the causes of mood disorders and into novel treatments [44].

Because of the polygenic, multifactorial nature of psychiatric disorders and the limitations of GWAS design, the genetic loci identified are generally small in effect size and individually of questionable clinical significance [45]. GWAS alone will

most likely yield limited translational advances to improve diagnostic accuracy and treatment effectiveness [42]. Our knowledge of expression and functions of genomic factors associated with a disorder is much more likely to be enhanced by a multidisciplinary approach that combines multiple omics data – integrated multidimensional omics to improve diagnosis, prognosis, and treatment development [46]. For example, a recent GWAS meta-analysis revealed a high degree of correlation [average genetic correlation (rg) = 0.40] among bipolar disorder, major depressive disorder (MDD), and schizophrenia [47]. However, a molecular profiling approach characterizing 181 proteins and small molecules in serum showed excellent potential to distinguish schizophrenia from healthy controls, as well as from subjects with MDD, bipolar disorder, and Asperger's syndrome [48]. Studies utilizing both research methods in the same cohort likely will lead to significant improvement in diagnostic accuracy [15].

One research group (Chang et al. 2018) [44] performed a meta-analysis of very large datasets obtained from two GWASs. The sets included 29,557 subjects with mood disorders and 32,056 control subjects. They found that single-nucleotide polymorphisms (SNPs) along the brain expressed protocadherin gene (PCDH17) region were associated with major mood disorders such as bipolar and depression. Furthermore, in primary neuronal cultures, higher than normal expression of PCDH17 showed changes in dendritic spines. These changes in dendritic spines can affect normal synaptic function and cause abnormalities in synaptic function. Because abnormal synaptic function is thought to be a basic aspect of brain dysfunction in major mood disorders, PCDH17 expression could be implicated in the pathophysiology of major mood disorders and provide a potential novel target for pharmacotherapy.

27.4.2.2 Gene Polymorphisms

Jimenez et al. [49] were also interested in finding a genetic association to mood disorders, specifically depression. The FGF20 gene is part of the fibroblast growth factor (FGF) family which is associated with neural function and development. Therefore, Jimenez et al. examined a functional polymorphism (rs12720208) in the FGF20 gene, which is modulated by miR-433 (a short non-coding RNA) and its association with depressive symptoms in young adults (mean age of 21 years). They did find an association between the functional polymorphism rs12720208 on the FGF20 gene and depressive symptoms.

However, Border et al. [50] obtained differing results when trying to test the validity of candidate genes for depression. They selected 18 candidate genes for depression well examined in at least 10 studies. They analyzed data from large population-based samples and case-control samples examining candidate gene polymorphism main effects and polymorphism-by-environment interaction for association with depression. They found no association between candidate gene polymorphisms and depression nor between polymorphism by environment and

depression. Their results conflict with earlier studies and they suggest that the earlier studies were false positives [50].

Changes in circadian rhythm genes associated with bipolar disorder have also been a focus of research. Mansour and colleagues [51] conducted a small case-control study, in which 234 patients with bipolar I disorder were compared with 180 controls. They focused on 44 SNPs of 8 circadian rhythm genes and found associations with SNPs for aryl hydrocarbon receptor nuclear translocator-like (ARNTL) and timeless circadian clock genes (TIMELESS) [51]. Benedetti and colleagues [52] examined the diurnal activity and nocturnal sleep in 39 patients diagnosed with bipolar disorder and evaluated the role of the rs1801260 SNP within the CLOCK gene. Higher activity levels in the evening, delayed sleep onset, and reduced total amount of sleep per night were associated with this SNP [52].

27.4.2.3 Epigenetics

Using data from the ESPRIT study (a community-based population of individuals > 65 years of age), Lam et al. [53] found that DNA methylation of the serotonin transporter gene (SLC6A4) was associated with depression status, but only in specific genotypes. In individuals homozygous for the short 5-HTTLPR and 5-HTTLPR/r25531 alleles, lower methylation at two CpGs was associated with depression. This study illustrates genotype-dependent associations between SLC6A4 methylation and depression and suggests that genetic variants may also play a role in influencing promoter methylation levels and its association with depression. In another DNA methylation-related study, Thaweethee-Sukjai et al. [54] examined the extent of methylation of the parvalbumin gene (PVALB) promoter in MDD patients with and without suicide attempts compared to healthy controls. PVALB methylation was significantly increased at CpG2 and decreased at CpG4 in the MDD group compared to the control group; however, there was no difference between non-suicidal and suicidal MDD subgroups. Their study demonstrates abnormalities of gene PVALB promoter methylation in MDD and its correlation with MDD severity indicating a role for epigenetics in MDD.

By analyzing monozygotic twin studies, Peng et al. [55] found that altered DNA methylation in stress-related genes was associated with depressive symptoms and postulated that this mediates the association of childhood trauma with depression occurring later in life. They noted that several candidate genes are involved in the stress response system (including glucocorticoid receptor (NR3C1), brain-derived neurotrophic factor (BDNF), serotonin transporter (SLC6A4), and monoamine oxidase (MAOA, MAOB)) and that depression may be a result of altered DNA methylation of these genes. In another study, Tyrka et al. [56] examined the 1F promoter region of NR3C1 in relation to early-life stress and psychiatric disorders and found lower levels of methylation to be associated with stress exposure-related psychiatric conditions. These findings suggest that childhood stress influences NR3C1 methylation and may be a risk factor for the development of psychopathology. In a third study, Humphreys et al. [57] prospectively examined DNA methylation levels at loci within six genes that have been implicated in HPA axis functioning

(i.e., FKBP5, NR3C1, NR3C2, CRH, CRHR1, and CRHR2) in 77 girls at low and high familial risk for MDD who had no past or current MDD diagnosis at baseline. These researchers found that DNA methylation levels within CpG sites in NR3C1, CRH, CRHR1, and CRHR2 were associated with risk for MDD across adolescence and young adulthood. When they reanalyzed their data controlling for genetic variation and for familial risk for MDD, methylation levels continued to be a significant predictor of the onset of MDD. These findings imply that factors which were not inherited such as those from the environment could foretell the onset of MDD through the variation of DNA methylation levels more so than the effects of familial risk and genetic variation. They also noted that genetic and epigenetic factors both probably contribute to depression risk, but because of the modifiability of DNA methylation, epigenetic markers may be more helpful independent predictors of MDD risk.

27.4.3 Serum and CSF Biomarkers of Depression

Possible serum biomarkers have included the concentration of 25-hydroxy-vitamin D, 25(OH)D. In 2014, Milaneschi et al. [58] measured serum levels of 25(OH)D in subjects with depression and controls. They found lower levels of 25(OH)D in the depressed subjects than controls. Furthermore, the 25(OH)D levels were inversely proportional to the depression severity. They suggest that low vitamin D may represent a risk for depression [58].

In contrast to the above 2014 study, 5 years later, Milaneschi et al. [59] applied genomic tools and found no evidence of direct causal effect of 25(OH)D on depression risk. Another study [60] also found that vitamin D concentrations were not associated with the development of depression.

Other potential serum biomarkers for depression are inflammatory markers. This is a vast literature, which space constraints preclude an adequate review. For example, in a case-control study, Mishra et al. [61] found that in late-onset depression (mean age 64.7 years), patients with depression had 40% higher levels of C-reactive protein (CRP) compared to age-matched nondepressed patients. In addition, there was a robust positive correlation between CRP levels and severity of depression [61]. Our group has made similar observations of pro-inflammatory cytokines in depression [62].

27.4.4 Transforming Diagnostic Approach

An example of the transforming diagnostic approach is the the Bipolar-Schizophrenia Network on Intermediate Phenotypes (BSNIP). The BSNIP study used statistical methods to sort cases into subgroups, based on multiple neurobiological measures. Biological and behavioral characteristics associated with psychosis were scrutinized in 1872 participants – patients diagnosed with schizophrenia, schizoaffective

disorder, and bipolar disorder with psychosis, their first-degree relatives, and healthy control subjects. Characteristics such as performance on thinking, planning, and memory tasks, eye tracking, inhibition, and brainwave responses to auditory stimuli determined groups of biomarkers that differentiated subgroups of patients. Three distinct psychosis-related biotypes were identified across clinical diagnosis boundaries. In addition, external measures – social functioning, brain structure, and rates of psychosis-related illness and biomarker patterns in patients' first-degree relatives – validated the neurobiological biotype subgroups more than they did the symptom-based categories, providing evidence of biological overlap between traditional, symptom-based diagnostic categories for disorders in which patients experience psychotic symptoms. "The biotypes outcome provides proof-of-concept that structural and functional brain biomarker measures can sort individuals with psychosis into groups that are neurobiologically distinctive and appear biologically meaningful" [28, 63].

Those with various biotypes differed in their types of psychosis-related impairments. For example, cases classified as biotype 1 showed the most impairment in a set of brain functions that the researchers combined into a concept they term "cognitive control" – the ability to flexibly exert control over attention and information processing to meet one's goals. The most socially impaired persons were biotype 1. Biotype 2 cases showed intermediate levels of impaired cognitive control but had normal to accentuated brain responses to sensory inputs and fast visual orienting, a set of brain functions called "sensorimotor reactivity" – the ability to detect and process sensory stimuli. Biotype 3 cases showed normal cognitive control and modestly impaired sensorimotor reactivity, were the least socially impaired, and had the lowest positive (e.g., hallucinations and delusions) and negative (e.g., blunted emotion) symptoms.

The BSNIP consortium has developed approaches to perfecting biomarkers and defining subtypes of psychosis using information about brain structure and function instead of clinical symptom characteristics. Brain structure differences also distinguish the three biotypes, further validating the categories. On MRI scans of the brain, biotype 1 cases – and to a lesser degree biotype 2 cases – showed reduced gray matter across several areas of the cortex known to process higher-order information. Alternatively, in biotype 3 cases, the largest of the groups, reduced gray matter was principally localized in emotion-processing areas in deeper brain regions. Biotypes 1 and 2 may successfully be examined with hereditary/genetic studies, while biotype 3 cases may produce more information about environmental contributions to psychosis risk. Treatments for biotype 1 should target cognitive control and enhance brain mechanisms for determining the relevance of environmental stimuli. Patients with biotypes 1 and 2 might be best treated with approaches that correct neuronal activity levels through effects on cellular potassium or calcium channels (Table 27.2) [28, 63].

Psychiatry is in critical need of functional and molecular biomarkers to generate therapeutic targets for drug development. Psychiatry has relied on trial and error for identifying treatments for too long. Moreover, knowledge of the specific neural alterations associated with and causally related to psychotic illness will assist in

Table 27.2 Biotype cluster characteristics (adapted from 28, 63)

Biotype 1	Biotype 2	Biotype 3
Very low cognition	Low cognition	Nearly NL cognition
Very low EEG power	High EEG power	Just low on EEG power
Low gray matter volume	N100, P300 (normal)	Fast visual orienting
Worst negative Sx	Low cortical volume, more focused	Low % affected relatives
Highest affected relatives	High affected relatives	Normal Sz polygene score
High Sz polygene score	Moderate cannabis use	High cannabis use
Lowest cannabis use		

Abbreviations: *EEG* electroencephalography, *NL* normal, *Sx* symptoms, *Sz* schizophrenia

defining actual brain changes, and this may help to diminish the stigma of serious mental illness. Knowledge of molecular, cellular, and biologic systems pathophysiology in psychotic diseases could greatly enhance prospective screening and prophylactic management of psychotic conditions, supporting the importance of early detection [28, 63].

27.5 Biomarkers and Treatment Response

A number of researchers have examined biomarkers in relationship to treatment response. For example, they have considered genetic markers and markers from blood and other peripheral measures.

27.5.1 Genetics

O'Connell et al. [64] examined the relationship between genotype at 16 candidate HPA axis single-nucleotide polymorphisms (SNPs) and treatment outcomes for 3 antidepressants (escitalopram, sertraline, and extended-release venlafaxine) in the 1000 patient iSPOT study. The rs28365143 variant within the corticotropin-releasing hormone binding protein (CRHBP) gene predicted antidepressant outcomes for remission, response, and symptom change. Persons homozygous for the G allele of rs28365143 variant had greater remission rates, response rates, and symptom reduction and responded significantly better to the selective serotonin reuptake inhibitors escitalopram and sertraline than A allele carriers. However, the rs28365143 genotype was not associated with better treatment responses for the serotonin-norepinephrine reuptake inhibitor, venlafaxine. The findings suggest that a specific CRHBP SNP, rs28365143, may have a role in predicting which patients will improve with antidepressants and which type of antidepressant may be most effective [64].

In a separate study, Marsche et al. [65] investigated five functional variants of the norepinephrine (SLC6A2, NET) and serotonin transporter (SLC6A4, SERT) genes

and remission in depressed older adults treated with venlafaxine. They found that NET rs2242446/T-182C may serve as a biomarker to predict the likelihood of remission with venlafaxine in older adults with major depression [65]. Kao et al. [66] evaluated whether the serotonin transporter (5-HTT or SERT or SLC6A4) mRNA expression could be used as a biomarker of treatment response in patients with major depression treated with the antidepressants duloxetine and paroxetine. Patients with 5-HTTPR long-form alleles and STin2.12 alleles had a poor antidepressant treatment response. The 5-HTT mRNA expression was correlated with treatment response [66]. Ising et al. [67] were able to demonstrate that a reduction in *FKBP5* gene and FKBP51 protein expression were associated with successful antidepressant treatment outcome in depressed patients, particularly in those patients who are carrying the risk allele of the *FKBP5* variant rs1360780. Their findings suggest an important role for *FKBP5* and FKBP51 in antidepressant treatment outcome and highlight a promising target for future antidepressant drug development [67].

In their review of convergent neurobiological predictors of mood and anxiety symptoms and treatment response, Jabbi and Nemeroff [68] examined the interaction between environmental-adversity and molecular-genetic mediators of brain correlates of affective symptoms. The molecular focus was on the *GTF2i*, *BDNF*, and *FKBP5* genes that are, respectively, involved in transcriptional, neurodevelopmental, and neuroendocrine pathways of affective functions. Major psychiatric syndromes including mood and anxiety disorders are classic examples of complex medical diseases caused by gene-environment interactions that impact neural development and, as research progresses, can be evaluated with biomarkers. The authors also emphasized the importance of studying gene-dosage effects in understanding the biological risk for affective disorders and how neurogenetic studies could guide identification of novel pharmacotherapeutic targets and help in the prediction of treatment response. They used the term “mental scars” and note that studies identifying these scars in terms of brain structural and functional correlates of affective disorders, along with computational applications to decipher the maladaptive behavioral effects of these mental scars, will result in a better biological understanding of affective disorders [68].

Zeier et al. [69] reviewed the literature for several commercial combinatorial pharmacogenetic decision support tools that have been evaluated in clinical settings. Although some of the preliminary published reports were promising, particularly with regard to the CYP450 gene variants and side effect burden, the authors concluded that there is insufficient evidence to support widespread use of combinatorial pharmacogenetic decision support tools in predicting antidepressant treatment response at this time [69].

27.5.2 Blood and Other Peripheral Measures

Several studies have attempted to identify factors to predict depression outcome over time. Salivary cortisol levels have been just such a candidate. Vreeburg et al. [70] examined salivary cortisol measures in relationship to a 2-year course of depression and anxiety disorders. They found that a lower cortisol awakening response had an increased risk of a poor 2-year chronic course trajectory for depression and anxiety disorders.

Vogelzangs et al. [71] tested several metabolic and inflammatory factors seeking an association with depression outcome at the 2-year point. The subjects were treated with antidepressants. Factors associated with a less favorable outcome were elevated interleukin-6 (IL-6) and metabolic factors including hypertriglyceridemia, low HDL cholesterol, and hyperglycemia. These results suggest that patients with metabolic and inflammatory dysregulation have a poorer response to antidepressants [71]. Rethorst et al. [72] also considered inflammatory factors as an indicator of depression response to antidepressants and whether exercise might be a beneficial addition to treatment. Their result showed that patients with a higher baseline level of tumor necrosis factor-α (TNF-α) responded better to exercise treatment, suggesting that in this particular subgroup, exercise is a viable treatment option for depression [72]. Our group [62] in a study of never-treated depressed patients reported multiple alterations in pro- and anti-inflammatory cytokines as well as in other immune measures. Clearly a sizable subtype of depressed patients exhibits immune system dysregulation including evidence in which inflammation in the CNS was measured in depressed patients with PET imaging [73].

27.6 Trauma as a Predictor of Diagnosis and Treatment

Williams et al. [74] evaluated the role of early-life trauma in predicting acute response outcomes to antidepressants in a large sample of well-characterized patients with major depressive disorder (MDD). The data were derived from the International Study to Predict Optimized Treatment for Depression (iSPOT-D), a randomized clinical trial with enrollment in five countries. The study sample was comprised of patients (n = 1008) meeting DSM-IV criteria for MDD and 336 matched healthy controls. Randomization was applied to 8 weeks of treatment with escitalopram, sertraline, or venlafaxine with dosage adjusted by the participant's treating clinician per routine clinical practice. The Early-Life Stress Questionnaire was used to evaluate exposure to 18 types of traumatic events before the age of 18. Depressed patients were significantly more likely to report early-life stress than controls. The higher rate of early-life trauma was most evident for experiences of interpersonal violation (emotional, sexual, and physical abuses). Abuse (and abuse occurring at $\leqslant$7 years of age) predicted poorer outcomes after 8 weeks of antidepressant treatment. Specific types of early-life trauma, particularly physical,

emotional, and sexual abuse, especially when occurring at ⩽7 years of age, are important moderators of antidepressant response in MDD [74].

Goldstein-Piekarski et al. [75] demonstrated that functional remission with antidepressants may be dependent on the degree of early-life stress (ELS), the degree of amygdala engagement during facial emotion viewing, and their interaction. They were able to predict with a high degree of accuracy (81%) who would and would not remit following pharmacotherapy with commonly prescribed antidepressants. Peng et al. [55] examined the combined association of DNA methylation at multiple CpG probes in five stress-related genes associated with depressive symptoms and tested whether these genes' methylation mediated the association between childhood trauma and depression in two monozygotic (MZ) twin studies. They found that gene-based or gene-set approaches revealed significant joint associations of DNA methylation in all five stress-related genes associated with depressive symptoms in both studies. Two CpG probes in the *BDNF* and *NR3C1* mediated approximately 20% of the association between childhood trauma and depressive symptoms. The authors indicated that their results highlight the importance of testing the combined effects of multiple CpG loci on complex traits and that this approach may unravel a molecular mechanism through which adverse early-life experiences are biologically embedded [55].

27.7 The Role of Neuroimaging

Neuroimaging studies and selected cognitive-emotional domains are being developed as biomarkers for mood disorders to predict disease subtypes and response to treatments. Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis has been frequently found in depressed patients and also is associated with the risk of suicide and the risk of PTSD in those with early-life trauma [11].

Human brain function properties that can be quantified in vivo (e.g., brain structure, cognition, molecular traits, functional behavioral outcomes) are a key to understanding pathophysiology and predicting outcomes in psychiatric conditions and for classifying brain disorders by types of pathophysiology regardless of clinical symptoms. When etiology is unknown, measures of brain function (biomarkers or intermediate phenotypes) are especially important for studying brain diseases. Without biomarkers for these disorders, only clinical signs and symptoms are used to classify and define diseases, an approach that is far from optimal for capturing distinctive neurobiological pathophysiology. Clinical manifestations are not reliable for classifying psychoses, because they are pleomorphic and vary within and across diagnoses. Technical advances have led to innovative tools in clinical neuroscience, which have advanced the biological knowledge in human brain diseases, including tools for brain imaging, cognition, and electrophysiology [37].

27.7.1 Functional Measures

EEG measures the brain's electrical activity directly, while other methods record changes in blood flow (e.g., SPECT, fMRI) or metabolic activity (e.g., PET), which are indirect markers of brain electrical activity.

27.7.1.1 Spatial Neuroimaging: The MRI, fMRI, and PET Scan

Vulnerability Both functional (fMRI) and structural (sMRI) magnetic resonance imaging have been utilized to determine what markers might be a predictor of depression development. In an fMRI study, low ventral striatum activation was shown to be a predictor of subthreshold or clinical depression 2 years later in adolescents with no previous history of depression [76]. Another study, using sMRI [77], evaluated markers of cortical neurodevelopment in patients with depression and controls. Greater local cortical gyrification (LGI) was found in certain regions in depressed subjects than controls and appeared to be associated with length of disease. These results show that abnormal cortical neurodevelopment may be a potential indicator of future depression [77].

Predictors of Treatment Response Because depression has a relatively low remission rate, it is important to be able to predict which individual will respond favorably to a specific treatment. Much effort has been put forth in this endeavor. Several studies have utilized neuroimaging and found potential indicators of which treatment would be optimal for a particular patient. For example, using PET, one study demonstrated that subjects with insula hypermetabolism responded well to escitalopram, while those with insula hypometabolism responded better to cognitive behavioral therapy [78]. Dunlop et al. evaluated the right anterior insula (rAI) metabolism biomarker as a predictor of outcome in depression. The subjects were depressed patients who had not responded to either CBT or escitalopram and were then given additional treatment. Results showed that when the added treatment matched biomarker-indicated treatment, the patients were more likely to have a favorable outcome than when the treatments were mismatched. Indeed the rAI appears to be a viable biomarker for selecting the best treatment for depression [79].

Schmaal et al. [80] attempted to identify neurobiological factors which could help forecast the outcome of major depression. They tested several neuroimaging metrics using fMRI and sMRI as well as clinical characteristics for predictive value. Neural responses to emotional faces had a better predictive value for depression outcome than clinical data. Finally, Ditcher et al. [81] evaluated the findings of previous fMRI studies and found several factors valid for predicting treatment response in MDD including visual recognition circuits and elevated connectivity between the frontal lobe and limbic system [81].

27.7.1.2 Electrophysiologic Neuroimaging: The EEG

EEG (electroencephalogram) measures have also been considered as a potential predictor of depression. A 2013 study [82] was the first to find an association between a neural measure of reward sensitivity and the initial episode of depression prospectively. The authors followed 68 never-depressed girls over 2 years and found blunted baseline reward sensitivity may be a predictor for the onset of depression. Their findings were substantiated by another study [83] which also found that low baseline reward sensitivity could predict the initial onset of depression. Both studies involved adolescents, which is the age group that the incidence of depression greatly increases, thus an important time to have a viable biomarker for depression risk [82, 83].

In addition, EEG has been considered as a predictor for treatment outcome in depression. Greater right frontal alpha oscillations have been linked to good outcomes with escitalopram and sertraline, though only in females [84]. In addition, baseline gamma oscillations have been associated with response to treatment with paroxetine [85]. However, other studies have found that while baseline EEG measures theta-band rACC-rAI connectivity [86] and rACC theta activity [87] could predict depression outcome, they had no value as predictors for specific treatment outcome. In addition, a meta-analysis study [88] found no predictive value for treatment outcome using QEEG (quantitative EEG).

Rolle et al. [89] studied whether EEG connectivity could reveal neural indicators of antidepressant treatment. In their study, greater alpha-band and lower gamma-band connectivity predicted better placebo outcomes and worse antidepressant outcomes. Their findings established the value of EEG-based connectivity analyses to assist the differentiation of placebo response from antidepressant response in clinical trials, whereas Wu et al. [90] developed a machine learning algorithm for resting-state EEG and applied it to the findings from a large imaging-coupled, placebo-controlled antidepressant study. Symptom improvement was predicted for sertraline. Also, the sertraline resting-state EEG was associated with prefrontal neural responsivity, as measured by concurrent transcranial magnetic stimulation and EEG. Their findings enhanced the neurobiological understanding of antidepressant treatment through an EEG-tailored computational model and help provide a clinical tool for personalized treatment of depression.

27.8 Information Technology in Precision Psychiatry

In the future, developments in technology will have a greater role in the determination of new biomarkers for depression. However, in spite of early enthusiasm, few technological tools have been created that are usable in clinical practice. Tools available now are mostly pharmacogenetic test kits (e.g., the FDA approved AmpliChip CYP450 test from Roche, Switzerland, and GeneSight from Assurex Health, OH, USA), but their utility is doubtful at best [91–94]. In order to have

personalized medicine, it is critical to have practical clinical tools. Extremely large datasets are now easier and more affordable to collect, store, and analyze. Electronic medical records (EMRs) enable clinical information to be stored and potentially available for analysis by researchers. Standardizing EMRs with national and international guidelines would render the data on EMRs more easily studied and comparable between records, such as those from the Department of Health [95].

The miniaturization of physiological sensors, allowing them to be integrated into wearable devices, is another potential advance for precision medicine. Some devices for ambulatory monitoring have existed since the 1960s (e.g., Holter monitors for electrocardiography, arterial pressure, and electroencephalography). However, not till recently have the devices become small enough that they are wearable and useful for studies. These devices include watches, jewelry, smartphones, patches, and more. Some vital signs can now be measured with miniaturized sensors, such as motion/heart rate, body and skin temperature, arterial blood pressure, blood oxygen saturation, electrocardiograms, electroencephalograms (EEGs), and respiration rate [96].

In addition, the connection of devices to the Internet and to each other, the so-called Internet of Things [97], also allows real-time streaming of data and real-time analyses. These wearable devices can be continuously connected to the Internet and permit the collection of data [98] through apps that allow users to insert information, as well as automatically collecting data via the sensors connected to smartphones. With these devices data and warnings can be sent to clinicians, allowing them to monitor their patients' conditions and intervene when necessary. Real-time information can also be sent to patients affording them better awareness of their condition. This approach has been very effective in monitoring pain, and recent studies have investigated the promise of continuous monitoring in subjects with psychiatric disorders (phone, wrist-worn activity monitor, stationary EEG system for periodic measurements, and novel "sock-integrated" electrodermal activity sensor) [99–102].

Electronic medical records and miniaturized sensors embedded in wearable devices, as well as genomics, epigenetics, transcriptomics, and proteomics assessments, enable the collection of a large amount of data for every patient. However, even when useful information is available, making predictions requires models that connect this information with an outcome. Machine learning integrates computer science, engineering, and statistics "that gives computers the ability to learn without being explicitly programmed." The family of machine learning procedures referred to as "supervised" can be used to develop predictive algorithms able to provide the best possible predictions when applied to new cases, for example, making a single-patient prediction of the expected response before a therapy is administered. A number of supervised methods have been developed, e.g., artificial neural network [103], support vector machine [104], random forest [105], and boosting [106], but also traditional statistical methods (i.e., from linear regression to the generalized linear model) can be used to develop predictive models. If predictors are unknown, the best opportunity to reveal them relies on either analysis of datasets already available or determining them from the current scientific evidence, as much as experts' own experience [13].

27.9 Conclusion

Personalized (or precision) medicine as applied to psychiatry is still a relatively new concept but is being actively investigated by numerous researchers and shows promise in helping to improve psychiatric care. In this chapter we have presented current and potential tools that can be used to aid the implementation of precision psychiatry as applied to depression. We have explored and discussed numerous biomarkers, including endophenotypes, gene variants/polymorphisms, epigenetic factors such as methylation, biochemical measures, circadian rhythm dysregulation, and neuroimaging findings. We also examined the role of early childhood trauma in relation to the development of and treatment of depression. Finally, we reviewed how new developments in technology may play an increasing role in the development of biomarkers for depression. In the future precision psychiatry is likely to play a greater role in the diagnosis and treatment of depression and thus help reduce the suffering from this major cause of morbidity and mortality.

Financial Disclosures

Candace Jones:

None.

Charles Nemeroff:

Research/grants:

National Institutes of Health (NIH).

Consulting (*last 3 years*):

Xhale; Takeda; Taisho Pharmaceutical Inc.; Signant Health; Sunovion Pharmaceuticals Inc.; Janssen Research & Development LLC; Magstim, Inc.; Navitor Pharmaceuticals, Inc.; TC MSO, Inc.; Intra-Cellular Therapies, Inc.; EMA Wellness; Gerson Lehrman Group (GLG); Acadia Pharmaceuticals.

Stockholder:

Xhale; Celgene; Seattle Genetics; AbbVie; OPKO Health, Inc.; Antares; BI Gen Holdings, Inc.; Corcept Therapeutics pharmaceuticals company; TC MSO, Inc.; Trends in Pharma Development, LLC; EMA Wellness.

Scientific advisory boards:

American Foundation for Suicide Prevention (AFSP), Brain and Behavior Research Foundation (BBRF), Xhale, Anxiety and Disorder Association of America (ADAA), Skyland Trail, Signant Health, Laureate Institute for Brain Research (LIBR), Inc.

Board of directors:

GratitudeAmerica, ADAA, Xhale Smart, Inc.

Income sources or equity of $10,000 or more:

American Psychiatric Publishing; Xhale; Signant Health; CME Outfitters; Intra-Cellular Therapies, Inc.; Magstim; EMA Wellness.

Patents:

Method and devices for transdermal delivery of lithium (*US 6,375,990B1*).

Method of assessing antidepressant drug therapy via transport inhibition of monoamine neurotransmitters by ex vivo assay (*US 7,148,027B2*).

Compounds, compositions, methods of synthesis, and methods of treatment (CRF receptor binding ligand) (*US 8551, 996 B2*).

Speakers bureau:

None.

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