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Peripheral Biomarkers of Major Depression and Antidepressant Treatment Response: Current Knowledge and Future Outlooks

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Abstract

Background—In recent years, we have accomplished a deeper understanding about the pathophysiology of major depressive disorder (MDD). Nevertheless, this improved comprehension has not translated to improved treatment outcome, as identification of specific biologic markers of disease may still be crucial to facilitate a more rapid, successful treatment. Ongoing research explores the importance of screening biomarkers using neuroimaging, neurophysiology, genomics, proteomics, and metabolomics measures.

Results—In the present review, we highlight the biomarkers that are differentially expressed in MDD and treatment response and place a particular emphasis on the most recent progress in advancing technology which will continue the search for blood-based biomarkers.

Limitations—Due to space constraints, we are unable to detail all biomarker platforms, such as neurophysiological and neuroimaging markers, although their contributions are certainly applicable to a biomarker review and valuable to the field.

Conclusions—Although the search for reliable biomarkers of depression and/or treatment outcome is ongoing, the rapidly-expanding field of research along with promising new technologies may provide the foundation for identifying key factors which will ultimately help direct patients toward a quicker and more effective treatment for MDD.

Keywords

depression; biomarkers; biosignatures; genomics; proteomics; metabolomics

1. Introduction

Major Depressive Disorder (MDD) is a prevalent psychiatric disorder associated with varied prognosis, chronic course, and duration of illness with reduced quality of life (Beck et al., 1961; Burton et al., 2015; Daly EJ, 2010). Most MDD patients stay on ineffective medications for too long, switch treatments too early, or simply drop out of care (Burton et al., 2015; Rush et al., 2008; Warden et al., 2007b). Compared to treatment of several other

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somatic diseases, antidepressant response rates are low, duration to attain therapeutic benefit is long, and treatment-emergent side effect burden is significant (Rush et al., 2011; Trivedi et al., 2006b; Warden et al., 2007a). Furthermore, treatments are selected not based on efficacy, but instead on patient or provider preferences. The factors that ultimately drive these decisions include cost, side effects, tolerability, and/or response during previous episode(s) (Meron et al., 2015). Unlike other specialty fields of medicine, such as breast cancer (Dowsett and Dunbier, 2008), asthma (Lima et al., 2009), macular degeneration (Lee et al., 2009), and multiple sclerosis (Vosslamber et al., 2009), there are no validated biomarkers for depression, thereby stalling the goal of offering precise, targeted treatment for this devastating disorder. Indeed, personalized treatment has the capacity to maximize the likelihood of treatment response or remission, while simultaneously minimizing detrimental side effects (Kessler et al., 2003; Murray et al., 2013).

The search for biomarkers is hindered by the heterogeneity of MDD (Hasler et al., 2004) and the limitation of its current diagnostic categories such as self-reports, measurement based scales, with a lack of understanding of the molecular blood testing compared to other diseases (Insel et al., 2010a). In clinical practice, efforts are made to understand the demographic features, (e.g., gender (Young et al., 2009), race (Friedman et al., 2009), employment status (Warden et al., 2007a)), illness characteristics (e.g., baseline severity of depression (Friedman et al., 2012), duration of illness (Rush et al., 2012), number of previous episodes (Trivedi et al., 2005), age of onset (Zisook et al., 2007), family history of mood disorders (Trivedi et al., 2005), presence of anxious features (Fava et al., 2008), depression symptoms and its subtypes (Friedman et al., 2009), co-morbid psychiatric disorders (Friedman et al., 2009), psychosocial functioning (Vittengl et al., 2009), and social factors (e.g., marital status (Trivedi et al., 2005), level of social support (Lesser et al., 2008), social status (Lesser et al., 2008)). Unfortunately, these have proven to be of limited utility due to the knowledge gap regarding cellular and molecular pathophysiology, blood tests, and events that occur during brain development and maturation in MDD. (Arnow et al., 2015; Bobo et al., 2011; Chan et al., 2012; Sung et al., 2012; Sung et al., 2013; Sung et al., 2015). The underlying biological factors that drive MDD may be better suited to serve as biomarkers for guiding personalized medicine, as they are objective and can be measured externally (2001; Strimbu and Tavel, 2010). The heterogeneity of MDD necessitates and/or allows for numerous biomarker classifications, as shown in Figure 1. Diagnostic biomarkers indicate presence and/or future development of disease. Most of the currently-identified biomarkers, identified below, are predictive, such that baseline levels will provide insight as to whether or not a patient will respond to treatment. Moderators are also characterized at baseline, though provide more detailed information, such that clinicians can predict how a patient will respond to a particular treatment. Mediators define markers that change following treatment initiation and may predict future performance with the same or alternative treatment methodology. To maximize the chances of success, we may also need to go beyond individual biomarkers and venture towards generating multidimensional biomarkers (i.e., biosignatures) by systematically evaluating combinations of both clinical and biological markers.

In this report, we briefly review currently available treatment for depression, though emphasize the necessity for biomarker identification to discriminate depression subtypes and

work toward personalized medicine. We present the tools available for biomarker discovery and discuss what these technologies have identified as hits to date. In addition, we discuss our own clinical trial study, EMBARC (Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care), which is exclusively designed to screen numerous putative biomarkers with the aim to identify biosignatures for depression response.

2. Antidepressant Treatment Strategies

Numerous modalities are available to treat individuals with depression. Unfortunately, no treatment is universally effective, although different molecules and neural circuits are targeted, promoting distinct physiological changes. Pharmacological medications continue to be the most commonly-recommended first-line treatment for MDD (Olfson and Marcus, 2009). While there are several ADM classes like selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and others (bupropion and mirtazapine), all similarly target monoamine neurotransmission (Ball et al., 2014; Feighner, 1999; Lin et al., 2011; Saragoussi et al., 2012). Despite the variety of molecular targets, two thirds of MDD patients fail to achieve remission after initial treatment, and almost one third fail to achieve remission even after four consecutive treatment trials (McGrath et al., 2006; Rush et al., 2006a; Rush et al., 2006b; Trivedi et al., 2006a; Warden et al., 2007a).

Outside of the widely-prescribed pharmacological therapies, alternative treatment strategies instead employ indirect mechanisms which may still affect brain physiology, such as psychotherapy, exercise, and somatic treatments. Although their central mechanism(s) of action remain largely unknown, each has demonstrated efficacy in clinical populations. For example, individual or group psychotherapy sessions (e.g., including cognitive-behavioral therapy (CBT), interpersonal therapy (IPT), and behavioral activation) show efficacy in treating depression (Craighead and Dunlop, 2014). Physical activity, including aerobic, anaerobic, and mindfulness ameliorates depressive symptomatology following both acute and chronic sessions. This is demonstrated in numerous studies, although it is important to point out that results are not always consistent, likely due to the heterogeneity of participants and treatment design (Blumenthal et al., 2012; Bridle et al., 2012; Rethorst and Trivedi, 2013; Silveira et al., 2013). Lastly, somatic treatments, including electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and vagus nerve stimulation (VNS) have evidence of some efficacy, though its use is often restricted to patients with treatment-resistant or moderate-to-severe depression (Meron et al., 2015).

In each case, these treatment options have demonstrated benefit alone or as an augmentation therapy to previously-described ADMs. The problem persists, however, that even by combining medications or treatment strategies, depressed patients frequently do not achieve response of remission. Discovery of biomarkers will help identify a personalized treatment strategy for each patient and thereby assist with quick and efficacious responsiveness.

3. Biomarker Discovery—Tools and Application

Technological advances over the last few decades has fueled the search for biomarkers which may predict individual response to particular antidepressant treatment strategies. In this section we detail the advanced methodologies with a particular focus on the strategies which enable screening of “Omics” biomarkers. Figure 2 denotes the cascade of events necessary for identifying a biomarker, including discovery and validation processing using high- and low-throughput methodology, respectively. These approaches hold promise, as they enable study of a wide variety of biological processing, ranging from genetic composition to protein breakdown, and any biological entity in between. Below we will review the methodological design and tools for pharmacogenomics, epigenomics, transcriptomics, proteomics, and metabolomics and provide examples of their employment thus far:

3.1. Pharmacogenomics, Epigenomics and Transcriptomics

Genomics enables the identification of one’s genetic makeup and post-translational modifications, ultimately providing insight regarding a target’s structure and function. Standard large scale genome-wide association studies (GWAS) as well newer, next-generation technologies will serve at the forefront of identifying genetic biomarkers. Large clinical trials [STAR*D (n = 1953) (Garriock et al., 2010), MARS (n = 339) (Ising et al., 2009), GENDEP (n= 706) (Uher et al., 2010), and PGRN-AMPS (n= 529) (Ji et al., 2013)] are harnessing the power of pharmacogenomics to help identify predictors of depression and/or treatment response.

To date, single nucleotide polymorphism (SNP) identification provides the longest list of potential hits in MDD research and treatment response. Current technology enables genotyping of 500,000 to 2.5 million SNPs across the genome (Lohoff, 2010), without a requirement for pre-selection of analytes. Thus, SNP research with GWAS helps to identify new and unbiased pathways involved in mood disorders (Lohoff, 2010). Notable SNP genotyping studies include: Sequenced Treatment Alternatives to Relieve Depression (STAR*D) (Garriock et al., 2010), the Munich Antidepressant Response Signature (MARS) (Ising et al., 2009), the Genome-based Therapeutic Drugs for Depression (GENDEP) (Uher et al., 2010), and the Mayo Clinic Pharmacogenomics Research Network Antidepressant Medication Pharmacogenomics Study (PGRN-AMPS) (Ji et al., 2013), and the ‘1000’ Genomes (Abo et al., 2012). While studies have failed to detect any particular gene of significant in predicting antidepressant response, numerous SNP hits have been identified which mediate several aspects of depression mechanisms and medication metabolism:

a. Drug Absorption:

Genetic polymorphisms in the multidrug-resistance gene (MDR1) are associated with both positive (Dong et al., 2009; Gex-Fabry et al., 2008; Kato et al., 2008; Nikisch et al., 2008; Uhr et al., 2008) and negative (Laika et al., 2006; Mihaljevic Peles et al., 2008; Peters et al., 2008) treatment outcomes. P-glycoprotein (P-gp) is the gene product of MDR1, resides at the blood brain barrier, and affects absorption of antidepressants. Thus, antidepressants which are substrates of P-gp

(e.g., citalopram, venlafaxine or paroxetine) are particularly susceptible to producing differential treatment outcomes.

b. Neurotransmitter Transport and Transmission:

Serotonin: Given the imbalance of monoamine levels associated with MDD, the serotonin (5HT) transporter and receptors have unsurprisingly been studied in numerous trials as a predictor of MDD risk and treatment outcome. Regarding the 5HT *transporter*, while no significant associations were initially identified with STAR*D participants (Kraft et al., 2007), follow-up analyses have shown differential treatment outcomes associated with the serotonin transporter linked polymorphic region (5-HTTLPR) of the SLC6A4 gene, notably in across races in response to treatment with SSRIs (Mrazek et al., 2009), although other groups have not been able to replicate these data several studies failed to find any association of 5-HTTLPR (Maron et al., 2009; Perlis et al., 2010; Serretti et al., 2013). Discovery and validation of SNPs in the serotonin *receptors* have been equally as complex. Data from both STAR*D (McMahon et al., 2006; Peters et al., 2009) and MARS (Lucae et al., 2010) indicate an association between the rs7997012 SNP of the serotonin receptor 2A gene and treatment outcome. However, other groups were unable to replicate this finding but found additional polymorphisms relating to treatment outcome (Horstmann et al., 2010; Uher et al., 2009).

Dopamine: A SNP at codon 158 of Catechol –O- Methyl Transferase (COMT) gene (rs4680) results in a valine-methionine substitution (i.e. met/met genotype) and is associated with decreased COMT activity (Chen et al., 2004; Lachman et al., 1996). COMT is the main catalytic enzyme of dopamine in the brain (Gogos et al., 1998; Kaenmaki et al., 2010; Sesack et al., 1998), and thus, this SNP has been reported to have favorable outcomes with antidepressants in some studies (Baune et al., 2008; Benedetti et al., 2009; Benedetti et al., 2010; Kocabas et al., 2010; Spronk et al., 2011; Tsai et al., 2009), but not others (Arias et al., 2006; Perlis et al., 2009; Serretti et al., 2013; Szegedi et al., 2005). In contrast, treatment-resistant patients with the val/val genotype higher response with ECT (Anttila et al., 2007), which was replicated in female patients (Domschke et al., 2010).

Glutamate receptor: Polymorphisms in glutamate ionotropic kainite receptor (GRIK) 4 gene were shown to be associated with treatment response in samples from STAR*D (Paddock et al., 2007), MARS (Horstmann et al., 2010) and others (Pu et al., 2013). Specifically, the rs1954787 SNP was most robust in STAR*D and was associated with the same directionality with the MARS and Chinese Han trials. However, other groups have failed to replicate these associations (Perlis et al., 2010; Serretti et al., 2012).

c. Monoamine Metabolism:

Type A Monoamine Oxidase-A (MAO-A) catabolizes monoamine transmitters, serotonin, norepinephrine, and dopamine, and therefore is a candidate player in

the onset, progression, and treatment of mood disorders, including depression. Combined with decreased levels of serotonin and norepinephrine, a genetic polymorphism which increases MAO-A expression is proposed as a key factor associated with MDD (Naoi et al., 2017). Further evidence indicates MAO-A as a promising biomarker; the SNP-rs6323 is predictive of treatment response with mirtazapine in women with bipolar disorder (Tadic et al., 2007). Studies examining fluoxetine and bupropion in Mexican and Caucasian populations, however, have shown no association with outcome (Peters et al., 2004; Tiwari et al., 2013).

Cytochrome P450 enzymes (CYPs) expression and function are altered by monoaminergic neurotransmission. Commercially-available kits enable identification of SNPs in P450 enzymes which may be used to classify individuals as extensive metabolizers, intermediate metabolizers, poor metabolizers or ultra-rapid metabolizers (Porcelli et al., 2011). While these polymorphisms can be helpful in predicting adverse effects due to drug metabolism (D'Empaire et al., 2011; Lim et al., 2014; Porcelli et al., 2011), their association with SSRI treatment response in STAR*D (Mihaljevic Peles et al., 2008; Peters et al., 2008), GENDEP (Hodgson et al., 2014; Hodgson et al., 2015) and other studies (Grasmader et al., 2004; Serretti et al., 2009; Shams et al., 2006) has at best been either negative or weakly positive (Lobello et al., 2010).

d. Immune-Regulation

FK506 binding protein 5 (FKBP5): The FKBP5 (rs1360780) gene, and particularly its epigenetic variants, is strongly associated with morphological brain changes in regions regulating emotions (Han et al., 2017) and displays a predisposition to developing MDD. FKBP5 genetic variants (including rs1360780, rs4713916, and rs3800373) have also shown a strong link in Caucasian subjects with various antidepressants treatments (Binder et al., 2004), which has been replicated by some groups (Binder et al., 2008; Gawlik et al., 2006). Following treatment with escitalopram or duloxetine, no association is observed with genetic variation and response (Perlis et al., 2010; Uher et al., 2009).

e. Multiple single nucleotide polymorphisms:

Given the discordance among studies investigating individual SNPs, an alternative approach is to investigate the interactive role of multiple SNPs. In a cohort of MDD outpatients of Asian ethnicity, Lim et al. found that responsiveness to SSRI could be predicted with 87% accuracy with a model incorporating SNPs of GRIK 2 (rs543196) and glutamate decarboxylase 1 (rs3828275 of GAD1), and haplotypes of tryptophan hydroxylase 2 (TPH2) and 5-HTTLPR (Lim et al., 2014). Their model was not accurate for predicting response to non-SSRI medications, however, supporting the notion that multiple SNP analyses could predict differential response to antidepressants.

Other genomics tools, including epigenetic modification, whole exome/gene sequencing, and transcriptomics/RNA Seq (i.e., “next generation sequencing”) are relatively new technologies, and thus their employment with MDD biomarker research is limited. However, early preliminary studies with MDD diagnostics suggest their feasibility and applicability:

Epigenetics refers to the study of heritable phenotypic traits which occur without any alterations in DNA sequence (Berger et al., 2009), such as post translational modification of histones, DNA methylation, and/or microRNA expression. Epigenetics has been used recently in depression research, both in clinical trials and in animal model studies (Maze et al., 2014; Oh et al., 2015). Oh et al. conducted DNA modification analysis in white blood cells from monozygotic twins discordant for MDD, in brain prefrontal cortex with MDD, and control subjects (total n = 304) using microarray fine mapping. Domschke et al. observed a higher methylation status of the SLC6A4 gene in MDD patients who showed a better response following 6 weeks treatment with escitalopram (Domschke et al., 2014). Epigenome-wide association studies (EWAS) have shown that the tricyclic antidepressants, amitriptyline and imipramine, as well as the SSRI paroxetine, reduced DNA methylation in rat primary astrocytes (Menke and Binder, 2014). Lopez et al. found that reduced histone H3 lysine 27 trimethylation (H3K27me3) significantly correlated with improvement in depressive symptoms and peripheral blood BDNF mRNA levels (Lopez et al., 2013). Thus, while the study of predictive biomarkers is still developing, preliminary studies demonstrate an association of epigenetic modifications with MDD.

Immediately downstream of epigenetics is transcriptomics, the study of gene transcription, which may help to identify pathways associated with the pathophysiology of mood disorders by examining gene expression and novel splice transcripts. For example, a preliminary study by Jansen et al. demonstrated strong gene expression differences between current MDD and control participants [current MDD (N=882), remitted MDD (N=635) and control (N=331)]. Further, RNA sequencing allowed them to associate the robustly-expressed MDD genes interleukin-6 signaling and natural killer cell pathways (Jansen et al., 2016) In an exploratory study of transcriptomic biomarkers with whole-genome expression of MDD remitters versus non-responders, Hennings et al. initially discovered messenger ribonucleic acid (mRNA) transcripts of interest and then used a replication sample of 142 patients from MARS study (Hennings et al., 2015). They found that lower pre-treatment mRNA levels of retinoid-related orphan receptor alpha (RORa), germinal center expressed transcript 2 (GCET2), and chitinase 3-like protein 2 (CHI3L2) were associated with greater likelihood of antidepressant response.

Pharmacogenomics-to-date has provided an interesting framework for future studies. Cumulative evidence supports the involvement of some genes and molecular pathways in MDD and antidepressant efficacy, notably those involved with monoamine transport and metabolism (SLC6A4, HTR2A, and cytochrome P450 genes). However, many of these hits demonstrate difficulty in validation. Although reasons for this could be due to retrospective analysis of biomarkers, low sample size, variations in data collection, or subjective clinical evaluation, there is a clear need for further characterization before they may be translated into the clinic.

3.2 Proteomics

Following gene transcription, a protein may be studied, either individually or in combination with others. The levels of several proteins, notably inflammatory factors, are implicated with MDD and are increasingly associated with treatment outcome. Proteomics methodology may be performed with a high-throughput discovery setup or targeted quantitation. Common techniques are based on size characterization or antibody/aptamer binding.

Two Dimensional Gel Electrophoresis (2DE) with Mass Spectrometry (MS) is a common methodology available to study the proteome, and has frequently been used with psychiatric disorders such as depression, schizophrenia, and bipolar disorder, as well as in studies of neurodegenerative disorders such as Alzheimer's disease (Lista et al., 2013; Martins-de-Souza et al., 2010; Schirle et al., 2012). In recent years, using 2D ITRAQ LC-MS with MDD samples, Xu et al. showed that several proteins (e.g., apolipoprotein D, B-100, ceruloplasmin histidine rich glyocprotein, semophorin, and α-2-macroglobulin) are significantly up- or downregulated (Xu et al., 2012). 2DE–MS-based proteomics is not without limitations, however. This technique shows difficulty with detecting proteins that are low-abundance, acidic, basic, or have an extremely high or low molecular weight.

Shotgun Proteomics is an alternative to the direct MS-based approach described above and can separate and identify thousands of proteins in one experiment. The liquid chromatography–tandem mass spectrometry (LC–MS) technique combines chromatographic steps in a high-throughput manner prior to MS analyses. Use of shotgun proteomics with MDD is limited, although it is capable of revealing differentially expressed proteins not found with 2DE methods (Martins-de-Souza et al., 2010; Schirle et al., 2012). Among the few MDD studies, shotgun LC-MS analysis of MDD patient samples with and without psychosis showed significant differences in proteomic profiles (Martins-de-Souza et al., 2010; Schirle et al., 2012). Mass spectrometry proteomics technology carries the beneficial capability of screening of a specimen's entire proteome, but sacrifices significant quantification power in the process. Furthermore, sample preparation in MS is not well-standardized and data interpretation is complicated due to the sheer amount of proteins assayed. As such, this technique requires more characterization before a reliable biomarker may be identified and translated to the clinic.

Multiplex Proteomics—The latest introduction of advanced multiplex luminex based technologies allow measurement of multiple analytes in individual small-volume samples, revolutionizing proteomic analyses. Different platforms include rules based medicine (RBM), bioplexes, meso-scale discovery (MSD), somalogic, and others which are suitable for developing convenient, rapid, sensitive, and specific assays for a wide range of diseases including major depression (Chen and Zhu, 2006; Xu et al., 2012). The technology employs multiplexed dye-coded microspheres, coated with specific capture reagents (antibodies and/or DNA-based aptamers) which may bind numerous analytes within a single biological sample. To date, multiplex technology varies from screening 10–1100 analytes in the same sample. This approach minimizes sampling errors, required sample volume, and cost for assay reagents. Multiplex-based technologies have been implicated in screening for putative biomarkers in Alzheimer's disease, Parkinson's disease, cancer, and infectious disorders, as

well as for psychiatric disorders like schizophrenia, depression, and bipolar (Chen and Zhu, 2006).

Inflammatory biomarkers, growth factors, and lipids have recently been studied with the rules based medicine (RBM) multiplex discovery platform (Bot et al., 2015; Diniz et al., 2015). Bot et al. conducted studies on 1589 participants from the Netherlands Study of Depression and Anxiety and found differences in protein level across current MDD, remitted MDD, and healthy control participants. The analytes predominantly associated with diverse cell communication and signal transduction processes, immune response, and protein metabolism (Bot et al., 2015). In a subsequent RBM study by Diniz et al., remitted MDD participants displayed differential expression of 24 proteins related to regulation of immune-inflammatory activity, intracellular signaling, cell survival, and protein and lipid homeostasis (Diniz et al., 2015). Several studies have evaluated peripheral blood levels of neurotrophic factors, but ultimately found no evidence for their utility as biomarker(s) of differential antidepressant treatment response (Brunoni et al., 2014; Buttenschon et al., 2015; Gorgulu and Caliyurt, 2009; Matrisciano et al., 2009; Molendijk et al., 2014; Ninan et al., 2014).

Antibody-based assays like western blots or enzyme linked immunosorbent assays (ELISA) have been around much longer than the other described proteomic assays, are very well-optimized, and have significant quantification advantages. ELISA technology may be used to quantify one specific protein or may be multiplexed to analyze several at the same time. They are frequently used in biomarker research and have produced many potential proteins of interest, particularly in inflammatory cascades. So far, meta-analyses have shown serum TNF-α, IL-6 CRP, BDNF and IL-1β levels as consistent proteomic markers associated with MDD and treatment response. Perhaps the most well-characterized inflammatory marker, however, is C-reactive protein (CRP), a marker of global inflammation, which has been reported as a biomarker of treatment response in several studies. Low (<1 mg/mL) baseline levels of CRP successfully identified patients who would respond better to escitalopram than nortriptyline in the GENDEP study (Uher et al., 2014). Correspondingly, higher baseline CRP levels were associated with greater reduction in depression severity with nortriptyline treatment. Raison et al. found that elevated high sensitivity CRP (> 5 mg/ml) at baseline was associated with a significantly greater likelihood of treatment response with infliximab as compared to placebo (Raison et al., 2013). In a more recent study, Jha et al. found that MDD patients with low baseline CRP levels (<1 mg/L) respond better to SSRI monotherapy, and patients with higher levels of CRP respond better to combination therapy of bupropion and SSRI (Jha et al., 2017).

Aside from CRP, ELISAs have been used to quantify other potential biomarkers, including protein p11 in natural killer (NK) cells and monocytes. Svenningsson et al. found that a reduction in p11 after 1 – 2 weeks of citalopram treatment was significantly correlated with subsequent reduction in depression severity (Svenningsson et al., 2014). Levels of many peripheral blood inflammatory cytokines are reduced with SSRI treatment (Hannestad et al., 2011). Janssen et al. found that antidepressants modulate cytokine functioning and directly influence treatment outcome in MDD (Janssen et al., 2010). Further, they showed that antidepressants normalize serum levels of cytokines including interleukin IL-6, IL-1β, tumor necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ). Maes et al. examined the

effects of clomipramine, sertraline, and trazadone on the stimulated production of IFN-γ and IL-10, and observed that all three antidepressants significantly increased the IFN-γ/IL-10 ratio (Maes, 2001). Lastly, a recent study by Gadad et al. identified only two of 31 potential inflammatory markers (Eotaxin/CCL11 and IFNγ) that significantly changed pre- to post-antidepressant treatment in the CO-MED study (Gadad et al., 2017, in press; Rush et al., 2011). Interestingly, increased levels of Eotaxin was associated with remission, whereas decreased IFNγ was associated with non-remission. Thus, antibody-based assays certainly provide a feasible platform for biomarker research, although their utility is somewhat hindered by the unavailability of protein-specific antibodies, low throughput, and high cost.

Interestingly, proteomics techniques are commonly combined in biomarker research. Oftentimes, a non-targeted approach (i.e., shotgun or multiplex) is used to identify putative markers, and ELISA or Western blot is used to validate the potential hits. This discovery/validation setup is crucial for biomarker research, as it is necessary to demonstrate that the differences found in a limited set of samples are applicable to a broader cohort. Lee et al. identified 10 proteins that were consistently upregulated or downregulated in MDD (n=5). Validation with ELISA demonstrated consistency with three of these: ceruloplasmin, inter-alpha-trypsin inhibitor heavy chain H4, and complement component 1qC (Lee et al., 2015). In addition, Stelzhammaer et al. used multiplex immunoassays and LC-MS with serum samples from MDD cohorts (first onset and antidepressant drug naïve) and matched controls independently. Results identified several possible biomarkers, including cytokines and interleukins, BDNF, cortisol, angiotensin-converting enzyme, and enzymes participating in the oxidative stress response (Stelzhammer et al., 2014).

Validation/Standardization—As proteomics is the most developed ‘omics platform thus far, its limitations are becoming well-characterized. 2DE, LC-MS, and shotgun or multiplex proteomics/metabolomics are used to evaluate the global expression in an individual biological sample. Although a powerful tool for simultaneously evaluating a wealth of markers, sensitivity and specificity are compromised. With ELISA, although relatively sensitive, attention must be paid closely to the possibility for inconsistent results. Samples are generally run simultaneously to prevent within-study variation, but assay detection can differ widely based on the company or antibody employed. Even within individuals, protein levels are susceptible to change with time of day or fasting status. Thus, for biomarker identification to be universally accepted and implemented in the clinic, all procedures, from collection of specimens to analysis of results, must be standardized. These markers have been consistently been reproduced and validated in several clinical trials.

3.3 Metabolomics

Metabolites are the final products of interactions between gene expression, protein function and the cellular environment (Fernie et al., 2004). Thus, metabolite profiling holds great promise for the identification of pathways involved in antidepressant response and pathophysiology of depression (Kaddurah-Daouk and Krishnan, 2009). In contrast to studies of DNA, RNA, or proteins, there is no building block equivalent like nucleic acids or amino acids in the metabolome, and the chemical diversity of metabolites makes their study particularly challenging. Like proteins, some individual metabolites can be assayed through

various detection methods: although the majority are currently detected via mass spectrometry.

Mass Spectrometry (MS) was initiated as a semi-quantitative method for providing either targeted or largescale metabolome analyses. Moreover, high-performance liquid chromatography, gas chromatography, and targeted electrochemistry based MS platforms have also been widely used to quantify abundant metabolic biomarkers in serum, plasma, and CSF from MDD participants (Martins-de-Souza, 2014). Many early depression metabolomic studies focused on broad metabolite classes, such as lipids (lipidomics). This was in part due to technologic limitations (Piomelli et al., 2007), although there was a known connection between lipids and neuronal signaling and disease (Allen et al., 2006; Donati and Rasenick, 2008). A meta-analysis of 14 studies comparing the total n-3 polyunsaturated fatty acids (n-3 PUFAs) levels in serum, plasma or erythrocytes in depressed vs non-depressed individuals demonstrated a significantly lower amount of n-3 PUFA in depressed populations (Lin et al., 2010). These findings have led to numerous clinical trials demonstrating efficacy of particular n-3 PUFAs as adjunct therapy for depression (Gertsik et al., 2012). Investigation into their mechanism of action has also generated further basic science inquiry about the pathophysiology of depression (Czysz and Rasenick, 2013). As lipidomics technologies have improved, however, research has expanded beyond n-3 PUFAs. In a large study of plasma from 742 participants with records of depression and anxiety related HADS-A/D and CES-D scores were compared to 148 phospho- and sphingolipids. Most notably the ratio of sphingomyelin 23:1 to sphingomyelin 16:0 was inversely related to depression severity (Demirkan et al., 2013). Furthermore, plasma and erythrocytes from 65 control and 137 MDD (19% currently depressed) participants in the DELTA study demonstrated lower levels of mono unsaturated and saturated fatty acids in depressed patients (Assies et al., 2010). Additionally, a small study of bipolar depressed patients investigated metabolomic changes following ketamine or esketamine treatment, and found more evidence for lipid changes (Rotroff et al., 2016). Targeted electrochemistry based metabolomics platform (LCECA) profiled serum samples from MDD patients and found that metabolites of the tryptophan metabolism pathway (e.g., kynurenine) were differentially regulated (Kaddurah-Daouk et al., 2013). When 800 metabolites were screened across plasma from depressed, remitted, or never depressed patients, results revealed that GABA, glycerate, citrate, glycerol, and 9,12,octadecadienoate were reduced in the currently depressed cohort (Paige, 2007).

More recent investigations have looked at a wider array of metabolites outside of lipids, including amino acids, hormones, and biogenic amines (Martins-de-Souza, 2014). These studies have aimed either to differentiate depressed from non-depressed patients (Paige, 2007) or predict patient response to drug therapy (Gupta et al., 2016; Kaddurah-Daouk et al., 2013; Kaddurah-Daouk et al., 2011).

Nuclear Magnetic Resonance Spectroscopy (NMR)—The initiation of high-resolution proton nuclear magnetic resonance spectroscopy (1H-NMR) provided a means of analyzing several thousands of metabolites with high throughput (Abo et al., 2012; Kaddurah-Daouk and Krishnan, 2009). Aside from blood, urine samples have been used for metabolomics analysis. Tian et al. measured small endogenous metabolites using NMR and

(Tian et al., 2014)reported that creatinine, taurine, 2-oxoglutarate, and xanthurenic acid increased significantly after treatment with the Chinese medication, xiaoyaosan, in MDD participants (Tian et al., 2014).

Multiplex-based metabolites screening is an advanced and quantitative method with the ability to quickly provide potential metabolic biomarker signatures (Rotroff et al., 2016). In combination with the targeted metabolomics kits currently available, it may be used for either exploratory or targeted analyses and provides reproducibility (Rotroff et al., 2016).

The above studies are somewhat limited by the heterogeneous mix of patients and/or pharmacotherapies. Other work has investigated metabolomics following treatment with specific antidepressants, including sertraline (Gupta et al., 2016; Kaddurah-Daouk et al., 2013; Kaddurah-Daouk et al., 2011), escitalopram (Ji et al., 2011), ketamine, and esketamine (Villasenor et al., 2014). Metabolite profiling of tryptophan metabolism in a 4-week double-blind placebo-controlled study showed that response to either sertraline or placebo was associated with metabolomics changes when post-treatment was compared to pre-treatment. Specifically, 5-methoxytryptophol and melatonin levels increased, while the kynurenine:melatonin and 3-hydroxykynurenine:melatonin ratios decreased (Zhu et al., 2013). Using the same samples in a separate study, Kaddurah-Daouk et al. found that pre-treatment levels of tryptophan, phenylalanine, purine, and tocopherol could predict responders versus non-responders (Kaddurah-Daouk et al., 2011). In a subsequent study, they found that a pre- to post-treatment decrease in branched chain amino acid (valine, leucine, and isoleucine) levels correlated with improvement in depression severity, notably in patients treated with sertraline (Kaddurah-Daouk et al., 2013). Other amino acids (glycine, glutamic acid, aspartic acid, asparagine) and the small molecule, hydroxylamine, have also been implicated as predictors of changes in QIDS-C score following escitalopram treatment (Ji et al., 2011). As mentioned above, the stability of many molecules is weak, and metabolites are especially susceptible given their quick turnover. Additionally, several mentioned above (fatty acids) are highly variable depending on fasting state. Thus, it will be of utmost importance to standardize collection materials should metabolomics of adipokines be a biomarker hit.

3.4 Data Driven Informatics

Bioinformatics, the study of information processing in biological systems, gained widespread prominence with the large volume of data arising from the human genome project (Hogeweg, 2011). Bioinformatics tools are now widely used to analyze the biological systems through various -omics studies like genomics, transcriptomics, epigenomics, proteomics, and metabolomics. The ongoing human connectome project (HCP; http://humanconnectome.org) is scanning 1200 healthy adults and utilizing robust informatics tools to analyze this large volume of data to map the neural network and understand the functional connections in the human brain (Toga et al., 2012). Arns et al. has brought these large datasets into the public domain, enabling the possibility of crowdsourcing biomarker discovery (Arns et al., 2015).

4. The Future of Biomarker Identification via Clinical Trial Analyses

The limitations of current diagnostic criteria for psychiatric illnesses have led to the Research Domain Criteria (RDoC) project by the NIMH (Insel et al., 2010b). Especially in the depression field, where clinical syndrome-based subtyping has failed to personalize treatment, the framework postulated in RDoC provides an exciting and promising future. RDoC aims to classify high level domains (or subtypes) from a heterogeneous population by integrating assessments from numerous systems, including emotional, cognitive, motivational, social behavioral, and potentially others, such as biological and physiological systems.

Among the biggest limitations of current depression biomarker research is the potpourri of studies looking at specific biomarker classes (e.g., genetics, metabolites, etc.) and focusing on one or two mutations, proteins, etc. rather than. When analyzed separately, there is an inability to detect how biomarkers may interact or synergize to promote the ultimate depression phenotype. Thus, to address the aims of RDoC and to hone in on specific subtypes, future clinical trials should take an integrative approach to biomarker research. Studies need to recruit large numbers of participants to accurately represent the population at-large. With the wealth of data which may ultimately be collected, both discovery and targeted analyses should be performed. Most of the tools described above are high-throughput, thereby enabling the identification of new ‘hits’. Also desired, will be the replication and validation of previously-implicated markers, such as those described above. Most importantly, however, future studies should attempt to identify multiple features (i.e., a biosignature) which together most-accurately predict response. This is the goal of the Establishing Moderators and Biosignatures of Antidepressant Response for Clinical Care (EMBARC) study (Trivedi et al., 2016).

The EMBARC study design, including inclusion and exclusion criteria, may be found at https://clinicaltrials.gov/ct2/show/NCT01407094. In summary, sertraline (an SSRI; (Bolden-Watson and Richelson, 1993; Owens et al., 2001)) and bupropion (a dopamine/norepinephrine reuptake inhibitor; (Ascher et al., 1995)) were selected as antidepressant medications for their different mechanisms of action. Placebo was included to establish the changes in clinical and biological markers that occur in the absence of pharmacologically active treatment (Dong and Blier, 2001; Li et al., 2002; Nomikos et al., 1989; Trivedi et al., 2016). The study includes two stages, with each stage lasting 8 weeks. At baseline, the study participants complete self-report clinical instruments and undergo neuroimaging, neurophysiological, and behavioral testing, then provide a blood sample. In addition to self-reporting, a research psychiatrist or psychologist completes clinician-rated instruments for clinical phenotyping. Metrics are repeated at a 1 week visit, and blood is collected at weeks 4, 8, 9 (if medication is switched), 12, and 16 (Trivedi et al., 2016).

4.1 Clinical and biological markers collected in EMBARC

Comprehensive clinical phenotyping in EMBARC is done with structured diagnostic assessments and self-report instruments to evaluate ongoing symptoms, antidepressant treatment history, trauma history, social functioning, sexual functioning, personality, and intelligence (Greenberg et al., 2015; Trivedi et al., 2016). Behavioral assessments include

psychomotor slowing (choice reaction time and word fluency task), cognitive control (Flanker task), working memory (A not B task), and reward responsiveness (probabilistic reward task). Neuroimaging includes structural assessments (DTI and three dimensional high resolution Magnetization-Prepared Rapid Gradient-Echo, MP-RAGE), functional imaging while performing challenge tasks (e.g., implicit emotion processing and regulation; and reward processing), and resting state imaging (e.g., blood-oxygen-level dependent (BOLD) and arterial spin labeling (ASL) (Webb et al., 2016). Neurophysiological assessments include resting EEG with eyes opened and closed, Low Resolution Electromagnetic Tomography (LORETA) to localize theta activity, and measurement of Loudness Dependence of Auditory Evoked Potentials (LDAEP) after presentation of 1000 Hz tones at 5 different intensity levels using a headphone. While imaging and EEG analysis have already begun to demonstrate the capacity for subtyping depression (Chase et al., 2015; Webb et al., 2016). Plasma and serum samples will next be analyzed using genomic, proteomic, and metabolomics technologies to potentially identify additional biomarkers.

4.2 Statistical innovations in EMBARC

Mixed effects models will be used to analyze individual variables for their role as mediators or moderators. The sample will then be randomly divided into exploratory and validation samples for generation and testing a differential treatment response index (DTRI) by using a combination of variables and interaction among variables that best predict treatment outcome (Chase et al., 2015; Trivedi et al., 2016). Based on the exploratory sample derived from stage 1 of the study, DTRI can be generated for levels of improvement expected with Sertraline treatment (data not shown). The validation sample will next be used to test DTRI. Side effect indices (IndexSE) will be generated in a similar manner using exploratory and validation samples.

4.3 Limitations of EMBARC

Generalizability of findings from EMBARC may be limited to the subgroup of MDD patients who meet the eligibility criteria of this study, especially due to restrictions on age of onset, chronicity, co-morbid psychiatric disorders, exclusionary medications and presence of treatment resistance. Similar to results from other clinical trials, we cannot be certain that the peripheral changes observed are in direct relation to changes observed centrally. Certainly, there are several ways in which peripheral molecules enter the brain (e.g., a weakened blood brain barrier, active transport, cerebrospinal fluid-lymph node interaction (Kim and Won, 2017{Robson, 2017 #366)}, although the intricacies and nuances of how the two systems directly relate remains elusive. Lastly, EMBARC was designed to generate candidate clinical and biological markers, and not to test a priori hypotheses. Thus, it may lack the adequate power necessary to draw definitive conclusions about mediators or moderators. Lack of assessment of clinical and biological markers of treatment outcomes with other antidepressant treatments like psychotherapy, exercise, novel antidepressant medications (e.g., ketamine), and somatic treatments is another limitation of EMBARC. A naturalistic follow-up study with longer term assessment may help to evaluate functional recovery, risk of relapse or recurrence, and efficacy of subtype treatment matching.

5. Conclusions and Future Perspectives

The ineffective treatment of depression necessitates biomarker discovery. We are equipped with complex and high throughput technologies, which combined with large-scale clinical trials, should enable detection of depression biosignatures and ultimately a higher change of remission. As demonstrated in Figure 3, to date, biomarker research has begun spanning the genome, proteome, and metabolome, and the utility of these technologies will only continue to grow. Presently there exists a potpourri of studies in each of these fields: SNP studies have identified genes related to monoaminergic and glutamatergic signaling. Protein studies have the most robust evidence for disturbances in immunologic pathways including interleukin IL-6, IL-1β, TNF-α, and IFNγ. Finally, metabolomics studies have identified a variety of candidate metabolites related to depression and drug response. A limited number of these results have been validated in additional patient cohorts, however. As a result, no individual or collection of biomarkers have translated into clinical practice for either diagnosis of depression or guidance of treatment selection. The heterogeneous pathology driving depression makes biomarker discovery particularly challenging, though provides the capability to hone in on numerous underlying biomarkers (i.e., a biosignature) to define specific subgroups. Robust techniques are necessary, as is the continuing refinement of both measurement and analytical tools for biomarker discovery. These technological advances combined with an increasing identification of putative biomarkers will help tailor depression treatment to individual patients, ultimately leading to faster and more efficacious treatment.

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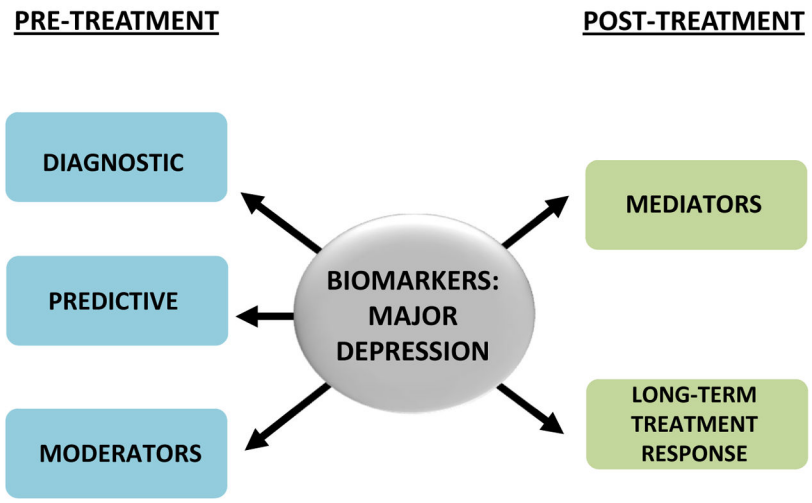

Figure 1. Biomarkers of major depression

Biomarkers identified before treatment initiation are classified as diagnostic, predictive, or moderators. Diagnostic markers classify an MDD patient, predictive markers determine overall likelihood of response/remission, and moderators determine likelihood of response/remission with a particular treatment. Mediators are biomarkers collected soon after treatment initiation and help predict overall likelihood of response/remission. Long-term treatment response may also be indicative of ultimate outcome

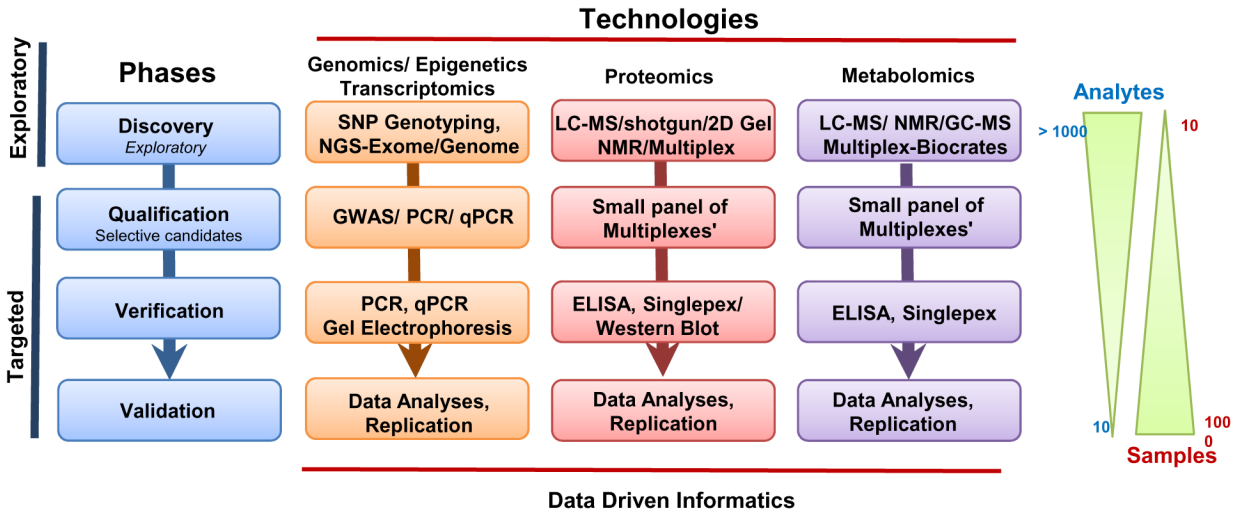

Figure 2. Tools and Technologies for the development biomarker candidates

Biomarker consists of four main phases- discovery, qualification, verification and validation. The tools and associated technologies are listed for pharmacogenomics, epigenetics, transcriptomics, proteomics and metabolomics. “Analytes” and “Samples” refer to the number of different protein targets or samples, respectively that are evaluated in each phase. LC-MS/MS, liquid chromatography tandem mass spectrometry; NGS, Next generation sequencing; PCR, Polymerase chain reaction.

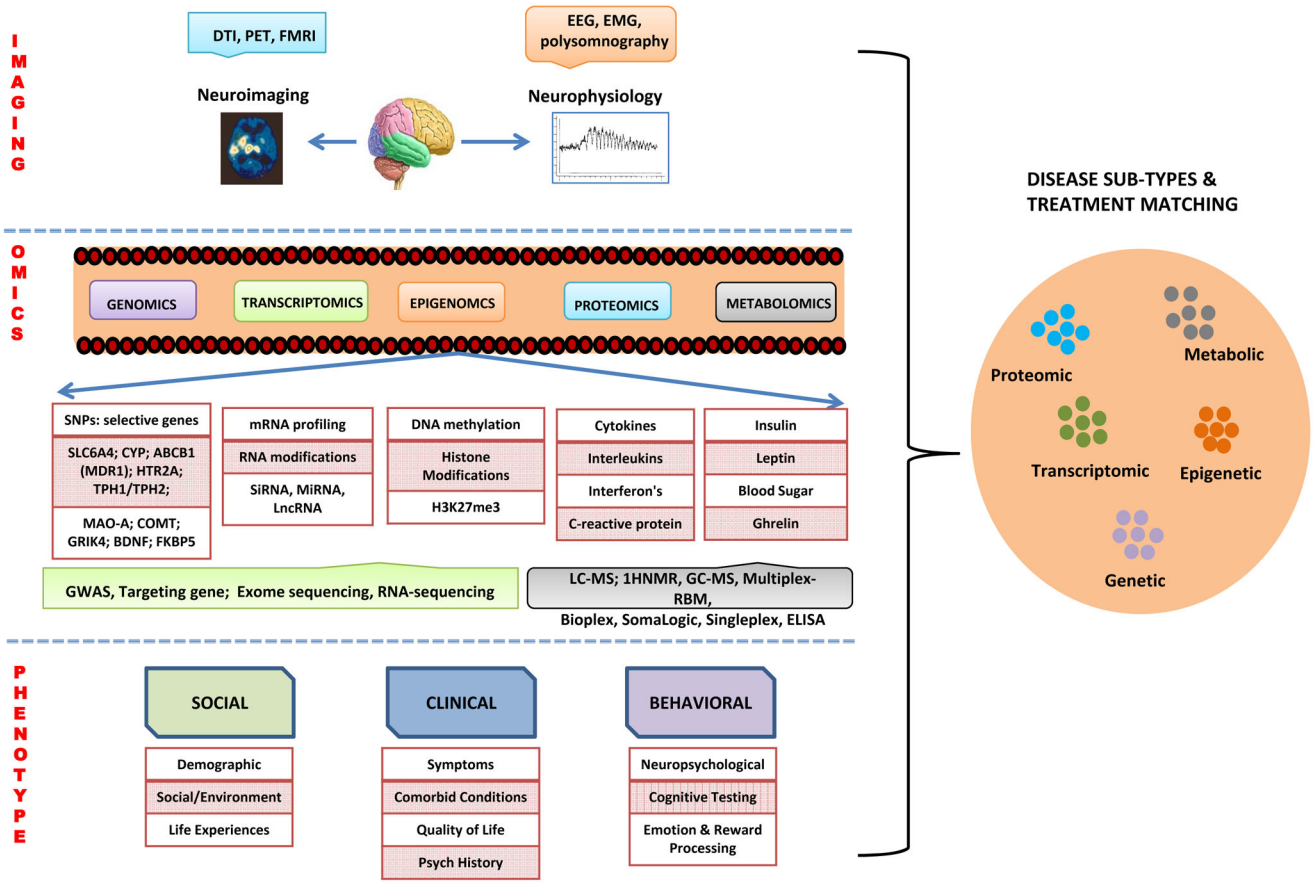

Figure 3. 'Omics based approach in major depression and treatment matching

Along with imaging and physiology, 'omics' and clinical phenotype are major components which may lead to treatment matching via unique biosignature. 'Omics include: genomics, proteomics, transcriptomics, epigenomics, and metabolomics. Phenotype includes social, clinical and behavioral. Overall, evaluation of these features may enable identification of different subtypes of depression, which may improve treatment matching.