Toward a Global Roadmap for Precision Medicine in Psychiatry: Challenges and Opportunities

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Abstract

Mental disorders represent a major public health burden worldwide. This is likely to rise in the next decade, with the highest increases predicted to occur in low- and middle-income countries. Current psychotropic medication treatment guidelines focus on uniform approaches to the treatment of heterogeneous disorders and achieve only partial therapeutic success. Developing a global precision medicine approach in psychiatry appears attractive, given the value of this approach in other fields of medicine, such as oncology and infectious diseases. In this horizon scanning analysis, we review the salient opportunities and challenges for precision medicine in psychiatry over the next decade. Variants within numerous genes involved in a range of pathways have been implicated in psychotropic drug response and might ultimately be used to guide choice of pharmacotherapy. Multipronged approaches such as multi-omics (genomics, proteomics, metabolomics) analyses and systems diagnostics together with high-throughput sequencing and genotyping technologies hold promise for identifying precise and targeted treatments in mental disorders. To date, however, the vast majority of pharmacogenomics work has been undertaken in high-income countries on a relatively small proportion of the global population, and many other challenges face the field. Opportunities and challenges for establishing a global roadmap for precision medicine in psychiatry are discussed in this article.

Introduction

MENTAL DISORDERS REPRESENT a major public health problem worldwide and are associated with significant functional impairment (Kessler et al., 2009). Direct costs encompass hospitalization and treatment, while indirect costs include loss of income due to unemployment (Insel, 2008). In 2010, 7.4% of the total global disease burden was attributable to mental and substance use disorders, and this burden is anticipated to rise (Whiteford et al., 2013), with the highest increases to occur in low- and middle-income countries (LMICs) (Baingana et al., 2015). In psychiatry, current treatment guidelines, including the World Health Organization (WHO) Mental Health Gap Action Programme (mhGAP), focus on uniform approaches to the treatment of

heterogeneous disorders and achieve only partial success. Thus, developing a global precision medicine approach in psychiatry appears attractive.

The aim of precision medicine is to prescribe the correct medication and dosages, at the right time, based on the demographics and genomic makeup of a particular group of patients categorized by similar conditions (Mirnezami et al., 2012; Ritchie, 2012). Significant resources and efforts have been put into this effort. For example, the Precision Medicine Initiative (PMI) aims to improve health and find cures for disease by advancing individualized care and will include ~1 million US citizens (www.nih.gov/precision-medicine-initiative-cohort-program). However, this work has predominantly been undertaken in high-income countries, while the vast majority of the world's population lives in LMICs.

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LMICs are also faced with several challenges in terms of genomic-based medicine, including high costs, a deficiency of trained scientists and clinicians, inadequate laboratories, a lack of awareness of the significance of genomics in public health, and gaps in policy frameworks for public health (Rehman et al., 2016; Tekola-Ayele and Rotimi, 2015). In this article, we discuss the emerging opportunities and challenges in establishing a global precision medicine strategy for psychiatry.

Moving to Precision Medicine in Psychiatry

Diagnosis in psychiatry is based on classification systems, such as the *Diagnostic and Statistical Manual of Mental Disorders (DSM)* (American Psychiatric Association, 2013), which group together relatively heterogeneous conditions. Treatment guidelines focus on these conditions and provide the clinician with general, evidence-based rules. This approach has only partial efficacy, and concerns have been expressed about the validity of *DSM-5* criteria in LMIC settings (Jacob and Patel, 2014). Thus, there is interest in alternative approaches to psychiatric diagnosis and assessment.

The National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative aims to group psychiatric phenotypes according to neurobiological dimensions or systems, based on neuroscience, rather than the classic categorical diagnostic criteria (Insel et al., 2010). The ultimate aim of RDoC is to incorporate precision medicine into clinical psychiatry by generating a comprehensive matrix of information for each patient, based on disease pathophysiology (Insel, 2014). However, the structure of RDoC constructs may be as complex as that of *DSM* categories, and for the foreseeable future, a range of phenotyping and endophenotyping approaches will be needed (Stein, 2014).

Psychiatrists often use a rational trial-and-error approach when selecting medications and determining optimal dosages (Mrazek, 2010; Smoller, 2014). Treatment response and tolerance vary from patient to patient (Lohoff and Ferraro, 2010). Only 60–70% of individuals achieve remission when taking antidepressants (Malhi et al., 2016), and 20–30% of people with schizophrenia do not respond to treatment with antipsychotics (Ackenheil and Weber, 2004). Furthermore, adverse drug reactions (ADRs) are relatively common and may lead to nonadherence or discontinuation of therapy. Evidence from twin studies, as well as genome-wide, single-nucleotide polymorphism-based investigations, have suggested that response to psychotropic medication may have relatively high heritability (Horáček et al., 2001; Tansey et al., 2013; Vojvoda et al., 1996; Wehmeier et al., 2005).

Pharmacogenomic testing may be useful in facilitating the selection of appropriate psychotropic medications for particular patients (Mrazek, 2010). Pharmacogenomic/genetic approaches, a key element of precision medicine (Johnson and Weitzel, 2016), have had some success in identifying genetic variants, which are able to predict negative drug response. For example, variants within the gene, cytochrome P450-2D6 (*CYP2D6*) that specifically catalyses the formation of morphine from codeine, are able to predict whether an individual is a poor, intermediate, extensive, or ultrarapid metabolizer of codeine (Crews et al., 2012). Another example of how pharmacogenetics has aided precision medicine is the profiling of

the human leukocyte antigen (*HLA*) when using carbamazepine; variants within the *HLA-B* gene place individuals at a higher risk of developing severe ADRs, such as Stevens–Johnson syndrome after carbamazepine (Kaniwa et al., 2010).

To date, many candidate gene-based association studies and genome-wide association studies (GWAS) have sought to identify genetic variants associated with psychotropic treatment response and these are discussed next.

Current Findings

Candidate gene approach

Recent reviews on the pharmacogenetics of various psychotropic treatments indicate that the most studied genes relevant to pharmacodynamics are those involved in neurotransmitter pathways, such as the dopamine (e.g., catechol-O-methyltransferase [*COMT*], monoamine oxidase A [*MAOA*], dopamine transporter [*DAT*], dopamine receptor D2 [*DRD2*]) and serotonin (e.g., tryptophan hydroxylase [*TPH*], solute carrier family 6 member 4 [*SLC6A4*], 5-hydroxytryptamine receptor 2A [*HTR2A*]) systems as well as genes involved in the hypothalamic-pituitary-adrenal (HPA)-axis (e.g., corticotropin releasing hormone receptor 1 [*CRHR1*]), neuroprotection (brain-derived neurotrophic factor [*BDNF*]), and circadian pathways (clock circadian regulator [*CLOCK*]) (Changasi et al., 2014; Fabbri and Serretti, 2015; Porcelli et al., 2011). Variations within the drug metabolizing gene *CYP2D6* have been most extensively investigated in terms of pharmacokinetics of psychotropic medication (Porcelli et al., 2011). Based on *CYP2D6* genotype, a patient can be classified as a poor, intermediate, or ultrarapid drug metabolizer (Bertilsson et al., 2002).

Genome-wide association studies

To date, ~30 GWAS studies have been conducted focused on treatment response or ADRs in psychiatry (www.ebi.ac.uk/gwas) (Burdett et al., 2015). Overall, <20 genome-wide significant hits (p -value $<5 \times 10^{-8}$) have been found (Table 1). The most significant hit was for a locus within the *HLA-A* region associated with cutaneous ADRs in Japanese individuals taking carbamazepine (Ozeki et al., 2011). A more recent study using gene-based and pathway analysis for GWAS data found that the inorganic cation transmembrane transporter activity pathway was associated with antidepressant response in individuals with major depressive disorder (MDD) (Cocchi et al., 2016). These findings suggest promise, but a meta-analysis of three large pharmacogenetic studies, namely, the Genome-Based Therapeutic Drugs for Depression (GENDEP), the Munich Antidepressant Response Signature (MARS), and the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) studies, found no genome-wide significant hits for antidepressant efficacy in individuals with MDD (GENDEP Investigators et al., 2013).

Taken together, few findings thus far are ready for translation into the clinic. Exceptions include the use of *HLA* profiling with carbamazepine treatment. Several commercial pharmacogenetic tests and pharmacogenetic-based decision support tools are available to psychiatrists. However, the validity and utility of these tests/tools are still uncertain, and as a result of limited evidence, recommendations for use in routine clinical are premature (Bousman and Hopwood, 2016). Another limitation of current genetic studies is that

TABLE 1. SIGNIFICANT GENOME-WIDE ASSOCIATION STUDY HITS FOR PHARMACOGENOMIC STUDIES IN PSYCHIATRY

<i>Outcome</i>	<i>Ancestry</i>	<i>Sample</i>	<i>Disorder/trait</i>	<i>Treatment</i>	<i>Reported gene(s)/regions</i>	<i>Replication of top hits</i>	<i>References</i>
Response to antipsychotic treatment	European, African American	738 Cases	Schizophrenia	Olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, clozapine	Intergenic	No	Åberg et al. (2010)
Response to antipsychotic treatment	European, African American	738 Cases	Schizophrenia	Olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, clozapine	<i>MEIS2, GPR98</i>	No	Adkins et al. (2011)
Response to antidepressant treatment	European, African American	1762 cases	MDD	Citalopram	<i>EMID2</i>	No	Adkins et al. (2012)
Response to antiepileptic drugs	European American	1334 cases	Schizophrenia, bipolar disorder, and MDD	Amisulpride, aripiprazole, clozapine, haloperidol, olanzapine, perphenazine, sertindole, risperidone, zuclopenthixol, amitriptyline, citalopram, escitalopram, mianserin, mirtazapine, sertraline, venlafaxine, lamotrigine, valproic Acid	<i>LOC100505718</i>	No	Athanasia et al. (2015)
Response to antipsychotic treatment	European, African American	738 cases	Schizophrenia	Olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, clozapine	Intergenic, <i>PDE4D</i>	No	Clark et al. (2013)
Response to antidepressant treatment	European	435 cases	MDD	Citalopram, escitalopram	<i>SEPT, LOC100132273, LOC388906, CYP2D6, CYP2C9, CYP2C19, TRIMLI</i>	No	Ji et al. (2014)
Response to antidepressant treatment	Korean	Discovery: 481 cases, replication: 230 cases, 159 cases	Unipolar depression	Escitalopram, sertraline, fluoxetine, paroxetine	<i>AUTS2</i>	Yes	Myung et al. (2015)
Response to anticonvulsant	Japanese	Discovery: 55 cases, 898 controls, replication: 61 cases, 376 controls	Carbamazepine induced ADRs	Carbamazepine	<i>HLA-A</i>	Yes	Ozeki et al. (2011)
Response to antidepressant treatment	European	706 cases	MDD	Escitalopram, nortriptyline	<i>UST</i>	No	Uher et al. (2010)
Response to lithium treatment	European, Japanese, Taiwanese	Discovery: 2563 cases, prospective: 73 cases	Bipolar disorder	Lithium	<i>AL157359.3, AL157359.4</i>	Yes, prospective cohort	Hou et al. (2016)

ADRs, adverse drug reactions; *CYP2D6* = cytochrome P450-2D6; *HLA*, human leukocyte antigen; MDD, major depressive disorder.

TABLE 2. SUMMARY OF THE TOP THREE CHALLENGES AND OPPORTUNITIES FOR GLOBAL PRECISION MEDICINE IN PSYCHIATRY

Challenges	Opportunities
<ul style="list-style-type: none"> • Phenotype classification based on standardized diagnostic criteria • Interindividual differences in the efficacy and tolerability of psychotropic treatment that are often underappreciated due to lack of robust global science and innovation policies • Systems Biology: mathematical models, molecular information from <i>in vitro</i>, <i>in vivo</i>, and <i>in silico</i> experiments are combined with multi-omics data to understand complex interactions and networks involved in drug response 	<ul style="list-style-type: none"> • RDoC—phenotypes classified according to neurobiological dimensions or systems, based on neuroscience. Caveat: The structure of RDoC constructs may be as complex as that of <i>DSM</i> categories. • NGS and hypothesis-free genomic and multi-omics methods to determine novel pharmacogenomic variants. • Consortia: might allow for extensive collaboration and data sharing necessary to achieve the sample sizes required to detect genetic variation of small effect.

DSM, *Diagnostic and Statistical Manual of Mental Disorders*; NGS, next-generation sequencing; RDoC, Research Domain Criteria.

most are conducted on individuals of European descent and findings are therefore not always applicable to other population groups.

In Table 2 and discussed more extensively below, we explore a number of opportunities in pharmacogenomics, with a focus on approaches that may be considered feasible, such as next-generation sequencing (NGS), increasing sample size through consortia, gene imaging analysis, and including the mitochondrial genome. We also describe a number of challenges in moving forward with a global precision medicine in psychiatry.

Opportunities

Next-generation sequencing

NGS may be vital to precision medicine, particularly in identifying rare variants in diverse genomes. This technology has already had some success in identifying variants in psychotropic drug response. For example, a whole-exome sequencing (WES) study found that variants in the gene bone morphogenetic protein 5 (*BMP5*) were associated with antidepressant response (Tammiste et al., 2013). A more recent WES study in patients with schizophrenia showed that variants in the genes myosin 7B (*MYO7B*) and 5-methyltetrahydrofolate-homocysteine methyltransferase reductase (*MTRR*) could potentially predict response to antipsychotics (Drögemöller et al., 2016). The use of these methods is still too expensive for some health systems, especially in LMICs, but the cost of NGS technologies is declining rapidly.

Consortia science

The discovery of clinically relevant pharmaco-variants for psychiatry will likely require very large sample sizes, in the order of tens of thousands (Smoller, 2014). Such samples are now being achieved through extensive collaboration and data sharing. Consortia, for example, the Psychiatric Genomics Consortium (PGC), are playing a crucial role in psychiatric research, and several are particularly interested in investigating pharmacogenomics. One such consortium is the Clinical Pharmacogenetics Implementation Consortium (CPIC), which aims to provide guidelines on how to prescribe

specific drugs based on genetic findings from the laboratory. Membership to the consortium is open to anyone with an interest in clinical pharmacogenetics (www.pharmgkb.org/page/cpic). Similarly, the Pharmacogenomics of Bipolar Disorder (PGBD) study seeks to identify genes for lithium response in a prospective cohort of patients with bipolar disorder, which will be achieved by conducting GWAS, meta-analysis, and follow-up with gene expression studies in pluripotent stem cells (Oedegaard et al., 2016), and the International SSRI Pharmacogenomics Consortium (ISPC) aims to identify genetic variation contributing to selective serotonin reuptake inhibitor (SSRI) response for patients with MDD (Biernacka et al., 2015).

Such consortia will increasingly include samples from globally distributed populations in the future (Dalvie et al., 2015). While consortia science can bring scientific discoveries to scale, we need to be mindful that research funding to smaller scale independent scientific laboratories is also maintained, together with independent academic analysis. The opportunities and tensions at the intersection of consortia science and smaller scale independent/artisan science are reviewed elsewhere (Dove and Özdemir, 2015).

Genes and imaging intersection

The use of neuroimaging techniques, such as volumetric and functional magnetic resonance imaging (fMRI), may also hold promise for advancing precision medicine in psychiatry. For example, an fMRI study found that variation in the *COMT* gene interacted with the effects of the antipsychotic olanzapine to improve cognition and negative symptoms in patients with schizophrenia (Bertolino et al., 2014). Another study found that variation within *BDNF* was associated with gray matter volume and antidepressant treatment response in individuals with MDD (Cardoner et al., 2013). However, numerous methodological challenges and limitations account for inconsistent and non-reproducible findings in neuroimaging studies, such as small study size for genetic analyses, presence of artifacts, comorbidities, variability in neuroimaging protocols, and poor study design, which limit the power to detect genotype $\times$ medicinal effects (Falcone et al., 2013; Weinberger and Radulescu, 2016).

Addressing these limitations may allow for neuroimaging studies to better investigate individual differences in

endophenotypes, disorders, and treatment responses and may further facilitate the development of individualized treatment strategies targeted to specific variant genotypes. The ENIGMA (Enhancing NeuroImaging Genetics through Meta-Analysis) network (<http://enigma.ini.usc.edu>) is an imaging genomics consortium, focused on neuropsychiatric disorders (Thompson et al., 2016), which has managed to overcome some of the limitations mentioned above. Ultimately, treatment interventions informed by genetic variance and neuroimaging may present a more powerful strategy for targeted therapy than either tool alone (Ray et al., 2008).

Mitochondrial dysfunctions

The mitochondrial genome has coevolved with the increase in human brain size to adapt to its increased energy demands (Martins-de-Souza et al., 2011). Thus, variation within mitochondrial genes and pathways may result in altered mitochondrial functioning and metabolism, and subsequent altered brain function (Martins-de-Souza et al., 2011). A number of microsomal (endoplasmic reticular) cytochrome P450 (CYP) enzymes involved in antipsychotic metabolism are bimodal (targeted to two separate subcellular locations) and are localized to the mitochondria of the liver, brain, heart, lungs, and other tissues (Avadhani et al., 2011; Sangar et al., 2010). These mitochondrial CYPs have also been shown to contribute to drug metabolism and drug-induced toxicity (Guengerich, 2001). For example, CYP2D6 has been shown to be localized to the mitochondria in liver tissue, where it is metabolically active (Avadhani et al., 2011; Sangar et al., 2009). Significant interindividual variation in the protein content of this enzyme has also been observed within liver tissue mitochondria (Sangar et al., 2009). Further work on assessing the role of mitochondrial CYPs in pharmacogenetics and pharmacodynamics is needed.

Challenges

Research in LMICs and diverse populations

It is particularly important to address the genetics of psychiatric disorders in LMICs and diverse populations (Dalvie et al., 2015). African genomes have higher levels of genetic diversity and shorter blocks of linkage disequilibrium (LD). This is due to ancestral Africans having a greater effective population size and there has been more time for recombination to reduce levels of LD. Non-African population groups have larger LD blocks possibly as a result of a founding event during the expansion of modern humans out of Africa within the past 100,000 years (Campbell and Tishkoff, 2008). With shorter LD blocks in African populations, more markers are required to tag shorter genomic regions, and existing microarrays may not effectively capture common haplotypes in African populations. There are therefore significant gaps in our ability to use genomic approaches to predict therapeutic responses to pharmacotherapy in this population.

Biological complexity

Systems biology represents a paradigm shift from the reductionist theory toward a more holistic approach, through which biological systems are investigated in entirety (Rodin et al., 2011; Zaraket et al., 2012). This is achieved by combining mathematical models, molecular information from

in vitro, *in vivo*, and *in silico* experiments, together with multi-omics data (Bender, 2015; Dimitrov, 2011; Kumar et al., 2015; Shao et al., 2015). Thus, a systems biology approach has the potential to aid in the understanding of the complex interactions and networks involved in complex phenotypes, such as psychiatric disorders (Zaraket et al., 2012). For example, the Integrative Personal Omics Profile (iPOP) combines genomic, transcriptomic, proteomic, metabolomic, and autoantibody profiles from a single individual over a 14-month period to generate a multidimensional view of healthy and diseased states (Chen et al., 2012). At the same time, the reality of biological complexity must be acknowledged. In the area of psychiatry in particular, multiple causal factors operating at different levels contribute to treatment outcome, so that even a detailed understanding of pharmacogenomics/pharmacodynamics may be insufficient to allow a fail-safe personalized medicine approach.

Noncoding variation and regulatory elements

Given that most common variants associated with clinical phenotypes occur in noncoding regions and that these regions remain underrepresented in current research, expanding research to focus on these genetic components may facilitate a better understanding of the complexity associated with pharmacogenomic intervention in psychiatry (Freedman et al., 2011). Noncoding variants within regulatory pathways may alter gene expression and present with larger effects than coding variation, due to their effects on global transcription and translation (Georgitsi et al., 2011). Nonetheless, there remains a paucity of studies on regulatory noncoding variants due to (1) an emphasis being placed on coding regions (e.g., WES) and (2) difficulty in studying these genomic regions due to factors, such as repeats and high GC content (Drögemöller et al., 2014; Ritchie et al., 2014; Schmidt et al., 2010).

Schizophrenia risk variants have shown to be enriched for alleles that are located within promoter or enhancer regions affecting gene expression (Roussos et al., 2014). Similarly, >97% of variants associated with attention-deficit/hyperactivity disorder (ADHD) are noncoding (Tong et al., 2016). In terms of treatment response, a recent GWAS found that the most significant locus associated with lithium response in bipolar disorder contained long, noncoding RNA genes (Hou et al., 2016). Our relative lack of knowledge in this area represents a key challenge in developing a global precision medicine approach in psychiatry.

Conclusions and Outlook

The burden of psychiatric disorders appears likely to continue to increase, especially in LMICs (Whiteford et al., 2013). Although novel candidates in disease pathophysiology have been proposed and there have been significant advances in the treatment of psychiatric disorders, there remains a considerable need for further improving treatment outcomes. Multifaceted approaches, such as multi-omic and pathway-based approaches in conjunction with high-throughput sequencing and genotyping technologies, hold promise for identifying additional specific treatment targets in mental disorders. In this study, we have considered the development of precision medicine in psychiatry from a global perspective, noting a number of opportunities (which make us hopeful about the future of the field) as well as a number of

challenges (which make us cautious). Indeed, we must be careful to differentiate hope from hype, in considering the establishment of a global and inclusive roadmap for precision medicine in psychiatry.

Author Disclosure Statement

The authors declare that no conflicting financial interests exist.

References

- Åberg K, Adkins DE, Bukszár J, et al. (2010). Genomewide association study of movement-related adverse antipsychotic effects. *Biol Psychiatry* 67, 279–282.
- Ackenheil M, and Weber K. (2004). Differing response to antipsychotic therapy in schizophrenia: Pharmacogenomic aspects. *Dialogues Clin Neurosci* 6, 71–77.
- Adkins DE, Åberg K, McClay JL, et al. (2011). Genomewide pharmacogenomic study of metabolic side effects to antipsychotic drugs. *Mol Psychiatry* 16, 321–332.
- Adkins D, Clark S, Åberg K, et al. (2012). Genome-wide pharmacogenomic study of citalopram-induced side effects in STAR*D. *Transl Psychiatry* 2, e129.
- American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders (DSM-5®)*. American Psychiatric Publishing, Arlington, VA.
- Athanasia L, Smorr LL, Tesli M, et al. (2015). Genome-wide association study identifies common variants associated with pharmacokinetics of psychotropic drugs. *J Psychopharmacol* 29, 884–891.
- Avadhani NG, Sangar MC, Bansal S, and Bajpai P. (2011). Bimodal targeting of cytochrome P450s to endoplasmic reticulum and mitochondria: The concept of chimeric signals. *FEBS J* 278, 4218–4229.
- Baingana F, Al'Absi M, Becker AE, and Pringle B. (2015). Global research challenges and opportunities for mental health and substance-use disorders. *Nature* 527, S172–S177.
- Bender E. (2015). Big data in biomedicine: 4 Big questions. *Nature* 527, S19.
- Bertilsson L, Dahl M, Dalén P, and Al-Shurbaji A. (2002). Molecular genetics of *CYP2D6*: Clinical relevance with focus on psychotropic drugs. *Br J Clin Pharmacol* 53, 111–122.
- Bertolino A, Caforio G, Blasi G, et al. (2014). Interaction of *COMT* Val108/158 met genotype and olanzapine treatment on prefrontal cortical function in patients with schizophrenia. *Am J Psychiatry* 161, 1798–1805.
- Biernacka J, Sangkuhl K, Jenkins G, et al. (2015). The international SSRI pharmacogenomics consortium (ISPC): A genome-wide association study of antidepressant treatment response. *Transl Psychiatry* 5, e553.
- Bousman CA, and Hopwood M. (2016). Commercial pharmacogenetic-based decision-support tools in psychiatry. *Lancet Psychiatry* 3, 585–590.
- Burdett T, Hall P, Hastings E, Hindorff L, and Junkins H. (2015). The NHGRI-EBI catalog of published genome-wide association studies. www.Ebiacuk/Gwas (last access: July 28, 2016).
- Campbell MC, and Tishkoff SA. (2008). African genetic diversity: Implications for human demographic history, modern human origins, and complex disease mapping. *Annu Rev Genomics Hum Genet* 9, 403–433.
- Cardoner N, Soria V, Gratacos M, et al. (2013). Val66Met *BDNF* genotypes in melancholic depression: Effects on brain structure and treatment outcome. *Depress Anxiety* 30, 225–233.
- Changasi AH, Shams TA, Pouget JG, and Müller DJ. (2014). Genetics of antipsychotic drug outcome and implications for the clinician: Into the limelight. *Transl Dev Psychiatry* 2, 24663–24677.
- Chen R, Mias GI, Li-Pook-Than J, et al. (2012). Personal omics profiling reveals dynamic molecular and medical phenotypes. *Cell* 148, 1293–1307.
- Clark SL, Souza RP, Adkins DE, et al. (2013). Genome-wide association study of patient-rated and clinician-rated global impression of severity during antipsychotic treatment. *Pharmacogenet Genomics* 23, 69–77.
- Cocchi E, Fabbri C, Han C, et al. (2016). Genome-wide association study of antidepressant response: Involvement of the inorganic cation transmembrane transporter activity pathway. *BMC Psychiatry* 16, 1.
- Crews K, Gaedigk A, Dunnenberger H, et al. (2012). Clinical pharmacogenetics implementation consortium (CPIC) guidelines for codeine therapy in the context of cytochrome P450 2D6 (*CYP2D6*) genotype. *Clin Pharmacol Ther* 91, 321.
- Dalvie S, Koen N, Duncan L, et al. (2015). Large scale genetic research on neuropsychiatric disorders in African populations is needed. *EBioMedicine* 2, 1259–1261.
- Dimitrov DV. (2011). The human gutome: Nutrigenomics of the host-microbiome interactions. *OMICS* 15, 419–430.
- Dove ES, and Özdemir V. (2015). What role for law, human rights, and bioethics in an age of big data, consortia science, and consortia ethics? The importance of trustworthiness. *Laws* 4, 515–540.
- Drögemöller BI, Emsley R, Chiliza B, et al. (2016). The identification of novel genetic variants associated with antipsychotic treatment response outcomes in first-episode schizophrenia patients. *Pharmacogenet Genomics* 26, 235–242.
- Drögemöller BI, Wright GE, and Warnich L. (2014). Considerations for rare variants in drug metabolism genes and the clinical implications. *Expert Opin Drug Metab Toxicol* 10, 873–884.
- Fabbri C, and Serretti A. (2015). Pharmacogenetics of major depressive disorder: Top genes and pathways toward clinical applications. *Curr Psychiatry Rep* 17, 1–11.
- Falcone M, Smith RM, Chenoweth MJ, et al. (2013). Neuroimaging in psychiatric pharmacogenetics research: The promise and pitfalls. *Neuropsychopharmacology* 38, 2327–2337.
- Freedman ML, Monteiro AN, Gayther SA, et al. (2011). Principles for the post-GWAS functional characterization of cancer risk loci. *Nat Genet* 43, 513–518.
- GENDEP Investigators, MARS Investigators, and STAR*D Investigators. (2013). Common genetic variation and antidepressant efficacy in major depressive disorder: A meta-analysis of three genome-wide pharmacogenetic studies. *Am J Psychiatry* 170, 207–217.
- Georgitsi M, Zukic B, Pavlovic S, and Patrinos GP. (2011). Transcriptional regulation and pharmacogenomics. *Pharmacogenomics* 12, 655–673.
- Guengerich FP. (2001). Common and uncommon cytochrome P450 reactions related to metabolism and chemical toxicity. *Chem Res Toxicol* 14, 611–650.
- Horáček J, Libiger C, Höschl K, Borzova I, and Hendrychová J. (2001). Clozapine-induced concordant agranulocytosis in monozygotic twins. *Int J Psychiatry Clin Pract* 5, 71–73.
- Hou L, Heilbronner U, Degenhardt F, et al. (2016). Genetic variants associated with response to lithium treatment in bi-

- polar disorder: A genome-wide association study. *Lancet* 387, 1085–1093.
- Insel TR. (2008). Assessing the economic costs of serious mental illness. *Am J Psychiatry* 165, 663–665.
- Insel TR. (2014). The NIMH research domain criteria (RDoC) project: Precision medicine for psychiatry. *Am J Psychiatry* 171, 395–397.
- Insel T, Cuthbert B, Garvey M, et al. (2010). Research domain criteria (RDoC): Toward a new classification framework for research on mental disorders. *Am J Psychiatry* 167, 748–751.
- Jacob KS, and Patel V. (2014). Classification of mental disorders: A global mental health perspective. *Lancet* 383, 1433–1435.
- Ji Y, Schaid DJ, Desta Z, et al. (2014). Citalopram and escitalopram plasma drug and metabolite concentrations: Genome-wide associations. *Br J Clin Pharmacol* 78, 373–383.
- Johnson J, and Weitzel K. (2016). Advancing pharmacogenomics as a component of precision medicine: How, where, and who? *Clin Pharmacol Ther* 99, 154–156.
- Kaniwa N, Saito Y, Aihara M, et al. (2010). HLA-B* 1511 is a risk factor for carbamazepine-induced Stevens-Johnson syndrome and toxic epidermal necrolysis in Japanese patients. *Epilepsia* 51, 2461–2465.
- Kessler RC, Aguilar-Gaxiola S, Alonso J, et al. (2009). The global burden of mental disorders: An update from the WHO world mental health (WMH) surveys. *Epidemiol Psychiatr Soc* 18, 23–33.
- Kumar A, Pathak RK, Gupta SM, Gaur VS, and Pandey D. (2015). Systems biology for smart crops and agricultural innovation: Filling the gaps between genotype and phenotype for complex traits linked with robust agricultural productivity and sustainability. *OMICS* 19, 581–601.
- Lohoff FW, and Ferraro TN. (2010). Pharmacogenetic considerations in the treatment of psychiatric disorders. *Expert Opin Pharmacother* 11, 423–439.
- Malhi GS, Lingford-Hughes AR, and Young AH. (2016). Antidepressant treatment response: ‘I want it all, and I want it now!’ *Br J Psychiatry* 208, 101–103.
- Martins-de-Souza D, Harris LW, Guest PC, and Bahn S. (2011). The role of energy metabolism dysfunction and oxidative stress in schizophrenia revealed by proteomics. *Antioxid Redox Signal* 15, 2067–2079.
- Mirnezami R, Nicholson J, and Darzi A. (2012). Preparing for precision medicine. *N Engl J Med* 366, 489–491.
- Mrazek DA. (2010). Psychiatric pharmacogenomic testing in clinical practice. *Dialogues Clin Neurosci* 12, 69–76.
- Myung W, Kim J, Lim S, et al. (2015). A genome-wide association study of antidepressant response in Koreans. *Transl Psychiatry* 5, e633.
- Oedegaard KJ, Alda M, Anand A, et al. (2016). The pharmacogenomics of bipolar disorder study (PGBD): Identification of genes for lithium response in a prospective sample. *BMC Psychiatry* 16, 1.
- Ozeki T, Mushiroda T, Yowang A, et al. (2011). Genome-wide association study identifies HLA-A*3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. *Hum Mol Genet* 20, 1034–1041.
- Porcelli S, Drago A, Fabbri C, and Gibiino S. (2011). Pharmacogenetics of antidepressant response. *J Psychiatry Neurosci* 36, 87.
- Ray R, Loughhead J, Wang Z, et al. (2008). Neuroimaging, genetics and the treatment of nicotine addiction. *Behav Brain Res* 193, 159–169.
- Rehman A, Awais M, and Baloch NU. (2016). Precision medicine and low-to middle-income countries. *JAMA Oncol* 2, 293–294.
- Ritchie GR, Dunham I, Zeggini E, and Flicek P. (2014). Functional annotation of noncoding sequence variants. *Nat Methods* 11, 294–296.
- Ritchie MD. (2012). The success of pharmacogenomics in moving genetic association studies from bench to bedside: Study design and implementation of precision medicine in the post-GWAS era. *Hum Genet* 131, 1615–1626.
- Rodin AS, Gogoshin G, and Boerwinkle E. (2011). Systems biology data analysis methodology in pharmacogenomics. *Pharmacogenomics* 12, 1349–1360.
- Roussos P, Mitchell AC, Voloudakis G, et al. (2014). A role for noncoding variation in schizophrenia. *Cell Rep* 9, 1417–1429.
- Sangar M, Anandatheerthavarada HK, Tang W, et al. (2009). Human liver mitochondrial cytochrome P450 2D6—individual variations and implications in drug metabolism. *FEBS J* 276, 3440–3453.
- Sangar MC, Bansal S, and Avadhani NG. (2010). Bimodal targeting of microsomal cytochrome P450s to mitochondria: Implications in drug metabolism and toxicity. *Expert Opin Drug Metab Toxicol* 6, 1231–1251.
- Schmidt D, Wilson MD, Ballester B, et al. (2010). Five-vertebrate ChIP-seq reveals the evolutionary dynamics of transcription factor binding. *Science* 328, 1036–1040.
- Shao WH, Chen JJ, Fan SH, et al. (2015). Combined metabolomics and proteomics analysis of major depression in an animal model: Perturbed energy metabolism in the chronic mild stressed rat cerebellum. *OMICS* 19, 383–392.
- Smoller JW. (2014). Psychiatric genetics and the future of personalized treatment. *Depress Anxiety* 31, 893–898.
- Stein DJ. (2014). An integrative approach to psychiatric diagnosis and research. *World Psychiatry* 13, 51–53.
- Tammiste A, Jiang T, Fischer K, et al. (2013). Whole-exome sequencing identifies a polymorphism in the *BMP5* gene associated with SSRI treatment response in major depression. *J Psychopharmacol* 27, 915–920.
- Tansey KE, Guipponi M, Hu X, et al. (2013). Contribution of common genetic variants to antidepressant response. *Biol Psychiatry* 73, 679–682.
- Tekola-Ayele F, and Rotimi CN. (2015). Translational genomics in low- and middle-income countries: Opportunities and challenges. *Public Health Genomics* 18, 242–247.
- Thompson PM, Andreassen OA, Arias-Vasquez A, et al. (2016). ENIGMA and the individual: Predicting factors that affect the brain in 35 countries worldwide. *NeuroImage*. DOI: 10.1016/j.neuroimage.2015.11.057
- Tong J, Hawi Z, Dark C, et al. (2016). Separating the wheat from the chaff: Systematic identification of functionally relevant noncoding variants in ADHD. *Mol Psychiatry* 1–10.
- Uher R, Perroud N, Ng MY, et al. (2010). Genome-wide pharmacogenetics of antidepressant response in the GENDEP project. *Am J Psychiatry* 167, 555–564.
- Vojvoda D, Grimmell K, Sernyak M, and Mazure C. (1996). Monozygotic twins concordant for response to clozapine. *Lancet* 347, 61.
- Wehmeier PM, Gebhardt S, Schmidtke J, Remschmidt H, Hebebrand J, and Theisen FM. (2005). Clozapine: Weight gain in a pair of monozygotic twins concordant for schizophrenia and mild mental retardation. *Psychiatry Res* 133, 273–276.

- Weinberger DR, and Radulescu E. (2016). Finding the elusive psychiatric “lesion” with 21st-century neuroanatomy: A note of caution. *Am J Psychiatry* 173, 27–33.
- Whiteford HA, Degenhardt L, Rehm J, et al. (2013). Global burden of disease attributable to mental and substance use disorders: Findings from the global burden of disease study 2010. *Lancet* 382, 1575–1586.
- Zaraket FA, Li J, Nokkari A, et al. (2012). Systems biology, bioinformatics, and biomarkers in neuropsychiatry. *Front Neurosci* 6, 187.

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Abbreviations Used

ADR = adverse drug reaction
 BDNF = brain-derived neurotrophic factor
 COMT = catechol-O-methyltransferase
 CYP = cytochrome P450
 CYP2D6 = cytochrome P450-2D6
 DSM = *Diagnostic and Statistical Manual of Mental Disorders*
 fMRI = functional magnetic resonance imaging
 GWAS = genome-wide association study
 HLA = human leukocyte antigen
 LD = linkage disequilibrium
 LMICs = low- and middle-income countries
 MDD = major depressive disorder
 NGS = next-generation sequencing
 RDoC = Research Domain Criteria
 SSRI = selective serotonin reuptake inhibitor
 WES = whole-exome sequencing
 WHO = World Health Organization