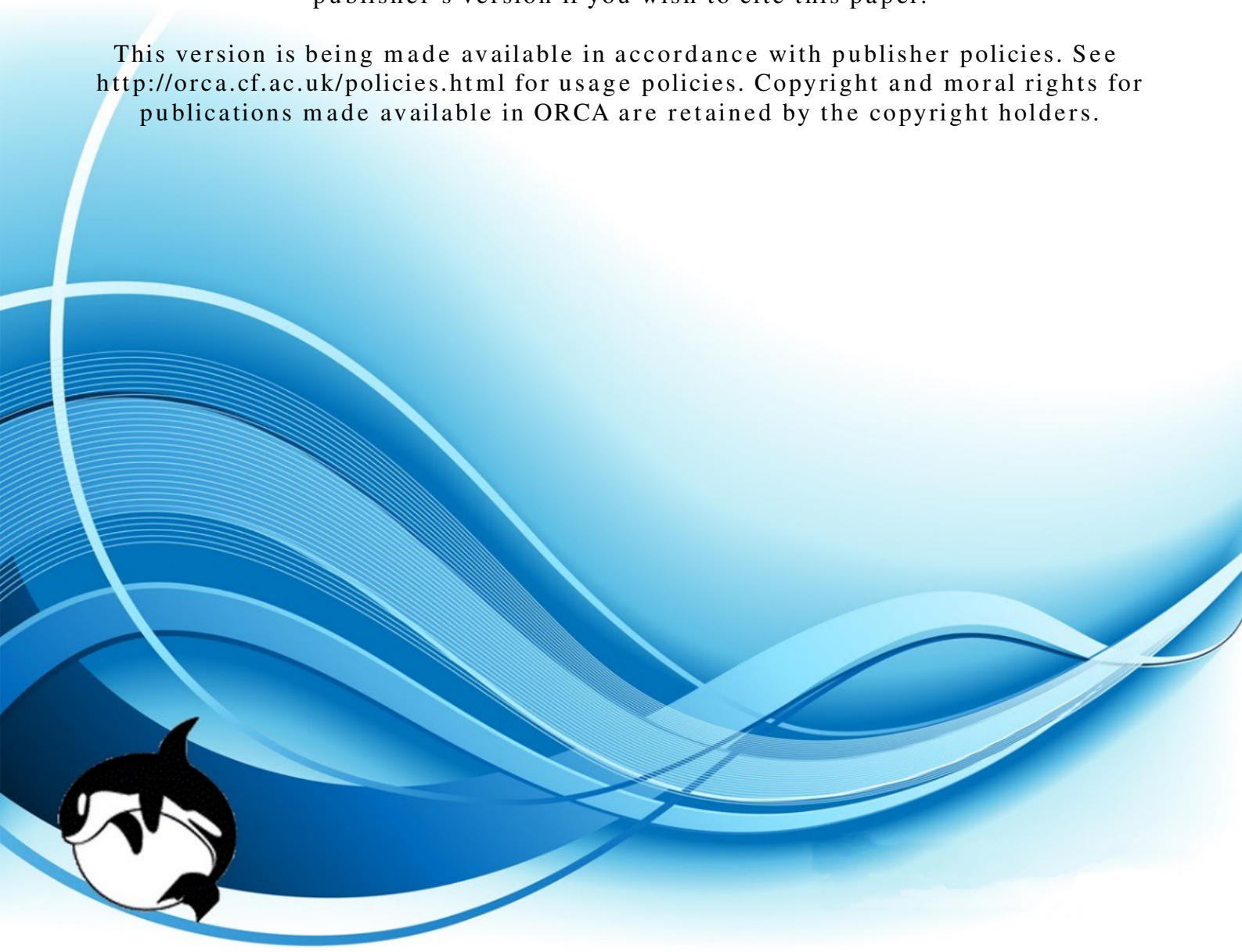


Pharmacogenomics: A road ahead for precision medicine in psychiatry

Antonio F. Pardiñas[1]; Michael J. Owen[1]*, James T. R. Walters[1].

[1] MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University School of Medicine, Hadyn Ellis Building, Maindy Road, Cardiff CF24 4HQ, United Kingdom.

***Corresponding author:**

E-mail address: OwenMJ@cardiff.ac.uk

ABSTRACT

Psychiatric genomics is providing insights into the nature of psychiatric conditions that in time should identify new drug targets and improve patient care. Less attention has been paid to psychiatric pharmacogenomics research, despite its potential to deliver more rapid change in clinical practice and patient outcomes. The pharmacogenomics of treatment response encapsulates both pharmacokinetic ("what the body does to a drug") and pharmacodynamic ("what the drug does to the body") effects. Despite early optimism and substantial research in both these areas, they have to date made little impact on clinical management in psychiatry. A number of bottlenecks have hampered progress including a lack of large-scale replication studies, inconsistencies in defining valid treatment outcomes across experiments, a failure to routinely incorporate adverse drug reactions and serum metabolite monitoring in study designs, and inadequate investment in the longitudinal data collections required to demonstrate clinical utility. Nonetheless advances in genomics and health informatics present distinct opportunities for psychiatric pharmacogenomics to enter a new and productive phase of research discovery and translation.

INTRODUCTION

Psychiatric disorders are major contributors to the global burden of disease, accounting for 19% of all years lived with disability worldwide (Rehm and Shield, 2019). The societal impact of these conditions arises from their high prevalence, with one in 5-6 adults affected annually (Baker, 2020), as well as their substantial effects on morbidity and premature mortality. Notably, the global burden of psychiatric disorders has remained high throughout recent decades (Jorm et al., 2017), in contrast to improvements seen in communicable, and other non-communicable diseases (Martinez et al., 2020; Murray et al., 2020). The reasons for the lack of progress in prevention and treatment are complex, but they include limited understanding of pathogenesis, pathophysiology and of the mode of action of existing treatments and why they are ineffective for many people. This is compounded by the inadequate provision of mental healthcare. Only 20% of individuals with common psychiatric disorders, such as depression and anxiety, have access to appropriate treatment in Europe and North America, and this "treatment gap" is likely to be even wider in low- and middle-income countries (Vigo et al., 2019).

Even among those who can access treatment, fewer than 50% will receive an "effective" therapy, broadly defined as one leading to a positive response with sustained improvement in therapeutic outcomes (De Silva et al., 2014; Wong et al., 2010). Established treatments for particular major mental health disorders also show broadly equivalent levels of effectiveness when assessed in large cohorts (Cipriani et al., 2018; Lieberman et al., 2005), and thus treatment decisions often centre around preferences based on generic adverse reaction profiles without knowledge of the patient's actual risks (National Collaborating Centre for Mental Health, 2014). Adverse drug reactions and lack of effectiveness are common reasons for psychiatric medication being discontinued (Legge et al., 2016), with only a minority of patients remaining on prescribed treatments for the full therapeutic course (Jones et al., 2006; Lieberman et al., 2005). These issues are exacerbated by the requirement for long-term treatment of many patients (Demyttenaere, 2019), and together these factors result in a large

fraction of those diagnosed with major psychiatric disorders failing to benefit from current standards of care (**Figure 1A**). While this is a criticism levelled at psychopharmacological treatments (Muscatello et al., 2020), many of these same issues also apply to the evidence-based psychological treatment approaches used in psychiatry (Holmes et al., 2018).

The prescription of drugs that are ineffective or cause harmful side effects has substantial implications for individuals and the resources of health systems (Fava et al., 2017; Muscatello et al., 2020). In part, this is a reflection of the "efficacy-effectiveness gap", the disconnect between the results of randomised controlled trials ("efficacy") of interventions and their real-world performance ("effectiveness"; Eichler et al., 2011), due in large part to the limited degree to which trial participants and processes reflect clinical practise. This phenomenon is apparent in all areas of medicine, indeed meta-reviews have highlighted that drugs routinely used in psychiatry have equivalent efficacy to those used in other specialities (Huhn et al., 2014; Leucht et al., 2012). These analyses also found large individual variability in response, including frequent remission under placebo, which creates an upper bound to the efficacy of treatments when measured as means across groups of patients.

Many factors have been associated with individual differences in treatment response in psychiatric disorders (Perna et al., 2020; Stern et al., 2018) including demographics and lifestyle traits (sex, age, ancestry, body mass index, smoking habits, socioeconomic status), symptom profiles (frequency, severity and stage of illness, age at onset, comorbidities) and treatment provision (primary or secondary care, treatment adherence monitoring, concomitant prescription of other drugs or psychotherapy). Recent research has explored potential explanations behind some of these associations, such as physiological differences between sexes (LeGates et al., 2019), and variation in markers of neurobiological function affecting response to particular medications (McCutcheon et al., 2019). More specifically, genetic variation makes important contributions to variability in treatment response, as well as to the occurrence of adverse effects of medication. This raises the possibility of applying the many advances in human genomics to understand and predict individual variability in drug response, which is the aim of pharmacogenomics research.

PHARMACOLOGICAL PROCESSES AND GENOMIC VARIATION

The relationship between the dose of a drug and its effect, broadly speaking, depends upon the combined action of two sets of processes, pharmacokinetics and pharmacodynamics (Hefner et al., 2013). Pharmacokinetics ("what the body does to a drug") refers to the set of biotransformations that a drug undergoes in the body, through absorption, distribution, metabolism, and excretion (ADME) processes. Whereas, pharmacodynamics ("what the drug does to the body") refers to the physiological and biological responses caused by that drug, mostly reflecting ligand-receptor occupancy and downstream effects. Pharmacogenomics seeks to identify the genetic basis of these processes, often with research targeted to specific drugs or drug-gene pairs (Krebs and Milani, 2019; Roden et al., 2019). This discipline was pioneered by the work of Friedrich Vogel, Arno Motulsky and Werner Kalow in the late 1950s and early 1960s, with important tenets, such as the transethnic variability of drug metabolising enzymes, becoming fully established by the 1980s (Müller and Rizhanovsky, 2020).

Early pharmacogenomics research was based upon the "candidate gene" analysis framework consolidated in the 1990s, which rapidly generated many drug-gene associations (Evans and

Johnson, 2001). Several of these advanced into Phase 1 clinical trials, sparking the interest of a pharmaceutical industry that saw pharmacogenomics as a potential solution to the "innovation deficit" of traditional drug development pipelines (Norton, 2001). However, as in other areas of genomic research, there were difficulties in replicating the results of candidate gene studies, a consequence of their limitations in establishing causal variants and controlling for genomic confounders (Peters et al., 2010; Walgren et al., 2005). Thus, few of the initial discoveries fulfilled the criteria necessary to demonstrate clinical utility, prompting the creation of international consortia to explicitly assess the actionability and therapeutic potential of pharmacogenomic evidence, such as the Dutch Pharmacogenetics Working Group (DPWG; Swen et al., 2008) and the Clinical Pharmacogenomics Implementation Consortium (CPIC; Relling and Klein, 2011). Despite criticisms of the field at that time (Ioannidis, 2013), the work of these consortia, together with the move towards genome-wide association studies (GWAS) as standard hypothesis-generating experimental designs, contributed to the consolidation of pharmacogenomics as one of the pillars of the "precision medicine" model of healthcare in the last decade (Hicks et al., 2019).

Currently, more than 1,000 basic research studies in pharmacogenomics are published every year (Müller and Rizhanovsky, 2020), and 165 guidelines on the use of pharmacogenomic information for specific drug-gene pairs are available in the PharmGKB repository as of May 2021, including 33 relevant for psychiatry (Bousman et al., 2021). Recommendations in these guidelines are derived from a thorough process of literature curation and standardised variant annotation (Barbarino et al., 2018), partially aligned with guideline standards from the US National Academy of Medicine (Caudle et al., 2014). They are increasingly recognised by industry and regulators in drug development and labelling processes (Schuck and Grillo, 2016; Yin and Vandell, 2019). PharmGKB guidelines also assess the quality of supporting evidence and, when indicated, make genotype-based prescribing recommendations (Relling et al., 2020). However, these guidelines have not been widely adopted by clinical services, including those providing psychiatric care, as in most cases the trials needed to demonstrate their clinical utility to the standards required by public healthcare settings have yet to be carried out (Caudle et al., 2014; Russell et al., 2021). Additionally, important financial and regulatory constraints are still being explored, particularly those regarding the circumstances in which to implement genetic testing and who should cover its cost (Mitropoulou et al., 2020).

GENOMICS OF DRUG METABOLISM

The majority of the established drug-gene pairs and associated dosing guidelines relate to pharmacokinetic effects (particularly drug metabolism). Due to the difficulty of directly studying molecular interactions *in vivo*, pharmacological studies of large cohorts typically rely on measuring markers of drug metabolism and response. Treatment outcomes are sometimes used as proxies, particularly if the aim of the study concerns specific treatment effects (Grady and Ritchie, 2011; Roden et al., 2019), but the plasma concentration of an active drug metabolite offers advantages over other proxy measures since it's a relatively close marker to biochemical pathways and a potential correlate of drug efficacy (Hefner et al., 2013). Metabolite concentrations can be also be analysed as precise quantitative phenotypes, and thus are well-suited to the statistical methods optimised for genetics and genomics studies (Grady and Ritchie, 2011; Suhre et al., 2011). This perhaps underlies the productivity of this line of research, which is responsible for most of the current drug-gene associations with potential

clinical applicability in psychiatric settings (**Table 1**; Bousman et al., 2021) and in general (Tornio and Backman, 2018).

The genes robustly identified by pharmacogenomics research, in both psychiatry and general medicine, include about 40% of the 266 human protein-coding genes that are known to be implicated in ADME processes (Tilleman et al., 2019), though this definition can be expanded to around 800 if known drug targets are also considered (Schärfe et al., 2017). ADME genes appear consistently in candidate gene studies of pharmacogenomic traits, although it is reassuring that they also often emerge through data-driven approaches, such as GWAS. Indeed, genome-wide assays are often enriched for these "usual suspects", and signals can be as narrow as to implicate individual alleles or SNPs within these genes (Loukola et al., 2015; Pardiñas et al., 2019). These pharmacogenomic studies also benefit from decades of *in vitro* and model organism studies, which have already clarified the role of many of the causal genes and pathways in ADME phenotypes (Neavin et al., 2016). They have also allowed the definition, for a restricted set of drug metabolising enzymes, of standardised metrics of protein function ("activity scores"). Such scores allow individuals to be classified into the rapid-poor metaboliser spectrum for specific drugs (Caudle et al., 2017) and have formed the basis of many pharmacogenetic prescribing guidelines including those for psychiatry (**Table 1**).

The fact that a small number of genes have been robustly implicated from analyses of relatively small samples in pharmacogenomic studies sits in contrast to large-scale genomic studies of complex traits and disorders which identify an ever-expanding number of associations reflecting polygenic genetic architectures (Visscher et al., 2017). This can be explained by the underlying relationship between genetic variation and pharmacokinetics, particularly drug metabolism. In general, the genomic studies of endogenous and xenobiotic metabolism have revealed fewer genetic determinants than equivalent studies in complex traits, with most metabolites showing oligogenic architectures characterised by a few common variants of large effect size (Timpson et al., 2018). Heritability estimates, however, are similarly large (Lauschke and Ingelman-Sundberg, 2019), which raises the possibility that genetic predictors of drug metabolism could be created using relatively small sets of genomic markers as recently shown possible by research on other oligogenic traits (Zhang et al., 2020).

The apparent simplicity of the genomic architecture of these pharmacogenomic traits is complicated by challenges in fully characterising the genomic variation within these genes. Several important ADME genes, of which the best known is probably CYP2D6, harbour structural variation that is not well-captured by standard genotyping protocols (Lauschke et al., 2017). As a consequence of this, insights and results from much of the early literature on these genes have to be cautiously interpreted (Yang et al., 2017), which compromises applications and trials in clinical settings (Cavallari et al., 2019). It should be noted that complex genomic regions within ADME genes are not uncommon, and originated from the evolution of gene clusters through duplication and homologous recombination (Meech et al., 2012; Thomas, 2007), favouring a genomic environment with relaxed natural selection where novel mutations tended to drift (Hovelson et al., 2017). Thus, despite successes in identifying potential causal variants from the analysis of metabolite concentrations and related metrics, pharmacogenomic traits are likely to still have substantial unexplained ("hidden" or "missing") heritability, which might require more complete sequencing and genotype-environment studies to be resolved (López-Cortegano and Caballero, 2019).

PHARMACOGENOMICS OF ADVERSE DRUG REACTIONS

Responses to drugs can include unwanted side effects. The preferred term for these is "adverse drug reactions" (ADRs) when they can be confidently assigned to a specific medication. ADRs are major causes of morbidity and mortality, and genetic variation makes important contributions to the risk of developing them (Carr and Pirmohamed, 2017). Many of the drug-gene pairings within PharmGKB resources highlight ADRs that are dependent on genotype (Relling et al., 2020), and these include treatments for psychiatric disorders.

In their simplest form, ADRs can be classified as "Type A" (pharmacological) or "Type B" (idiosyncratic). Pharmacological reactions arise from an adverse response to the known mechanism of action of a drug, occur in a dose-dependent fashion, and can be understood and potentially predicted from the drug's known targets. Thus, genetic variation contributing to pharmacokinetic mechanisms can be relevant for these ADRs, and there are already several examples of highly penetrant risk alleles within genes encoding drug-metabolizing enzymes, such as CYP2C9 and bleeding on warfarin treatment, or CYP2D6 and opiate-induced respiratory depression (Carr and Pirmohamed, 2017). On the other hand, idiosyncratic ADRs are not predictable from the known pharmacological profile of the drug, are rarer (20% of all ADRs), but can be life-threatening and cause severe organ damage. Immunological processes have been implicated in many of these ADRs and the majority of guidelines relate them to polymorphisms within immune response genes, particularly the HLA system (Manson et al., 2020).

ADRs have a significant impact on health systems given their frequency and potential severity; 6–7% of hospital admissions in the UK have been attributed to ADRs and 19% of hospital inpatients experience significant ADRs (Pirmohamed et al., 2004), a rate that is likely higher in children and older people (Laatikainen et al., 2017; Sutherland et al., 2019). Their relevance in psychiatry is related to the fact that polypharmacy, the prescription of multiple medications, is common in psychiatric care and can lead to increased rates of ADRs through drug-drug interactions (Hefner et al., 2020). In addition, many psychiatric medications are so-called "dirty drugs", having actions at multiple receptor targets with associated broad adverse effect profiles (Agid et al., 2007; Caraci et al., 2017). This is a counterpart to the classic idea of "magic bullet" drug development, whereby single-target drugs would improve treatment by minimising adverse effects. This approach has not yet led to advances in psychiatric treatment (Roth et al., 2004), which raises the question of whether the multi-target action of many medications may be central to their effectiveness (Ramsay et al., 2018).

These observations highlight the potential for developing prediction algorithms for ADRs to benefit patient safety and resource utilisation. Medications with pharmacogenomic indications, in which genomic data could be used to prevent or minimise ADRs, are slightly overrepresented among those prescribed in routine care (Barbarino et al., 2018), and it has been estimated that at least 65% of primary care patients are exposed to them over a 5-year period (Kimpton et al., 2019). The utility of this information is now being examined at scale, with the prospect of standardised pharmacogenomic variation being stored on routine health records and incorporated to alert and monitoring systems to guide prescribing decisions (Denny and Collins, 2021; Erika et al., 2017; Relling et al., 2020).

RISE, FALL AND PLATEAU OF PSYCHIATRIC PHARMACOGENOMICS

There is a long history of pharmacogenomic studies of medications for mental health conditions, and the specific drug-gene pairs that have been identified from this work have been comprehensively reviewed elsewhere (Cacabelos, 2020; Lam and Someya, 2019). Early findings established effects of genetic variation in ADME enzymes on psychotropic medications (Coutts et al., 1999), prompting a large body of subsequent work which, despite its potential, has largely failed to be translated to clinical impact. In 2008, the field seemed to be "at the forefront of the use of pharmacogenomics in medicine" together with oncology, and five genetic tests were being marketed in the USA to support psychiatric treatment management (de Leon, 2009). However, these tests were soon discontinued or became outdated due to uncertain clinical utility and low consumer uptake, and have not been adopted by healthcare providers (de Leon, 2016). This experience reflects the paucity of research to support the clinical use of pharmacogenetic testing and reinforces the need to further develop the evidence base for the practical relevance of pharmacogenomic testing in common psychiatric conditions, including major depression and schizophrenia, and the limitations of commercial tests in providing the levels of reliable guidance demanded by clinicians, patients and regulators (Rakesh et al., 2020).

A major barrier to the implementation of pharmacogenomic testing in psychiatric care has been the lack of primary data of therapeutic utility for the vast majority of drug-gene pairs (Bousman et al., 2021). This is a prerequisite for the commissioning of new tests or interventions in many healthcare settings, as is the need to demonstrate health economic benefits. Advances are being made in this area with the advent of psychiatric clinical trials assessing the impact of testing for specific drug-gene pairs on psychiatric outcomes, although to date these have failed to demonstrate major therapeutic advantages. For example, there have been substantial efforts to assess the benefits of genomic testing for the treatment of major depression (Bousman et al., 2019), a necessary first step towards the clinical adoption of these procedures (**Figure 1B)**. The largest trial of this kind, GUIDED, did not show a beneficial effect of pharmacogenomic guided prescribing for its primary outcome of symptom improvement against antidepressant standard-care (Greden et al., 2019). Results on treatment response and remission outcomes were more positive, although these were secondary analyses that have been questioned on conceptual and statistical grounds (Goldberg, 2019; Smith and Nemeroff, 2020). This lack of supportive evidence, coupled with the negative results of other studies (Perlis et al., 2020; Zeier et al., 2018), underlies the lack of support from the FDA, CPIC or DPWG for all current claims of genetic markers as potential predictors of antidepressant response or indeed any other pharmacodynamic outcome (Bousman et al., 2021). Nonetheless, all these organisations currently recognise that pharmacogenomic variation could be of relevance for antidepressant therapeutic management mainly due to its effects on pharmacokinetics (Bousman et al., 2021). This avenue, explored but not found significant in GUIDED, has however shown some promising results in recent prospective trials conducted within small-scale clinical settings (Papastergiou et al., 2021).

In terms of healthcare impact, the most effective pharmacogenomic intervention in psychiatry is currently the assessment of rare HLA-B alleles for prevention of Stevens-Johnson syndrome and toxic epidermal necrolysis caused by carbamazepine, an anticonvulsant now most commonly used in psychiatry as a second-line treatment for bipolar disorder (Goodwin, 2003). With 77.4% sensitivity and 94.4% specificity in Han Chinese individuals, prescription changes

and screening protocols based on this finding have substantially reduced the incidence of this ADR across East Asia (Nguyen et al., 2019a; Pan et al., 2017). Similar procedures, again for carbamazepine, have been implemented outside of East Asia for genotyping HLA-A alleles to prevent hypersensitivity reactions (Phillips et al., 2018). Reflecting this evidence, in 2020 the FDA included carbamazepine and its structural analogue oxcarbazepine in its official review table of pharmacogenomic associations. To date, these are the only psychiatric drug-gene pairs labelled with explicit recommendations of pharmacovigilance informed, though not substituted, by preventative genotyping (U.S. Food and Drug Administration, 2021).

Whilst no other findings in psychiatric pharmacogenomics have achieved this level of clinical impact, cautious support is emerging for the potential utility of testing more widely. The International Society of Psychiatric Genetics (ISPG; McMahon et al., 2019) has recognised the potential benefits of the CPIC/DPWG guidelines in the prescription of certain antidepressants and antipsychotics (**Table 1**), a stance supported by a recent systematic review of CYP2C19 and CYP2D6 enzyme activity for these classes of medication (Milosavljević et al., 2020). Although these two genes are implicated to a degree in the metabolism of 80% of psychiatric medications and are increasingly recognised in regulator-approved drug labels (Müller et al., 2013; van Schaik et al., 2020), it is worth noting that many psychiatric drugs do not yet have replicated pharmacogenomic associations with these genes or indeed any other ADME gene despite the large body of basic research on this topic (Kose and Cetin, 2018). Additionally, even in well-established associations between genetic markers and drug metabolism, downstream effects on drug response or ADRs need to be explicitly evaluated, not just inferred. Difficulties in both identifying primary associations and carrying out therapeutic evaluations are related to the broad challenges of psychiatric pharmacogenomic research that we outline below, particularly around underpowered "candidate gene" designs (Kose and Cetin, 2018; Kranzler et al., 2017). These challenges are reinforced by the lack of funding for large longitudinal studies that have proven beneficial in other areas of medicine (Pirmohamed et al., 2013; The SEARCH Collaborative Group, 2008). Consequently, recent comparisons between psychiatry and general medicine, particularly oncology, have found the latter to have a clear lead in terms of immediate healthcare impact, with psychiatric pharmacogenomics remaining a promise with unrealised potential (de Leon, 2016; Kranzler et al., 2017).

In summary, while most psychiatric care is supported by the prescription of medications, psychiatric drugs are not currently effective for large numbers of those living with mental health disorders, and treatment changes and discontinuation are commonplace. A genetic basis for individual differences in both therapeutic and adverse drug responses is well established, but has not yet been translated into real-world therapeutic improvements in psychiatry. The hope that this translation is possible comes from progress in other areas of medicine, the fact that psychiatric drugs are not less efficacious than non-psychiatric medications, and the repeated successes of genomic approaches in finding robust and replicable associations for drug metabolism and ADRs. It is thus worth exploring the reasons behind this slow advance, and whether specific improvements can be made to accelerate the pace and robustness of discoveries in psychiatric pharmacogenomics. This research might improve psychiatric drug efficacy by contributing to better drug design, but it is perhaps more likely to deliver its benefits through the offering of tailored treatments within the "precision medicine" paradigm. Here, it will be important to demonstrate valid stratification of groups of patients in terms of their

response to a specific treatment (**Figure 1B**). However, treatment response can be a particularly hard concept to define in psychiatry, a limitation that has hampered research progress.

MEASURING TREATMENT OUTCOMES AND RESPONSE

Arguably the biggest challenge for psychiatric pharmacogenomics is the lack of widespread use of consistent, operationalised definitions of response to treatment. There are no diagnostic biomarkers in psychiatry, which forces diagnostic procedures to rely upon clinician assessment of subjective and observed clinical symptoms and their impact on patients' functioning. Similarly, "treatment response" is a multifaceted concept that can incorporate many features in research settings, including changes in symptoms, assessment of functional level or metrics of health service use such as admission to hospital (Sajatovic et al., 2010; Salagre et al., 2018). In the absence of surrogate biomarkers to track drug response, the methods to measure these diverse outcomes become critical to advancing pharmacogenomic research.

In many areas of medicine the measurement of whether an individual benefits from a drug is conceptualised as a surrogate of survival or other "ultimate" treatment endpoints (Woodcock, 2010). However, these are generally less applicable in psychiatry as mortality is rarely a short term outcome and is not a primary part of pathophysiology (Leucht et al., 2012). The most popular methods to measure psychiatric drug response rely on defined changes in scores of pre- and post-treatment symptom rating scales (Leucht et al., 2009). While an in-depth review of their psychometric properties is outside the scope of this article, it is worth noting that most rating scales exchange sensitivity in favour of internal consistency and applicability in diverse settings (Fava et al., 2017). Additionally, when used on their own, symptom scales largely ignore the broad impacts psychiatric treatment can have on psychological and social function, as well as quality of life (Demyttenaere, 2019).

Valid assessment of treatment outcome requires longitudinal measurement of these multifaceted elements of symptom and functional level. This requirement has been recognised in several consensus outcome definitions in psychosis (Andreasen et al., 2005; Howes et al., 2017), with equivalent initiatives also developing in depression research (Gaynes et al., 2020). Nonetheless, whilst these measures have been adopted in some clinical trials and observational research, they have not been widely used in pharmacogenomic studies.

The majority of recommendations for the assessment of treatment response have relied on data from the prospective measurement of symptoms and functioning. Other initiatives have defined therapeutic outcomes by applying retrospective assessment of clinical records, notably for lithium treatment in bipolar disorder (Grof et al., 2002), and this approach has shown its utility for observational pharmacogenomic research (Hou et al., 2016). As an important note, ADRs are not always considered as part of drug response criteria (Jordan et al., 2018) despite the fact that they are often primary causes of treatment discontinuation (Lahijani and Harris, 2017; Legge et al., 2016). The standardisation of phenotypic definitions of ADRs has benefitted other areas of pharmacogenomic research by aiding replication and supporting accurate meta-analyses and psychiatry could benefit from similar initiatives (Carr and Pirmohamed, 2017). An alternative approach used in pragmatic trials has been reliance on all-cause treatment discontinuation as a primary outcome measure of medication response, given its ability to capture both the efficacy and tolerability of medications (Kahn et al., 2008; Lieberman et al., 2005).

A final crucial aspect in defining response is the assessment of treatment adherence. Whilst adherence can be assessed through patient self-reports or information on health records, for example prescription refills (Rossom et al., 2016; Sajatovic et al., 2010), the gold standard remains the measurement of serum or plasma levels of the drug. Many drug response analyses are not conducted in parallel with therapeutic drug monitoring (TDM) or serum level measurements, and thus lack a biochemical perspective that permits insights into drug metabolism, as well as confirmation of adherence (Hiemke, 2016). The integration of this information into consensus measures has already been recommended by several reviews on major psychiatric disorders (Fornaro et al., 2018; Gadad et al., 2018; Lally and Gaughran, 2019). Furthermore, the inclusion of ADRs and drug metabolism into treatment response measurements would result in more robust and generalisable evidence in psychiatric treatment research by following the triangulation principle that has been widely successful in epidemiological studies (Lawlor et al., 2017).

In summary, in order to advance pharmacogenomics research, operationalised definitions of treatment response are required that incorporate measures of symptomatic and functional change, ADRs and adherence, ideally through measurement of serum levels. This would allow the dissection of treatment response into its pharmacokinetic and pharmacodynamic elements which are currently conflated in much treatment response research. Such developments would help advance the investigation of the complex biological and clinical landscape underlying drug effectiveness (Nordon et al., 2016), with downstream benefits for genomic and epidemiological research seeking to elucidate causal mechanisms.

THE (A)TYPICAL STORY OF CLOZAPINE

The results of extensive research on the second-generation (or “atypical”) antipsychotic clozapine illustrate many of the challenges and opportunities to advance psychiatric pharmacogenomics research. Clozapine is the only evidence-based medication for treatment-resistant schizophrenia, a condition affecting up to a third of those diagnosed with this disorder (Flanagan et al., 2020; Siskind et al., 2021). It is efficacious in around 40% of treated individuals, with greater effectiveness if administered early in the course of the disorder, but it is widely underutilised due to the perceived complexity of its prescribing (Remington et al., 2016), including a gradual titration period which requires careful physical monitoring (Stanworth et al., 2012). Whilst there can be multiple dose-related ADRs, the most prominent adverse effect is a rare blood dyscrasia which can escalate to agranulocytosis, a frequently fatal loss of white blood cells (De Berardis et al., 2018). The unpredictability of this idiosyncratic reaction, which affects less than 1% of treated individuals, prompted the establishment of recurrent blood monitoring services, which have to be used by all those prescribed clozapine (Nielsen et al., 2016). Among several other ADRs, weight gain is common and frequently severe (Flanagan et al., 2020), and sedation constitutes the main reason for voluntary treatment discontinuation together with lack of monitoring compliance (Legge et al., 2016). The search for pharmacogenomic markers to facilitate the management of clozapine-treated individuals and lighten the burden of routine blood monitoring has been an explicit research goal for many years (Arranz et al., 2000; Legge and Walters, 2019; Lieberman et al., 1990), although the relationships between treatment efficacy, side effects and clozapine pharmacokinetics are still unclear (Mauri et al., 2018).

Clozapine undergoes first-pass metabolism in the liver in which up to 90% of the drug is converted to norclozapine (N-desmethylclozapine). This reaction is mediated primarily by the CYP1A2 enzyme, though CYP3A4 and CYP2C19 can also act as catalysts. The main design chosen by clozapine pharmacogenomic studies follows this pathway (**Figure 2**), tracking the plasma concentrations of clozapine and norclozapine in treated individuals, and genotyping or sequencing the exonic segments of the genes coding the aforementioned enzymes and perhaps a few others. Results of these "candidate" studies have accumulated during the past two decades but have led to inconsistent findings (Li et al., 2018), potentially contributing to erroneous pharmacogenomic guidance (Rahman et al., 2017) and have been unsupported by recent GWAS in larger samples (Pardiñas et al., 2019; Smith et al., 2020).

Hampering advances in this field is uncertainty around the biological mechanisms responsible for the efficacy and adverse effect profile of clozapine, and there is still debate about whether norclozapine is itself of any pharmacological relevance (Hellman et al., 2016; Nucifora et al., 2017). Additionally, the first-pass metabolism of clozapine leads to a secondary compound, clozapine N-oxide, that has rarely been studied in this line of research. This is likely because its plasma concentrations are not often assayed for monitoring treatment adherence, which is the main clinical use of clozapine and norclozapine TDM (Flanagan et al., 2020). Nevertheless, high clozapine doses can promote the formation of clozapine N-oxide, which is capable of interacting with a broad array of neurotransmitter receptors (Diaz et al., 2014). Furthermore, all clozapine metabolites can cross the blood-brain barrier through a yet-unknown transporter (Dickens et al., 2018; Hellman et al., 2016), participating in further biological pathways which are poorly understood. While these would be arguably the most relevant processes to study particularly in a genomic setting (McMillan and Tyndale, 2018), research is still scarce as directly measuring the amount of active clozapine in the *in vivo* brain is currently impractical outside of animal models, and predictive chemoinformatics algorithms are still of limited application (Wong et al., 2019).

In summary, despite unparalleled effectiveness and after 30 years of intense research, clozapine remains a drug for which the active metabolite, site and mechanism of action remain unknown, demonstrating the challenges of moving from informative pharmacogenomic research studies to achieving actionable or clinically translatable evidence (Cremers et al., 2012). While by terminology it is an "atypical" antipsychotic, these knowledge gaps and translational challenges are typical of many other psychiatric drugs, limiting the advance of therapeutic developments (Alavijeh et al., 2005; Kose and Cetin, 2018). Nonetheless, in the last decade, there have been significant advances in our knowledge of clozapine's metabolism and the origin of its adverse effect profile through the international application of unbiased genome-wide methods to routinely collected samples with clear phenotypic definitions (Goldstein et al., 2014; Legge et al., 2017; Pardiñas et al., 2019; Smith et al., 2020). For these insights and derived findings to advance research into the pharmacogenomics of treatment response, they will have to be explored further at scale. As obtaining high-quality data from large samples using traditional methods (i.e. personal follow-up) can be very costly and time-consuming, developing and consolidating population-scale phenotyping methods is an avenue with immense potential to advance psychiatric pharmacogenomics research (Smoller, 2018).

RESEARCH WIDELY, IMPLEMENT LOCALLY

Advances in health informatics have made possible the routine collection, storage and analysis of electronic health records (eHRs) within healthcare systems, leading to this area of research becoming another pillar for the "precision medicine" approach (Denny and Collins, 2021). Datasets based on eHRs offer the potential for research at the level of the population, promising representativity and real-world relevance beyond the ascertainment and inclusion biases that have hindered clinical research to date. The integration of genomic data into eHRs offers many benefits but also challenges (Grebe et al., 2020), although pharmacogenomic alleles were some of the earliest data to be incorporated into routine records (Abul-Husn and Kenny, 2019). In addition to the potential utility of easily accessible pharmacogenomic variants to guide treatment decisions (**Figure 1C**), the longitudinal real-world phenotypes from eHRs could also become invaluable for pharmacogenomic research. As well as the availability of detailed prescribing information and therapeutic drug monitoring results, eHR data could help define treatment response, particularly in psychiatry where much of the relevant data is stored in free-text narrative notes (Aaslestad, 2016). While the analysis of clinical notes, and raw text in general, has traditionally been considered difficult, methodological advances in Natural Language Processing (NLP) and Artificial Intelligence give grounds for optimism and can feasibly unlock this data for clinical research purposes (Jackson et al., 2017). This would not, however, avoid the presence of confounders and biases, which could stem from patient, clinician or even healthcare system factors (Dueñas et al., 2020). Addressing these difficulties should take advantage of both the population-wide scale of clinical databases and the multidisciplinary nature of eHR-based research (**Figure 3**), as both open up opportunities for identifying these problems rapidly and early, as well as exploring solutions in which data curation and quality control algorithms are informed by clinical expertise (Rees et al., 2019).

Currently, several worldwide biobanks are working on incorporating information from eHRs into drug-specific pharmacogenomic studies or clinical trials (Hoffman et al., 2020), and recent results from Danish, British and Estonian Biobanks support previous observations that 90%-99% of the population has at least one clinically actionable pharmacogenomic allele (Lunenburg et al., 2021; McInnes et al., 2020; Reisberg et al., 2018). In psychiatry, the value of routinely collected phenotypes has been demonstrated by studies examining the antidepressant escitalopram (Jukić et al., 2018) and the antipsychotics aripiprazole and risperidone (Jukić et al., 2019), performed in thousands of records from a therapeutic drug monitoring service. This research used drug switching as one of its outcomes (referred to as "therapeutic failure", equivalent to all-cause treatment discontinuation referred to above), and showed that individuals with certain CYP2C19 and CYP2D6 activity scores (ultrarapid and poor metabolisers) were more prone to a change of prescription early in the course of treatment. Importantly, this happened despite clinicians commonly altering doses during treatment in reaction to drug response, thus not being completely agnostic of metabolism and other underlying pharmacological processes. Similar studies conducted on child and adolescent cohorts replicated these results (Aldrich et al., 2019; Jallaq et al., 2020), suggesting that genetic variants determining enzyme activities could be beneficial in clinical decision-making even if non-genetic factors, such as the co-prescription of enzyme inhibitors, are already considered. While none of these experiments were explicitly designed for causal inference, complementary data of metabolite concentrations on those same individuals supported the hypothesis that drug switching was prompted by insufficient clinical response or the appearance of adverse effects. This triangulation and replication of evidence, based on a broad but consistently defined

treatment outcome, has now become part of pharmacogenomic guidelines for these medications (Bousman et al., 2021) and serve as exemplars for the field. While this is only the first step on the long road to eventual healthcare application, it demonstrates the willingness of the psychiatric pharmacogenomics community to embrace new findings based on robust research.

Clinical trials, particularly randomised controlled trials (RCTs), are the gold standard experimental designs to evaluate the robustness of research findings and, ultimately, the utility of interventions derived from them (Lawlor et al., 2017). The design of pharmacogenomic RCTs is not straightforward and financial incentives to support them are not always apparent (Russell et al., 2021), which has likely limited the scale of these studies in psychiatry. In fact, most of those carried out to date have been industry-sponsored, focusing on antidepressant use and following the more numerous PharmGKB guidelines for these medications (**Table 1**). A recent synthesis of this RCT evidence, including the GUIDED trial discussed before, showed that individuals who receive genotype-guided drug dosing are 1.71 times more likely to achieve remission than those on standard care (Bousman et al., 2019), although the context of these findings needs to be considered in light of frequent multiple secondary outcomes and post-hoc analyses undertaken as part of the primary research studies. Furthermore it is worth noting that several of these trials recruited only participants with prior inadequate treatment response, although there is little reason to think that the benefits of pharmacogenomics will be restricted to this patient group. Basic research to demonstrate this wider utility could explore, for example, the stratification of patient cohorts by treatment response or outcome (**Figure 3**), which could result in further insights regarding the genetic basis of these traits (Fabbri et al., 2021).

The declaration of a drug-gene association as therapeutically useful, even within regulator-approved product labelling, does not ensure its adoption into routine clinical work (van Schaik et al., 2020). Importantly, pharmacogenomic guidelines do not advise on which therapeutic situations, if any, should prompt a clinician to order a genetic test, instead working as "decision-support tools" when testing is already available in a particular healthcare setting (McMahon et al., 2019). This is still uncommon and can result in substantial public and private costs and implementation challenges, which at the moment are being explored in health systems across the world (Krebs and Milani, 2019). The application of these tests and the need for patient support in the form of counselling, as well as other resource implications, are yet to be fully assessed within psychiatry (Moldovan et al., 2019). Recent surveys show that psychiatrists are generally accepting of incorporating pharmacogenomic information in their routine clinical work, though they also recognise that their training is likely inadequate to take on the added responsibilities that this would entail (Ward et al., 2019). Public perceptions, on the other hand, seem to be more cautious and mostly interested in the effects test results could have on clinical decisions (Liko et al., 2020). Responding to these views requires psychiatric pharmacogenomics to be implemented in a multidisciplinary way, involving psychiatrists, genetic counsellors, pharmacists, and patients, with a strong emphasis on outreach and educational practices (Hicks et al., 2019). The experience of some clinics applying these principles shows that local pharmacogenomic support services can sustainably contribute to psychiatric community healthcare (Arwood et al., 2020; Dunnenberger et al., 2016), effectively reducing the amount of trial-and-error needed to find efficacious medications in a sizeable

proportion of individuals. Similar outcomes have been obtained, though not specifically in psychiatry, by integrating pre-emptive genetic testing services into existing clinical pharmacy frameworks (Thornley et al., 2021). Thus, it becomes plausible that the development and adoption of these specialist services could act as the gateway through which pharmacogenomics knowledge becomes integrated into the psychiatric standard of care (**Figure 1A**, **Figure 1B**), revealing a road from "precision medicine" into "precision psychiatry".

PHARMACOGENOMIC PHENOTYPES: SIMPLE TRAIT GENOMICS?

In basic science settings, the next stage of pharmacogenomics research is likely to be focussed on ascertaining rare and structural genomic variation primarily within key ADME proteins (**Figure 2**), and ideally in diverse worldwide populations to fully characterise pharmacogenomic variation across ancestries (Lauschke and Ingelman-Sundberg, 2019; Schwarz et al., 2019). However, rare variant associations can require novel effect annotations, complex sequencing protocols and larger sample sizes than GWAS to achieve strong statistical support, which also complicates the evaluation of their impact in RCT settings and for clinical implementation (van Schaik et al., 2020). Nonetheless, as we have outlined, we believe that confronting these challenges will help demonstrate biologically-valid strata within many of the complex, heterogeneous psychiatric disorders, and thus invigorate mechanistic research to identify the causal basis of treatment response. Whilst this may appear more tractable for pharmacogenomic phenotypes, given their relatively simpler genetic architectures, the key hurdles of human genomics research remain particularly in moving from genetic association to biological understanding, supporting the need for functional genomic and biological experimental follow up (**Figure 3**). A recent cautionary example from the analysis of a diabetes biomarker shows how a putatively causal variant in a membrane transporter ended up being a confounded signal from an unrelated population-specific blood trait (Chai et al., 2020). Without similar and careful evaluations, genomic studies are vulnerable to attempting to derive causal mechanisms from incomplete information on gene function, tempted by the "narrative potential" of the human genome (Goldstein et al., 2013). Lack of mechanistic follow-up on pharmacogenomic studies could be partly behind the current heterogeneity seen on genetic testing panels, which use a variety of SNPs and sequence variants to call the same alleles or enzyme activity scores (Tilleman et al., 2019). This is an issue in both clinical and research settings, as it further complicates the accurate determination of metaboliser status in some particularly complex genes, such as CYP2D6, risking inaccurate results if panels lacking the appropriate coverage of structural variants are used (Jarvis et al., 2019). Finally, resolving genomic associations into single or sets of putatively causal markers would allow for using statistical approaches such as Mendelian Randomisation (MR) to facilitate the design of downstream biological experiments and clarify the relationships between different metabolic traits (Tin and Köttgen, 2020). If enough potentially causal variants are available, this latter use could help in the identification of potential drug-drug interactions at the pharmacokinetic level (Pardiñas et al., 2019), which are an important cause of ADRs in psychiatric pharmacotherapy (Hefner et al., 2020).

Though these considerations pertain to pharmacokinetic phenotypes, they do not necessarily apply to the analysis of pharmacodynamic outcomes, including drug response, which may well have more complex, polygenic genetic architectures given their multifactorial aetiology

(Roden et al., 2019; Rohde and Kristensen, 2020). Robust pharmacogenomic analyses of response to psychiatric drugs are pressingly needed, as no replicated pharmacodynamic associations have yet been found (Bousman et al., 2021). Indeed it has been recently argued that the focus of new genomic studies should be disease outcomes, rather than the presence of disease as traditionally assayed with case-control experimental designs, if such studies are to deliver the goal of target identification and improved therapeutics (Paternoster et al., 2017). The field of depression research has progressed this idea by extensively exploring mechanisms behind associations between genes in the hypothalamus-pituitary-adrenocortical system and treatment response (Ising et al., 2019; O'Connell et al., 2018). More widely, a retrospective study has shown that pharmacodynamic variants on genes encoding drug targets are predictive of ADRs affecting specific organ systems (Nguyen et al., 2019b). There is also preliminary evidence that rare genetic variation could be associated with differential drug response, supporting the use of mutation burden analyses to highlight pharmacodynamic genes (Wolking et al., 2020). This approach is increasingly tractable with the advent of whole-exome and whole-genome sequencing but again requires well-characterised samples stratified for response and non-response. Another interesting avenue is that drug metabolism, rightly considered a strong mediator of drug response, could also act as a moderator in certain cases. This would manifest as the pharmacogenomic effect sizes of variants in the targets of a given drug depending on the activity of relevant metabolic enzymes (Baranova et al., 2017). Needless to say, very large samples would be needed to detect such dependencies with reliability, of at least four times the size needed to detect the main pharmacogenomic effects (Brookes et al., 2004). A way of partially addressing this scenario in more limited conditions could be to include predictors of drug metabolism, such as phenoconversions, as part of drug response analyses, because the ignorance of these is known to hinder the discoverability of pharmacogenomic markers (Matthaei et al., 2016). Other predictors could also be genomic variants themselves or composite markers, inspired by the growing body of literature on genetic predisposition in psychiatry and the potential benefits for research of sample stratification in polygenic extremes (Murray et al., 2021). While these holistic experimental designs are less common than other approaches, they could be facilitated by the ongoing development of health informatics algorithms to exploit routinely-collected eHRs (Hoffman et al., 2020), and would follow recent recommendations for the inclusion of more individual- and drug-related characteristics in pharmacogenomic analyses (Thorn et al., 2019).

PHARMACOGENOMICS NEEDS TO BE GLOBALLY FOCUSSED

One issue that remains a pressing concern (Denny and Collins, 2021). is the realisation that since the allele frequencies of actionable pharmacogenomic variants often differ by ancestry, their clinical use needs to be implemented in such a way as to avoid reinforcing the structural inequalities that lead to treatment gaps and health disparities among ethnic groups in many countries (Martin et al., 2017; Olivier and Williams-Jones, 2014). Increasing awareness of this issue among drug industry regulators is encouraging (Tan-Koi et al., 2019), but the research community must contribute to this discussion and to rectifying the under-representation of those of non-European ancestries in pharmacogenomic studies, a disappointing constant across medical genetics research (Mills and Rahal, 2020). It is an indictment that only 5% of pharmacogenomics research publications explicitly state the ethnicity or ancestry of their participants (Popejoy, 2019). Without these data, the reliable assessment of population-specific

pharmacogenomic effects, known in principle for at least the last four decades, is impossible. Moreover, genetic markers with strong ancestral stratification, of uncertain utility in global populations when applied to predictive tasks, can mistakenly become incorporated in genetic testing panels marketed to large amounts of individuals (Manrai et al., 2016). Thus, improved consistency in the reporting of genetic ancestry and ethnic variability is required, ideally following standardised criteria (Huddart et al., 2019), a necessity if the full potential of pharmacogenomic interventions is to be realised across the world.

CONCLUSIONS

Genomics offers two main prospects for psychiatry. First, it provides a potentially unbiased route to understanding pathogenesis and pathophysiology. Second, it can potentially provide novel predictive tests for research and clinical practice (Owen and O'Donovan, 2020). These two elements come together in pharmacogenomics, which will be central to delivering precision medicine and within it, precision psychiatry. Pharmacogenomics offers a way to improve our understanding of the metabolism, safety and efficacy of psychiatric drugs, whilst potentially contributing to their development or repurposing (Schuck and Grillo, 2016; Yin and Vandell, 2019). It will also allow us to delineate groups of individuals who could benefit from particular therapeutic strategies (Rees and Owen, 2020). Psychiatric pharmacogenomic insights are likely closer to clinical implementation than those derived from wider psychiatric genomics, given the relative simplicity of the genomic architectures of many pharmacogenomic phenotypes (particularly those of ADME traits) and their manifest clinical applicability. If psychiatry can overcome the obstacles and roadblocks described in this review and seize the opportunites offered by new technologies (**Figure 3**), we can be optimistic that the rate at which these insights are generated will increase.

ACKNOWLEDGEMENTS

AFP is supported by an Academy of Medical Sciences "Springboard" award (SBF005\1083). This work was supported by the following grants to Cardiff University: European Union's Seventh Framework Programme (279227), Medical Research Council Centre (MR/L010305/1), Program (G0800509), and Project (MR/L011794/1; MC-PC-17212).

DECLARATION OF INTERESTS

JTRW is a shareholder of Meomics Technology Ltd. JTRW and MO have received a collaborative research grant from Takeda Pharmaceuticals. Takeda played no part in the conception, design, implementation, or interpretation of this study.

Table 1: Summary of psychiatric pharmacogenomic drug-gene associations reflected in current PharmGKB guidelines, all with CPIC evidence codes "A" or "B" indicating a recommendation for genotype-guided prescribing. Original data from Bousman et al. (2021). Advice based on regulator-approved product labels is not reflected here as inconsistencies have been noted in some psychiatric drugs (van Schaik et al., 2020). Further details about PharmGKB recommendations and their adherence to evidence-based medical guideline standards are available in Caudle et al. (2014).

Note: "PM" - "Poor metabolisers"; "UM" - "Ultrarrapid metabolisers"

Medication class	Drug(s)	Biological mechanisms	Gene	Main supporting evidence
Antidepressants	Amytriptyline, citalopram, clomipramine, doxepin, escitalopram, imipramine, sertraline, trimipramine,	Pharmacokinetics	CYP2C19	Treatment discontinuation more likely in PMs/UMs
	Amytriptyline, clomipramine, desipramine, doxepin, fluvoxamine, imipramine, nortriptyline, paroxetine, trimipramine, venlafaxine	Pharmacokinetics	CYP2D6	Treatment discontinuation more likely in PMs/UMs
Antipsychotics	Aripiprazole, brexiprazole, haloperidol, pimozide, risperidone, zuclopenthixol	Pharmacokinetics	CYP2D6	Treatment discontinuation more likely in PMs
Mood stabilisers	Phenytoin	Pharmacokinetics	CYP2C9	ADRs more likely in PMs
	Carbamazepine, oxcarbazepine, phenytoin	Inmunological	HLA-A, HLA-B	HLA-A*31:01 and HLA-B*15:02 likely causal for severe ADRs
ADHD medications	Atomoxetine	Pharmacokinetics	CYP2D6	ADRs more likely in PMs

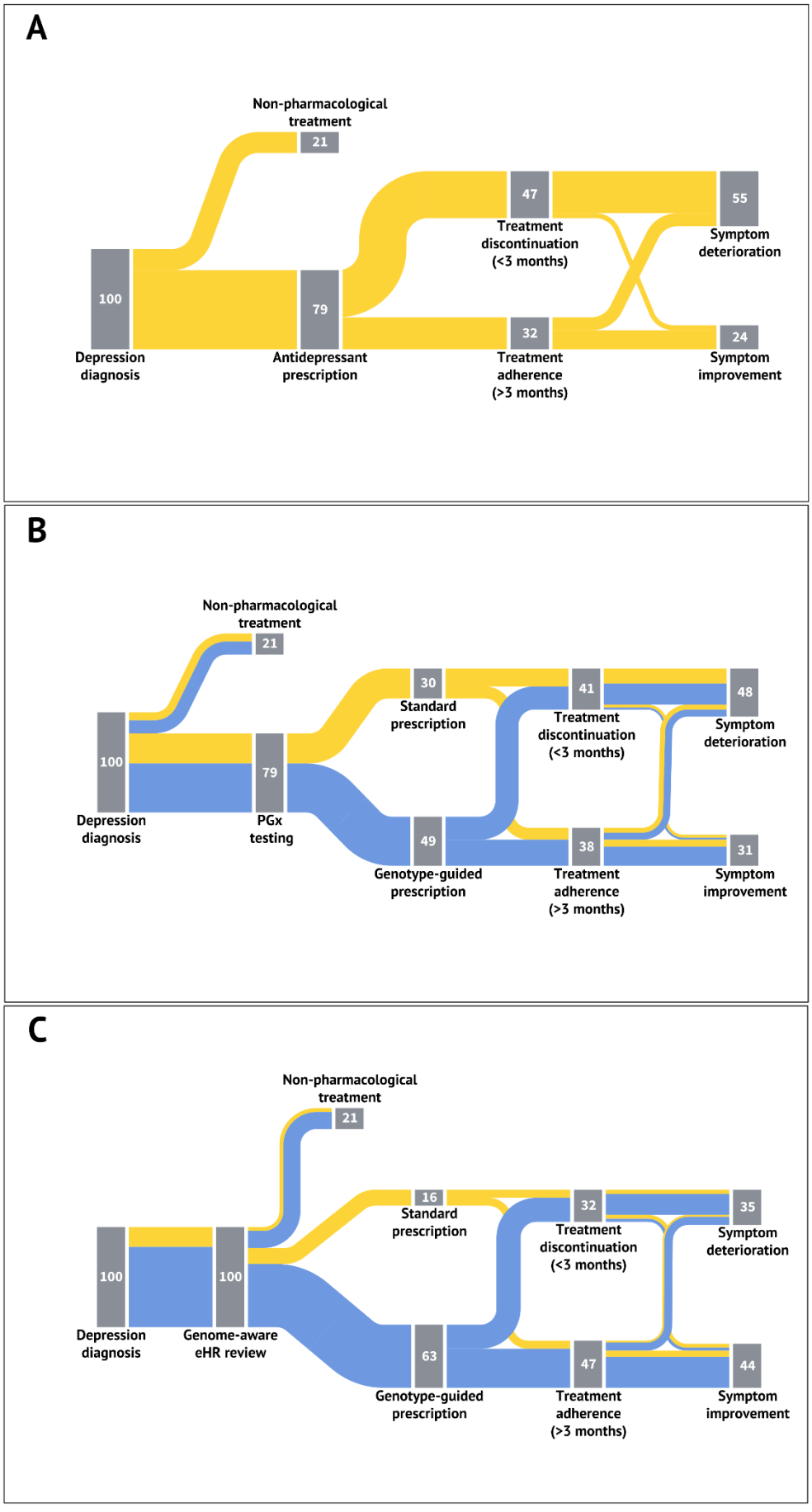

A
Non-pharmacological treatment
21
100
Depression diagnosis
79
Antidepressant prescription
47
Treatment discontinuation (<3 months)
32
Treatment adherence (>3 months)
55
Symptom deterioration
24
Symptom improvement
B
Non-pharmacological treatment
21
100
Depression diagnosis
79
PGx testing
30
Standard prescription
49
Genotype-guided prescription
41
Treatment discontinuation (<3 months)
38
Treatment adherence (>3 months)
48
Symptom deterioration
31
Symptom improvement
C
Non-pharmacological treatment
21
100
Depression diagnosis
100
Genome-aware eHR review
16
Standard prescription
63
Genotype-guided prescription
32
Treatment discontinuation (<3 months)
47
Treatment adherence (>3 months)
35
Symptom deterioration
44
Symptom improvement

Figure 1: Journey of 100 people through an initial diagnosis of Major Depressive Disorder under several current and potential healthcare models. (A) Standard genetics-agnostic care in high-income countries with extensive public health systems. (B) Near-future scenario in which the clinical implementation of psychiatric pharmacogenomics (PGx) testing has cleared all current barriers and became introduced before an eventual antidepressant prescription. (C) Future (post-2030, following Denny and Collins, 2021) scenario following the above development and in which information from electronic health records (eHR) systems is easily accessible before drug prescription and enriched with genetic data.

For reference, panel A contains the following assumptions: (i) 79% of those with a diagnosis of depression are initially prescribed pharmacotherapy (Treviño et al., 2017); (ii) at least 60% of people discontinue their first antidepressant within three months (Jung et al., 2016; Rossom et al., 2016); (iii) while the symptomatology of some individuals can improve or remit without treatment (Kato et al., 2021), 40% of people who adhere to antidepressant treatment do not obtain any therapeutic benefit (Rottenberg et al., 2018), and early discontinuation is associated with an 8-fold increase in this rate (Ho et al., 2016). Panel B follows the same proportions, additionally assuming that: (i) 62.4% of individuals in the population carry a PGx actionable variant for commonly prescribed antidepressants, as shown in blue (rate in European UK Biobank participants; Dr Gregory McInnes, personal communication); (ii) PGx testing is freely available to everyone, detects genotypes without error and clinicians always follow genotype-dosing guidelines when they are available. (iii) PGx-informed antidepressant treatment leads to a 1.7-fold improvement in therapeutic benefit (Bousman et al., 2019) and has a similar effect on treatment adherence (Jessel et al., 2020). Finally, for panel C we have optimistically considered that: (i) in eHR-driven healthcare, the therapeutic improvement of PGx-guided care increases to 2.5-fold and (ii) even standard prescriptions would be more effective (1.5-fold) than in current practice due to the use of routinely collected personal and exposure data in clinical decision-making (Denny and Collins, 2021).

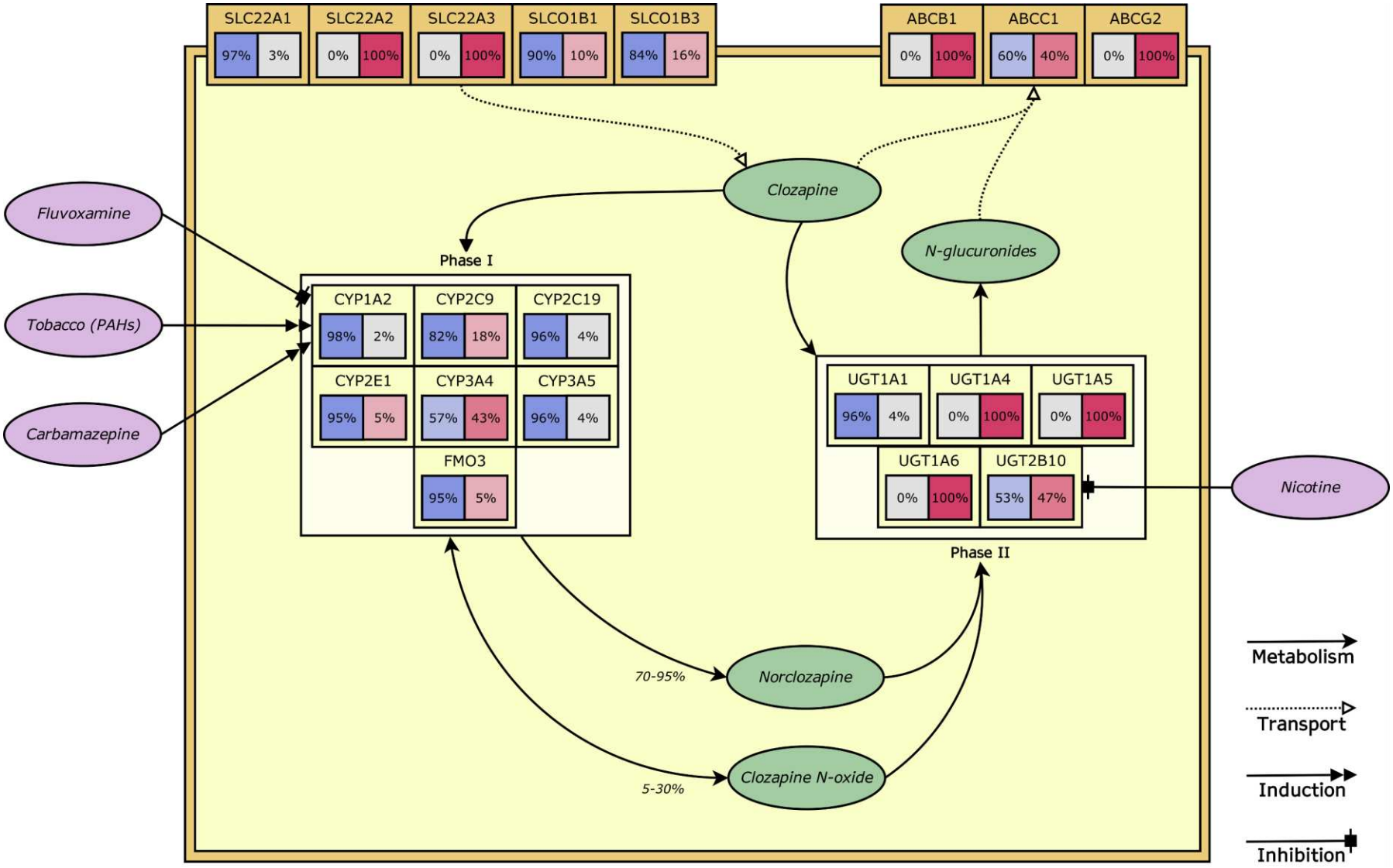

SLC22A1
97%
3%
SLC22A2
0%
100%
SLC22A3
0%
100%
SLCO1B1
90%
10%
SLCO1B3
84%
16%
ABCB1
0%
100%
ABCC1
60%
40%
ABCG2
0%
100%
Clozapine
N-glucuronides
Fluvoxamine
Tobacco (PAHs)
Carbamazepine
Phase I
CYP1A2
98%
2%
CYP2C9
82%
18%
CYP2C19
96%
4%
CYP2E1
95%
5%
CYP3A4
57%
43%
CYP3A5
96%
4%
FMO3
95%
5%
UGT1A1
96%
4%
UGT1A4
0%
100%
UGT1A5
0%
100%
UGT1A6
0%
100%
UGT2B10
53%
47%
Nicotine
Phase II
70-95%
Norclozapine
5-30%
Clozapine N-oxide
Metabolism
Transport
Induction
Inhibition

Figure 2: Schematic depiction of a hepatocyte illustrating current knowledge about the clozapine metabolic pathway, which highlights proteins identified in the latest PharmGKB review (Thorn et al., 2018) and those encoded by ADME genes found in GWAS approaches (Legge et al., 2017; Pardiñas et al., 2019; Smith et al., 2020). Following the analysis of the ExAC database by Ingelman-Sundberg et al. (2018), boxes within each protein indicate the percentage of functional genic variation expected to be common (MAF≥1%, left box, blue) or rare (MAF<1%, right box, red).

CHALLENGES

ROADBLOCKS AND LIMITATIONS

Sample collection

Manual phenotyping of small samples

Strong ancestry/ethnicity bias in recruitment

Lack of funding for longitudinal studies

Study design

Inconsistent definitions of treatment response

Limited knowledge of drug effects in brain

Focus on “candidate” genes and variants

Results

Harder replication of studies

Uncertain generalisability

Slow progress and lack of impact

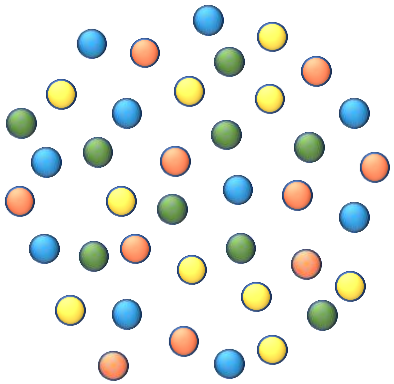
Psychiatric disorders

Multifactorial aetiology

Socioeconomic risk factors

Complex genetic architecture

Large variability in drug response



Sample collection

Semi-automatic phenotyping enabled by NLP

Population-scale routine electronic health records

Resources and opportunities to involve underrepresented populations and disorders

Study design

Operationalised drug response definitions

Pharmacological data for assessing outcomes, adverse reactions and treatment adherence

Genome/exome-wide analyses, inference of credible causal variants and biological follow-up

Results

Potentially straightforward replication

Real-world parallels favour designing RCTs

Faster progress from basic to translational research

ADVANCES AND SOLUTIONS

Figure 3: Inherent challenges of psychiatric pharmacogenomics research (center, red), its usual roadblocks and limitations (left, silver) and needed solutions to advance into the precision psychiatry framework (right, gold). Coloured spheres illustrate the demographic, genetic, and socioeconomic diversity of the population of those affected by mental illness. Note that the study designs that we advocate for future psychiatric pharmacogenomics are not limited to assessing larger samples, but contain methodological innovations which would implicitly make these samples more diverse and representative.

REFERENCES

Aaslestad, P. (2016). The patient as text: the role of the narrator in psychiatric notes, 1890-1990 (CRC Press).

Abul-Husn, N.S., and Kenny, E.E. (2019). Personalized Medicine and the Power of Electronic Health Records. Cell 177, 58-69.

Agid, Y., Buzsáki, G., Diamond, D.M., Frackowiak, R., Giedd, J., Girault, J.-A., Grace, A., Lambert, J.J., Manji, H., Mayberg, H., *et al.* (2007). How can drug discovery for psychiatric disorders be improved? Nature Reviews Drug Discovery 6, 189-201.

Alavijeh, M.S., Chishty, M., Qaiser, M.Z., and Palmer, A.M. (2005). Drug metabolism and pharmacokinetics, the blood-brain barrier, and central nervous system drug discovery. NeuroRX 2, 554-571.

Aldrich, S.L., Poweleit, E.A., Prows, C.A., Martin, L.J., Strawn, J.R., and Ramsey, L.B. (2019). Influence of CYP2C19 Metabolizer Status on Escitalopram/Citalopram Tolerability and Response in Youth With Anxiety and Depressive Disorders. Frontiers in Pharmacology 10.

Andreasen, N.C., Carpenter, W.T., Kane, J.M., Lasser, R.A., Marder, S.R., and Weinberger, D.R. (2005). Remission in Schizophrenia: Proposed Criteria and Rationale for Consensus. Am J Psychiatry 162, 441-449.

Arranz, M.J., Munro, J., Birkett, J., Bolonna, A., Mancama, D., Sodhi, M., Lesch, K.P., Meyer, J.F.W., Sham, P., Collier, D.A., *et al.* (2000). Pharmacogenetic prediction of clozapine response. The Lancet 355, 1615-1616.

Arwood, M.J., Dietrich, E.A., Duong, B.Q., Smith, D.M., Cook, K., Elchynski, A., Rosenberg, E.I., Huber, K.N., Nagoshi, Y.L., Wright, A., *et al.* (2020). Design and Early Implementation Successes and Challenges of a Pharmacogenetics Consult Clinic. Journal of Clinical Medicine 9, 2274.

Baker, C. (2020). Briefing Paper 6988: Mental health statistics for England: prevalence, services and funding (London, UK: House of Commons Library).

Baranova, E.V., Verhoef, T.I., Ragia, G., le Cessie, S., Asselbergs, F.W., de Boer, A., Manolopoulos, V.G., Maitland-van der Zee, A.H., and group, t.E.-P. (2017). Dosing algorithms for vitamin K antagonists across VKORC1 and CYP2C9 genotypes. Journal of Thrombosis and Haemostasis 15, 465-472.

Barbarino, J.M., Whirl-Carrillo, M., Altman, R.B., and Klein, T.E. (2018). PharmGKB: A worldwide resource for pharmacogenomic information. WIREs Systems Biology and Medicine 10, e1417.

Bousman, C.A., Arandjelovic, K., Mancuso, S.G., Eyre, H.A., and Dunlop, B.W. (2019). Pharmacogenetic tests and depressive symptom remission: a meta-analysis of randomized controlled trials. Pharmacogenomics 20, 37-47.

Bousman, C.A., Bengesser, S.A., Aitchison, K.J., Amare, A.T., Aschauer, H., Baune, B.T., Asl, B.B., Bishop, J.R., Burmeister, M., Chaumette, B., *et al.* (2021). Review and Consensus on Pharmacogenomic Testing in Psychiatry. Pharmacopsychiatry 54, 5-17.

Brookes, S.T., Whitely, E., Egger, M., Smith, G.D., Mulheran, P.A., and Peters, T.J. (2004). Subgroup analyses in randomized trials: risks of subgroup-specific analyses;: power and sample size for the interaction test. J Clin Epidemiol 57, 229-236.

Cacabelos, R. (2020). Pharmacogenomics of drugs used to treat brain disorders. Expert Review of Precision Medicine and Drug Development 5, 181-234.

Caraci, F., Leggio, G., Salomone, S., and Drago, F. (2017). New drugs in psychiatry: focus on new pharmacological targets [version 1; peer review: 3 approved]. F1000Research 6.

Carr, D.F., and Pirmohamed, M. (2017). Biomarkers of adverse drug reactions. Exp Biol Med 243, 291-299.

Caudle, K.E., Dunnenberger, H.M., Freimuth, R.R., Peterson, J.F., Burlison, J.D., Whirl-Carrillo, M., Scott, S.A., Rehm, H.L., Williams, M.S., Klein, T.E*., et al.* (2017). Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). Genetics in Medicine 19, 215-223.

Caudle, K.E., Klein, T.E., Hoffman, J.M., Muller, D.J., Whirl-Carrillo, M., Gong, L., McDonagh, E.M., Sangkuhl, K., Thorn, C.F., Schwab, M*., et al.* (2014). Incorporation of Pharmacogenomics into Routine Clinical Practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline Development Process. Current Drug Metabolism 15, 209-217.

Cavallari, L.H., Van Driest, S.L., Prows, C.A., Bishop, J.R., Limdi, N.A., Pratt, V.M., Ramsey, L.B., Smith, D.M., Tuteja, S., Duong, B.Q*., et al.* (2019). Multi-site investigation of strategies for the clinical implementation of CYP2D6 genotyping to guide drug prescribing. Genetics in Medicine 21, 2255-2263.

Chai, J.F., Kao, S.L., Wang, C., Lim, V.J., Khor, I.W., Dou, J., Podgornaia, A.I., Chothani, S., Cheng, C.Y., Sabanayagam, C*., et al.* (2020). Genome-Wide Association for HbA1c in Malay Identified Deletion on SLC4A1 that Influences HbA1c Independent of Glycemia. J Clin Endocrinol Metab 105.

Cipriani, A., Furukawa, T.A., Salanti, G., Chaimani, A., Atkinson, L.Z., Ogawa, Y., Leucht, S., Ruhe, H.G., Turner, E.H., Higgins, J.P.T*., et al.* (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. The Lancet 391, 1357-1366.

Coutts, R.T., Fang, j., Bourin, M., and Baker, G.B. (1999). Principles of Drug Metabolism, with an Emphasis on Psychiatric Drugs. In Cell Neurobiology Techniques, A.A. Boulton, G.B. Baker, and A.N. Bateson, eds. (Totowa, NJ: Humana Press), pp. 255-286.

Cremers, T.I.F.H., Flik, G., Hofland, C., and Stratford, R.E. (2012). Microdialysis Evaluation of Clozapine and N-Desmethylclozapine Pharmacokinetics in Rat Brain. Drug Metabolism and Disposition 40, 1909-1916.

De Berardis, D., Rapini, G., Olivieri, L., Di Nicola, D., Tomasetti, C., Valchera, A., Fornaro, M., Di Fabio, F., Perna, G., Di Nicola, M*., et al.* (2018). Safety of antipsychotics for the treatment of schizophrenia: a focus on the adverse effects of clozapine. Therapeutic Advances in Drug Safety 9, 237-256.

de Leon, J. (2009). Pharmacogenomics: The Promise of Personalized Medicine for CNS Disorders. Neuropsychopharmacology 34, 159-172.

de Leon, J. (2016). Pharmacogenetic Tests in Psychiatry: From Fear to Failure to Hype. J Clin Psychopharmacol 36, 299-304.

De Silva, M.J., Lee, L., Fuhr, D.C., Rathod, S., Chisholm, D., Schellenberg, J., and Patel, V. (2014). Estimating the coverage of mental health programmes: a systematic review. Int J Epidemiol 43, 341-353.

Demyttenaere, K. (2019). What is treatment resistance in psychiatry? A "difficult to treat" concept. World psychiatry : official journal of the World Psychiatric Association (WPA) 18, 354-355.

Denny, J.C., and Collins, F.S. (2021). Precision medicine in 2030—seven ways to transform healthcare. Cell 184, 1415-1419.

Diaz, F.J., Eap, C.B., Ansermot, N., Crettol, S., Spina, E., and de Leon, J. (2014). Can valproic acid be an inducer of clozapine metabolism? Pharmacopsychiatry 47, 89-96.

Dickens, D., Rädisch, S., Chiduza, G.N., Giannoudis, A., Cross, M.J., Malik, H., Schaeffeler, E., Sison-Young, R.L., Wilkinson, E.L., Goldring, C.E.*, et al.* (2018). Cellular Uptake of the Atypical Antipsychotic Clozapine Is a Carrier-Mediated Process. Molecular Pharmaceutics 15, 3557-3572.

Dueñas, H.R., Seah, C., Johnson, J.S., and Huckins, L.M. (2020). Implicit bias of encoded variables: frameworks for addressing structured bias in EHR–GWAS data. Hum Mol Genet 29, R33-R41.

Dunnenberger, H.M., Biszewski, M., Bell, G.C., Sereika, A., May, H., Johnson, S.G., Hulick, P.J., and Khandekar, J. (2016). Implementation of a multidisciplinary pharmacogenomics clinic in a community health system. Am J Health Syst Pharm 73, 1956-1966.

Eichler, H.-G., Abadie, E., Breckenridge, A., Flamion, B., Gustafsson, L.L., Leufkens, H., Rowland, M., Schneider, C.K., and Bloechl-Daum, B. (2011). Bridging the efficacy–effectiveness gap: a regulator's perspective on addressing variability of drug response. Nature Reviews Drug Discovery 10, 495-506.

Erika, C., Rossana, R., Hendrik, J.G., Giuseppe, T., and for the Ubiquitous Pharmacogenomics, C. (2017). Ubiquitous Pharmacogenomics (U-PGx): The Time for Implementation is Now. An Horizon2020 Program to Drive Pharmacogenomics into Clinical Practice. Current Pharmaceutical Biotechnology 18, 204-209.

Evans, W.E., and Johnson, J.A. (2001). Pharmacogenomics: The Inherited Basis for Interindividual Differences in Drug Response. Annu Rev Genomics Hum Genet 2, 9-39.

Fabbri, C., Pain, O., Hagenaars, S.P., Lewis, C.M., and Serretti, A. (2021). Transcriptome-wide association study of treatment-resistant depression and depression subtypes for drug repurposing. Neuropsychopharmacology.

Fava, G.A., Tomba, E., and Bech, P. (2017). Clinical Pharmacopsychology: Conceptual Foundations and Emerging Tasks. Psychother Psychosom 86, 134-140.

Flanagan, R.J., Lally, J., Gee, S., Lyon, R., and Every-Palmer, S. (2020). Clozapine in the treatment of refractory schizophrenia: a practical guide for healthcare professionals. Br Med Bull.

Fornaro, M., De Berardis, D., Anastasia, A., Novello, S., Fusco, A., Cattaneo, C.I., Solmi, M., Monaco, F., Veronese, N., Kim, Y.-K., and de Bartolomeis, A. (2018). The identification of biomarkers predicting acute and maintenance lithium treatment response in bipolar disorder: A plea for further research attention. Psychiatry Res 269, 658-672.

Gadad, B.S., Jha, M.K., Czysz, A., Furman, J.L., Mayes, T.L., Emslie, M.P., and Trivedi, M.H. (2018). Peripheral biomarkers of major depression and antidepressant treatment response: Current knowledge and future outlooks. J Affect Disord 233, 3-14.

Gaynes, B.N., Lux, L., Gartlehner, G., Asher, G., Forman-Hoffman, V., Green, J., Boland, E., Weber, R.P., Randolph, C., Bann, C.*, et al.* (2020). Defining treatment-resistant depression. Depress Anxiety 37, 134-145.

Goldberg, J.F. (2019). Does Pharmacogenomic Testing Meaningfully Improve Antidepressant Treatment Outcomes When Looking Only at Patients Taking Phase I Hepatically Metabolized Drugs? A Little. The Journal of clinical psychiatry 80, 0-0.

Goldstein, D.B., Allen, A., Keebler, J., Margulies, E.H., Petrou, S., Petrovski, S., and Sunyaev, S. (2013). Sequencing studies in human genetics: design and interpretation. Nature Rev Genet 14, 460-470.

Goldstein, J.I., Fredrik Jarskog, L., Hilliard, C., Alfirevic, A., Duncan, L., Fourches, D., Huang, H., Lek, M., Neale, B.M., Ripke, S.*, et al.* (2014). Clozapine-induced agranulocytosis is associated with rare HLA-DQB1 and HLA-B alleles. Nature Communications 5, 4757.

Goodwin, G. (2003). Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. J Psychopharmacol (Oxf) 17, 149-173.

Grady, B.J., and Ritchie, M.D. (2011). Statistical Optimization of Pharmacogenomics Association Studies: Key Considerations from Study Design to Analysis. Current Pharmacogenomics and Personalized Medicine 9, 41-66.

Grebe, T.A., Khushf, G., Chen, M., Bailey, D., Brenman, L.M., Williams, M.S., Seaver, L.H., Acmg Social, E., and Legal Issues, C. (2020). The interface of genomic information with the electronic health record: a points to consider statement of the American College of Medical Genetics and Genomics (ACMG). Genetics in Medicine 22, 1431-1436.

Greden, J.F., Parikh, S.V., Rothschild, A.J., Thase, M.E., Dunlop, B.W., DeBattista, C., Conway, C.R., Forester, B.P., Mondimore, F.M., Shelton, R.C.*, et al.* (2019). Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: A large, patient- and rater-blinded, randomized, controlled study. J Psychiatr Res 111, 59-67.

Grof, P., Duffy, A., Cavazzoni, P., Grof, E., Garnham, J., MacDougall, M., and Alda, M. (2002). Is response to prophylactic lithium a familial trait? The Journal of clinical psychiatry 63, 942-947.

Hefner, G., Laib, A.K., Sigurdsson, H., Hohner, M., and Hiemke, C. (2013). The value of drug and metabolite concentration in blood as a biomarker of psychopharmacological therapy. International Review of Psychiatry 25, 494-508.

Hefner, G., Wolff, J., Hahn, M., Hiemke, C., Toto, S., Roll, S.C., Messer, T., and Klimke, A. (2020). Prevalence and sort of pharmacokinetic drug–drug interactions in hospitalized psychiatric patients. J Neural Transm 127, 1185-1198.

Hellman, K., Aadal Nielsen, P., Ek, F., and Olsson, R. (2016). An ex Vivo Model for Evaluating Blood–Brain Barrier Permeability, Efflux, and Drug Metabolism. ACS Chemical Neuroscience 7, 668-680.

Hicks, J.K., Aquilante, C.L., Dunnenberger, H.M., Gammal, R.S., Funk, R.S., Aitken, S.L., Bright, D.R., Coons, J.C., Dotson, K.M., Elder, C.T., *et al.* (2019). Precision pharmacotherapy: Integrating pharmacogenomics into clinical pharmacy practice. JACCP: JOURNAL OF THE AMERICAN COLLEGE OF CLINICAL PHARMACY 2, 303-313.

Hiemke, C. (2016). Consensus Guideline Based Therapeutic Drug Monitoring (TDM) in Psychiatry and Neurology. Current Drug Delivery 13, 353-361.

Ho, S.C., Chong, H.Y., Chaiyakunapruk, N., Tangiisuran, B., and Jacob, S.A. (2016). Clinical and economic impact of non-adherence to antidepressants in major depressive disorder: A systematic review. J Affect Disord 193, 1-10.

Hoffman, J.M., Flynn, A.J., Juskewitch, J.E., and Freimuth, R.R. (2020). Biomedical Data Science and Informatics Challenges to Implementing Pharmacogenomics with Electronic Health Records. Annual Review of Biomedical Data Science 3, 289-314.

Holmes, E.A., Ghaderi, A., Harmer, C.J., Ramchandani, P.G., Cuijpers, P., Morrison, A.P., Roiser, J.P., Bockting, C.L.H., O'Connor, R.C., Shafran, R., *et al.* (2018). The *Lancet Psychiatry* Commission on psychological treatments research in tomorrow's science. The Lancet Psychiatry 5, 237-286.

Hou, L., Heilbronner, U., Degenhardt, F., Adli, M., Akiyama, K., Akula, N., Ardau, R., Arias, B., Backlund, L., Banzato, C.E.M., *et al.* (2016). Genetic variants associated with response to lithium treatment in bipolar disorder: a genome-wide association study. The Lancet 387, 1085-1093.

Hovelson, D.H., Xue, Z., Zawistowski, M., Ehm, M.G., Harris, E.C., Stocker, S.L., Gross, A.S., Jang, I.-J., Ieiri, I., Lee, J.-E., *et al.* (2017). Characterization of ADME gene variation in 21 populations by exome sequencing. Pharmacogenetics and Genomics 27, 89-100.

Howes, O.D., McCutcheon, R., Agid, O., de Bartolomeis, A., van Beveren, N.J.M., Birnbaum, M.L., Bloomfield, M.A.P., Bressan, R.A., Buchanan, R.W., Carpenter, W.T., *et al.* (2017). Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. Am J Psychiatry 174, 216-229.

Huddart, R., Fohner, A.E., Whirl-Carrillo, M., Wojcik, G.L., Gignoux, C.R., Popejoy, A.B., Bustamante, C.D., Altman, R.B., and Klein, T.E. (2019). Standardized Biogeographic Grouping System for Annotating Populations in Pharmacogenetic Research. Clin Pharmacol Ther 105, 1256-1262.

Huhn, M., Tardy, M., Spineli, L.M., Kissling, W., Förstl, H., Pitschel-Walz, G., Leucht, C., Samara, M., Dold, M., Davis, J.M., and Leucht, S. (2014). Efficacy of Pharmacotherapy and Psychotherapy for Adult Psychiatric Disorders: A Systematic Overview of Meta-analyses. JAMA Psychiatry 71, 706-715.

Ingelman-Sundberg, M., Mkrtchian, S., Zhou, Y., and Lauschke, V.M. (2018). Integrating rare genetic variants into pharmacogenetic drug response predictions. Human genomics 12, 26.

Ioannidis, J.P.A. (2013). To Replicate or Not to Replicate: The Case of Pharmacogenetic Studies. Circulation: Cardiovascular Genetics 6, 413-418.

Ising, M., Maccarrone, G., Brückl, T., Scheuer, S., Hennings, J., Holsboer, F., Turck, C.W., Uhr, M., and Lucae, S. (2019). FKBP5 Gene Expression Predicts Antidepressant Treatment Outcome in Depression. International Journal of Molecular Sciences 20, 485.

Jackson, R.G., Patel, R., Jayatilleke, N., Kolliakou, A., Ball, M., Gorrell, G., Roberts, A., Dobson, R.J., and Stewart, R. (2017). Natural language processing to extract symptoms of severe mental illness from clinical text: the Clinical Record Interactive Search Comprehensive Data Extraction (CRIS-CODE) project. BMJ Open 7, e012012.

Jallaq, S.A., Verba, M., Strawn, J.R., Martin, L.J., DelBello, M.P., and Ramsey, L.B. (2020). CYP2D6 Phenotype Influences Aripiprazole Tolerability in Pediatric Patients with Mood Disorders. J Child Adolesc Psychopharmacol 0.

Jarvis, J.P., Peter, A.P., and Shaman, J.A. (2019). Consequences of CYP2D6 Copy-Number Variation for Pharmacogenomics in Psychiatry. Frontiers in Psychiatry 10.

Jessel, C.D., Mostafa, S., Potiriadis, M., Everall, I.P., Gunn, J.M., and Bousman, C.A. (2020). Use of antidepressants with pharmacogenetic prescribing guidelines in a 10-year depression cohort of adult primary care patients. Pharmacogenet Genomics 30, 145-152.

Jones, P.B., Barnes, T.R.E., Davies, L., Dunn, G., Lloyd, H., Hayhurst, K.P., Murray, R.M., Markwick, A., and Lewis, S.W. (2006). Randomized Controlled Trial of the Effect on Quality of Life of Second- vs First-Generation Antipsychotic Drugs in Schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry 63, 1079-1087.

Jordan, S., Logan, P.A., Panes, G., Vaismoradi, M., and Hughes, D. (2018). Adverse Drug Reactions, Power, Harm Reduction, Regulation and the ADRe Profiles. Pharmacy 6, 102.

Jorm, A.F., Patten, S.B., Brugha, T.S., and Mojtabai, R. (2017). Has increased provision of treatment reduced the prevalence of common mental disorders? Review of the evidence from four countries. World Psychiatry 16, 90-99.

Jukić, M.M., Haslemo, T., Molden, E., and Ingelman-Sundberg, M. (2018). Impact of CYP2C19 Genotype on Escitalopram Exposure and Therapeutic Failure: A Retrospective Study Based on 2,087 Patients. Am J Psychiatry 175, 463-470.

Jukić, M.M., Smith, R.L., Haslemo, T., Molden, E., and Ingelman-Sundberg, M. (2019). Effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole: a retrospective, cohort study. The Lancet Psychiatry 6, 418-426.

Jung, W.-Y., Jang, S.-H., Kim, S.-G., Jae, Y.-M., Kong, B.-G., Kim, H.-C., Choe, B.-M., Kim, J.-G., and Kim, C.-R. (2016). Times to Discontinue Antidepressants Over 6 Months in Patients with Major Depressive Disorder. Psychiatry Investig 13, 440-446.

Kahn, R.S., Fleischhacker, W.W., Boter, H., Davidson, M., Vergouwe, Y., Keet, I.P.M., Gheorghe, M.D., Rybakowski, J.K., Galderisi, S., Libiger, J.*, et al.* (2008). Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. The Lancet 371, 1085-1097.

Kato, M., Hori, H., Inoue, T., Iga, J., Iwata, M., Inagaki, T., Shinohara, K., Imai, H., Murata, A., Mishima, K., and Tajika, A. (2021). Discontinuation of antidepressants after remission with antidepressant medication in major depressive disorder: a systematic review and meta-analysis. Mol Psychiatry 26, 118-133.

Kimpton, J.E., Carey, I.M., Threapleton, C.J.D., Robinson, A., Harris, T., Cook, D.G., DeWilde, S., and Baker, E.H. (2019). Longitudinal exposure of English primary care patients to pharmacogenomic drugs: An analysis to inform design of pre-emptive pharmacogenomic testing. Br J Clin Pharmacol 85, 2734-2746.

Kose, S., and Cetin, M. (2018). Psychiatric pharmacogenomics in the age of neuroscience: promises and challenges. Psychiatry and Clinical Psychopharmacology 28, 231-235.

Kranzler, H.R., Smith, R.V., Schnoll, R., Moustafa, A., and Greenstreet-Akman, E. (2017). Precision medicine and pharmacogenetics: what does oncology have that addiction medicine does not? Addiction 112, 2086-2094.

Krebs, K., and Milani, L. (2019). Translating pharmacogenomics into clinical decisions: do not let the perfect be the enemy of the good. Human Genomics 13, 39.

Laatikainen, O., Miettunen, J., Sneck, S., Lehtiniemi, H., Tenhunen, O., and Turpeinen, M. (2017). The prevalence of medication-related adverse events in inpatients—a systematic review and meta-analysis. Eur J Clin Pharmacol 73, 1539-1549.

Lahijani, S.C., and Harris, K.A. (2017). Medical Complications of Psychiatric Treatment: An Update. Crit Care Clin 33, 713-734.

Lally, J., and Gaughran, F. (2019). Treatment resistant schizophrenia – review and a call to action. Irish Journal of Psychological Medicine 36, 279-291.

Lam, Y.W.F., and Someya, T. (2019). Pharmacogenomics in Psychiatric Disorders. In Pharmacogenomics (Second Edition), Y.W.F. Lam, and S.A. Scott, eds. (Academic Press), pp. 181-225.

Lauschke, V.M., and Ingelman-Sundberg, M. (2019). Prediction of drug response and adverse drug reactions: From twin studies to Next Generation Sequencing. Eur J Pharm Sci 130, 65-77.

Lauschke, V.M., Milani, L., and Ingelman-Sundberg, M. (2017). Pharmacogenomic Biomarkers for Improved Drug Therapy—Recent Progress and Future Developments. The AAPS Journal 20, 4.

Lawlor, D.A., Tilling, K., and Davey Smith, G. (2017). Triangulation in aetiological epidemiology. Int J Epidemiol 45, 1866-1886.

LeGates, T.A., Kvarta, M.D., and Thompson, S.M. (2019). Sex differences in antidepressant efficacy. Neuropsychopharmacology 44, 140-154.

Legge, S.E., Hamshere, M., Hayes, R.D., Downs, J., O'Donovan, M.C., Owen, M.J., Walters, J.T.R., and MacCabe, J.H. (2016). Reasons for discontinuing clozapine: A cohort study of patients commencing treatment. Schizophr Res 174, 113-119.

Legge, S.E., Hamshere, M.L., Ripke, S., Pardiñas, A.F., Goldstein, J.I., Rees, E., Richards, A.L., Leonenko, G., Jorskog, L.F., Goldstein, J.I., *et al.* (2017). Genome-wide common and rare variant analysis provides novel insights into clozapine-associated neutropenia. Mol Psychiatry 22, 1502-1508.

Legge, S.E., and Walters, J.T.R. (2019). Genetics of clozapine-associated neutropenia: recent advances, challenges and future perspective. Pharmacogenomics 20, 279-290.

Leucht, S., Davis, J.M., Engel, R.R., Kissling, W., and Kane, J.M. (2009). Definitions of response and remission in schizophrenia: recommendations for their use and their presentation. Acta Psychiatr Scand 119, 7-14.

Leucht, S., Hierl, S., Kissling, W., Dold, M., and Davis, J.M. (2012). Putting the efficacy of psychiatric and general medicine medication into perspective: review of meta-analyses. Br J Psychiatry 200, 97-106.

Li, K.J., Solomon, H.V., and DeLisi, L.E. (2018). Clozapine pharmacogenomics: a review of efficacy, pharmacokinetics, and agranulocytosis. Current Opinion in Psychiatry 31.

Lieberman, J.A., Stroup, T.S., McEvoy, J.P., Swartz, M.S., Rosenheck, R.A., Perkins, D.O., Keefe, R.S.E., Davis, S.M., Davis, C.E., Lebowitz, B.D., *et al.* (2005). Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia. N Engl J Med 353, 1209-1223.

Lieberman, J.A., Yunis, J., Egea, E., Canoso, R.T., Kane, J.M., and Yunis, E.J. (1990). HLA-B38, DR4, DQw3 and Clozapine-Induced Agranulocytosis in Jewish Patients With Schizophrenia. Arch Gen Psychiatry 47, 945-948.

Liko, I., Lai, E., Griffin, R.J., Aquilante, C.L., and Lee, Y.M. (2020). Patients' Perspectives on Psychiatric Pharmacogenetic Testing. Pharmacopsychiatry.

López-Cortegano, E., and Caballero, A. (2019). Inferring the Nature of Missing Heritability in Human Traits Using Data from the GWAS Catalog. Genetics 212, 891-904.

Loukola, A., Buchwald, J., Gupta, R., Palviainen, T., Hällfors, J., Tikkanen, E., Korhonen, T., Ollikainen, M., Sarin, A.-P., Ripatti, S., *et al.* (2015). A Genome-Wide Association Study of a Biomarker of Nicotine Metabolism. PLoS Genet 11, e1005498.

Lunenburg, C.A.T.C., Thirstrup, J.P., Bybjerg-Grauholm, J., Bækvad-Hansen, M., Hougaard, D.M., Nordentoft, M., Werge, T., Børglum, A.D., Mors, O., Mortensen, P.B., and Gasse, C. (2021). Pharmacogenetic genotype and phenotype frequencies in a large Danish population-based case-cohort sample. Translational Psychiatry 11, 294.

Manrai, A.K., Funke, B.H., Rehm, H.L., Olesen, M.S., Maron, B.A., Szolovits, P., Margulies, D.M., Loscalzo, J., and Kohane, I.S. (2016). Genetic Misdiagnoses and the Potential for Health Disparities. N Engl J Med 375, 655-665.

Manson, L.E.N., Swen, J.J., and Guchelaar, H.-J. (2020). Diagnostic Test Criteria for HLA Genotyping to Prevent Drug Hypersensitivity Reactions: A Systematic Review of Actionable HLA Recommendations in CPIC and DPWG Guidelines. Frontiers in pharmacology 11, 567048-567048.

Martin, A., Downing, J., Maden, M., Fleeman, N., Alfirevic, A., Haycox, A., and Pirmohamed, M. (2017). An assessment of the impact of pharmacogenomics on health disparities: a systematic literature review. Pharmacogenomics 18, 1541-1550.

Martinez, R., Lloyd-Sherlock, P., Soliz, P., Ebrahim, S., Vega, E., Ordunez, P., and McKee, M. (2020). Trends in premature avertable mortality from non-communicable diseases for 195 countries and territories, 1990–2017: a population-based study. The Lancet Global Health 8, e511-e523.

Matthaei, J., Tzvetkov, M., Strube, J., Sehrt, D., Sachse-Seeboth, C., Hjelmborg, J., Möller, S., Halekoh, U., Hofmann, U., Schwab, M.*, et al.* (2016). Heritability of Caffeine Metabolism: Environmental Effects Masking Genetic Effects on CYP1A2 Activity but Not on NAT2. Clin Pharmacol Ther 100, 606-616.

Mauri, M.C., Paletta, S., Di Pace, C., Reggiori, A., Cirnigliaro, G., Valli, I., and Altamura, A.C. (2018). Clinical Pharmacokinetics of Atypical Antipsychotics: An Update. Clin Pharmacokinet 57, 1493-1528.

McCutcheon, R.A., Pillinger, T., Mizuno, Y., Montgomery, A., Pandian, H., Vano, L., Marques, T.R., and Howes, O.D. (2019). The efficacy and heterogeneity of antipsychotic response in schizophrenia: A meta-analysis. Mol Psychiatry.

McInnes, G., Lavertu, A., Sangkuhl, K., Klein, T.E., Whirl-Carrillo, M., and Altman, R.B. (2020). Pharmacogenetics at scale: An analysis of the UK Biobank. bioRxiv, 2020.2005.2030.125583.

McMahon, F., Degenhardt, F., Aitchison, K., Alliey, N., Amare, A.T., Aschauer, H., Austin, J., Barta, C., Bohlen, K., Bousman, C.*, et al.* (2019). Genetic Testing and Psychiatric Disorders. (International Society of Psychiatric Genetics).

McMillan, D.M., and Tyndale, R.F. (2018). CYP-mediated drug metabolism in the brain impacts drug response. Pharmacol Ther 184, 189-200.

Meech, R., Miners, J.O., Lewis, B.C., and Mackenzie, P.I. (2012). The glycosidation of xenobiotics and endogenous compounds: Versatility and redundancy in the UDP glycosyltransferase superfamily. Pharmacol Ther 134, 200-218.

Mills, M.C., and Rahal, C. (2020). The GWAS Diversity Monitor tracks diversity by disease in real time. Nat Genet 52, 242-243.

Milosavljević, F., Bukvić, N., Pavlović, Z., Miljević, Č., Pešić, V., Molden, E., Ingelman-Sundberg, M., Leucht, S., and Jukić, M.M. (2020). Association of CYP2C19 and CYP2D6

Poor and Intermediate Metabolizer Status With Antidepressant and Antipsychotic Exposure: A Systematic Review and Meta-analysis. JAMA Psychiatry.

Mitropoulou, C., Litinski, V., Kabakchiev, B., Rogers, S., and P Patrinos, G. (2020). PARC report: health outcomes and value of personalized medicine interventions: impact on patient care. Pharmacogenomics 21, 797-807.

Moldovan, R., McGhee, K.A., Coviello, D., Hamang, A., Inglis, A., Ingvoldstad Malmgren, C., Johansson-Soller, M., Laurino, M., Meiser, B., Murphy, L.*, et al.* (2019). Psychiatric genetic counseling: A mapping exercise. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 180, 523-532.

Müller, D.J., Kekin, I., Kao, A.C.C., and Brandl, E.J. (2013). Towards the implementation of CYP2D6 and CYP2C19 genotypes in clinical practice: Update and report from a pharmacogenetic service clinic. International Review of Psychiatry 25, 554-571.

Müller, D.J., and Rizhanovsky, Z. (2020). From the Origins of Pharmacogenetics to First Applications in Psychiatry. Pharmacopsychiatry.

Murray, C.J.L., Abbafati, C., Abbas, K.M., Abbasi, M., Abbasi-Kangevari, M., Abd-Allah, F., Abdollahi, M., Abedi, P., Abedi, A., Abolhassani, H.*, et al.* (2020). Five insights from the Global Burden of Disease Study 2019. The Lancet 396, 1135-1159.

Murray, G.K., Lin, T., Austin, J., McGrath, J.J., Hickie, I.B., and Wray, N.R. (2021). Could Polygenic Risk Scores Be Useful in Psychiatry?: A Review. JAMA Psychiatry 78, 210-219.

Muscatello, M.R.A., Zoccali, R.A., and Bruno, A. (2020). Is there a time when prescribing pharmacotherapy in psychiatry is futile? Expert Opinion on Pharmacotherapy 21, 733-735.

National Collaborating Centre for Mental Health (2014). National Institute for Health and Clinical Excellence: Guidance. In Psychosis and Schizophrenia in Adults: Treatment and Management: Updated Edition 2014 (London: National Institute for Health and Care Excellence (UK)).

Neavin, D., Kaddurah-Daouk, R., and Weinshilboum, R. (2016). Pharmacometabolomics informs pharmacogenomics. Metabolomics 12, 121.

Nguyen, D.V., Vidal, C., Chu, H.C., and van Nunen, S. (2019a). Developing pharmacogenetic screening methods for an emergent country: Vietnam. World Allergy Organization Journal 12, 100037.

Nguyen, P.A., Born, D.A., Deaton, A.M., Nioi, P., and Ward, L.D. (2019b). Phenotypes associated with genes encoding drug targets are predictive of clinical trial side effects. Nature Communications 10, 1579.

Nielsen, J., Young, C., Ifteni, P., Kishimoto, T., Xiang, Y.T., Schulte, P.F., Correll, C.U., and Taylor, D. (2016). Worldwide Differences in Regulations of Clozapine Use. CNS Drugs 30, 149-161.

Nordon, C., Karcher, H., Groenwold, R.H.H., Ankarfeldt, M.Z., Pichler, F., Chevrou-Severac, H., Rossignol, M., Abbe, A., and Abenhaim, L. (2016). The “Efficacy-Effectiveness Gap”: Historical Background and Current Conceptualization. Value in Health 19, 75-81.

Norton, R.M. (2001). Clinical pharmacogenomics: applications in pharmaceutical R&D. Drug Discovery Today 6, 180-185.

Nucifora, F.C., Mihaljevic, M., Lee, B.J., and Sawa, A. (2017). Clozapine as a Model for Antipsychotic Development. Neurotherapeutics 14, 750-761.

O'Connell, C.P., Goldstein-Piekarski, A.N., Nemeroff, C.B., Schatzberg, A.F., Debattista, C., Carrillo-Roa, T., Binder, E.B., Dunlop, B.W., Craighead, W.E., Mayberg, H.S., and Williams, L.M. (2018). Antidepressant Outcomes Predicted by Genetic Variation in Corticotropin-Releasing Hormone Binding Protein. Am J Psychiatry 175, 251-261.

Olivier, C., and Williams-Jones, B. (2014). Global pharmacogenomics: Where is the research taking us? Global Public Health 9, 312-324.

Owen, M.J., and O'Donovan, M.C. (2020). Large-scale genomics: a paradigm shift in psychiatry? Biol Psychiatry, [in press].

Pan, R.Y., Dao, R.L., Hung, S.I., and Chung, W.H. (2017). Pharmacogenomic Advances in the Prediction and Prevention of Cutaneous Idiosyncratic Drug Reactions. Clin Pharmacol Ther 102, 86-97.

Papastergiou, J., Quilty, L.C., Li, W., Thiruchselvam, T., Jain, E., Gove, P., Mandlsohn, L., van den Bemt, B., and Pojskic, N. (2021). Pharmacogenomics guided versus standard antidepressant treatment in a community pharmacy setting: A randomized controlled trial. Clinical and Translational Science [in press].

Pardiñas, A.F., Nalmpanti, M., Pocklington, A.J., Legge, S.E., Medway, C., King, A., Jansen, J., Helthuis, M., Zammit, S., MacCabe, J.*, et al.* (2019). Pharmacogenomic Variants and Drug Interactions Identified Through the Genetic Analysis of Clozapine Metabolism. Am J Psychiatry 176, 477-486.

Paternoster, L., Tilling, K., and Davey Smith, G. (2017). Genetic epidemiology and Mendelian randomization for informing disease therapeutics: Conceptual and methodological challenges. PLoS Genet 13, e1006944.

Perlis, R.H., Dowd, D., Fava, M., Lencz, T., and Krause, D.S. (2020). Randomized, controlled, participant- and rater-blind trial of pharmacogenomic test-guided treatment versus treatment as usual for major depressive disorder. Depress Anxiety 37, 834-841.

Perna, G., Alciati, A., Daccò, S., Grassi, M., and Caldirola, D. (2020). Personalized Psychiatry and Depression: The Role of Sociodemographic and Clinical Variables. Psychiatry Investig 17, 193-206.

Peters, B.J.M., Rodin, A.S., De Boer, A., and Maitland-van der Zee, A.-H. (2010). Methodological and statistical issues in pharmacogenomics. J Pharm Pharmacol 62, 161-166.

Phillips, E.J., Sukasem, C., Whirl-Carrillo, M., Müller, D.J., Dunnenberger, H.M., Chantratita, W., Goldspiel, B., Chen, Y.-T., Carleton, B.C., George Jr., A.L.*, et al.* (2018). Clinical Pharmacogenetics Implementation Consortium Guideline for HLA Genotype and Use of Carbamazepine and Oxcarbazepine: 2017 Update. Clin Pharmacol Ther 103, 574-581.

Pirmohamed, M., Burnside, G., Eriksson, N., Jorgensen, A.L., Toh, C.H., Nicholson, T., Kesteven, P., Christersson, C., Wahlström, B., Stafberg, C.*, et al.* (2013). A Randomized Trial of Genotype-Guided Dosing of Warfarin. N Engl J Med 369, 2294-2303.

Pirmohamed, M., James, S., Meakin, S., Green, C., Scott, A.K., Walley, T.J., Farrar, K., Park, B.K., and Breckenridge, A.M. (2004). Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 329, 15-19.

Popejoy, A.B. (2019). Diversity In Precision Medicine And Pharmacogenetics: Methodological And Conceptual Considerations For Broadening Participation. Pharmacogenomics and personalized medicine 12, 257-271.

Rahman, T., M. Ash, D., Lauriello, J., and Rawlani, R. (2017). Misleading Guidance From Pharmacogenomic Testing. Am J Psychiatry 174, 922-924.

Rakesh, G., Sumner, C.R., Alexander, J.L., Gross, L.S., Pine, J., Slaby, A., Garakani, A., and Baron, D. (2020). Pharmacogenomic Testing in Psychiatry: Ready for Primetime? The Journal of Nervous and Mental Disease 208.

Ramsay, R.R., Popovic-Nikolic, M.R., Nikolic, K., Uliassi, E., and Bolognesi, M.L. (2018). A perspective on multi-target drug discovery and design for complex diseases. Clinical and Translational Medicine 7, 3.

Rees, E., and Owen, M.J. (2020). Translating insights from neuropsychiatric genetics and genomics for precision psychiatry. Genome Medicine 12, 43.

Rees, S., Akbari, A., Collins, H., Lee, S.C., Marchant, A., Rees, A., Thayer, D., Wang, T., Wood, S., and John, A. (2019). Developing a standardised approach to the aggregation of inpatient episodes into person-based spells in all specialties and psychiatric specialties. BMC Medical Informatics and Decision Making 19, 246.

Rehm, J., and Shield, K.D. (2019). Global Burden of Disease and the Impact of Mental and Addictive Disorders. Current Psychiatry Reports 21, 10.

Reisberg, S., Krebs, K., Lepamets, M., Kals, M., Mägi, R., Metsalu, K., Lauschke, V.M., Vilo, J., and Milani, L. (2018). Translating genotype data of 44,000 biobank participants into clinical pharmacogenetic recommendations: challenges and solutions. Genetics in Medicine.

Relling, M., and Klein, T. (2011). CPIC: Clinical Pharmacogenetics Implementation Consortium of the Pharmacogenomics Research Network. Clin Pharmacol Ther 89, 464-467.

Relling, M.V., Klein, T.E., Gammal, R.S., Whirl-Carrillo, M., Hoffman, J.M., and Caudle, K.E. (2020). The Clinical Pharmacogenetics Implementation Consortium: 10 Years Later. Clin Pharmacol Ther 107, 171-175.

Remington, G., Lee, J., Agid, O., Takeuchi, H., Foussias, G., Hahn, M., Fervaha, G., Burton, L., and Powell, V. (2016). Clozapine's critical role in treatment resistant schizophrenia: ensuring both safety and use. Expert Opinion on Drug Safety 15, 1193-1203.

Roden, D.M., McLeod, H.L., Relling, M.V., Williams, M.S., Mensah, G.A., Peterson, J.F., and Van Driest, S.L. (2019). Pharmacogenomics. The Lancet 394, 521-532.

Rohde, P.D., and Kristensen, T.N. (2020). Untangling the genetic basis of drug response. Pharmacogenomics 21, 87-89.

Rossom, R.C., Shortreed, S., Coleman, K.J., Beck, A., Waitzfelder, B.E., Stewart, C., Ahmedani, B.K., Zeber, J.E., and Simon, G.E. (2016). ANTIDEPRESSANT ADHERENCE ACROSS DIVERSE POPULATIONS AND HEALTHCARE SETTINGS. Depress Anxiety 33, 765-774.

Roth, B.L., Sheffler, D.J., and Kroeze, W.K. (2004). Magic shotguns versus magic bullets: selectively non-selective drugs for mood disorders and schizophrenia. Nature Reviews Drug Discovery 3, 353-359.

Rottenberg, J., Devendorf, A.R., Kashdan, T.B., and Disabato, D.J. (2018). The Curious Neglect of High Functioning After Psychopathology: The Case of Depression. Perspectives on Psychological Science 13, 549-566.

Russell, L.E., Zhou, Y., Almousa, A.A., Sodhi, J.K., Nwabufo, C.K., and Lauschke, V.M. (2021). Pharmacogenomics in the Era of Next Generation Sequencing – from Byte to Bedside. Drug Metab Rev, 1-79.

Sajatovic, M., Velligan, D.I., Weiden, P.J., Valenstein, M.A., and Ogedegbe, G. (2010). Measurement of psychiatric treatment adherence. J Psychosom Res 69, 591-599.

Salagre, E., Dodd, S., Aedo, A., Rosa, A., Amoretti, S., Pinzon, J., Reinares, M., Berk, M., Kapczinski, F.P., Vieta, E., and Grande, I. (2018). Toward Precision Psychiatry in Bipolar Disorder: Staging 2.0. Frontiers in Psychiatry 9.

Schärfe, C.P.I., Tremmel, R., Schwab, M., Kohlbacher, O., and Marks, D.S. (2017). Genetic variation in human drug-related genes. Genome Medicine 9, 117.

Schuck, R.N., and Grillo, J.A. (2016). Pharmacogenomic Biomarkers: an FDA Perspective on Utilization in Biological Product Labeling. The AAPS Journal 18, 573-577.

Schwarz, U.I., Gulilat, M., and Kim, R.B. (2019). The Role of Next-Generation Sequencing in Pharmacogenetics and Pharmacogenomics. Cold Spring Harbor Perspectives in Medicine 9.

Siskind, D., Orr, S., Sinha, S., Yu, O., Brijball, B., Warren, N., MacCabe, J.H., Smart, S.E., and Kisely, S. (2021). Rates of treatment-resistant schizophrenia from first-episode cohorts: systematic review and meta-analysis. Br J Psychiatry, 1-6.

Smith, R.L., O'Connell, K., Athanasiu, L., Djurovic, S., Kringen, M.K., Andreassen, O.A., and Molden, E. (2020). Identification of a novel polymorphism associated with reduced clozapine concentration in schizophrenia patients—a genome-wide association study adjusting for smoking habits. Translational Psychiatry 10, 198.

Smith, T.L., and Nemeroff, C.B. (2020). Pharmacogenomic testing and antidepressant response: problems and promises. Brazilian Journal of Psychiatry 42, 116-117.

Smoller, J.W. (2018). The use of electronic health records for psychiatric phenotyping and genomics. American Journal of Medical Genetics Part B: Neuropsychiatric Genetics 177, 601-612.

Stanworth, D., Hunt, N.C.A., and Flanagan, R.J. (2012). Clozapine—A dangerous drug in a clozapine-naïve subject. Forensic Sci Int 214, e23-e25.

Stern, S., Linker, S., Vadodaria, K.C., Marchetto, M.C., and Gage, F.H. (2018). Prediction of response to drug therapy in psychiatric disorders. Open Biology 8, 180031.

Suhre, K., Shin, S.-Y., Petersen, A.-K., Mohney, R.P., Meredith, D., Wägele, B., Altmaier, E., Deloukas, P., Erdmann, J., Grundberg, E.*, et al.* (2011). Human metabolic individuality in biomedical and pharmaceutical research. Nature 477, 54-60.

Sutherland, A., Phipps, D.L., Tomlin, S., and Ashcroft, D.M. (2019). Mapping the prevalence and nature of drug related problems among hospitalised children in the United Kingdom: a systematic review. BMC Pediatrics 19, 486.

Swen, J., Wilting, I., De Goede, A., Grandia, L., Mulder, H., Touw, D., De Boer, A., Conemans, J., Egberts, T., and Klungel, O. (2008). Pharmacogenetics: from bench to byte. Clin Pharmacol Ther 83, 781-787.

Tan-Koi, W.C., Limenta, M., Mohamed, E.H.M., and Lee, E.J.D. (2019). The Importance of Ethnicity Definitions and Pharmacogenomics in Ethnobridging and Pharmacovigilance. In Pharmacogenomics (Second Edition), Y.W.F. Lam, and S.A. Scott, eds. (Academic Press), pp. 289-327.

The SEARCH Collaborative Group (2008). SLCO1B1 Variants and Statin-Induced Myopathy — A Genomewide Study. N Engl J Med 359, 789-799.

Thomas, J.H. (2007). Rapid Birth–Death Evolution Specific to Xenobiotic Cytochrome P450 Genes in Vertebrates. PLoS Genet 3, e67.

Thorn, C.F., Müller, D.J., Altman, R.B., and Klein, T.E. (2018). PharmGKB summary: clozapine pathway, pharmacokinetics. Pharmacogenetics and genomics 28, 214-222.

Thorn, C.F., Whirl-Carrillo, M., Hachad, H., Johnson, J.A., McDonagh, E.M., Ratain, M.J., Relling, M.V., Scott, S.A., Altman, R.B., and Klein, T.E. (2019). Essential Characteristics of Pharmacogenomics Study Publications. Clin Pharmacol Ther 105, 86-91.

Thornley, T., Esquivel, B., Wright, D.J., Dop, H.v.d., Kirkdale, C.L., and Youssef, E. (2021). Implementation of a Pharmacogenomic Testing Service through Community Pharmacy in the Netherlands: Results from an Early Service Evaluation. Pharmacy 9, 38.

Tilleman, L., Weymaere, J., Heindryckx, B., Deforce, D., and Nieuwerburgh, F.V. (2019). Contemporary pharmacogenetic assays in view of the PharmGKB database. Pharmacogenomics 20, 261-272.

Timpson, N.J., Greenwood, C.M.T., Soranzo, N., Lawson, D.J., and Richards, J.B. (2018). Genetic architecture: the shape of the genetic contribution to human traits and disease. Nature Rev Genet 19, 110-124.

Tin, A., and Köttgen, A. (2020). Genome-Wide Association Studies of CKD and Related Traits. Clinical Journal of the American Society of Nephrology 15, 1643-1656.

Tornio, A., and Backman, J.T. (2018). Cytochrome P450 in Pharmacogenetics: An Update. In Adv Pharmacol, K. Brøsen, and P. Damkier, eds. (Academic Press), pp. 3-32.

Treviño, L.A., Ruble, M.W., Treviño, K., Weinstein, L.M., and Gresky, D.P. (2017). Antidepressant Medication Prescribing Practices for Treatment of Major Depressive Disorder. Psychiatr Serv 68, 199-202.

U.S. Food and Drug Administration (2021). Table of Pharmacogenetic Associations.

van Schaik, R.H.N., Müller, D.J., Serretti, A., and Ingelman-Sundberg, M. (2020). Pharmacogenetics in Psychiatry: An Update on Clinical Usability. Frontiers in Pharmacology 11.

Vigo, D.V., Kestel, D., Pendakur, K., Thornicroft, G., and Atun, R. (2019). Disease burden and government spending on mental, neurological, and substance use disorders, and self-harm: cross-sectional, ecological study of health system response in the Americas. The Lancet Public Health 4, e89-e96.

Visscher, P.M., Wray, N.R., Zhang, Q., Sklar, P., McCarthy, M.I., Brown, M.A., and Yang, J. (2017). 10 Years of GWAS Discovery: Biology, Function, and Translation. Am J Hum Genet 101, 5-22.

Walgren, R.A., Meucci, M.A., and McLeod, H.L. (2005). Pharmacogenomic Discovery Approaches: Will the Real Genes Please Stand Up? J Clin Oncol 23, 7342-7349.

Ward, E.T., Kostick, K.M., and Lázaro-Muñoz, G. (2019). Integrating Genomics into Psychiatric Practice: Ethical and Legal Challenges for Clinicians. Harv Rev Psychiatry 27, 53-64.

Wolking, S., Moreau, C., Nies, A.T., Schaeffeler, E., McCormack, M., Auce, P., Avbersek, A., Becker, F., Krenn, M., Møller, R.S.*, et al.* (2020). Testing association of rare genetic variants with resistance to three common antiseizure medications. Epilepsia 61, 657-666.

Wong, E.H.F., Yocca, F., Smith, M.A., and Lee, C.-M. (2010). Challenges and opportunities for drug discovery in psychiatric disorders: the drug hunters' perspective. International Journal of Neuropsychopharmacology 13, 1269-1284.

Wong, Y.C., Centanni, M., and de Lange, E.C.M. (2019). Physiologically Based Modeling Approach to Predict Dopamine D2 Receptor Occupancy of Antipsychotics in Brain: Translation From Rat to Human. The Journal of Clinical Pharmacology 59, 731-747.

Woodcock, J. (2010). Assessing the Clinical Utility of Diagnostics Used in Drug Therapy. Clin Pharmacol Ther 88, 765-773.

Yang, Y., Botton, M.R., Scott, E.R., and Scott, S.A. (2017). Sequencing the CYP2D6 gene: from variant allele discovery to clinical pharmacogenetic testing. Pharmacogenomics 18, 673-685.

Yin, O., and Vandell, A. (2019). Incorporating Pharmacogenomics in Drug Development: A Perspective From Industry. In Pharmacogenomics (Second Edition), Y.W.F. Lam, and S.A. Scott, eds. (Academic Press), pp. 81-101.

Zeier, Z., Carpenter, L.L., Kalin, N.H., Rodriguez, C.I., McDonald, W.M., Widge, A.S., and Nemeroff, C.B. (2018). Clinical Implementation of Pharmacogenetic Decision Support Tools for Antidepressant Drug Prescribing. Am J Psychiatry 175, 873-886.

Zhang, Q., Sidorenko, J., Couvy-Duchesne, B., Marioni, R.E., Wright, M.J., Goate, A.M., Marcora, E., Huang, K.-l., Porter, T., Laws, S.M.*, et al.* (2020). Risk prediction of late-onset Alzheimer's disease implies an oligogenic architecture. Nature Communications 11, 4799.