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Pharmacogenomics: A road ahead for precision medicine in psychiatry

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1 **ABSTRACT**

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

16

17 **INTRODUCTION**

18 Psychiatric disorders are major contributors to the global burden of disease, accounting for
19 19% of all years lived with disability worldwide (Rehm and Shield, 2019). The societal impact
20 of these conditions arises from their high prevalence, with one in 5-6 adults affected annually
21 (Baker, 2020), as well as their substantial effects on morbidity and premature mortality.
22 Notably, the global burden of psychiatric disorders has remained high throughout recent
23 decades (Jorm et al., 2017), in contrast to improvements seen in communicable, and other non-
24 communicable diseases (Martinez et al., 2020; Murray et al., 2020). The reasons for the lack
25 of progress in prevention and treatment are complex, but they include limited understanding of
26 pathogenesis, pathophysiology and of the mode of action of existing treatments and why they
27 are ineffective for many people. This is compounded by the inadequate provision of mental
28 healthcare. Only 20% of individuals with common psychiatric disorders, such as depression
29 and anxiety, have access to appropriate treatment in Europe and North America, and this
30 “treatment gap” is likely to be even wider in low- and middle-income countries (Vigo et al.,
31 2019).

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

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

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

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

29 **PHARMACOLOGICAL PROCESSES AND GENOMIC VARIATION**

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

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

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

16 Currently, more than 1,000 basic research studies in pharmacogenomics are published every
17 year (Müller and Rizhanovsky, 2020), and 165 guidelines on the use of pharmacogenomic
18 information for specific drug-gene pairs are available in the PharmGKB repository as of May
19 2021, including 33 relevant for psychiatry (Bousman et al., 2021). Recommendations in these
20 guidelines are derived from a thorough process of literature curation and standardised variant
21 annotation (Barbarino et al., 2018), partially aligned with guideline standards from the US
22 National Academy of Medicine (Caudle et al., 2014). They are increasingly recognised by
23 industry and regulators in drug development and labelling processes (Schuck and Grillo, 2016;
24 Yin and Vandell, 2019). PharmGKB guidelines also assess the quality of supporting evidence
25 and, when indicated, make genotype-based prescribing recommendations (Relling et al., 2020).
26 However, these guidelines have not been widely adopted by clinical services, including those
27 providing psychiatric care, as in most cases the trials needed to demonstrate their clinical utility
28 to the standards required by public healthcare settings have yet to be carried out (Caudle et al.,
29 2014; Russell et al., 2021). Additionally, important financial and regulatory constraints are still
30 being explored, particularly those regarding the circumstances in which to implement genetic
31 testing and who should cover its cost (Mitropoulou et al., 2020).

32 **GENOMICS OF DRUG METABOLISM**

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

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

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

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

30 The apparent simplicity of the genomic architecture of these pharmacogenomic traits is
31 complicated by challenges in fully characterising the genomic variation within these genes.
32 Several important ADME genes, of which the best known is probably CYP2D6, harbour
33 structural variation that is not well-captured by standard genotyping protocols (Lauschke et al.,
34 2017). As a consequence of this, insights and results from much of the early literature on these
35 genes have to be cautiously interpreted (Yang et al., 2017), which compromises applications
36 and trials in clinical settings (Cavallari et al., 2019). It should be noted that complex genomic
37 regions within ADME genes are not uncommon, and originated from the evolution of gene
38 clusters through duplication and homologous recombination (Meech et al., 2012; Thomas,
39 2007), favouring a genomic environment with relaxed natural selection where novel mutations
40 tended to drift (Hovelson et al., 2017). Thus, despite successes in identifying potential causal
41 variants from the analysis of metabolite concentrations and related metrics, pharmacogenomic
42 traits are likely to still have substantial unexplained (“hidden” or “missing”) heritability, which
43 might require more complete sequencing and genotype-environment studies to be resolved
44 (López-Cortegano and Caballero, 2019).

1 PHARMA COGENOMICS OF ADVERSE DRUG REACTIONS

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

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

21 ADRs have a significant impact on health systems given their frequency and potential severity;
22 6–7% of hospital admissions in the UK have been attributed to ADRs and 19% of hospital
23 inpatients experience significant ADRs (Pirmohamed et al., 2004), a rate that is likely higher
24 in children and older people (Laatikainen et al., 2017; Sutherland et al., 2019). Their relevance
25 in psychiatry is related to the fact that polypharmacy, the prescription of multiple medications,
26 is common in psychiatric care and can lead to increased rates of ADRs through drug-drug
27 interactions (Hefner et al., 2020). In addition, many psychiatric medications are so-called “dirty
28 drugs”, having actions at multiple receptor targets with associated broad adverse effect profiles
29 (Agid et al., 2007; Caraci et al., 2017). This is a counterpart to the classic idea of “magic bullet”
30 drug development, whereby single-target drugs would improve treatment by minimising
31 adverse effects. This approach has not yet led to advances in psychiatric treatment (Roth et al.,
32 2004), which raises the question of whether the multi-target action of many medications may
33 be central to their effectiveness (Ramsay et al., 2018).

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

43 RISE, FALL AND PLATEAU OF PSYCHIATRIC PHARMA COGENOMICS

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

17 A major barrier to the implementation of pharmacogenomic testing in psychiatric care has been
18 the lack of primary data of therapeutic utility for the vast majority of drug-gene pairs (Bousman
19 et al., 2021). This is a prerequisite for the commissioning of new tests or interventions in many
20 healthcare settings, as is the need to demonstrate health economic benefits. Advances are being
21 made in this area with the advent of psychiatric clinical trials assessing the impact of testing
22 for specific drug-gene pairs on psychiatric outcomes, although to date these have failed to
23 demonstrate major therapeutic advantages. For example, there have been substantial efforts to
24 assess the benefits of genomic testing for the treatment of major depression (Bousman et al.,
25 2019), a necessary first step towards the clinical adoption of these procedures (**Figure 1B**). The
26 largest trial of this kind, GUIDED, did not show a beneficial effect of pharmacogenomic guided
27 prescribing for its primary outcome of symptom improvement against antidepressant standard-
28 care (Greden et al., 2019). Results on treatment response and remission outcomes were more
29 positive, although these were secondary analyses that have been questioned on conceptual and
30 statistical grounds (Goldberg, 2019; Smith and Nemeroff, 2020). This lack of supportive
31 evidence, coupled with the negative results of other studies (Perlis et al., 2020; Zeier et al.,
32 2018), underlies the lack of support from the FDA, CPIC or DPWG for all current claims of
33 genetic markers as potential predictors of antidepressant response or indeed any other
34 pharmacodynamic outcome (Bousman et al., 2021). Nonetheless, all these organisations
35 currently recognise that pharmacogenomic variation could be of relevance for antidepressant
36 therapeutic management mainly due to its effects on pharmacokinetics (Bousman et al., 2021).
37 This avenue, explored but not found significant in GUIDED, has however shown some
38 promising results in recent prospective trials conducted within small-scale clinical settings
39 (Papastergiou et al., 2021).

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

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

9 Whilst no other findings in psychiatric pharmacogenomics have achieved this level of clinical
10 impact, cautious support is emerging for the potential utility of testing more widely. The
11 International Society of Psychiatric Genetics (ISPG; McMahon et al., 2019) has recognised the
12 potential benefits of the CPIC/DPWG guidelines in the prescription of certain antidepressants
13 and antipsychotics (**Table 1**), a stance supported by a recent systematic review of CYP2C19
14 and CYP2D6 enzyme activity for these classes of medication (Milosavljević et al., 2020).
15 Although these two genes are implicated to a degree in the metabolism of 80% of psychiatric
16 medications and are increasingly recognised in regulator-approved drug labels (Müller et al.,
17 2013; van Schaik et al., 2020), it is worth noting that many psychiatric drugs do not yet have
18 replicated pharmacogenomic associations with these genes or indeed any other ADME gene
19 despite the large body of basic research on this topic (Kose and Cetin, 2018). Additionally,
20 even in well-established associations between genetic markers and drug metabolism,
21 downstream effects on drug response or ADRs need to be explicitly evaluated, not just inferred.
22 Difficulties in both identifying primary associations and carrying out therapeutic evaluations
23 are related to the broad challenges of psychiatric pharmacogenomic research that we outline
24 below, particularly around underpowered “candidate gene” designs (Kose and Cetin, 2018;
25 Kranzler et al., 2017). These challenges are reinforced by the lack of funding for large
26 longitudinal studies that have proven beneficial in other areas of medicine (Pirmohamed et al.,
27 2013; The SEARCH Collaborative Group, 2008). Consequently, recent comparisons between
28 psychiatry and general medicine, particularly oncology, have found the latter to have a clear
29 lead in terms of immediate healthcare impact, with psychiatric pharmacogenomics remaining
30 a promise with unrealised potential (de Leon, 2016; Kranzler et al., 2017).

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

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

3 **MEASURING TREATMENT OUTCOMES AND RESPONSE**

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

13 In many areas of medicine the measurement of whether an individual benefits from a drug is
14 conceptualised as a surrogate of survival or other "ultimate" treatment endpoints (Woodcock,
15 2010). However, these are generally less applicable in psychiatry as mortality is rarely a short
16 term outcome and is not a primary part of pathophysiology (Leucht et al., 2012). The most
17 popular methods to measure psychiatric drug response rely on defined changes in scores of
18 pre- and post-treatment symptom rating scales (Leucht et al., 2009). While an in-depth review
19 of their psychometric properties is outside the scope of this article, it is worth noting that most
20 rating scales exchange sensitivity in favour of internal consistency and applicability in diverse
21 settings (Fava et al., 2017). Additionally, when used on their own, symptom scales largely
22 ignore the broad impacts psychiatric treatment can have on psychological and social function,
23 as well as quality of life (Demyttenaere, 2019).

24 Valid assessment of treatment outcome requires longitudinal measurement of these
25 multifaceted elements of symptom and functional level. This requirement has been recognised
26 in several consensus outcome definitions in psychosis (Andreasen et al., 2005; Howes et al.,
27 2017), with equivalent initiatives also developing in depression research (Gaynes et al., 2020).
28 Nonetheless, whilst these measures have been adopted in some clinical trials and observational
29 research, they have not been widely used in pharmacogenomic studies.

30 The majority of recommendations for the assessment of treatment response have relied on data
31 from the prospective measurement of symptoms and functioning. Other initiatives have defined
32 therapeutic outcomes by applying retrospective assessment of clinical records, notably for
33 lithium treatment in bipolar disorder (Grof et al., 2002), and this approach has shown its utility
34 for observational pharmacogenomic research (Hou et al., 2016). As an important note, ADRs
35 are not always considered as part of drug response criteria (Jordan et al., 2018) despite the fact
36 that they are often primary causes of treatment discontinuation (Lahijani and Harris, 2017;
37 Legge et al., 2016). The standardisation of phenotypic definitions of ADRs has benefitted other
38 areas of pharmacogenomic research by aiding replication and supporting accurate meta-
39 analyses and psychiatry could benefit from similar initiatives (Carr and Pirmohamed, 2017).
40 An alternative approach used in pragmatic trials has been reliance on all-cause treatment
41 discontinuation as a primary outcome measure of medication response, given its ability to
42 capture both the efficacy and tolerability of medications (Kahn et al., 2008; Lieberman et al.,
43 2005).

1 A final crucial aspect in defining response is the assessment of treatment adherence. Whilst
2 adherence can be assessed through patient self-reports or information on health records, for
3 example prescription refills (Rossom et al., 2016; Sajatovic et al., 2010), the gold standard
4 remains the measurement of serum or plasma levels of the drug. Many drug response analyses
5 are not conducted in parallel with therapeutic drug monitoring (TDM) or serum level
6 measurements, and thus lack a biochemical perspective that permits insights into drug
7 metabolism, as well as confirmation of adherence (Hiemke, 2016). The integration of this
8 information into consensus measures has already been recommended by several reviews on
9 major psychiatric disorders (Fornaro et al., 2018; Gadad et al., 2018; Lally and Gaughran,
10 2019). Furthermore, the inclusion of ADRs and drug metabolism into treatment response
11 measurements would result in more robust and generalisable evidence in psychiatric treatment
12 research by following the triangulation principle that has been widely successful in
13 epidemiological studies (Lawlor et al., 2017).

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

22 **THE (A)TYPICAL STORY OF CLOZAPINE**

23 The results of extensive research on the second-generation (or “atypical”) antipsychotic
24 clozapine illustrate many of the challenges and opportunities to advance psychiatric
25 pharmacogenomics research. Clozapine is the only evidence-based medication for treatment-
26 resistant schizophrenia, a condition affecting up to a third of those diagnosed with this disorder
27 (Flanagan et al., 2020; Siskind et al., 2021). It is efficacious in around 40% of treated
28 individuals, with greater effectiveness if administered early in the course of the disorder, but it
29 is widely underutilised due to the perceived complexity of its prescribing (Remington et al.,
30 2016), including a gradual titration period which requires careful physical monitoring
31 (Stanworth et al., 2012). Whilst there can be multiple dose-related ADRs, the most prominent
32 adverse effect is a rare blood dyscrasia which can escalate to agranulocytosis, a frequently fatal
33 loss of white blood cells (De Berardis et al., 2018). The unpredictability of this idiosyncratic
34 reaction, which affects less than 1% of treated individuals, prompted the establishment of
35 recurrent blood monitoring services, which have to be used by all those prescribed clozapine
36 (Nielsen et al., 2016). Among several other ADRs, weight gain is common and frequently
37 severe (Flanagan et al., 2020), and sedation constitutes the main reason for voluntary treatment
38 discontinuation together with lack of monitoring compliance (Legge et al., 2016). The search
39 for pharmacogenomic markers to facilitate the management of clozapine-treated individuals
40 and lighten the burden of routine blood monitoring has been an explicit research goal for many
41 years (Arranz et al., 2000; Legge and Walters, 2019; Lieberman et al., 1990), although the
42 relationships between treatment efficacy, side effects and clozapine pharmacokinetics are still
43 unclear (Mauri et al., 2018).

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

11 Hampering advances in this field is uncertainty around the biological mechanisms responsible
12 for the efficacy and adverse effect profile of clozapine, and there is still debate about whether
13 norclozapine is itself of any pharmacological relevance (Hellman et al., 2016; Nucifora et al.,
14 2017). Additionally, the first-pass metabolism of clozapine leads to a secondary compound,
15 clozapine N-oxide, that has rarely been studied in this line of research. This is likely because
16 its plasma concentrations are not often assayed for monitoring treatment adherence, which is
17 the main clinical use of clozapine and norclozapine TDM (Flanagan et al., 2020). Nevertheless,
18 high clozapine doses can promote the formation of clozapine N-oxide, which is capable of
19 interacting with a broad array of neurotransmitter receptors (Diaz et al., 2014). Furthermore,
20 all clozapine metabolites can cross the blood-brain barrier through a yet-unknown transporter
21 (Dickens et al., 2018; Hellman et al., 2016), participating in further biological pathways which
22 are poorly understood. While these would be arguably the most relevant processes to study
23 particularly in a genomic setting (McMillan and Tyndale, 2018), research is still scarce as
24 directly measuring the amount of active clozapine in the *in vivo* brain is currently impractical
25 outside of animal models, and predictive cheminformatics algorithms are still of limited
26 application (Wong et al., 2019).

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

43 **RESEARCH WIDELY, IMPLEMENT LOCALLY**

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

24 Currently, several worldwide biobanks are working on incorporating information from eHRs
25 into drug-specific pharmacogenomic studies or clinical trials (Hoffman et al., 2020), and recent
26 results from Danish, British and Estonian Biobanks support previous observations that 90%-
27 99% of the population has at least one clinically actionable pharmacogenomic allele
28 (Lunenburg et al., 2021; McInnes et al., 2020; Reisberg et al., 2018). In psychiatry, the value
29 of routinely collected phenotypes has been demonstrated by studies examining the
30 antidepressant escitalopram (Jukić et al., 2018) and the antipsychotics aripiprazole and
31 risperidone (Jukić et al., 2019), performed in thousands of records from a therapeutic drug
32 monitoring service. This research used drug switching as one of its outcomes (referred to as
33 “therapeutic failure”, equivalent to all-cause treatment discontinuation referred to above), and
34 showed that individuals with certain CYP2C19 and CYP2D6 activity scores (ultrarapid and
35 poor metabolisers) were more prone to a change of prescription early in the course of treatment.
36 Importantly, this happened despite clinicians commonly altering doses during treatment in
37 reaction to drug response, thus not being completely agnostic of metabolism and other
38 underlying pharmacological processes. Similar studies conducted on child and adolescent
39 cohorts replicated these results (Aldrich et al., 2019; Jallaq et al., 2020), suggesting that genetic
40 variants determining enzyme activities could be beneficial in clinical decision-making even if
41 non-genetic factors, such as the co-prescription of enzyme inhibitors, are already considered.
42 While none of these experiments were explicitly designed for causal inference, complementary
43 data of metabolite concentrations on those same individuals supported the hypothesis that drug
44 switching was prompted by insufficient clinical response or the appearance of adverse effects.
45 This triangulation and replication of evidence, based on a broad but consistently defined

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

6 Clinical trials, particularly randomised controlled trials (RCTs), are the gold standard
7 experimental designs to evaluate the robustness of research findings and, ultimately, the utility
8 of interventions derived from them (Lawlor et al., 2017). The design of pharmacogenomic
9 RCTs is not straightforward and financial incentives to support them are not always apparent
10 (Russell et al., 2021), which has likely limited the scale of these studies in psychiatry. In fact,
11 most of those carried out to date have been industry-sponsored, focusing on antidepressant use
12 and following the more numerous PharmGKB guidelines for these medications (**Table 1**). A
13 recent synthesis of this RCT evidence, including the GUIDED trial discussed before, showed
14 that individuals who receive genotype-guided drug dosing are 1.71 times more likely to achieve
15 remission than those on standard care (Bousman et al., 2019), although the context of these
16 findings needs to be considered in light of frequent multiple secondary outcomes and post-hoc
17 analyses undertaken as part of the primary research studies. Furthermore it is worth noting that
18 several of these trials recruited only participants with prior inadequate treatment response,
19 although there is little reason to think that the benefits of pharmacogenomics will be restricted
20 to this patient group. Basic research to demonstrate this wider utility could explore, for
21 example, the stratification of patient cohorts by treatment response or outcome (**Figure 3**),
22 which could result in further insights regarding the genetic basis of these traits (Fabbri et al.,
23 2021).

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

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

8 **PHARMACOGENOMIC PHENOTYPES: SIMPLE TRAIT GENOMICS?**

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

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

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

33 **PHARMACOGENOMICS NEEDS TO BE GLOBALLY FOCUSED**

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

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

8 **CONCLUSIONS**

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

24 **ACKNOWLEDGEMENTS**

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29 **DECLARATION OF INTERESTS**

30 JTRW is a shareholder of Meomics Technology Ltd. JTRW and MO have received a
31 collaborative research grant from Takeda Pharmaceuticals. Takeda played no part in the
32 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” - “Ultrarapid metabolisers”

Medication class	Drug(s)	Biological mechanisms	Gene	Main supporting evidence
<i>Antidepressants</i>	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
<i>Antipsychotics</i>	Aripiprazole, brexiprazole, haloperidol, pimozide, risperidone, zuclopenthixol	Pharmacokinetics	CYP2D6	Treatment discontinuation more likely in PMs
<i>Mood stabilisers</i>	Phenytoin	Pharmacokinetics	CYP2C9	ADRs more likely in PMs
	Carbamazepine, oxcarbazepine, phenytoin	Immunological	HLA-A, HLA-B	HLA-A*31:01 and HLA-B*15:02 likely causal for severe ADRs
<i>ADHD medications</i>	Atomoxetine	Pharmacokinetics	CYP2D6	ADRs more likely in PMs

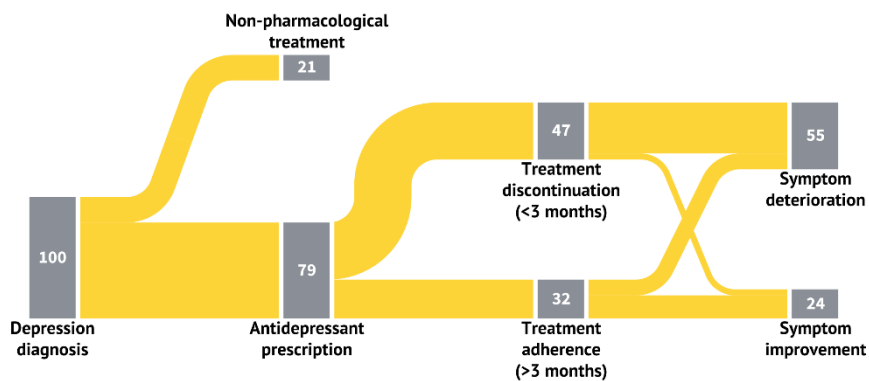
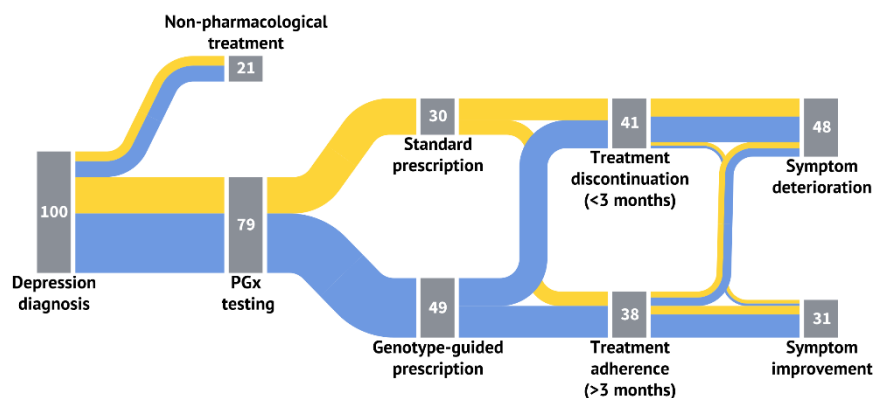
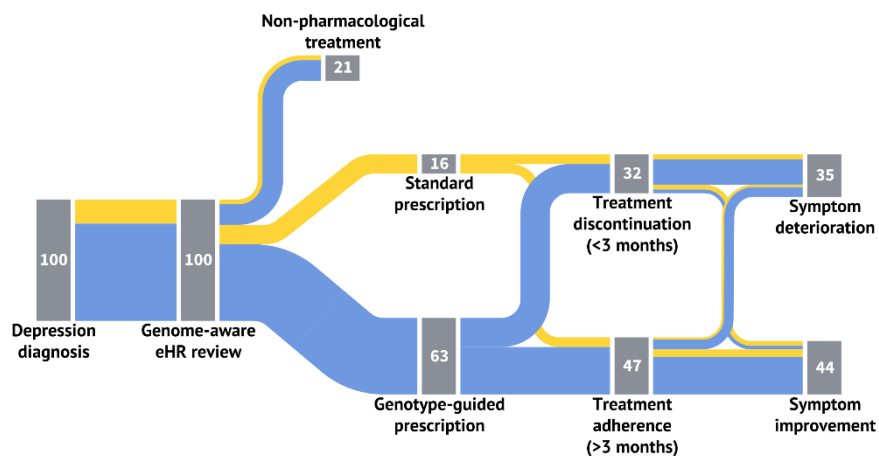
A**B****C**

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).

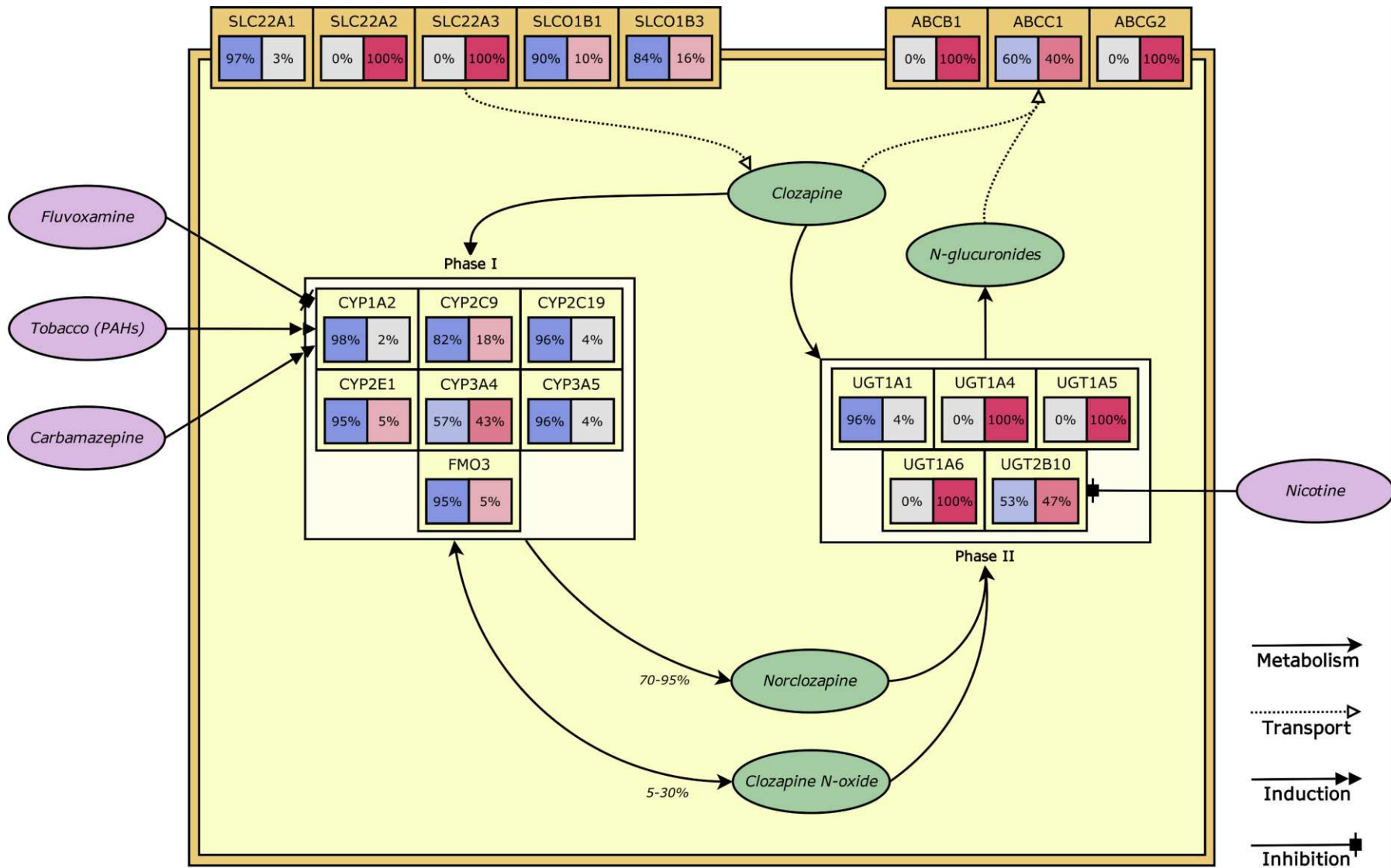


Figure 2: Schematic depiction of a hepatocyte illustrating current knowledge about the clozapine metabolic pathway, which highlights proteins identified in the latest PharmGKB review (Thorn et al., 2018) and those encoded by ADME genes found in GWAS approaches (Legge et al., 2017; Pardiñas et al., 2019; 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 ($MAF \geq 1\%$, left box, blue) or rare ($MAF < 1\%$, right box, red).

CHALLENGES

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

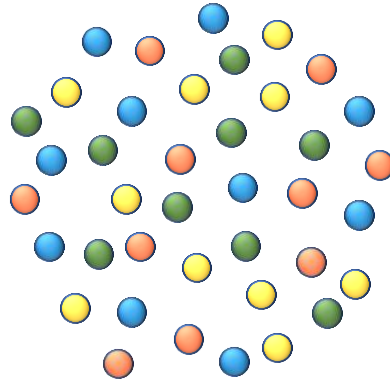


Results

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

ROADBLOCKS AND LIMITATIONS

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.

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