Review and Consensus on Pharmacogenomic Testing in Psychiatry

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Key words

precision medicine, pharmacogenetics, prescribing

received 09.07.2020
revised 05.10.2020
accepted 07.10.2020
published online 04.11.2020

Bibliography
Pharmacopsychiatry 2021; 54: 5–17
DOI 10.1055/a-1288-1061
ISSN 0176-3679

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ABSTRACT

The implementation of pharmacogenomic (PGx) testing in psychiatry remains modest, in part due to divergent perceptions of the quality and completeness of the evidence base and diverse perspectives on the clinical utility of PGx testing among psychiatrists and other healthcare providers. Recognizing the current lack of consensus within the field, the International Society of Psychiatric Genetics assembled a group of experts to conduct a narrative synthesis of the PGx literature, prescribing guidelines, and product labels related to psychotropic medications as well as the key considerations and limitations related to the use of PGx testing in psychiatry. The group concluded that to inform medication selection and dosing of several commonly-used antidepressant and antipsychotic medications, current published evidence, prescribing guidelines, and product labels support the use of PGx testing for 2 cytochrome P450 genes (*CYP2D6, CYP2C19*). In addition, the evidence supports testing for human leukocyte antigen genes when using the mood stabilizers carbamazepine (*HLA-A and HLA-B*), oxcarbazepine (*HLA-B*), and phenytoin (*CYP2C9, HLA-B*). For valproate, screening for variants in certain genes (*POLG, OTC, CSP1*) is recommended when a mitochondrial disorder or a urea cycle disorder is suspected. Although barriers to implementing PGx testing remain to be fully resolved, the current trajectory of discovery and innovation in the field suggests these barriers will be overcome and testing will become an important tool in psychiatry.

Introduction

The treatment of psychiatric disorders commonly involves the use of psychotropic medications such as antidepressants, antipsychotics, mood stabilizers, anxiolytics/hypnotics, stimulants, or anti-addiction medications. However, recipients of these medications often experience a lengthy trial-and-error process marked by poorly managed symptoms and/or adverse drug reactions before the right medications and doses are established. As such, strategies to predict or mitigate these poor responses are needed. Current pharmacological strategies include scheduled titrations over time (sometimes guided by therapeutic drug monitoring) [1] until a patient receives a standard target dose thought to be sufficient for clinical efficacy. Yet the same dose may not be the correct one for all individuals. Another emerging and complementary strategy is the implementation of pharmacogenomic (PGx) testing to inform medication selection and dosing decisions [2]. PGx testing examines genetic variation involved in medication metabolism and action to facilitate individualized prescribing, thus reducing undesirable outcomes. To date, this strategy has been implemented in a growing number of medical centres around the world and has fueled a burgeoning commercial PGx testing sector [3–5]. However, widespread implementation and adoption of this strategy has not yet occurred in psychiatry, in part due to diverging perceptions of the quality and completeness of the PGx evidence base, variable knowledge among psychiatrists about genetics, and mixed views related to the utility of PGx testing in clinical practice. Recognizing the current lack of consensus within the field, the International Society of Psychiatric Genetics (ISPG) assembled a group of experts to provide an overview of PGx mechanisms, summarize the current evidence and treatment recommendations related to PGx in psychiatry, and provide consensus recommendations for the use of PGx testing in clinical practice [6]. This review discusses the evidence that was considered by the ISPG and provides an up-to-date summary of recent developments that clinicians should know when considering PGx testing for their patients.

Pharmacogenomic Mechanisms

Pharmacokinetics

The majority of medications used to treat psychiatric conditions undergo hepatic metabolism, although some, such as lithium, are eliminated only through the kidneys. A number of genes encoding oxidative (Phase 1) and conjugative (Phase 2) metabolizing enzymes contain variants known to influence enzymatic activity. In addition, genetic variation in drug transporters expressed in the liver, gut, and at the blood brain barrier may alter the distribution of drugs and thereby alter their pharmacokinetic profile. The drug metabolizing enzymes that are currently the most clinically relevant to commonly used psychiatric medications are the cytochrome P450 (CYP) enzymes CYP2C9, CYP2C19, and CYP2D6 [7]. While genes encoding conjugative enzymes, such as UDP-glucuronosyltransferase (*UGT*) and catechol-O-methyltransferase (*COMT*) enzymes along with the P-glycoprotein (*ABCB1*) drug trans-

porter, may also be relevant, their clinical utility has not yet been established.

The CYP superfamily is arguably the most important enzyme system for drug metabolism. Allelic variants of *CYP* genes are commonly referred to using the star (*) nomenclature [8, 9]. Genotypes (reported as star diplotypes, e. g., *CYP2D6 * 1/ * 2*) are then translated into metabolizer phenotypes. The most widely used phenotype classification system includes: ultrarapid metabolizers (UMs), rapid metabolizers (RMs), normal metabolizers (NMs, activity of reference or sum of allelic variants with activity that is similar to that of the reference), intermediate metabolizers (IMs), and poor metabolizers (PMs, little or no enzyme activity) [10]. In this context, "activity" refers to the metabolic capacity of an enzyme, which broadly includes catalytic activity and enzyme abundance [10].

Pharmacodynamics

Pharmacodynamics refers to the biochemical, cellular, and physiologic effects of medications and their mechanism of action [11]. In psychiatric PGx, the focus has historically been on variation in genes encoding neurotransmitter receptors and reuptake transporters that are located on the pre- or postsynaptic cell membranes. More recently, the focus has expanded to include genes involved in signal transduction, gene transcription, and protein folding and trafficking. However, our understanding of how genetic variation affects the pharmacodynamics of psychiatric medications is still evolving.

Immunologic mechanisms

Immunologic mechanisms are often involved in drug hypersensitivity reactions. Variations in some human leukocyte antigen (*HLA*) genes are implicated in the risk for potentially severe and fatal hypersensitivity reactions to certain anticonvulsants/mood stabilizers [12]. More details are provided below in the section related to mood stabilizers.

Pharmacogenomic Evidence and Guidelines for Psychiatry

Antidepressants

Evidence

The bulk of antidepressant PGx evidence has been derived from studies on major depressive disorder and has focused on pharmacokinetic mechanisms, which have been reviewed in detail elsewhere [13]. In brief, findings have shown that genetic variants in *CYP2C19* and *CYP2D6* are associated with antidepressant blood concentrations, adverse drug reactions, and, to a lesser extent, clinical outcomes such as treatment discontinuation or symptom response [14, 15]. From a pharmacodynamic perspective, the Sequenced Treatment Alternatives to Relieve Depression (STAR * D) study [16], the Genome-based Therapeutic Drugs for Depression (GENDEP) project [17, 18], and the Munich Antidepressant Response Signature (MARS) [19], as well as the International SSRI Pharmacogenomics Consortium GWAS analysis [20], have not consistently supported any single pharmacodynamic gene variant as a significant predictor of antidepressant treatment response. The Pharmacogenomics Knowledgebase (PharmGKB) contains clinical annotations summarizing literature findings for associations between antidepressant efficacy and potentially relevant genes such as *SLC6A4* (serotonin transporter), *HTR2A* (serotonin 2A receptor), *GRIK4* (glutamate ionotropic receptor kainate 4), and *FKBP5* (FK506 binding protein 5). However, the associations have only moderate or low levels of evidence [21].

Guidelines

There is disagreement about the role of PGx testing in antidepressant prescribing. A recent safety communication from the US Food and Drug Administration (FDA) cautioned against using PGx testing to guide antidepressant prescribing, citing lack of evidence [22]. However, as clarified by us previously [23], 17 antidepressants have been included in published PGx-based prescribing guidelines [13, 24] or product labels for associations with *CYP2C19* and/or *CYP2D6* (▶ **Table 1**). The Clinical Pharmacogenetic Implementation Consortium (CPIC) guidelines for *CYP2C19* PMs suggest a 50 % reduction of the recommended starting dose of citalopram, escitalopram, sertraline, and tertiary amine tricyclic antidepressants (e. g., amitriptyline); whereas RMs/UMs treated with citalopram, escitalopram, and tertiary amine tricyclic antidepressants would likely have inadequate treatment response due to inadequate circulating antidepressant blood levels and thus may benefit from an alternative antidepressant [13, 24]. For *CYP2D6* PMs, CPIC recommends up to a 50 % reduction of most tricyclic antidepressants, fluvoxamine, and paroxetine doses, while for UMs, it is advised to select an alternative antidepressant that is not predominantly metabolized by *CYP2D6*13, 24]. In addition, the Dutch Pharmacogenetics Working Group (DPWG) recommends reduced dosing (amount unspecified) of venlafaxine for *CYP2D6* PMs and up to 150 % increased dosing for UMs [25, 26].

Antipsychotics

Evidence

Most antipsychotics are hepatically metabolized by one or more CYP450 enzymes. To date, studies of pharmacokinetic genes have predominantly focused on *CYP2D6* genetic variation, with risperidone and aripiprazole receiving the most recent attention [27–29]. In contrast, evidence relating to the impact of pharmacodynamic genes on antipsychotics drug response is still emerging. It is well established that antipsychotics act primarily via antagonism [30] or partial-antagonism [31] of the dopamine D_2 receptor. However, evidence linking genetic variation in the dopamine D_2 receptor (*DRD2*) gene to antipsychotic efficacy or adverse reactions has been inconsistent [32].

Guidelines

To date, 10 antipsychotics have product labels or prescribing guidelines [25] that offer selection or dosing recommendations based on *CYP2D6* metabolizer status (▶ **Table 2**). For all of these drugs, the guidelines or product labels recommend that *CYP2D6* PMs receive lower starting doses or an alternative drug not primarily metabolized by *CYP2D6*. In addition, the DPWG guidelines recommend reductions in the starting dose for pimozide and zuclopenthixol among *CYP2D6* IMs, while for UMs they recommend the use of an alternative drug or titration to the maximum dose for haloperidol,

▶ **Table 1** Actionable pharmacogenetic guidelines and product labels by antidepressants.

	Actionable Guideline Available[1]		Product Label[2]			
Antidepressant	**CPIC**	**DPWG**	**FDA**	**EMA**	**PMDA**	**HCSC**
Amitriptyline	CYP2C19, CYP2D6	CYP2D6	CYP2D6	–	–	–
Amoxapine	–	–	CYP2D6	–	–	–
Citalopram	CYP2C19	CYP2C19	CYP2C19	–	–	CYP2C19
Clomipramine	CYP2C19, CYP2D6	CYP2D6	CYP2D6	–	–	–
Desipramine	CYP2D6	–	CYP2D6	–	–	–
Doxepin	CYP2C19, CYP2D6	CYP2D6	CYP2C19, CYP2D6	–	–	–
Duloxetine	–	–	CYP2D6	CYP2D6	–	–
Escitalopram	CYP2C19	CYP2C19	–	–	CYP2C19	–
Fluvoxamine	CYP2D6	–	CYP2D6	–	–	–
Imipramine	CYP2C19, CYP2D6	CYP2C19, CYP2D6	CYP2D6	–	–	–
Nortriptyline	CYP2D6	CYP2D6	CYP2D6	–	–	CYP2D6
Paroxetine	CYP2D6	CYP2D6	–	–	–	–
Protriptyline	–	–	CYP2D6	–	–	–
Sertraline	CYP2C19	CYP2C19	–	–	–	–
Trimipramine	CYP2C19, CYP2D6	–	CYP2D6	–	–	–
Venlafaxine	–	CYP2D6	CYP2D6	–	–	–
Vortioxetine	–	–	CYP2D6	CYP2D6	–	CYP2D6

CPIC: Clinical Pharmacogenetics Implementation Consortium; DPWG: Dutch Pharmacogenetics Working Group; EMA: European Medicines Agency; FDA: US Food and Drug Administration; HCSC: Health Canada (Santé Canada); PMDA: Pharmaceuticals and Medical Devices Agency, Japan. [1]Only guidelines where a clinical action has been recommended were included. [2]Product label information was extracted from the Pharmacogenomics Knowledgebase (PharmGKB), only labels coded as "actionable," "test recommended," or "test required" by PharmGKB curators were included. For a description of these categories (PGx levels) and the drug label curation process, see https://www.pharmgkb.org/page/drugLabelLegend. Drugs reviewed that did not have an actionable guideline or product label included: agomelatine, buproprion, desvenlafaxine, fluoxetine, levomilnacipran, mianserin, mirtazapine, milnacipran, nefazodone, phenelzine, reboxetine, selegiline, tranylcypromine, trazodone, and vilazodone.

▶ **Table 2** Actionable pharmacogenetic guidelines and product labels by antipsychotics.

	Actionable Guideline Available[1]		Product Label[2]			
Antipsychotic	**CPIC**	**DPWG**	**FDA**	**EMA**	**PMDA**	**HCSC**
Aripiprazole	–	CYP2D6	CYP2D6	CYP2D6	–	CYP2D6
Brexpiprazole	–	CYP2D6	CYP2D6	CYP2D6	–	–
Clozapine	–	–	CYP2D6	–	–	–
Haloperidol	–	CYP2D6	–	–	–	–
Iloperidone	–	–	CYP2D6	–	–	–
Perphenazine	–	–	CYP2D6	–	CYP2D6	–
Pimozide	–	CYP2D6	CYP2D6	–	–	–
Risperidone	–	CYP2D6	–	–	–	–
Thioridazine	–	–	CYP2D6	–	–	–
Zuclopenthixol	–	CYP2D6	–	–	–	–

CPIC: Clinical Pharmacogenetics Implementation Consortium; DPWG: Dutch Pharmacogenetics Working Group; EMA: European Medicines Agency; FDA: US Food and Drug Administration; HCSC: Health Canada (Santé Canada); PMDA: Pharmaceuticals and Medical Devices Agency, Japan. [1]Only guidelines where a clinical action has been recommended were included. [2]Product label information was extracted from the Pharmacogenomics Knowledgebase (PharmGKB), only labels coded as "actionable," "test recommended," or "test required" by PharmGKB curators were included. For a description of these categories (PGx levels) and the drug label curation process, see https://www.pharmgkb.org/page/drugLabelLegend. Drugs reviewed that did not have an actionable guideline or product label included: asenapine, cariprazine, chlorpromazine, fluphenazine, loxapine, lurasidone, olanzapine, paliperidone, promethazine, quetiapine, thiothixene, trifluoperazine, and ziprasidone.

risperidone, and zuclopenthixol. Of note, the FDA product label for clozapine suggest *CYP2D6* PMs may require a dose reduction, despite CYP2D6's minor role (6 %) in the metabolism of clozapine [33], and a recent study that showed *CYP2D6* genotype-predicted enzyme activity explained a minimal amount of the variance (3 %–7 %) in dose-adjusted clozapine levels and psychotic symptom severity [34]. In addition, the FDA product label for pimozide states *CYP2D6* genetic testing should be performed if doses above 0.05

▶ **Table 3** Actionable pharmacogenetic guidelines and product labels by mood stabilizers/anticonvulsants.

	Actionable Guideline Available[1]		Product Label[2]			
Mood stabilizers/ anticonvulsants	**CPIC**	**DPWG**	**FDA**	**EMA**	**PMDA**	**HCSC**
Carbamazepine	HLA-A, HLA-B	–	HLA-A, HLA-B	–	HLA-A, HLA-B	HLA-A, HLA-B
Oxcarbazepine	HLA-B	–	HLA-B	–	–	HLA-B
Phenytoin	CYP2C9, HLA-B	CYP2C9	HLA-B	–	–	HLA-B
Valproic acid	–	–	OTC, POLG	–	CPS1, OTC	OTC, POLG

CPIC: Clinical Pharmacogenetics Implementation Consortium; DPWG: Dutch Pharmacogenetics Working Group; EMA: European Medicines Agency; FDA: US Food and Drug Administration; HCSC: Health Canada (Santé Canada); PMDA: Pharmaceuticals and Medical Devices Agency, Japan. [1]Only guidelines where a clinical action has been recommended were included. [2]Product label information was extracted from the Pharmacogenomics Knowledgebase (PharmGKB), only labels coded as "actionable," "test recommended," or "test required" by PharmGKB curators were included. For a description of these categories (PGx levels) and the drug label curation process, see https://www.pharmgkb.org/page/drugLabelLegend. Drugs reviewed that did not have an actionable guideline or product label included: eslicarbazepine, gabapentin, lamotrigine, levetiracetam, lithium, phenobarbital, pregabalin, topiramate, vigabatrin, and zonisamide.

mg/kg/day in children or above 4 mg/day in adults will be used. However, other regulatory agencies seem not to mention testing for *CYP2D6* on their pimozide labels (▶ **Table 2**).

Mood stabilizers/anticonvulsants

Evidence

In contrast to antidepressants and antipsychotics, there is limited evidence supporting a link between genetic variation in pharmacokinetic genes and mood stabilizer/anticonvulsant treatment outcomes. An exception is the strong associations between *CYP2C9* IMs and PMs and increased phenytoin plasma concentrations [35]. Furthermore, there are no robust associations between pharmacodynamic gene variants and mood stabilizer/anticonvulsant treatment outcomes. Three independent GWASs have identified SNPs associated with lithium response, but each study implicates a different locus [36–38]. Polygenic risk scores derived from schizophrenia and depression GWAS have been associated with lithium response [39, 40], but none of these findings have been replicated.

The immunologic genes *HLA-A* and *HLA-B* are robustly linked to rare, but potentially fatal, severe cutaneous adverse reactions (SCARs) (e. g., Stevens-Johnson syndrome [SJS] and toxic epidermal necrolysis [TEN]) following exposure to carbamazepine, oxcarbazepine, and phenytoin [41]. Specifically, *HLA-A * 31:01* and *HLA-B * 15:02* alleles are associated with a higher risk of SCARs if exposed to carbamazepine [12], while only the *HLA-B * 1502* allele is linked to a higher risk of SCARs following exposure to oxcarbazepine and phenytoin [42]. Notably, a recent meta-analysis of 11 studies in Asian (Chinese, Korean, and Thai) populations found a pooled odds ratio of 2.4 for risk of lamotrigine-induced SJS/TEN in *HLA-B * 15:02* carriers [43].

Guidelines

Product labels and prescribing guidelines are available for carbamazepine, oxcarbazepine, and phenytoin (▶ **Table 3**). For carbamazepine and oxcarbazepine, the FDA-approved labels recommend testing for the *HLA-B * 1502* allele prior to prescribing these medications to "genetically at-risk populations." Current evidence suggests at-risk individuals are those of Han Chinese, Thai, Vietnamese, Indonesian, Malay, Filipino, or Indian descent, who carry this allele more frequently (3–36 %) [44, 45]. In fact, in Taiwan [46], Hong Kong [47], and Thailand [48], HLA testing prior to prescribing carbamazepine and oxcarbazepine is standard practice. The FDA-approved label for carbamazepine also provides information about *HLA-A * 31:01* and *HLA-B * 1502*. Other regulatory agencies such as Health Canada (HCSC) and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan also note the risk of prescribing carbamazepine to individuals that carry the *HLA-A * 31:01* or *HLA-B * 1502* alleles. Aligned with these product label recommendations, CPIC recommends use of alternative medications for individuals who test positive for *HLA-A * 31:01* (carbamazepine) or *HLA-B * 1502* (carbamazepine, oxcarbazepine, and phenytoin). Furthermore, the CPIC guideline for phenytoin recommends a 50 % dose reduction for *CYP2C9* PMs, assuming the individual is not a carrier of the *HLA-B * 1502* allele [35, 44].

Finally, FDA, HCSC, and the PMDA product labels include language that valproic acid is contraindicated or recommend genetic tests before prescribing valproic acid to individuals suspected (e. g., by family history) of having certain rare metabolic disorders. Sequencing of the gene *POLG* (mitochondrial DNA polymerase γ) is recommended in patients suspected of having a mitochondrial disorder, while patients suspected of having a urea cycle disorder should be screened for mutations in the genes *OTC* (ornithine transcarbamylase) and *CPS1* (carbamoyl-phosphate synthase 1). Use of valproic acid by these individuals can induce liver toxicity, hyperammonemia, and encephalopathy [49].

Anxiolytics/hypnotics

Evidence

Most anxiolytic/hypnotic medications are preferentially metabolized by *CYP3A4*, *CYP3A5*, and *CYP2C19*[21]. Links between anxiolytic/hypnotic treatment outcomes and *CYP3A4* or *CYP3A5* genetic variation have been inconsistent [21], while associations between *CYP2C19* allelic variation and anxiolytic/hypnotic concentrations are more robust. This is particularly the case for clobazam and, to a lesser extent, diazepam. Serum concentrations of clobazam were increased 30–50 % and norclobazam (active metabolite) concentrations were up to 7-fold higher in *CYP2C19* PMs relative to other metabolizer groups [50], with single and repeated dosing half-lives in PMs of 130 hours and 289 hours, respectively [51]. Likewise, for diazepam and its active metabolite (nordiazepam), *CYP2C19* PMs had 40 % and 75 % higher plasma half-lives compared to NMs, re-

spectively [52]. There is also some evidence linking the *UGT2B15* (UDP-glucuronosyltransferase 2B15) rs1902023:AA genotype with reduced clearance of lorazepam and oxazepam [21]. In contrast, the limited available data do not suggest that any pharmacodynamic gene or variant is robustly associated with response to anxiolytic/hypnotic medications [53].

Guidelines

There are 2 actionable gene-drug pairs included on FDA-approved product labels, *CYP2C19* and clobazam and *CYP2C19* and diazepam. For clobazam, the FDA recommends that *CYP2C19* PMs receive a starting dose of 5mg/day, with up-titrations proceeding slowly according to body weight. For diazepam, the label does not provide specific dosing recommendations but does note that *CYP2C19* PMs could present with marked differences in drug clearance, suggesting caution and additional monitoring is warranted when prescribing this drug to *CYP2C19* PMs.

ADHD medications

Evidence

Stimulants, including methylphenidate and amphetamine, and the nonstimulant atomoxetine, are generally the first line treatments to alleviate core ADHD symptoms. To date, the strongest evidence for the impact of *CYP2D6* genotype on atomoxetine has come from pharmacokinetic studies and clinical outcomes in large fixed-dose treatment trials. This body of work, recently reviewed by CPIC and summarized in their consensus guideline [54], demonstrates that using standard dosing approaches, non-PMs are less likely than PMs to achieve blood concentrations (> ~ 200ng/ml) necessary for clinical effectiveness. In contrast, PMs are more likely to experience improvement in ADHD symptoms, but due to their absence of CYP2D6 metabolic activity, they are at also at increased risk of having side effects from atomoxetine and may therefore require lower doses. From a pharmacodynamic perspective, there are a number of interesting findings warranting further investigation related to dopamine and norepinephrine disposition in the brain (e. g., *COMT*), as well as the contribution of genetic variability in *CES1* (carboxylesterase 1) to methylphenidate metabolism [55]. However, the clinical efficacy and utility of testing for these genes remains unknown.

Guidelines

At the present time, only *CYP2D6* is noted as a PGx biomarker that may be helpful in guiding treatment with atomoxetine. Official FDA product labeling, CPIC [54], and DPWG [25] all note the clinical relevance of *CYP2D6* genetic variation for atomoxetine prescribing. In the product labeling, patients taking a *CYP2D6* inhibitor or who are known *CYP2D6* PMs are recommended to start at the same dose as NMs, but to approach dose escalation differently by only considering increases after 4 weeks if the drug is tolerated and symptoms do not improve. CPIC guidelines offer more specific recommendations with respect to *CYP2D6* genotype-informed therapy (i. e., specific starting doses, titration, and drug exposure/plasma verification recommendations for children and adults) [54].

Addiction medications

Evidence

Among substance use disorders and behaviors, several pharmacokinetic and pharmacodynamic genes have been studied, some of which are promising. Markers in the nicotine-metabolizing gene *CYP2A6* have repeatedly been associated with cessation treatment success [56–58] and a randomized, double-blind placebo-controlled trial suggested that *CYP2A6* genotype-guided therapy could help improve outcomes for various smoking cessation interventions [59]. Likewise, for *CYP2B6,* particularly the **6* decreased function allele, has repeatedly been associated with higher methadone plasma concentrations [60], but the magnitude of this effect casts doubt upon the suitability of this marker for use in the clinic [61].

Beyond pharmacokinetics, a number of GWAS have identified candidate variants for tobacco, alcohol, and opioid use behaviors [62, 63], although replication of these findings is still required. However, recent work has demonstrated that variation in the α5 nicotinic cholinergic receptor (*CHRNA5*) gene has prognostic significance for smoking cessation and response to nicotine replacement therapy [56–58]. Specifically, individuals with *CHRNA5* genetic variants that increase the risk for heavy smoking and tobacco use disorder are also more likely to benefit from pharmacotherapy for smoking cessation, compared to those who lack the risk variants. In people with alcohol dependence, a variant of the mu opioid receptor gene (*OPRM1*), rs1799971 (A118G), has been repeatedly associated with reduced analgesic response to exogenous opioids as well as reduced relapse rates during naltrexone treatment [61]. However, a large meta-analysis study has indicated that the effect of the A118G variant on substance dependence per se is only modest [64].

Guidelines

At the time of this review, there were no PGx guidelines or product labels for addiction medications due to the relatively limited evidence base.

Pharmacogenomic Testing in Psychiatry

The PGx evidence to date suggests genetic variation in *CYP2D6*, *CYP2C19*, *CYP2C9, HLA-A,* and *HLA-B* should be considered when prescribing several medications used in psychiatry. However, to facilitate the implementation of PGx into clinical practice, the mechanisms for testing, reporting, and interpreting the genomic variations associated with the tested genes, as well as understanding the complexities and limitations of testing, are required [65]. In this section, we provide an overview of PGx testing as it relates to psychiatry and highlight some of the challenges and limitations one should consider when using PGx in clinical practice.

Test providers

PGx test providers are typically classified into 2 groups: commercial and non-commercial. The number of test providers in each of these groups is difficult to estimate. Recent estimates suggest there are over 75 laboratories in the US that offer PGx testing [3]. In addition, many laboratories participate in the Genetic Testing Registry that is maintained by the National Center for Biotechnology Information (https://www.ncbi.nlm.nih.gov/gtr/), and CPIC lists a growing number of clinics, medical centers, and healthcare organizations/systems around the world that have implemented PGx into clinical practice.

The 2 most frequently used implementation models by commercial providers are the gatekeeper and the direct-to-consumer

(DTC) models [66]. The major difference between these 2 models is the degree to which a healthcare provider's involvement is required to order and/or interpret test results. Within the gatekeeper model, a healthcare provider must be involved in the ordering and interpretation, or in some cases only the ordering or only the interpretation of the test. In contrast, the DTC model does not require the involvement of a healthcare provider in the ordering or interpretation process, although some DTC companies offer consultation/interpretation services with an in-house pharmacist or physician. Non-commercial PGx test providers (i. e., healthcare organizations/systems) typically restrict testing to their specific patient population and require ordering and interpretation of test results by a healthcare provider. However, delivery of the test results varies by non-commercial providers due to differences in the clinical workflows, reimbursement environment, and information technology resources available [66].

Test content

PGx tests may include a single gene or a panel of genes, although multiple-gene panels have become the norm [3, 4]. Evaluations of commercial PGx testing panels have shown that gene content varies from test-to-test and often includes genes lacking sufficient evidence to guide prescribing in psychiatry (e. g., *COMT*, *CYP1A2, DRD2, SLC6A4*) [4, 67, 68]. Thus, the number of genes included on a testing panel is not an adequate metric for test selection. In psychiatry, the gene content most relevant to clinical practice, as discussed in the preceding sections, includes *CYP2D6, CYP2C19*, *CYP2C9, HLA-A, and HLA-B B*[65] and most commercial and non-commercial providers test for *CYP2D6, CYP2C19,* and *CYP2C9* [67]. However, even when the same genes appear on a testing panel, the number of sequence variations, or alleles, assayed within those genes can substantially vary among tests [68]. Unfortunately, regulatory standards for PGx test content have not been established. The FDA has recently issued warnings related to PGx testing that has specifically questioned the testing of particular gene-drug pairs to inform prescribing of psychiatric medications [22], which has commenced a discussion on FDA's role in the regulation of PGx testing [23] and has raised concerns related to the content validity and potential detrimental impact of PGx testing panels that include genes with limited supporting evidence [69]. However, the Association for Molecular Pathology (AMP) and College of American Pathologists (CAP) have published recommendations for clinical genotyping allele selection for *CYP2C9* [70] and *CYP2C19* [71] with a *CYP2D6* allele selection guide underway. To enable full use of these guides, test providers should be transparent about which SNPs are tested and not just provide genotype calls or genotype-derived phenotype assignments. A decision tree for guiding test selection is provided elsewhere [72].

Test analytical validity

PGx testing is ideally performed in laboratories that have been evaluated and accredited according to national regulatory standards to ensure a high level of analytical validity (i. e., ability of a test to detect whether a specific genetic variant is present or absent). However, analytical validity does vary among accredited laboratories. This variability stems from challenges in accurately calling "star" alleles (or haplotypes) from the variants tested, identification of structural variation (e. g., gene copy number variants, or CNVs), and the presence of novel or rare allelic variants that might affect PCR-based amplification and subsequent genotyping/sequencing. Genotyping technologies are less uniform in the detection of structural variants than in the detection of SNPs or short insertion/deletion polymorphisms. For example, many tests that detect *CYP2D6* CNVs often only report the presence of a "duplication" without specifying which allele is "duplicated" and default the copy number to "2" without determining how many copies of the gene are actually present. This can lead to inaccurate phenotype assignments, which in turn may lead to inaccurate recommendations. There are also numerous so-called hybrid genes that are part *CYP2D6* and part *CYP2D7* and do not usually encode a functional enzyme. Detailed descriptions of these structural variants and their impact for psychiatry are described elsewhere [73, 74].

Another challenge for PGx testing is the detection of rare variants. Current PGx testing panels do not typically include rare variants and are also not designed to detect novel variants. Sequencing has the advantage of detecting rare variants that are not part of PGx panels. It has been estimated that rare variants may account for up to 20–30 % of the variance in interindividual response to medications [75]. However, it needs to be emphasized that the functional impact of a rare or novel allele may be uncertain or unknown, and thus clinical interpretation of genotypes containing such variants is often difficult.

Test feasibility

The feasibility of PGx testing can be a challenge in clinical settings and is dependent on 1) availability of testing, 2) patient and provider acceptability of testing, 3) testing turnaround times, and 4) testing affordability. The exponential growth of PGx testing over the last decade, particularly in the US, has resulted in an increase in testing availability. Likewise, providers and the general public report positive opinions related to PGx testing [76–80], and patient's perception of care improves when testing is delivered [81]. However, strategies for reducing turnaround times and the monetary costs of performing PGx testing are still evolving. Turnaround times range from 1 day to 3 weeks [4], which can reduce the practicality of testing particularly in acute care settings, where expedited prescribing decisions are required. This situation will improve as rapid testing technologies delivering results within an hour emerge [82, 83]. From a cost perspective, PGx testing remains unattainable for many due to the high out-of-pocket expense and limited third-party reimbursement, although several third-party payers have recently announced limited coverage of testing or are actively evaluating the value of offering such coverage [84].

Test clinical efficacy and cost-effectiveness

Establishing clinical efficacy and cost-effectiveness of PGx testing is vital to widespread clinical uptake and adoption. Two meta-analytic evaluations of the clinical efficacy of commercial PGx testing in psychiatry have been conducted for prospective and retrospective clinical trials and showed that testing improves the likelihood of achieving symptom remission compared to treatment as usual [85, 86]. However, recent inconclusive or negative trial findings have been reported [87, 88], leading some to conclude that commercial PGx testing is not ready for widespread use in psychiatry

[89]. Furthermore, evidence of clinical efficacy has primarily been constrained to adults of European-ancestry with major depressive disorder who had a history of antidepressant non-response or adverse drug reactions, suggesting evaluations of clinical efficacy in other clinical populations (e. g., non-Europeans, treatment-naïve, children, schizophrenia) are required.

The cost-effectiveness of PGx testing has been evaluated in retrospective [90, 91] and prospective clinical trials [92–94] for both psychotropic and non-psychotropic drugs in diverse clinical settings. The majority of these evaluations have concluded that PGx testing is a cost-effective or cost-saving strategy relative to treatment as usual [90, 95], although limitations have been noted [92], and most economic studies have been completed by providers of commercial PGx testing. Nevertheless, findings to date are aligned with the notion that tailoring drug therapy to an individual's PGx profile can reduce visits to healthcare providers and pharmacy costs related to medication switching as well as emergency room visits and hospitalizations due to adverse drug reactions.

Test results interpretation and delivery

For most psychiatrists and other healthcare professionals, the interpretation of PGx test results can be a challenge without accompanying clinical decision support. Clinical decision support can be provided in a variety of forms, most commonly through interpretative clinical reports that translate raw PGx data into clinical recommendations and in ideal cases interruptive alerts implemented within the electronic medical record.

The translation process, however, is not trivial. The process includes assigning a function to the alleles possessed by an individual and then combining those functions to derive a phenotype. For some genes, such as *CYP2D6*, recommendations have been published with the goal to standardize the genotype to phenotype translation [96]. However, this process remains inconsistent across test providers and no gold standard approach exists. Some providers combine information from several genes (combinatorial approach) and employ proprietary algorithms that utilize—to varying degrees—the published literature, product labels, and/or guidelines developed by expert groups to derive recommendations [97]. This variability in genotype to phenotype translation and clinical decision support from one test provider to another can lead to potential discordant recommendations [98]. In addition, third-party analytic applications are now ubiquitously available and are capable of analyzing the raw data available from DTC providers, although the validity of the results produced by these applications have been questioned [99].

Beyond PGx information, other factors such as age [100], sex [101], concomitant medications [102], renal/hepatic function [103], inflammation [104, 105], lifestyle (e. g., smoking, diet), and weight [106] are also important considerations when applying PGx test results (see [107] for a detailed review of these factors). However, most PGx test providers do not typically account for these factors in their clinical decision support, and as such, it is the responsibility of the healthcare provider to be aware and understand how these factors may influence the PGx-based recommendations being offered. For example, an individual genotyped as a NM for a CYP enzyme who is taking a strong inhibitor of that enzyme will phenotypically resemble a PM, while a UM may convert to an IM. Weak inhibitors may convert a NM to an IM and a UM to a NM. This phenomenon is known as phenocopying. Likewise, an individual genotyped as a NM for a CYP enzyme who is taking a potent inducer of that enzyme will phenotypically resemble an UM. In these clinical scenarios, recommendations provided by a typical PGx test report, which does not account for the presence of concomitant inhibitors or inducers, could be misleading or lead to inappropriate medication selection or dosing. When possible, the use of therapeutic drug monitoring in conjunction with PGx testing in these scenarios can confirm suspected phenocopying and ensure more appropriate medication selection or dosing [108, 109].

Finally, ancestry is an important factor to consider when interpreting PGx results. There are marked differences in allele frequencies across ancestry groups for most of the genes of key drug metabolizing enzymes. In addition, there are also many non-functional alleles that are relatively rare and have been found in only some populations but not in others [110], resulting in notable differences in phenotype frequencies (▶ **Table 4**) [21]. This makes it particularly challenging to design "one-size-fits-all" test panels, and in practice, most panels are biased toward alleles observed in individuals of European ancestry. As a consequence, PGx testing panels can inaccurately assign metabolizer phenotypes. For example, the *CYP2D6* *29 decreased function allele is uncommon among individuals of European ancestry (0.1 %, range: 0–2 %) but common among those of African ancestry (9 %, range: 4–20 %) [111]. A PGx panel that did not include this allele would incorrectly assign the *1 or *2 alleles (depending on the other variants being tested). The *1 allele is a default (not tested) allele that is assigned when none of the tested alleles are detected, while the *2 is a tested allele that has some overlap with the *29 allele. Both the *1 and *2 alleles are interpreted as "normal," and, as such, inadvertent assignment of these alleles could lead to inaccurate metabolizer phenotype predictions (e. g., assigning a person as a NM when they are an IM). Thus, a "normal" genotype result for an individual, particularly those of non-European ancestry, should be interpreted in the context of the alleles that were tested to avoid potential inappropriate medication selection or dosing decisions. Additional information and examples regarding the assignment of alleles can be found in the *CYP2C19* [112] and *CYP2D6* [74] GeneFocus papers.

Conclusions

PGx testing should be viewed as a decision-support tool to assist in thoughtful implementation of good clinical care, enhancing rather than offering an alternative to standard treatment protocols. In this context, genetic markers can supplement demographic (e. g., age, sex, family history), clinical (e. g., concomitant medications), and lifestyle (e. g., diet, smoking) information to help guide treatment decisions. At this time, the published evidence, prescribing guidelines, and product labels support use of PGx testing to guide medication selection and dosing in several clinical contexts, particularly for antidepressants (*CYP2C19* and *CYP2D6*), antipsychotics (*CYP2D6*), anticonvulsants (*CYP2C9, HLA-A*, and *HLA-B*), and the ADHD medication atomoxetine (*CYP2D6*). The current evidence does not support the use of genetic variants in pharmacodynamic genes (e. g., *SLC6A4, COMT, MTHFR*) to inform prescribing of psychiatric medications. Clinicians and patients are encouraged to edu-

▶ **Table 4** Estimated phenotype frequency by ancestry for CYP2D6, CYP2C19, CYP2C9, HLA-A and HLA-B.

Genotype-predicted phenotypes	African	African American	Caucasian (European + North American)	Near Eastern	East Asian	South/ Central Asian	Americas	Latino	Oceanian
CYP2D6									
Ultrarapid Metabolizer	4.4%	4.5%	3.1%	9.5%	0.7%	2.2%	5.5%	4.4%	20.0%
Normal Metabolizer	43.4%	55.7%	51.1%	54.7%	51.9%	62.1%	63.6%	59.2%	67.0%
Intermediate Metabolizer	43.5%	36.2%	39.0%	29.9%	39.2%	29.5%	23.6%	29.1%	10.1%
Poor Metabolizer	1.5%	2.3%	6.5%	2.2%	0.9%	2.3%	2.2%	3.1%	0.4%
CYP2C19									
Ultrarapid Metabolizer	3.0%	4.3%	4.7%	3.7%	0.0%	2.9%	0.7%	2.8%	0.3%
Rapid Metabolizer	19.0%	23.7%	27.2%	25.7%	2.5%	18.6%	13.6%	24.1%	2.1%
Normal Metabolizer	30.1%	32.8%	39.6%	45.2%	38.1%	29.6%	62.8%	52.5%	3.5%
Intermediate Metabolizer	36.2%	31.4%	26.0%	23.5%	45.9%	40.8%	21.4%	19.0%	36.9%
Likely Intermediate Metabolizer	4.0%	2.8%	0.1%	0.0%	0.1%	0.0%	0.0%	0.4%	0.0%
Poor Metabolizer	6.3%	4.1%	2.4%	1.9%	13.0%	8.2%	1.5%	1.1%	57.1%
Likely Poor Metabolizer	1.4%	0.7%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
CYP2C9									
Normal metabolizer	73.1%	75.9%	62.9%	61.1%	83.8%	60.0%	83.1%	74.6%	91.2%
Intermediate metabolizer	26.3%	23.6%	34.5%	36.0%	15.2%	36.3%	16.4%	24.5%	8.7%
Poor metabolizer	0.5%	0.5%	2.6%	3.0%	0.6%	3.8%	0.4%	1.0%	0.1%
HLA									
A * 31:01	0.8%	1.0%	2.6%	1.1%	3.5%	3.3%	6.2%	4.5%	1.1%
B * 15:02	0.0%	0.1%	0.0%	0.0%	4.6%	2.6%	0.2%	0.0%	0.8%
Frequency data retrieved from the PharmGKB: https://www.pharmgkb.org/page/pgxGeneRef; accessed 22-Sept-2020.									

cate themselves or consult an expert prior to ordering a PGx test. This is particularly important given that PGx testing is currently not regulated, and many of the available tests include genes that have little to no support for clinical implementation. Recommendations produced by these tests could lead to inappropriate medication selection and dosing decisions. Various resources to assist in the interpretation and implementation of test results exist, but these resources do not supplant clinical judgement.

A number of larger PGx studies, such as the Ubiquitous Pharmacogenomics Project in Europe [113] and the Precision Medicine in Mental Health Care Study in the United States (NCT03170362) are underway. We expect with the completion of these studies and others that the PGx evidence will continue to evolve, barriers to testing will be cleared, and the uptake of genome sequencing and population-level precision medicine initiatives will increase. As such, we anticipate PGx testing will become an important tool in psychiatry, mitigating the trial-and-error process that too many individuals currently endure.

Funding

The work was supported in part by an Alberta Innovates Strategic Research Project G2018000868 (Drs. Aitchison and Bousman), the Neuroscience and Mental Health Institute and Department of Psychiatry, University of Alberta (Ms. Behroozi Asi), NARSAD Young Investigator Grant from the Brain & Behaviour Research Foundation (Dr. Amare), the Foundation Bettencourt-Schueller (Dr. Chaumette), the European COST Action EnGagE CA17130 (Dr. Degenhardt), the German Federal Ministry of Education and Research e:Med programme (Dr. Degenhardt), the NIH/NHGRI U24 HG010615 (Drs. Klein and Sangkuhl), the NIH/NIGMS R24 GM123930 (Dr. Gaedigk), the NIDA R01 DA038076 (Dr. Li-Shiun), and the NIMH Intramural Research Program (Dr. McMahon).

Author Contribution

All authors were involved in the conception of this work. All authors either drafted or critically revised the content and approved the final version. All authors accept accountability for all aspects of the work.

Data Availability

Data availability is not applicable to this article as no new data were created or analyzed in this study.

Conflict of Interest

Dr. Bousman reports a grant from Alberta Innovates Strategic Research Project G2018000868, during the conduct of the study; and he has received in-kind testing kits from Myriad Neuroscience, CNSDose, Genomind, and AB-Biotics for research purposes but has not received payments

or received any equity, stocks, or options in these companies or any other pharmacogenetic companies. Dr. Bengesser has nothing to disclose. Dr. Aitchison reports grants from Alberta Innovates Strategic Research Project G2018000868, other from Neuroscience and Mental Health Institute, other from Department of Psychiatry, during the conduct of the study; non-financial support from HLS Therapeutics, grants from Janssen Inc., Canada, outside the submitted work; and Member, Pharmacogene Variation Consortium (PharmVar); Coauthor, Haplotype Translators for CYP2D6 and CYP2C19; Member, Alberta Cannabis Research and Innovation Network; Member, Schizophrenia Society of Alberta; Board Member, Canadian Consortium for Early Intervention in Psychosis. Dr. Amare has nothing to disclose. Dr. Aschauer has nothing to disclose. Dr. Baune has nothing to disclose. Ms. Behroozi Asl reports grants from Alberta Innovates, during the conduct of the study. Dr. Bishop reports personal fees from OptumRx, outside the submitted work; and he is a member of the Clinical Pharmacogenetics Implementation Consortium. Dr. Burmeister reports personal fees from Chinese University of Hong Kong (Shen Zhen), personal fees from Research Grants Council (RGC) of Hong Kong, personal fees from Alexander von Humboldt Foundation, outside the submitted work. Dr. Chaumette reports personal fees from Janssen-Cilag, grants from Fondation Bettencourt-Schueller, outside the submitted work. Dr. Chen has nothing to disclose. Dr. Cordner has nothing to disclose. Dr. Deckert reports grants from DFG, grants from BMBF, grants from Vogel-Foundation, grants from EU, grants from Bavarian Secretary of Commerce, outside the submitted work. Dr. Degenhardt has nothing to disclose. Dr. DeLisi has nothing to disclose. Dr. Folkersen has nothing to disclose. Dr. Kennedy has a patent 'PGx of Antipsychotic Response'; and 'PGx of Wt Gain' both pending. No licensees. Dr. Kennedy's affiliated hospital, (which is not his employer) the Centre for Addiction and Mental Health, is a part owner of the Canadian subsidiary of Myriad Neuroscience, USA. Dr. Klein reports grants from NIH/NHGRI, during the conduct of the study. Dr. McClay has nothing to disclose. Dr. McMahon has nothing to disclose. Dr. Musil reports personal fees from Otsuka/Lundbeck, outside the submitted work. Dr. Saccone reports that her spouse is listed as an inventor on Issued U.S. Patent 8,080,371, "Markers for Addiction" covering the use of certain single nucleotide polymorphisms in determining the diagnosis, prognosis, and treatment of addiction. Dr. Sangkuhl reports grants from NIH/NHGRI, during the conduct of the study. Dr. Stowe has nothing to disclose. Dr. Tan has nothing to disclose. Dr. Tiwari reports that he is a co-investigator on two pharmacogenetic studies where genetic test kits were provided as in-kind contribution by Assurex Health (Myriad Neuroscience) but he did not receive any payments or any equity, stocks, or options from this company or any other pharmacogenetic companies. Dr. Tiwari is also a co-inventor on a patent assessing risk for antipsychotic-induced weight gain. Dr. C. Zai has a patent for suicide markers issued, and a patent for antipsychotic-induced weight gain markers pending. Dr. G. Zai has nothing to disclose. Dr. Zhang has nothing to disclose. Dr. Gaedigk has nothing to disclose. Dr. Müller reports to be a co-investigator on two pharmacogenetic studies where genetic test kits were provided as in-kind contribution by Myriad Neuroscience. He did not receive any payments or any equity, stocks, or options from any pharmacogenetic companies. Dr. Müller is also a co-inventor on two patent assessing risk for antipsychotic-induced weight gain (pending).

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Notice

This article was changed on December 11, 2020.
Conflict of Interest:
some details were incorrect and they have been corrected.