Review and Consensus on Pharmacogenomic Testing in Psychiatry

Authors

Affiliations
1 Departments of Medical Genetics, Psychiatry, Physiology & Pharmacology, University of Calgary, Calgary, AB, Canada
2 Hotchkiss Brain Institute, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada
3 Alberta Children’s Hospital Research Institute, Calgary, AB, Canada
4 Department of Psychiatry, Melbourne Medical School, The University of Melbourne, Melbourne, VIC, Australia
5 Department of Psychiatry and Psychotherapeutic Medicine, Medical University of Graz, Austria
6 Departments of Psychiatry, Medical Genetics and the Neuroscience and Mental Health Institute, University of Alberta, Edmonton, AB, Canada
7 Discipline of Psychiatry, School of Medicine, University of Adelaide, Adelaide, SA, Australia
8 South Australian Health and Medical Research Institute (SAHMRI), Adelaide, SA, Australia
9 Biopsychosocial Corporation (BioPsyC), non-profit association, Vienna, Austria
10 Department of Psychiatry and Psychotherapy, University of Münster, Germany
11 The Florey Institute of Neuroscience and Mental Health, The University of Melbourne, Parkville, VIC, Australia
12 Department of Experimental and Clinical Pharmacology, University of Minnesota College of Pharmacy and Department of Psychiatry, University of Minnesota Medical School, Minneapolis, MN, USA
13 Michigan Neuroscience Institute and Departments of Computational Medicine & Bioinformatics, Human Genetics and Psychiatry, The University of Michigan, Ann Arbor MI, USA
14 Institute of Psychiatry and Neuroscience of Paris, GHU Paris Psychiatrie & Neurosciences, University of Paris, Paris, France
15 Department of Psychiatry, McGill University, Montreal, Canada
16 Departments of Psychiatry and Genetics, Washington University School of Medicine in St. Louis, USA
17 Department of Psychiatry & Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA
18 Department of Psychiatry, Psychosomatics and Psychotherapy, Center of Mental Health, Würzburg, Germany
19 Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany
20 Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital Essen, University of Duisburg-Essen, Duisburg, Germany
21 Department of Psychiatry, Harvard Medical School, Cambridge Health Alliance, Cambridge, Massachusetts, USA
22 Institute of Biological Psychiatry, Capital Region Hospitals, Copenhagen, Denmark
23 Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada
24 Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada
25 Department of Biomedical Data Science, Stanford University, Stanford, California, USA
26 Department of Pharmacotherapy and Outcome Science, Virginia Commonwealth University School of Pharmacy, Richmond, VA, USA
27 Human Genetics Branch, National Institute of Mental Health, Bethesda, MD, USA
28 Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University, Munich, Germany
29 Departments of Psychiatry and Neurology (Medicine), University of British Columbia, USA
30 KK Research Centre, KK Women’s and Children’s Hospital, Singapore, Singapore
31 Department of Psychiatry, Weill Cornell Medical College, New York-Presbyterian Westchester Division, White Plains, NY, USA
32 Division of Clinical Pharmacology, Toxicology & Therapeutic Innovation, Children’s Mercy Kansas City, Kansas City and School of Medicine, University of Missouri-Kansas City, Kansas City, MO, USA

Key words
precision medicine, pharmacogenetics, prescribing

received 09.07.2020
revised 05.10.2020
accepted 07.10.2020
published online 04.11.2020
### 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 poor 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]. How- ever, widespread implementation and adoption of this strategy has not yet occurred in psychiatry, in part due to divergent perceptions of the quality and completeness of the evidence base and diverge 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.

### 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., \*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 (\textit{\textsuperscript{\textlongrightarrow} 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 Pharmacogenomics 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\textsubscript{2} receptor. However, evidence linking genetic variation in the dopamine D\textsubscript{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 (\textit{\textsuperscript{\textlongrightarrow} 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,
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 mg.

### Table 1  Actionable pharmacogenetic guidelines and product labels by antidepressants.

<table>
<thead>
<tr>
<th>Antidepressant</th>
<th>Actionable Guideline Available</th>
<th>Product Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>CYP2C19, CYP2D6</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>–</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Citalopram</td>
<td>CYP2C19</td>
<td>CYP2C19</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>CYP2C19, CYP2D6</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Desipramine</td>
<td>CYP2D6</td>
<td>–</td>
</tr>
<tr>
<td>Doxepin</td>
<td>CYP2C19, CYP2D6</td>
<td>CYP2C19, CYP2D6</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>–</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>CYP2C19</td>
<td>–</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>CYP2D6</td>
<td>–</td>
</tr>
<tr>
<td>Imipramine</td>
<td>CYP2C19, CYP2D6</td>
<td>CYP2C19, CYP2D6</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>CYP2D6</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>CYP2D6</td>
<td>–</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>–</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Sertraline</td>
<td>CYP2C19</td>
<td>–</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>CYP2C19, CYP2D6</td>
<td>–</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>–</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Vortioxetine</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

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. 1Only guidelines where a clinical action has been recommended were included. 2Product 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](https://www.pharmgkb.org/page/drugLabelLegend). Drugs reviewed that did not have an actionable guideline or product label included: agomelatine, bupropion, desvenlafaxine, fluoxetine, levomilnacipran, mianserin, mirtazapine, milnacipran, nefazodone, phenelzine, reboxetine, selegiline, tranylcypromine, trazodone, and vilazodone.

### Table 2  Actionable pharmacogenetic guidelines and product labels by antipsychotics.

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Actionable Guideline Available</th>
<th>Product Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>–</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>–</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Clozapine</td>
<td>–</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>–</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Loperidone</td>
<td>–</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>–</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Pimozide</td>
<td>–</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Risperidone</td>
<td>–</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>–</td>
<td>CYP2D6</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>–</td>
<td>CYP2D6</td>
</tr>
</tbody>
</table>

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. 1Only guidelines where a clinical action has been recommended were included. 2Product 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](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 mg.
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 HLA-B *15:02* allele prior to prescribing these medications. 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), CYP2C9 PMs had 40 % and 75 % higher plasma half-lives compared to NMs, re-

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Actionable pharmacogenetic guidelines and product labels by mood stabilizers/anticonvulsants.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood stabilizers/anticonvulsants</td>
<td>Actionable Guideline Available</td>
</tr>
<tr>
<td></td>
<td>CPIC</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>HLA-A, HLA-B</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>HLA-B</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>CYP2C9, HLA-B</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>–</td>
</tr>
</tbody>
</table>

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. ¹Only guidelines where a clinical action has been recommended were included. ²Product 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.
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 non-stimulant 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 risk 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 genes 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 [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.
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 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 allele 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-
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.

---

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

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

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, Pharmacogenome 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 BMGF, 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. Folkerssen has nothing to disclose. Dr. Kennedy has a patent ‘PGx of Antipsychotic Response’; and ‘PGx of Weight 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 patient assessing risk for antipsychotic-induced weight gain (pending).

References


[51] Chen Z, Liew D, Kwan P. Effects of a HLA-B*15:02 screening policy on antiepileptic drug use and severe skin reactions. Neurology 2014; 83: 2077–2084


Bousman CA et al. Review and Consensus on... Pharmacopsychiatry 2021; 54: 5–17 | © 2020. Thieme. All rights reserved.


[73] Nozfriz C, Paulmichl M. Accurately genotyping CYP2D6: not for the faint of heart. Pharmacogenomics 2018; 19: 999–1002


[84] Paterson J. Pharmacogenetic testing a growing area as pilot projects, research get underway. benefitscanada.com. February 1 2018;


This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.
[98] Bousman CA, Dunlop BW. Genotype, phenotype, and medication recommendation agreement among commercial pharmacogenetic-based decision support tools. Pharmacogenomics J 2018; 18: 613–622


[111] PharmGKB. PGx gene-specific information tables www.pharmgkb.org/page/pgxGeneRef accessed September 15, 2020


Notice

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