EXPERT REVIEW

Gene-drug pairings for antidepressants and antipsychotics: level of evidence and clinical application

Lara E. Murphy[1,2,9], Trehani M. Fonseka[1,9], Chad A. Bousman[3,4,5] and Daniel J. Müller[1,2,6,7,8,9]✉

Substantial inter-individual discrepancies exist in both therapeutic effectiveness and adverse effects of antidepressant and antipsychotic medications, which can, in part, be explained by genetic variation. Here, we searched the Pharmacogenomics Knowledge Base for gene-antidepressant and gene-antipsychotic pairs with the highest level of evidence. We then extracted and compared the associated prescribing recommendations for these pairs developed by the Clinical Pharmacogenomics Implementation Consortium, the Dutch Pharmacogenetics Working Group or approved product labels in the US, Canada, Europe, and Asia. Finally, we highlight key economical, educational, regulatory, and ethical issues that, if not appropriately considered, can hinder the implementation of these recommendations in clinical practice. Our review indicates that evidence-based guidelines are available to assist with the implementation of pharmacogenetic-guided antidepressant and antipsychotic prescribing, although the maximum impact of these guidelines on patient care will not be realized until key barriers are minimized or eliminated.

Molecular Psychiatry; https://doi.org/10.1038/s41380-021-01340-6

INTRODUCTION

Recent advancements within pharmacogenomic research are fueling precision medicine initiatives and facilitating the integration of pharmacogenetic testing into clinical practice. These innovations are of particular interest to psychiatrists and their patients who, dissatisfied with the current "trial-and-error" approach to drug selection and dosing, are demanding more modern approaches [1–4].

Pharmacogenetic tests in psychiatry are widely available and typically focus on two cytochrome P450 (CYP) genes, *CYP2D6* and *CYP2C19*. These genes encode enzymes that are involved in the hepatic metabolism of most psychiatric medications [5]. The presence or absence of functional variants in these genes is used to infer an individual's metabolizer status (i.e., poor, intermediate, normal, rapid, or ultrarapid metabolizer). An individual's metabolizer status is then used to inform medication selection and dosing based on the available guidelines.

Several expert groups, such as the Clinical Pharmacogenetic Implementation Consortium (CPIC) and the Royal Dutch Association for the Advancement of Pharmacy - Pharmacogenetics Working Group (DPWG) [6–8], develop prescribing guidelines based on the current pharmacogenetic evidence, which is cataloged in the Pharmacogenomics Knowledge Base (PharmGKB) [6, 7]. In PharmGKB, clinical annotations for gene-drug pairings are assigned a Level of Evidence rating from 1 A to 4 based on the evidence supporting the association, with 1 A being the highest level assigned [9, 10].

Recent studies have shown that effective integration of pharmacogenetic testing into treatment can improve clinical outcomes [11–15]. However, while the relationship between genetic variation and drug metabolism has strong support, there are limitations to the current body of evidence surrounding the clinical validity and utility of all relevant gene-drug pairs. Many currently available commercial tests include variants with limited or conflicting evidence supporting their clinical use. Furthermore, barriers continue to exist with translating findings into the reality of daily practice. Therefore, it is important to identify the gene-drug pairs and the genes' corresponding variants with guidelines supporting their association and clinical use, summarize the recommendations, and provide their clinical context in pharmacogenomic translation. In this review, we summarize CPIC and/or DPWG guidelines for actionable gene-antidepressant and gene-antipsychotic pairs, and provide a discussion of considerations for translating such guidelines into clinical practice.

METHODS

Selection of gene-drug pairings for inclusion

Gene-drug pairs as of April 2021 were included in this review, if they met one of the following inclusion criteria: (1) classification of level 1 A or 1B by PharmGKB denoting the two highest Level of Evidence ratings, (2) actionable DPWG guidelines present, or (3) actionable CPIC guidelines present.

[1]Pharmacogenetics Research Clinic, Centre for Addiction and Mental Health, Toronto, ON, Canada. [2]Temerty Faculty of Medicine, University of Toronto, Toronto, ON, Canada. [3]Departments of Medical Genetics, Psychiatry, Physiology & Pharmacology, and Community Health Sciences, University of Calgary, Calgary, AB, Canada. [4]Hotchkiss Brain Institute, University of Calgary, Calgary, AB, Canada. [5]Alberta Children's Hospital Research Institute, University of Calgary, Calgary, AB, Canada. [6]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada. [7]Department of Psychiatry, University of Toronto, Toronto, ON, Canada. [8]Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany. [9]These authors contributed equally: Lara E. Murphy and Trehani M. Fonseka. ✉email: daniel.mueller@camh.ca

Received: 13 May 2021 Revised: 23 September 2021 Accepted: 1 October 2021
Published online: 09 November 2021

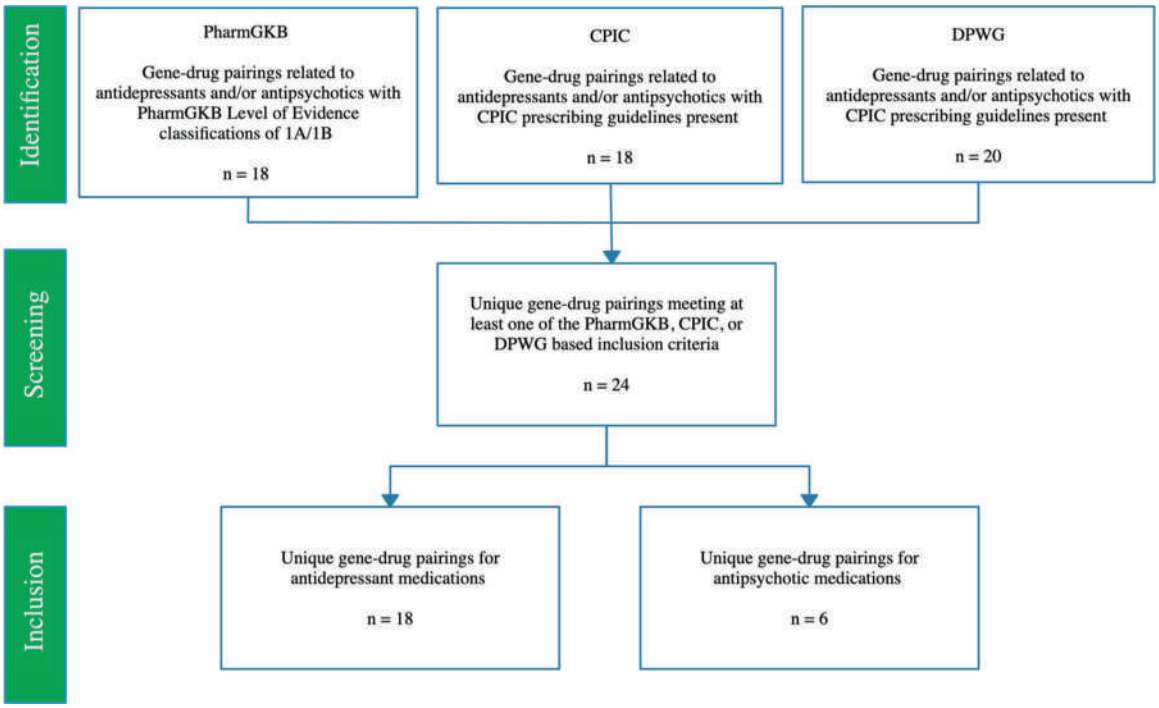

Fig. 1 Flow diagram outlining the study process for identifying and selecting the gene-drug pairings. n number of gene-drug pairings identified, CPIC Clinical Pharmacogenetics Implementation Consortium, DPWG Dutch Pharmacogenetics Working Group, PharmGKB Pharmacogenomics Knowledge Base.

Prescribing guideline assessment

Prescribing guidelines included on drug labels for each of the gene-drug pairs meeting inclusion criteria were also assessed. Only drug labels approved by one of the following agencies: the Food and Drug Administration (FDA), European Medicines Agency (EMA), Health Canada, and Japan's Pharmaceuticals and Medical Devices Agency (PMDA) were included.

Search strategy

To identify gene-drug pairings that met our inclusion criteria, PharmGKB, DPWG guidelines, and CPIC guidelines were consulted individually (Fig. 1). PharmGKB Level of Evidence ratings for clinical annotations were searched for major CYP isoforms, including CYP1A1, CYP1A2, CYP1B1, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. All CPIC and DPWG gene-drug guidelines were screened for prescribing guidelines relevant to antidepressants and/or antipsychotics.

RESULTS

Twenty-four gene-drug pairs with pharmacogenetic-based prescribing guidelines were identified. Eighteen of the gene-drug pairs included an antidepressant (Table 1), and six included an antipsychotic (Table 2). Sixteen of these pairs included *CYP2D6* and eight included *CYP2C19*.

Tricyclic antidepressants

Twelve gene-drug pairings for TCAs were identified (*CYP2D6* with trimipramine, clomipramine, doxepin, imipramine, desipramine, nortriptyline, and amitriptyline; *CYP2C19* with amitriptyline, doxepin, imipramine, trimipramine, and clomipramine). CPIC guidelines were present for all 12 pairings, whereas DPWG guidelines were only present for eight [8, 15]. The guidelines differed between these groups for all 12 pairings, with the only overlap in recommendations for amitriptyline and *CYP2D6* intermediate metabolizers.

The current pharmacogenomic knowledge for TCAs is predominantly based on studies of amitriptyline and nortriptyline. The 2016 CPIC guidelines apply evidence to develop dosing recommendations based on the assumption that TCA metabolism is similar between doses. Thus, findings from studies using single doses to assess the impact of *CYP2C19* and *CYP2D6* genetic variation on TCA pharmacokinetics are applied to the usage of multiple doses clinically [16]. The current 2016 CPIC guidelines note that due to the similar pharmacokinetic profiles of TCAs, findings from studies assessing amitriptyline and nortriptyline can be extrapolated to the recommendations for other TCAs [16]. Contrastingly, the DPWG guidelines vary in dose alteration recommendations between the different pairings in this drug class [8].

Selective serotonin (and norepinephrine) reuptake inhibitors

Five gene-drug pairings for SSRIs were identified (*CYP2D6* with fluvoxamine and paroxetine; *CYP2C19* with sertraline, citalopram, and escitalopram). Both CPIC and DPWG guidelines are available for all five pairings [8, 17, 18]. For all five pairings, there were discrepancies in the guidelines for the recommendations provided, most often related to those given for poor and intermediate metabolizer classes.

One SNRI was identified as having an actionable gene-drug pairing (*CYP2D6* with venlafaxine), and only DPWG had available guidelines [8].

Antipsychotics

Six antipsychotics were identified as having an actionable gene-drug pairing (*CYP2D6* with aripiprazole, pimozide, risperidone, zuclopenthixol, brexpiprazole, and haloperidol). Only DPWG had available guidelines for all six pairings [8].

DISCUSSION

Our review revealed an extensive list of recommendations and guidelines for antidepressant and antipsychotic medications

Table 1. Guideline and class rating assessments for CYP2D6 and CYP2C19 genotype guided dosing and selection of antidepressants.

Medication	Gene	Phenotype	CPIC Recommendation	Strength of Recommendation	DPWG Recommendations	DPWG Class	CPIC Class	PharmGKB Class	EMA	Health Canada	FDA
Tricyclic Antidepressants											
Amitriptyline	CYP2D6 CYP2C19	Ultrarapid	Avoid use due to potential inefficacy, consider increasing dose if use is warranted	CYP2D6: Strong CYP2C19: Optional	CYP2D6: 140% increase of recommended starting dose, with clinical monitoring for cardiotoxic metabolites; Avoid use of amitriptyline if dose increase is not desirable CYP2C19: No action required	CYP2D6: 3C CYP2C19: 3A	A	1A	N.A	N.A	Actionable
		Normal	Initiate therapy at standard starting dose	Strong	No guidelines	-					
		Intermediate	CYP2D6: Consider 25% reduction of standard starting dose CYP2C19: Initiate therapy at standard starting dose	CYP2D6: Moderate CYP2C19: Strong	CYP2D6: 25% reduction of recommended starting dose with clinical monitoring CYP2C19: No action required	CYP2D6: 3C CYP2C19: 4A					
		Poor	Avoid use due to potential for side effects, consider decreasing starting dose by 50% if use is warranted	CYP2D6: Strong CYP2C19: Moderate	CYP2D6: 30% reduction of recommended starting dose with clinical monitoring CYP2C19: No action required	CYP2D6: 3A CYP2C19: 4A					
Nortriptyline	CYP2D6	Ultrarapid	Avoid use due to potential inefficacy, consider increasing dose if use is warranted	Strong	170% increase of recommended starting dose with clinical monitoring for cardiotoxic metabolites; Avoid use of nortriptyline if dose increase is not desirable	3C	A	1A	N.A	Actionable	Actionable
		Normal	Initiate therapy at standard starting dose	Strong	No guidelines	-					
		Intermediate	CYP2D6: Consider 25% reduction of standard starting dose CYP2C19: Initiate therapy at standard starting dose	Moderate	40% reduction of recommended starting dose with clinical monitoring	4C					
		Poor	Avoid use due to potential for side effects, consider decreasing starting dose by 50% if use is warranted	Strong	60% reduction of recommended starting dose with clinical monitoring	3C					
Desipramine	CYP2D6	Ultrarapid	Avoid use due to potential inefficacy, consider increasing dose if use is warranted	Optional	No guidelines	N.A	B	1A	N.A	N.A	Actionable
		Normal	Initiate therapy at standard starting dose	Strong		-					

Table 1 continued

Medication	Gene	Phenotype	CPIC Recommendation	Strength of Recommendation	DPWG Recommendations	DPWG Class	CPIC Class	PharmGKB Class	EMA	Health Canada	FDA
		Intermediate	CYP2D6: Consider 25% reduction of standard starting dose CYP2C19: Initiate therapy at standard starting dose	Optional		N.A					
		Poor	Avoid use due to potential for side effects, consider decreasing starting dose by 50% if use is warranted	Optional		N.A					
Doxepin	CYP2D6 CYP2C19	Ultrarapid	Avoid use due to potential inefficacy, consider increasing dose if use is warranted	Optional	CYP2D6: 200% increase in recommended starting dose, with clinical monitoring for cardiotoxic metabolites; Avoid use of doxepin if dose increase is not desirable CYP2C19: No action required	CYP2D6: 3A CYP2C19: N.A	B	1A	N.A	N.A	Actionable
		Normal	Initiate therapy at standard starting dose	Strong	No guidelines	-					
		Intermediate	CYP2D6: Consider 25% reduction of standard starting dose CYP2C19: Initiate therapy at standard starting dose	Optional	CYP2D6: 40% reduction of recommended starting dose with clinical monitoring CYP2C19: No action required	CYP2D6: 3A CYP2C19: 3A					
		Poor	Avoid use due to potential for side effects, consider decreasing starting dose by 50% if use is warranted	Optional	CYP2D6: 60% reduction of recommended starting dose with clinical monitoring CYP2C19: No action required	CYP2D6: 3F CYP2C19: 3A					
Imipramine	CYP2D6 CYP2C19	Ultrarapid	Avoid use due to potential inefficacy, consider increasing dose if use is warranted	Optional	CYP2D6: 170% increase in recommended starting dose, with clinical monitoring for cardiotoxic metabolites; Avoid use of imipramine if dose increase is not desirable CYP2C19: No action required	CYP2D6: 4A CYP2C19: 4A	B	1A	N.A	N.A	Actionable
		Normal	Initiate therapy at standard starting dose	Strong	No guidelines	-					
		Intermediate	CYP2D6: Consider 25% reduction of standard starting dose CYP2C19: Initiate therapy at standard starting dose	Optional	CYP2D6: 30% reduction of recommended starting dose with clinical monitoring CYP2C19: No action required	CYP2D6: 4A CYP2C19: 4A					

Table 1 continued

Medication	Gene	Phenotype	CPIC Recommendation	Strength of Recommendation	DPWG Recommendations	DPWG Class	CPIC Class	PharmGKB Class	EMA	Health Canada	FDA
		Poor	Avoid use due to potential for side effects, consider decreasing starting dose by 50% if use is warranted	Optional	CYP2D6: 70% reduction of recommended starting dose with clinical monitoring CYP2C19: 30% dose reduction with clinical monitoring or avoid use	CYP2D6: 4C CYP2C19: 4A					
Trimipramine	CYP2D6 CYP2C19	Ultrarapid	Avoid use due to potential inefficacy, consider increasing dose if use is warranted	Optional	No guidelines	N.A	B	1A	N.A	N.A	Actionable
		Normal	Initiate therapy at standard starting dose	Strong		-					
		Intermediate	CYP2D6: Consider 25% reduction of standard starting dose CYP2C19: Initiate therapy at standard starting dose	Optional		N.A					
		Poor	Avoid use due to potential for side effects, consider decreasing starting dose by 50% if use is warranted	Optional		N.A					
Clomipramine	CYP2C19 CYP2D6	Ultrarapid	Avoid use due to potential inefficacy, consider increasing dose if use is warranted	Optional	CYP2D6: 150% increase in recommended starting dose, with clinical monitoring for cardiotoxic metabolites; Avoid use of trimipramine if dose increase is not desirable CYP2C19: No action required for treatment of depression	CYP2D6: 3C CYP2C19: 3A	B	1A	N.A	N.A	Actionable
		Normal	Initiate therapy at standard starting dose	Strong	No guidelines	-					
		Intermediate	CYP2D6: Consider 25% reduction of standard starting dose CYP2C19: Initiate therapy at standard starting dose	Optional	CYP2D6: 30% reduction of recommended starting dose with clinical monitoring CYP2C19: No action required	CYP2D6: 4C CYP2C19: 4A					
		Poor	Avoid use due to potential for side effects, consider decreasing starting dose by 50% if use is warranted	Optional	CYP2D6: 50% dose reduction of recommended starting dose with clinical monitoring to set maintenance dose; Avoid use if dose reduction is not effective CYP2C19: No action required	CYP2D6: 4C CYP2C19: 4A					

Table 1 continued

Medication	Gene	Phenotype	CPIC Recommendation	Strength of Recommendation	DPWG Recommendations	DPWG Class	CPIC Class	PharmGKB Class	EMA	Health Canada	FDA
Selective Serotonin Reuptake Inhibitors											
Sertraline	CYP2C19	Ultrarapid	Initiate therapy at standard starting dose, consider alternative drug if a lack of response is observed	Optional	No action required	4AA	B	1A	N.A	N.A	N.A
		Normal	Initiate therapy at standard starting dose	Strong	No guidelines	-					
		Intermediate	Initiate therapy at standard starting dose	Strong	No action required	4A					
		Poor	Avoid use due to potential for side effects, consider decreasing starting dose by 50% if use is warranted	Optional	Do not exceed dosing of 75mg/day with clinical monitoring	4C					
Fluvoxamine	CYP2D6	Ultrarapid	No recommendations due to lack of data	Optional	No action required	N.A	B	1A	N.A	N.A	Actionable
		Normal	Initiate therapy at standard starting dose	Strong	No guidelines	-					
		Intermediate	Initiate therapy at standard starting dose	Moderate	No action required	4B					
		Poor	Avoid use due to potential for side effects, consider decreasing starting dose by 25-50% if use is warranted	Optional	No action required	3A					
Paroxetine	CYP2D6	Ultrarapid	Avoid use due to potential inefficacy	Strong	Avoid use, select alternative drug	4C	A	1A	N.A	N.A	Informative
		Normal	Initiate therapy at standard starting dose	Strong	No guidelines	-					
		Intermediate	Initiate therapy at standard starting dose	Moderate	No action required	4A					
		Poor	Avoid use due to potential for side effects, consider decreasing starting dose by 50% if use is warranted	Optional	No action required	4A					
Citalopram	CYP2C19	Ultrarapid	Avoid use due to potential inefficacy	Moderate	No action required	3AA	A	1A	N.A	Actionable	Actionable
		Normal	Initiate therapy at standard starting dose	Strong	No guidelines	-					
		Intermediate	Initiate therapy at standard starting dose	Strong	For individuals 65 or younger: do not exceed a dose of 30mg/day as tablets or 22mg/day as drops. For individuals older than 65: do not exceed a dose of 15mg/day as tablets or 10mg/day as drops	4A					

Table 1 continued

Medication	Gene	Phenotype	CPIC Recommendation	Strength of Recommendation	DPWG Recommendations	DPWG Class	CPIC Class	PharmGKB Class	EMA	Health Canada	FDA
		Poor	Avoid use due to potential for side effects, consider decreasing starting dose by 50% if use is warranted	Moderate	50% reduction of recommended starting dose; For individuals 65 or younger: do not exceed dose of 20mg/day as tablets or 16mg/day as drops. For individuals older than 65: do not exceed a dose of 10mg/day as tablets or 8mg/day as drops	4A					
Escitalopram	CYP2C19	Ultrarapid	Avoid use due to potential inefficacy	Moderate	Avoid use, select alternative drug	4C	A	1A	N.A	N.A	Actionable
		Normal	Initiate therapy at standard starting dose	Strong	No guidelines	-					
		Intermediate	Initiate therapy at standard starting dose	Strong	25% reduction of recommended starting dose; For individuals younger than 65: do not exceed a dose of 15mg/day. For individuals 65 or over: do not exceed a dose of 7.5mg/day	4A					
		Poor	Avoid use due to potential for side effects, consider decreasing starting dose by 50% if use is warranted	Moderate	50% reduction of recommended starting dose; For individuals younger than 65: do not exceed a dose of 10mg/day. For individuals 65 or over: do not exceed a dose of 5mg/day	4C					
Serotonin–Norepinephrine Reuptake Inhibitors											
Venlafaxine	CYP2D6	Ultrarapid	N/a		Clinically monitor response, increase dose by 150% if lack of effect is observed. Select an alternative drug if increase is not possible or effective	4A	A/B	2A	N.A	N.A	Actionable
		Normal			No guidelines	-					
		Intermediate			Limited data; precautionary recommendation to select an alternative drug, or if use is warranted implement clinical monitoring with dose decrease if side effects occur	4C					
		or Poor				4C					

CPIC clinical pharmacogenetic implementation consortium, *DPWG* Royal Dutch Association for the advancement of pharmacy - pharmacogenetics working group, *PharmGKB* pharmacogenomics knowledge base, *FDA* food and drug administration, *EMA* European medicines agency.

Table 2. Guideline and class rating assessments for CYP2D6 genotype guided dosing and selection of antipsychotics.

Medication	Phenotype	DPWG Recommendations (Yes/No)	DPWG Class	CPIC Class	PharmGKB Class	EMA	Health Canada	FDA
Aripiprazole	Ultrarapid	No action required	3AA	B	3	Actionable	Actionable	Actionable
	Normal	No guidelines	-					
	Intermediate	No action required	4B					
	Poor	25–33% reduction of recommended starting dose Do not exceed dose of 10 mg/day or 300 mg/month	4C					
Pimozide	Ultrarapid	No action required	3AA	A/B	3	N.A	N.A	Testing Required
	Normal	No guidelines	-					
	Intermediate	20% reduction of recommended starting dose Adults: 16 mg/day Children: 0.08 mg/kg per day to a max of 3 mg/day	3A					
	Poor	50% reduction of recommended starting dose Adults: 10 mg/day Children: 0.05 mg/kg per day to a max of 2 mg/day	3A					
Risperidone	Ultrarapid	Select alternative drug or titrate to the maximum dose of the active metabolite paliperidone Children ≥15 weighing ≥51 kg: oral 12 mg/day Children ≥15 weighing <51kg: 6 mg/day or intramuscular 7 mg/2 weeks	4C	B	1B	N.A	Informative	Informative
	Normal	No guidelines	-					
	Intermediate	No action required	4C					
	Poor	33% decrease from standard dose, with a further decrease to 50% of standard dose if side effects occur	4D					
Zuclopenthixol	Ultrarapid	150% dose increase or select an alternative drug	N.A	B/C	3	N.A	N.A	N.A
	Normal	No guidelines	-					
	Intermediate	Select alternative drug or decrease starting dose by 25%	4A					
	Poor	Select alternative drug or decrease starting dose by 50%	4A					
Brexpiprazole	Ultrarapid	No action required	0A	B/C	N.A	Actionable	N.A	Actionable
	Normal	No guidelines	-					
	Intermediate	No action required	4AA					
	Poor	50% decrease in recommended standard dose	0A					
Haloperidol	Ultrarapid	Limited data; precautionary recommendation for clinical monitoring, dose increase based on clinical judgement, or selection of an alternative drug	4C	B/C	3	N.A	N.A	N.A
	Normal	No guidelines	-					
	Intermediate	No action required	4A					
	Poor	Select alternative drug or decrease starting dose by 50%	4E					

CPIC clinical pharmacogenetic implementation consortium, *DPWG* Royal Dutch Association for the advancement of pharmacy - pharmacogenetics working group, *PharmGKB* pharmacogenomics knowledge base, *FDA* food and drug administration, *EMA* European medicines agency.

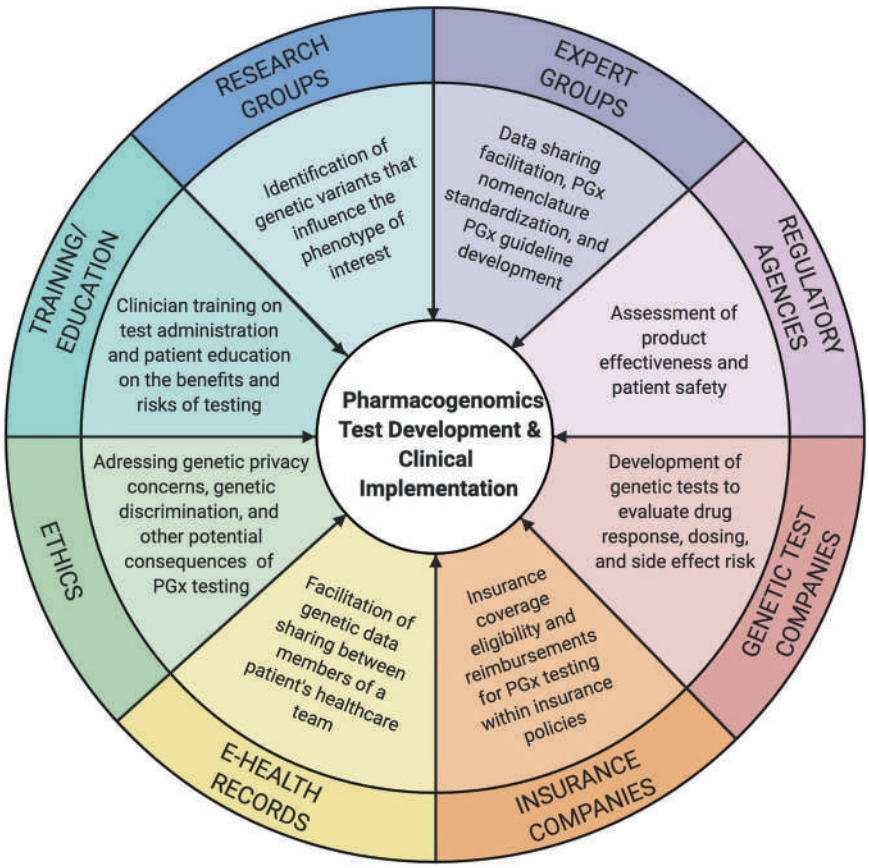

Fig. 2 Factors contributing to pharmacogenomic test development and implementation. Created with BioRender.com.

metabolized by *CYP2D6* and *CYP2C19*. These recommendations provide support for the benefits of *CYP2D6* and *CYP2C19* testing for many antidepressants of TCA and SSRI subclasses, as well as one SNRI. *CYP2D6* testing may have similar benefits for many major antidepressants. However, there is no standardization across expert groups in what drugs are included in the recommendations provided and what the specific recommendations are for the drug pairings. This was highlighted by past work comparing differences in methodology, allele terminology and classifications, and therapeutic recommendations between CPIC and DPWG [17, 19]. Both CPIC and DPWG guidelines have been endorsed by multiple professional societies [20, 21]. Regarding practical implementation, these recommendations are not yet widely adopted by healthcare providers, although a growing number of institutions and treatment centers worldwide are offering pharmacogenetic testing to patients. Implementation has been furthered by commercial companies that produce genetic testing panels, however, such companies tend to add additional gene-drug variants that lack clinical evidence or which sometimes use their own interpretations or combinatorial approaches that are difficult to validate. For a summary of relevant factors contributing to pharmacogenomic test development and implementation, see Fig. 2.

For novel interventions to be implemented, criteria within analytical validity, clinical validity, and clinical utility come into play. Analytical validity describes the ability of an assay to detect specific variants within targeted genes. Clinical validity in this context refers to the strength of the association between genetic variants and treatment response or adverse effects. Clinical utility describes the usefulness and relevance of the genetic test in clinical practice.

Regarding analytic validity, gene assays with high levels of validity are available, however, all tests should be conducted in accredited labs for the highest quality control purposes. As for the clinical validity, expert groups have clearly indicated the presence of moderate to strong associations between *CYP2D6* and *CYP2C19* genetic variants and drug treatment outcomes. However, the clinical utility of testing for these variants remains the subject of active investigations due to various factors, the most important of which are addressed below.

Cost-effectiveness and reimbursement

Many of the major challenges for global pharmacogenomics testing implementation relate to the cost-effectiveness of testing and reimbursement for testing. Multiple studies have shown that pharmacogenomics testing can be cost-effective in the context of psychiatry in the United States [22–25] and that improving outcomes through testing implementation may have larger economic impacts by increasing population productivity [22, 25]. While new evidence and test enhancements are to be expected, the clinical implications of new test results on extreme ends of the drug metabolism spectrum—such as ultrarapid and poor metabolizers—will likely remain unchanged throughout the lifespan. However, economic evaluations may not be representative of all pharmacogenetic tests and there have not been published economic evaluations inclusive of all antidepressants and antipsychotics with significant genetic associations [25]. If future cost-analyses are inconclusive, efforts should be taken to identify cost-draining aspects of testing provision and address gaps in testing design, access, and payment models. There have been recent improvements in the cost-effectiveness of genetic testing, with a downward trend in the pricing of testing in recent years, which is expected to be continually compounded by the future enhancement of pharmacogenetic testing technology [25].

A major consideration in clinical usage and service accessibility is the coverage of pharmacogenetic testing by third-party payers. In the US, an increasing number of third-party payers have started to recognize the benefits of pharmacogenetic testing and have created coverage policies or have made testing available through commercial partnerships [26, 27]. In the US, pharmacogenetic testing for many psychotropic drugs is covered by Medicare and Medicaid, national health insurance programs, as well as commercial health insurance programs [28, 29]. As of 2017, the single-gene test for CYP2D6 had the highest insurance coverage [28]. Pressure for increased coverage of pharmacogenetic testing has grown in recent years in the United States, highlighted by a current proposed local coverage determination (LCD) for pharmacogenetic testing under Centers for Medicare & Medicaid Services [30].

However, while growing, the coverage provided by third-party payers has slowed the adoption of genetic testing [31]. Further independent investigation into the cost-effectiveness of routine pharmacogenetic testing in diverse patient populations and into other clinical utility factors, such as improving test economic accessibility and logistical concerns regarding wait times, can strengthen the support of testing coverage and thus accelerate implementation.

Regulatory agencies

Regulatory agencies are increasingly adopting pharmacogenetic recommendations. The Food and Drug Administration (FDA) has the broadest authority to regulate genetic tests in the United States [32]. The FDA has acknowledged the potential benefit of pharmacogenetic testing in personalizing psychiatric medications and has integrated pharmacogenetic information into their recommendations for psychiatric medications (Table 1) [33, 34]. In some cases, the FDA mandates that approved drug labels include pharmacogenetic information on safety and effectiveness [29]. As of April 2021, information has been added for 38 gene-drug pairs across 35 psychiatric medications [34].

The FDA has disputed some companies' test results, stating their recommendations do not have an adequate scientific basis [34]. To improve the quality of the tests and results provided by pharmacogenetic test companies, the FDA has made a commitment to improving regulatory oversight of pharmacogenetic tests, including laboratory-developed tests [34]. A comparable regulatory system exists in Canada, where control over pharmacogenomic tests is divided between the federal and provincial governments. In Canada, however, inconsistencies exist in the regulation of direct-to-consumer (DTC) genetic testing and traditional testing in a healthcare setting [30]. There is a lack of strict and standardized federal legislation regulating DTC genetic testing, which has been highlighted by many national health organizations advocating for increased oversight [36, 37]. However, federal and provincial legislation regarding genetic information privacy provides security regulation of test production companies [35]. Health Canada has also been adopting pharmacogenetic information in drug labeling (Table 1), albeit at a slower rate than the FDA [38].

The European Medicines Agency (EMA) has also integrated pharmacogenetic information in drug labeling (Table 1) [39], with such details being included for a significant amount of EMA authorized medications [40]. Further, the EMA has published pharmacogenomic guidelines and both recommendations and requirements for the investigation and implementation of pharmacogenomic data [39]. Japan has additionally adopted pharmacogenetics information on drug labels [41].

Recommendations are not consistent across agencies, and communication from such agencies has at times been contradictory [42], which highlights the necessity for harmonization and consistency internationally. Clarifying and standardizing such recommendations and regulations has important ramifications for medical practice concerning claims of medical malpractice for use, or lack thereof, of genetic testing for patients who have adverse or insufficient responses to psychotropic medications [43].

Training and education

Another challenge is the lack of pharmacogenetic training in current curricula. Hence, more training in genetics should be offered to clinicians, in addition to encouraging patient education and building stronger partnerships between clinicians and pharmacists [44]. Such training has progressed through curricula in many medical and pharmacy schools incorporating pharmacogenetics in the current education of incoming medical professionals [45]. However, the depth and content of such training is not standardized, and integration may falter for interdisciplinary healthcare providers, such as nurse practitioners. Recommendations to improve training programs have been posed and include placing a greater focus on precision health in curricula to meet the reality of evolving treatment approaches [46, 47]. Regarding training update by practicing physicians, data showing positive physician opinions on the use of pharmacogenetic testing [1, 45] and patient benefits suggest there is growing clinical interest in pharmacogenomics [13, 48, 49].

To uphold a patient-centered approach to pharmacogenetic testing implementation, it is vital that physician education initiatives also focus on improving patient understanding of the clinical utility and limitations of testing results. Physicians must thus be provided with sufficient knowledge on informing patients about how testing results will be integrated into their care and the potential for the treatment plan to, or to not, be consequently altered.

Pharmacogenomics testing and equity in care

It is vital to note that in academic writing on genetic variation, comparisons in allele prevalence are often erroneously made between different racial groups. In education for practitioners on the implementation of genetic variance between populations, the language should refer to difference in geographical ancestry, which has genetic implications, and not race, which is socially constructed and not biologically founded [50]. The failure to do so can fuel false rhetoric of biological racial differences and consequent harmful errors in treatment decision making [51].

Pharmacogenomics testing companies

A growing interest in pharmacogenetic data from both providers and patients resulting from psychiatric treatment challenges has led to the emergence of numerous commercial pharmacogenetic tests [52, 53]. Two recent meta-analyses have suggested the superiority of some gene-guided treatment panels compared to treatment as usual [12, 15]. However, evidence for some commercial tests is still emerging and independent validation of study findings has yet to be established.

In fact, tests vary substantially in the selection of gene-drug pairs, in the alleles investigated, in the provided reports, their price, and with some companies analyzing gene-gene interactions (i.e., "combinatorial approaches") which are more difficult to validate [52, 54]. There are also concerns about marketing practices used by testing companies that could have important consequences for consumers. One recent study found that adolescent patients with major depressive disorder who had combinatorial testing results available were more likely to be prescribed medications with less evidence of their efficacy than patients without combinatorial testing results [55]. Proper regulation of commercial testing companies' communication to consumers and providers on the clinical use of their tests is therefore crucial to ensure that the results are not erroneously used to sway treatment decision-making without sufficient evidence of the efficacy of the results. Altogether, these concerns have sparked controversy about the clinical utility of commercial tests.

Electronic medical records

To support the optimization of pharmacogenomic testing in clinical practice, genetic test reports should be integrated into electronic medical records (EMRs). To do so, genetic reports need to be simplified and standardized to improve interpretability by clinicians, in turn maximizing their usefulness in therapeutic planning. Reporting terms for allele function and phenotype are not currently standardized, although consensus terminology has been proposed [56]. EMR systems could be supplemented to generate automated alerts that notify clinicians if affected medications are prescribed or dispensed [57]. Although the successful integration of pharmacogenetics into EMRs is limited, notable institutions have developed successful approaches. For example, Vanderbilt University Medical Center developed an EMR system that can order genotyping, either preemptively or in response to a drug indication(s). Resultant pharmacogenetic reports are then isolated from other medical records until there is sufficient evidence to warrant clinical action. The program also generates summaries of drug-gene interactions, treatment recommendations and alerts, and updates genetic records. Beyond clinicians, genetic reports within the EMR are accessible to patients [58].

This example of pharmacogenetic-EMR integration has provided a model for other healthcare systems to learn from. In doing so, extra vigilance is required to ensure genetic results are free from error before being integrated into a patient's lifetime medical record. In addition, as pharmacogenetic evidence evolves, information available to clinicians in EMRs must be updatable to ensure a high quality of care.

Ethical considerations

The implementation of pharmacogenomic testing occurs in tandem with various ethical considerations. For one, psychological distress could result if findings indicate a patient has a high likelihood of not responding to a treatment method [59]. Further concerns include genetic privacy, particularly regarding unauthorized disclosure of test results to insurers leading to discrimination in respect to treatment access and coverage, for both patients and their families [59]. Safeguards are therefore required to ensure confidentiality throughout the testing process. In the U.S., the Genetic Information Nondiscrimination Act of 2008 provides privacy protection for genetic test results by preventing genetic-based discrimination within the workplace and for most health insurance policies [60]. A similar Genetic Non-Discrimination Act was introduced in Canada in 2017 [61]. Despite the listed concerns, pharmacogenetic testing has been supported in clinical practice by patient populations based on the benefits of its use [62].

It is critical that patients be informed of the potential consequences of pharmacogenetic testing prior to consenting, including the type of information the test generates, how incidental findings and surplus biospecimens will be handled, who can access the results, and how results can affect treatment. Genetic counseling should be available, if needed, for additional education. Ultimately, patients should reserve the right to refuse to undergo testing.

Limitations and future directions

While psychiatric pharmacogenetics is still facing various challenges, implementation is rapidly growing and contributing to improved treatment care. One limitation of our review article is that we have reviewed recommendations provided by expert groups without validating recommendations by conducting our own literature reviews. Some of these recommendations were based on evidence reviews conducted in 2015 and 2016 for SSRIs and TCAs, respectively, and were thus not inclusive of recent evidence [16, 17]. However, the validity of the recommendations produced by expert groups such as CPIC and DPWG are supported by the use of high standard quality criteria and independence of commercial bias or interest [63]. The validity of these guidelines is further supported by endorsements from professional organizations [64, 65] and consensus from other expert groups such as the International Society of Psychiatric Genetics (ISPG) [66].

While additional recommendations exist for gene-drug pairs in psychiatry, due to space limitations, we have not reviewed CPIC guidelines such as CYP2D6 and atomoxetine [67], the HLA-A/HLA-B enzymes and carbamazepine/oxcarbazepine [68], and CYP2C9 and phenytoin [69], all of which show a high level of evidence for implementation [70, 71]. Finally, genetic variation is only one contributor to inter-individual differences in drug response, and this review does not touch on the complexity of integrating environmental, behavioral, and other biological factors into one's response. Future studies need to integrate the interaction between multiple genes and their corresponding variants, as their effects can compound for the resulting drug outcome variability. Current and near-future work strives towards the integration of polygenic risk scores as an additional assessment of an individual's genetic profile relevant to medication outcome [72].

CONCLUSIONS

There is currently consensus among experts in pharmacogenetics that *CYP2D6* and *CYP2C19* genotype information should be used to inform treatment recommendations for a large number of antidepressants and antipsychotics. This strategy is increasingly applied in routine clinical care, particularly for patients showing poor response to previous treatments. While other genes have shown promising associations with drug response and/or side effects for these drug classes, measurable clinical effects are limited [60], and therefore, might only be useful within additive risk models. Future algorithms need to be developed that incorporate demographic, clinical, and biomarker information for the advent of precision medicine.

REFERENCES

1. Walden LM, Brandl EJ, Changasi A, Sturgess JE, Soibel A, Notario JFD, et al. Physicians' opinions following pharmacogenetic testing for psychotropic medication. Psychiatry Res. 2015;229:913–8.
2. Stanek EJ, Sanders CL, Taber KAJ, Khalid M, Patel A, Verbrugge RR, et al. Adoption of pharmacogenomic testing by US physicians: results of a nationwide survey. Clin Pharm Ther. 2012;91:450–8.
3. Haga SB, O'Daniel JM, Tindall GM, Lipkus IR, Agans R. Survey of US public attitudes toward pharmacogenetic testing. Pharmacogenomics J. 2012;12:197–204.
4. McKillip RP, Borden BA, Galecki P, Ham SA, Patrick-Miller L, Hall JP, et al. Patient perceptions of care as influenced by a large institutional pharmacogenomic implementation program. Clin Pharm Ther. 2017;102:106–14.
5. Müller DJ, Rizhanovsky Z. From the origins of pharmacogenetics to first applications in psychiatry. Pharmacopsychiatry. 2020;53:155–61.
6. Thorn CF, Klein TE, Altman RB, Pharm GKB. In: Innocenti F, editor. Pharmacogenomics: Methods and Protocols. Totowa, NJ: Humana Press; 2005. p. 179–91.
7. Prioritization. https://cpicpgx.org/prioritization/. Accessed 26 November 2020.
8. Pharmacogenetics. 2018. https://www.knmp.nl/patientenzorg/medicatiebewaking/farmacogenetica/pharmacogenetics-1/pharmacogenetics. Accessed 20 April 2021.
9. Clinical annotation levels of evidence. https://www.pharmgkb.org/page/clinAnnLevels. Accessed 26 July 2021.
10. Whirl-Carrillo M, Huddart R, Gong L, Sangkuhl K, Thorn CF, Whaley R, et al. An evidence-based framework for evaluating pharmacogenomics knowledge for personalized medicine. Clin Pharmacol Ther. 2021;110:563–72.
11. Rosenblat JD, Lee Y, McIntyre RS. Does pharmacogenomic testing improve clinical outcomes for major depressive disorder? a systematic review of clinical trials and cost-effectiveness studies. J Clin Psychiatry. 2017;78:720–9.
12. Rosenblat JD, Lee Y, McIntyre RS. The effect of pharmacogenomic testing on response and remission rates in the acute treatment of major depressive disorder: a meta-analysis. J Affect Disord. 2018;241:484–91.
13. Greden JF, Parikh SV, Rothschild AJ, Thase ME, Dunlop BW, DeBattista C, et al. Impact of pharmacogenomics on clinical outcomes in major depressive disorder in the GUIDED trial: a large, patient- and rater-blinded, randomized, controlled study. J Psychiatr Res. 2019;111:59–67.

14. Pérez V, Salavert A, Espadaler J, Tuson M, Saiz-Ruiz J, Sáez-Navarro C, et al. Efficacy of prospective pharmacogenetic testing in the treatment of major depressive disorder: results of a randomized, double-blind clinical trial. BMC Psychiatry. 2017;17:250.
15. Bousman CA, Arandjelovic K, Mancuso SG, Eyre HA, Dunlop BW. Pharmacogenetic tests and depressive symptom remission: a meta-analysis of randomized controlled trials. Pharmacogenomics. 2019;20:37–47.
16. Hicks JK, Sangkuhl K, Swen JJ, Ellingrod VL, Müller DJ, Shimoda K, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of tricyclic antidepressants: 2016 update. Clin Pharm Ther. 2017;102:37–44.
17. Hicks JK, Bishop JR, Sangkuhl K, Muller DJ, Ji Y, Leckband SG, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors. Clin Pharm Ther. 2015;98:127–34.
18. Bank PCD, Caudle KE, Swen JJ, Gammal RS, Whirl-Carrillo M, Klein TE, et al. Comparison of the guidelines of the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenetics Working Group. Clin Pharm Ther. 2017;103:599–618.
19. Abdullah-Koolmees H, van Keulen A, Nijenhuis M, Deneer V. Pharmacogenetics guidelines: overview and comparison of the DPWG, CPIC, CPNDS, and RNPGx guidelines. Front Pharm. 2021;11:595219.
20. Endorsements. https://cpicpgx.org/endorsements/. Accessed 26 July 2021.
21. Statement of support for the use of European pharmacogenomic guidelines [Internet]. Ubiquitous Pharmacogenomics Project; 2021. https://upgx.eu/wp-content/uploads/2018/09/Statement-of-support-Horizon-2020-U-PGx-final-sep-2018.pdf. Accessed 27 July 2021.
22. Hornberger J, Li Q, Quinn B. Cost-effectiveness of combinatorial pharmacogenomic testing for treatment-resistant major depressive disorder patients. Am J Manag Care. 2015;21:e357–65.
23. Maciel A, Cullors A, Lukowiak AA, Garces J. Estimating cost savings of pharmacogenetic testing for depression in real-world clinical settings. Neuropsychiatr Dis Treat. 2018;14:225–30.
24. Brown LC, Lorenz RA, Li J, Dechairo BM. Economic utility: combinatorial pharmacogenomics and medication cost savings for mental health care in a primary care setting. Clin Ther. 2017;39:592–602.e1.
25. Verbelen M, Weale ME, Lewis CM. Cost-effectiveness of pharmacogenetic-guided treatment: are we there yet? Pharmacogenomics J. 2017;17:395–402.
26. United Healthcare. Pharmacogenetic testing. 2020. https://www.uhcprovider.com/content/dam/provider/docs/public/policies/comm-medical-drug/pharmacogenetic-testing.pdf. Accessed 21 April 2021.
27. Centers for Medicare and Medicaid Services. Local coverage determination (LCD): MolDX: pharmacogenomics testing (L38294). 2020. https://www.cms.gov/medicare-coverage-database/details/lcd-details.aspx?LCDId=38294&ver=16. Accessed 21 April 2021.
28. Anderson HD, Crooks KR, Kao DP, Aquilante CL. The landscape of pharmacogenetic testing in a US managed care population. Genet Med. 2020;22:1247–53.
29. Heitz D. Medicare now covers genetic tests for targeting depression drugs. Healthline Media. 2014. https://www.healthline.com/health-news/medicare-now-covers-genetic-tests-for-depression-drugs-111814. Accessed 20 November 2020.
30. Proposed Local Coverage Determination (LCD): Pharmacogenomics Testing (DL39063). Centers for Medicare & Medicaid Services; 2021.
31. L Rogers S, Keeling NJ, Giri J, Gonzaludo N, Jones JS, Glogowski E, et al. PARC report: a health-systems focus on reimbursement and patient access to pharmacogenomics testing. Pharmacogenomics. 2020;21:785–96.
32. Regulation of genetic tests. https://www.genome.gov/10002335/regulation-of-genetic-tests/. Accessed 20 November 2020.
33. Office of the Commissioner. FDA announces collaborative review of scientific evidence to support associations between genetic information and specific medications. 2020. https://www.fda.gov/news-events/press-announcements/fda-announces-collaborative-review-scientific-evidence-support-associations-between-genetic. Accessed 20 November 2020.
34. Center for Drug Evaluation, Research. Table of pharmacogenomic biomarkers. 2020. https://www.fda.gov/drugs/science-and-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling. Accessed 20 November 2020.
35. Caulfield T, McGuire AL. Direct-to-consumer genetic testing: perceptions, problems, and policy responses. Annu Rev Med. 2012;63:23–33.
36. Canadian Medical Association. Direct-to-consumer genetic testing. 2017. p. 1–4. Available from: https://www.cma.ca/sites/default/files/2018-11/cma-policy-direct-to-consumer-genetic-testing-pd17-05-e.pdf.
37. Office of the Privacy Commissioner of Canada. Direct-to-consumer genetic testing and privacy. 2017. https://www.priv.gc.ca/en/privacy-topics/health-genetic-and-other-body-information/02_05_d_69_gen/. Accessed 27 November 2020.
38. Loucks CM, Groeneweg G, Roy C, Lee DK, Rieder MJ, Lebel D, et al. Pharmacogenomic testing: enhancing personalized medication use for patients. Can Fam Physician. 2020;66:241–3.
39. Ehmann F, Caneva L, Prasad K, Paulmichl M, Maliepaard M, Llerena A, et al. Pharmacogenomic information in drug labels: European Medicines Agency perspective. Pharmacogenomics J. 2015;15:201–10.
40. Ehmann F, Caneva L, Papaluca M. European Medicines Agency initiatives and perspectives on pharmacogenomics. Br J Clin Pharm. 2014;77:612–7.
41. Otsubo Y, Asahina Y, Noguchi A, Sato Y, Ando Y, Uyama Y. Similarities and differences between US and Japan as to pharmacogenomic biomarker information in drug labels. Drug Metab Pharmacokinet. 2012;27:142–9.
42. Hicks JK, Bishop JR, Gammal RS, Sangkuhl K, Bousman CA, Leeder JS, et al. A call for clear and consistent communications regarding the role of pharmacogenetics in antidepressant pharmacotherapy. Clin Pharm Ther. 2020;107:50–2.
43. Eichmeyer J, Rogers S, Formea CM, Giri J, Jones JS, Schnettler E, et al. PARC report: a perspective on the state of clinical pharmacogenomics testing. Pharmacogenomics. 2020;21:809–20.
44. Nurnberger JI Jr, Austin J, Berrettini WH, Besterman AD, DeLisi LE, Grice DE, et al. What should a psychiatrist know about genetics? review and recommendations from the residency education committee of the international society of psychiatric genetics. J Clin Psychiatry. 2018;80:17nr12046.
45. Kuželički KN, Žitnik PI, Gurwitz D, Llerena A, Cascorbi I, Siest S, et al. Pharmacogenomics education in medical and pharmacy schools: conclusions of a global survey. Pharmacogenomics. 2019;20:643–57.
46. Anderson DW, Bousman CA, Chapman K. Engaging in building the educational support needed to deliver precision health in Canada. Health Manag Forum. 2020;33:135–9.
47. Just KS, Turner RM, Dolžan V, Cecchin E, Swen JJ, Gurwitz D, et al. Educating the next generation of pharmacogenomics experts: global educational needs and concepts. Clin Pharm Ther. 2019;106:313–6.
48. Singh AB. Improved antidepressant remission in major depression via a pharmacokinetic pathway polygene pharmacogenetic report. Clin Psychopharmacol Neurosci. 2015;13:150–6.
49. Bradley P, Shiekh M, Mehra V, Vrbicky K, Layle S, Olson MC, et al. Improved efficacy with targeted pharmacogenetic-guided treatment of patients with depression and anxiety: a randomized clinical trial demonstrating clinical utility. J Psychiatr Res. 2018;96:100–7.
50. Bonham VL, Green ED, Pérez-Stable EJ. Examining how race, ethnicity, and ancestry data are used in biomedical research. JAMA. 2018;320:1533–4.
51. Hollingshead NA, Matthias MS, Bair MJ, Hirsh AT. Impact of race and sex on pain management by medical trainees: a mixed methods pilot study of decision making and awareness of influence. Pain Med. 2015;16:280–90.
52. Bousman CA, Hopwood M. Commercial pharmacogenetic-based decision-support tools in psychiatry. Lancet Psychiatry. 2016;3:585–90.
53. Hachad H, Ramsey LB, Scott SA. Interpreting and implementing clinical pharmacogenetic tests: perspectives from service providers. Clin Pharm Ther. 2019;106:298–301.
54. Bousman CA, Dunlop BW. Genotype, phenotype, and medication recommendation agreement among commercial pharmacogenetic-based decision support tools. Pharmacogenomics J. 2018;18:613–22.
55. Vande Voort JL, Orth SS, Shekunov J, Romanowicz M, Geske JR, Ward JA, et al. A randomized controlled trial of combinatorial pharmacogenetics testing in adolescent depression. J Am Acad Child Adolesc Psychiatry. 2021;S0890-8567:00220–3.
56. Caudle KE, Dunnenberger HM, Freimuth RR, Peterson JF, Burlison JD, Whirl-Carrillo M, et al. Standardizing terms for clinical pharmacogenetic test results: consensus terms from the Clinical Pharmacogenetics Implementation Consortium (CPIC). Genet Med. 2017;19:215–23.
57. Hicks JK, Crews KR, Hoffman JM. A clinician-driven automated system for integration of pharmacogenetic interpretations into an electronic medical record. Clin Pharm Ther. 2012;92:563–6.
58. Peterson JF, Bowton E, Field JR, Beller M, Mitchell J, Schildcrout J, et al. Electronic health record design and implementation for pharmacogenomics: a local perspective. Genet Med. 2013;15:833–41.
59. McCarthy MJ, Chen Y, Demodena A, Fisher E, Golshan S, Suppes T, et al. Attitudes on pharmacogenetic testing in psychiatric patients with treatment-resistant depression. Depress Anxiety. 2020;37:842–50.
60. Katsanis SH, Katsanis N. Molecular genetic testing and the future of clinical genomics. Nat Rev Genet. 2013;4:415–26.
61. Legislative Services Branch. Genetic Non-Discrimination Act. 2019. https://laws.justice.gc.ca/eng/AnnualStatutes/2017_3/FullText.html. Accessed 18 August 2020.
62. Lanktree MB, Zai G, Vanderbeek LE, Giuffra DE, Smithson DS, Kipp LB, et al. Positive perception of pharmacogenetic testing for psychotropic medications. Hum Psychopharmacol. 2014;29:287–91.
63. Caudle KE, Klein TE, Hoffman JM, Muller DJ, Whirl-Carrillo M, Gong L, et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical

Pharmacogenetics Implementation Consortium (CPIC) guideline development process. Curr Drug Metab. 2014;15:209–17.
64. Endorsed Documents. https://www.ashp.org/Pharmacy-Practice/Policy-Positions-and-Guidelines/Browse-by-Document-Type/Endorsed-Documents?loginreturnUrl=SSOCheckOnly. Accessed 18 February 2021.
65. Moore M, Hancock S. Tools and Resources. Tru64 UNIX Troubleshooting, Elsevier; 2003. p. 27–66.
66. Bousman CA, Bengesser SA, Aitchison KJ, Amare AT, Aschauer H, Baune BT, et al. Review and consensus on pharmacogenomic testing in psychiatry. Pharmacopsychiatry. 2020. 4 November 2020. https://doi.org/10.1055/a-1288-1061.
67. Brown J, Bishop J, Sangkuhl K, Nurmi E, Mueller DJ, Dinh J, et al. Clinical pharmacogenetics implementation consortium guideline for cytochrome P450 (CYP)2D6 genotype and atomoxetine therapy. Clin Pharm Ther. 2019;106:94–102.
68. Phillips EJ, Sukasem C, Whirl-Carrillo M, Müller DJ, Dunnenberger HM, Chantratita W, et al. Clinical Pharmacogenetics Implementation Consortium guideline for HLA genotype and use of carbamazepine and oxcarbazepine: 2017 update. Clin Pharm Ther. 2018;103:574–81.
69. Caudle KE, Rettie AE, Whirl-Carrillo M, Smith LH, Mintzer S, Lee MTM, et al. Clinical pharmacogenetics implementation consortium guidelines for CYP2C9 and HLA-B genotypes and phenytoin dosing. Clin Pharm Ther. 2014;96:542–8.
70. Fan M, Bousman CA. Commercial pharmacogenetic tests in psychiatry: do they facilitate the implementation of pharmacogenetic dosing guidelines? Pharmacopsychiatry. 2020;53:174–8.
71. Bousman C, Maruf AA, Müller DJ. Towards the integration of pharmacogenetics in psychiatry: a minimum, evidence-based genetic testing panel. Curr Opin Psychiatry. 2019;32:7–15.
72. Fullerton JM, Nurnberger JI. Polygenic risk scores in psychiatry: will they be useful for clinicians? F1000Res. 2019;8:F1000 Faculty Rev-1293.

ACKNOWLEDGEMENTS

CAB is supported by the Alberta Children's Hospital Research Foundation and the University of Calgary Cumming School of Medicine. DJM is supported by the Canadian Institutes of Health Research (CIHR Operating Grant PJT - 169114), the Centre for Addiction and Mental Health Foundation (Joanne Murphy Professorship), and the Canadian Biomarker Integration Network for Depression (CAN-BIND). LEM received partial funding from the Jasmine Quigley Memorial Award, as part of the University of Toronto Institute of Medical Science Summer Undergraduate Research Program. The content of this paper is solely the responsibility of the authors and does not necessarily represent the official views of these organizations.

AUTHOR CONTRIBUTIONS

All authors had full access to the data presented in this review and take responsibility for the integrity of the data and the accuracy of the data interpretation. Study concept and design: TMF, DJM, LEM. Acquisition of data: TMF, LEM. Interpretation of data: TMF, LEM, CAB, DJM. Drafting of the paper: TMF, LEM. Critical revision of the paper for important intellectual content: TMF, LEM, CAB, DJM. Study supervision: DJM. All authors have given approval for the final version of the article to be published.

COMPETING INTERESTS

DJM and CAB are members of the Clinical Pharmacogenomics Implementation Consortium. TMF and LEM have no conflicts to declare. DJM was a co-investigator on two pharmacogenetic studies where genetic test kits were provided as in-kind contributions by Myriad Neuroscience. DJM did not receive any payments or any equity, stocks, or options from any pharmacogenetic companies. DJM is also a co-inventor on two patents assessing risk for antipsychotic-induced weight gain (pending). CAB is founder and equity holder in Sequence2Script Inc.

SUPPLEMENTARY INFORMATION

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Daniel J. Müller.