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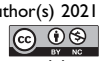

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Encountering Pharmacogenetic Test Results in the Psychiatric Clinic

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Introduction

Pharmacogenetic (PGx) testing is a personalized prescribing approach that utilizes a person's genetic information to inform medication selection and dosing decisions. This approach has been successfully implemented by numerous medical centers/health systems across North America, Europe and Asia,[1,2] is supported by an expert review and consensus[3] and endorsed by professional pharmacy and pharmacology organizations.[4,5] In addition, a recent meta-analysis of five randomized controlled trials showed patients with major depressive disorder that received pharmacogenetic-guided prescribing were 71% times more likely to achieve symptom remission relative to those that received treatment as usaul.[6] However, PGx testing remains controversial in psychiatry and consensus on its utility in day-to-day management of patients has not been reached.

In Canada, PGx testing is primarily performed by commercial laboratories, some offering testing directly to patients.[7] Therefore, psychiatrists should expect to be presented with and asked to use PGx test results by their patients. In addition, psychiatrists are likely to be asked by other psychiatry or family practice colleagues to provide advice on how to interpret the results of PGx testing. While some psychiatrists will feel comfortable providing consults, managing and perhaps integrating these test results into their practice, many will feel unsure about the merits of PGx testing or how to interpret and act on the results. This article addresses these common concerns and offers strategies and resources to prepare psychiatrists for patient care situations, where PGx test results are encountered.

Assessing the Validity of the Pharmacogenetic Test

PGx tests offered by laboratories in Canada and abroad are largely unregulated, unstandardized, and are not equivalent.[8] In fact, in 2018 the US Food and Drug Administration raised concerns about unapproved claims about the ability to predict response to specific medications using genetic testing[9] and later in 2019 issued a warning letter to Inova Genomics Laboratory for deceptive marketing practices and questionable clinical validity.[10] As such, each PGx test's analytical validity (i.e., the test's ability to detect genetic variants of interest) and clinical validity (i.e., how well the test results correlate with medication efficacy or tolerability) should be checked prior to interpreting and implementing the results. We recognize that formal evaluation of every test encountered in practice is not feasible and as such we recommend looking for three test characteristics that when present, can boost confidence in the results provided.

Characteristic 1: The Laboratory That Performed the Test Should Be Accredited. The Standards Council of Canada offers laboratory accreditation aligned with standards developed by the International Organization of Standardization, referred to as ISO 15189. However, the Canadian Association for

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Laboratory Accreditation (CALA), the College of American Pathologists (CAP), and the Clinical Laboratory Improvement Amendments (CLIA) also offer accreditation to laboratories providing PGx testing in Canada. Of note, several provinces (i.e., Alberta, British Columbia, Manitoba, Ontario, and Saskatchewan) have their own accreditation bodies but all provinces follow one or more of the standards mentioned above for accrediting laboratories.[11] If one of these or an equivalent accreditations is not evident, the analytical validity of the test could be questionable and caution in using the test results is advised.

Characteristic 2: The Genes and Alleles Tested Should Be Associated With Medication Pharmacokinetics, Efficacy or Tolerability. There are over 25 genes with evidence-based guidelines developed by expert groups such as the Clinical Pharmacogenetics Implementation Consortium (CPIC),[12] Dutch Pharmacogenetics Working Group (DPWG),[13] and Canadian Pharmacogenomics Network for Drug Safety (CPNDS)[14] as well as regulatory bodies such as Health Canada and the FDA. However, only five of these genes (*CYP2D6, CYP2C19, CYP2C9, HLA-A, HLA-B*) are associated with the pharmacokinetics, efficacy or tolerability of one or more psychiatric medications. Figure 1 (Supplementary Table 1) shows the five genes and 33 associated medications with evidence-based guidelines. To our knowledge, all PGx test panels available in Canada include *CYP2D6*, *CYP2C19* and *CYP2C9*, while less than half include *HLA-A* or *HLA-B*.[7] The absence of the *HLA* genes should only be a concern if the treatment plan involves the use of carbamazepine, oxcarbazepine, phenytoin, of fosphenytoin. Of greater concern is that laboratories often test and report results for genes with limited or no association to medication pharmacokinetics, efficacy or tolerability. Examples of genes commonly appearing on psychiatry test panels that lack sufficient evidence or expert developed guidelines include: *ABCB1, ADRA2A, ANK3, ANKK1, BDNF, CACNA1C, COMT, CYP1A2, CYP3A4, CYP2C8, DRD2, FKBP5, GNB3, GRIK1, HTR2A, HTR2C, MC4R, MTHFR*, and *SLC6A4*. Although many of these genes have excellent face validity and biological plausibility, there are limited or no data on clinical validity for these genes and they are not currently mentioned in a prescribing guideline. Test panels including these genes should be viewed critically and recommendations linked to these genes used with caution.

In addition to the genes, it is also worth examining the list of alleles (e.g., single nucleotide variants, copy number variants) that are tested for each gene, particularly the five genes relevant to psychiatry. The optimum number of tested alleles varies by gene and for most genes a consensus set of alleles has not been established, but in general as the number of alleles tested increases so does the sensitivity and specificity of the PGx test and the more applicable it will likely be across different populations (e.g., European, Asian, African, Indigenous). This latter point is particularly important when interpreting PGx test results of a patient of non-European ancestry because most panels are biased toward alleles observed in individuals of European ancestry. As a result, some panels are more likely to omit gene variants that are rarely observed in individuals of European ancestry but are more common in those of non-European ancestry.[3] Of note, minimum allele sets that take into account ancestry have been proposed for *CYP2C9* (*2, *3, *5, *6, *8, *11),[15] *CYP2C19* (*2, *3, *17),[16,17] *CYP2D6* (*3, *4, *5, *6, *10, *17, *41, *1xN, *2xN),[17] HLA-A (*31:01),[17] and HLA-B (*15:02).[17]

Characteristic 3: Prescribing Recommendations Should Be Supported by an Evidence-Based Guideline. Prescribing recommendations without reference to an evidence-based guideline (e.g., CPIC, DPWG, FDA, Health Canada) should be viewed skeptically as the source of the recommendation may lack sufficient clinical validity for use in practice. For example, some laboratories offer prescribing recommendations based on an association reported in a single clinical study or selectively cite studies that support the recommendations without disclosing the number of studies that failed to find the association. Acting on recommendations that have not undergone a rigorous review process, such as that used by guideline developers,[12] increases the risk of unexpected and potentially harmful outcomes.[18]

Assuming these three test characteristics are met, it is reasonable to consider the PGx test results as part of the overall medication selection and dosing decision-making process. However, the presence of these characteristics does not ensure the results will be clinically useful. To maximize the usefulness of PGx testing, thoughtful interpretation and implementation of the results are required.

Interpreting and Implementing Pharmacogenetic Test Results

When interpreting and implementing PGx-based prescribing recommendations into practice a number of questions often emerge. Here we address a few of the most frequently asked questions.

What Does the '' Mean?.* Testing laboratories typically reported PGx results as a genotype using the star (*) nomenclature. For example, *CYP2D6* *4/*5. The *4 and *5 are star alleles, each representing a unique group of genetic variants that are inherited together (i.e., haplotypes), one from each parent. Each star allele is assigned a function (i.e., no, decreased, normal, increased, unknown, or uncertain) based on the current evidence, such as that curated by the Pharmacogene Variation Consortium (PharmVar).[19,20] By combining the function of the two star alleles, laboratories can infer a person's phenotype, such as medication metabolizer status (i.e., poor, intermediate, normal, rapid,

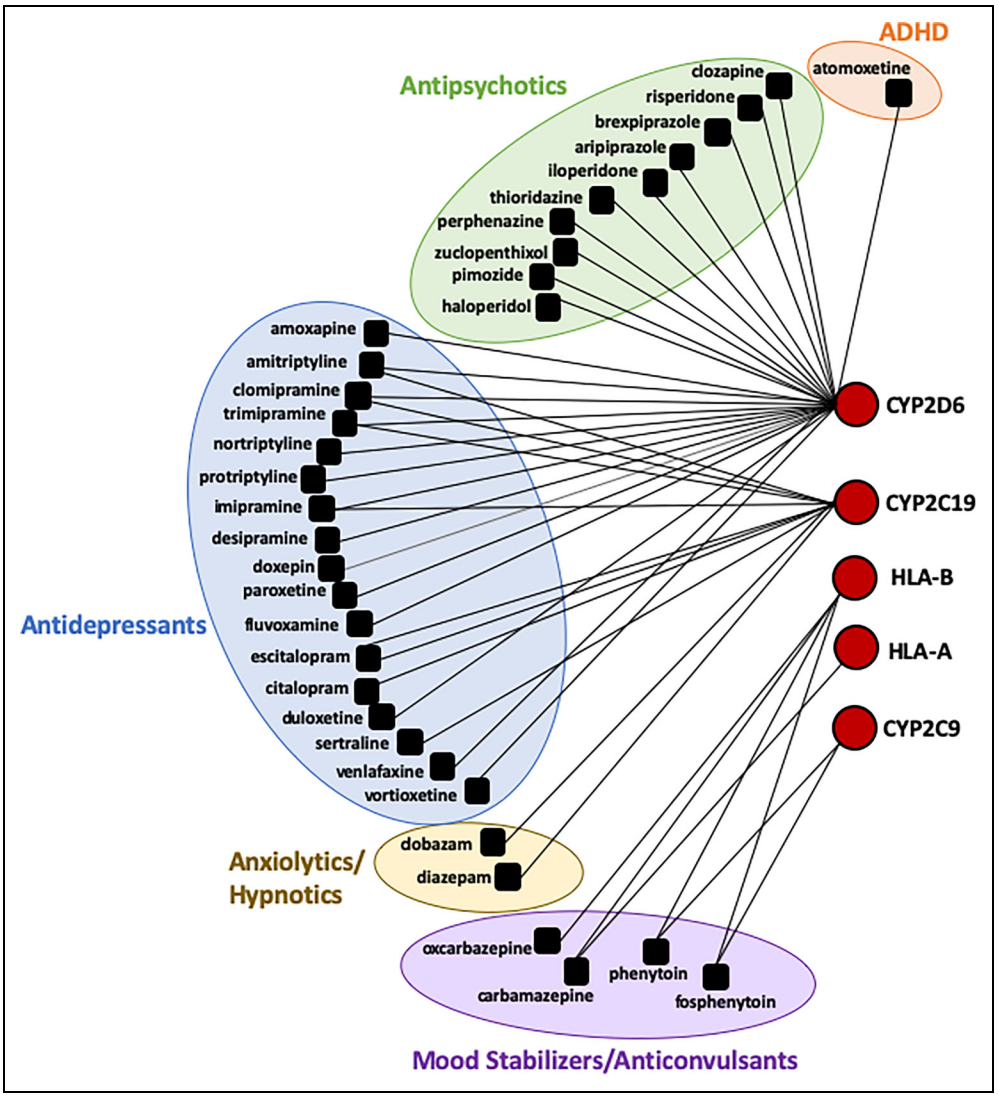

Figure 1. Psychotropic medications with pharmacogenetic-based prescribing guidelines developed by the Clinical Pharmacogenetics Implementation Consortium (CPIC), Dutch Pharmacogenetics Working Group (DPWG), Canadian Pharmacogenomics Network for Drug Safety, Health Canada, or FDA according to the Pharmacogenetics Knowledgebase (PharmGKB) as of 1-April-2021.

ultrarapid), medication transporter function (i.e., increased, normal, decreased, poor), or high-risk medication sensitivity status (i.e., positive, negative).[21] In our example, the *CYP2D6* *4 and *5 alleles have no function and the combination of these two alleles result in a poor metabolizer phenotype. In contrast, if the *CYP2D6* genotype was *1/*1 this would translate to a normal metabolizer because the *1 allele is a normal function allele and the combination of two normal function alleles results in a normal metabolizer phenotype. These genotype-inferred phenotypes are the basis from which medication selection and dosing recommendations are made.

Are Prescribing Recommendations Medication Specific?. Recommendations are made at the level of each gene-medication pair. Two medications in the same class will not necessarily have equivalent recommendations. The reason is typically due to differences in how the medications are metabolized. For example, escitalopram and paroxetine are both selective serotonin reuptake inhibitors but escitalopram is primarily metabolized by *CYP2C19*, whereas paroxetine is primarily metabolized by *CYP2D6*. Thus, an individual that is a *CYP2C19* normal metabolizer and *CYP2D6* poor metabolizer would receive a recommendation for escitalopram that suggests initiating therapy at the standard starting dose. Whereas, the recommendation for paroxetine would suggest selecting an alternative medication or reducing the staring dose due to their *CYP2D6* poor metabolizer status.

What Other Factors Can Impact the Interpretation of PGx Results?. Several demographic (e.g., age,[22] sex[23]) and clinical

(e.g., concomitant medications,[24] pregnancy,[25,26] inflammation[24,27]) factors can influence the interpretation of PGx-based recommendations. For example, a genotype-inferred *CYP2C19* normal metabolizer that commences use of esomeprazole to treat gastroesophageal reflux would likely be converted to an intermediate or poor metabolizer, depending on the esomeprazole dose taken. This conversion is a result of esomeprazole being an inhibitor of *CYP2C19* enzyme activity.[28,29] Conversely, if the same individual instead began taking St John's wort (a *CYP2C19* inducer), they would likely be converted to a rapid or ultrarapid metabolizer. In both of these scenarios the medication recommendations associated with their *CYP2C19* normal metabolizer phenotype could be inappropriate and may require adjustment before clinical implementation.

Adjusting recommendations provided by PGx testing laboratories can be a challenge without access to proper resources. To assist physicians, some testing laboratories offer web-based tools or consultations with one of their pharmacists or physicians. If these tools or consultations are not available, some health authorities have centralized consult services. For example, Alberta Health Services supports a Clinical Pharmacology Physician Consultation Service capable of assisting with PGx-related inquiries. There are also free web-based tools, such as Sequence2Script (sequence2script.com)[30] that enable physicians to (re)generate evidence-based prescribing recommendations for their patients while accounting for concomitant medications.

Interpretation of results may also be impacted by the strategy employed by PGx testing laboratories to translate genotypes to recommendations. Some commercial testing laboratories deliberately conceal – for proprietary reasons – the process by which pharmacogenetic testing results are translated into clinical recommendations. This so called 'black box' strategy is in conflict with open and peer-reviewed approaches adopted by CPIC and other clinical guideline development groups and significantly impairs critical appraisal of results produced using this strategy.[31] Fortunately, there are tools and resources, such as the Pharmacogenetics Knowledgebase (PharmGKB)[32] and Sequence2Script,[30] that can help 'by-pass' the black box via direct interpretation of the raw genotype (e.g., CYP2D6 *1/*4) or phenotype (e.g., CYP2D6 intermediate metabolizer) results provided by these testing companies. Notably, this by-pass procedure can be time consuming and no evidence exists on whether this approach produces recommendations that are superior to those provided by black box approaches. It does however, offer full transparency.

Why Are Medications I Prescribe Not on the PGx Report?. PGx testing laboratories differ on the medications they support. Some laboratories focus on medications relevant to specific practice settings (e.g., psychiatry, cardiology). What is important is that the medications that do appear in the report are supported by the current scientific evidence (Figure 1). For example, certain benzodiazepines (e.g., alprazolam), ACE inhibitors (e.g., enalpril), antipsychotics (e.g., quetiapine, olanzapine), antidepressants (e.g., bupropion, desvenlafaxine), and analgesics (e.g., aspirin) are commonly included on PGx testing panels[33] despite the absence of PGx-based guidelines for these medications. Implementing recommendations for medications that are not supported by evidence-based guidelines could do more harm than good.[18]

Am I at Risk for Litigation If I Don't Act on PGx Test Results?. With an increase in the clinical use of genetic testing, there are concerns of increased liability exposure to physicians for failure to use or misuse PGx information.[34] Any patient has the right to lodge a complaint and pursue litigation if they believe that their physician's failure to act on PGx test results caused injury. The potential liability is further amplified by the availability of PGx prescribing guidelines as well as regulatory bodies (e.g., Health Canada, FDA) increasingly requiring drug manufactures to include PGx information on their product labels.[34-37] To reduce litigation risk, physicians should become familiar with these guidelines and product labels, particularly those relevant to medications they most frequently prescribe. Physicians should also consider PGx test results when they are available and use them to facilitate shared decision-making with their patients, including efforts to set realistic expectations about how the results can be reasonably used.[38] We would also suggest documentation of this shared decision-making process in the patient's medical record and when appropriate, encourage seeking expert consultation.

How Long Are PGx Test Results Valid?. As prescribing recommendations are based on an individual's genetic information and this information does not change, the PGx test results remain valid over a person's lifetime. However, as the evidence evolves, the number of medications with PGx-based recommendations will increase and some recommendations will be refined. Therefore, even though a person's genes do not change, the recommendations associated with them might. Regular updates will ensure PGx recommendations remain valid over a patient's lifetime. However, unlike many clinical workflows that are integrated within the electronic health record (EHR), most PGx results encountered in psychiatry are in formats that do not facilitate direct integration into the EHR. In most settings PGx test results are scanned into the EHR. Fortunately, new EHR systems have been designed to receive and store PGx data in a manner that allows for easy updates and enables automated prescribing alerts.

Conclusion

When a patient presents for an appointment with PGx test results in hand or a colleague requests advise from you on

how best to interpret these results, common initial reactions may include sceptical, uncomfortable and perplexed. Given that the results are unexpected and the source is often unfamiliar, these types of reactions are understandable and predictable. However, it is important not to allow these reactions to trigger premature dismissal of PGx information and with it the potential opportunity to improve care and engage patients in treatment decision-making. Practical strategies and accessible resources are available to assist psychiatrists in effective consideration, interpretation and implementation of PGx test results that they encounter in their practice. In combination with existing strategies for prescribing, PGx testing can serve as an informative complement to the psychiatrist's toolbox.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: CAB has received in-kind testing kits from Myriad Neuroscience, CNSDose, Genomind, and AB-Biotics for research purposes but has not received payments or received any equity, stocks, or options in these companies or any other pharmacogenetic companies. CAB is also the founder and shareholder of Sequence2Script Inc. GM and RD are employees and equity holders at GeneYouIn Inc, provider of Pillcheck pharmacogenetic testing. DJM 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. DJM is also a co-inventor on two patent assessing risk for antipsychotic-induced weight gain (pending). XM and RT have nothing to disclose.

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Supplemental Material

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