PGx2
Evidence-Based Pharmacogenomic Testing for Psychiatry and Pain Management

Biron

Summary
Genetics affects how we tolerate and respond to medications. Pharmacogenomics, the study of how genetic variants influence our exposure, efficacy and tolerability to medications, has gained increasing support, and prompted the creation of expert groups and the publication of peer-reviewed clinical guidelines. However, to be integrated into clinical practice, clinicians require a more comprehensive solution. Here, describe Biron's methodology in creating a comprehensive and evidence-based pharmacogenomic test for patients in psychiatry and pain management.

Introduction

When selecting a course of treatment for a patient, clinicians often gather and consider a variety of clinically relevant data, including the patient's symptoms, prior and recent clinical history, family history, comorbidities, and personal preference. This process reflects an effort to comprehend the patient's particular genetic background and the source of the illness. The clinician must then use strict treatment algorithms that are not really tailored for any particular endophenotype to steer pharmacotherapy via trial-and-error, a process that may actually lengthen or complicate the clinical course before a positive outcome is attained.

Approved pharmacological treatments are safe and effective when evaluated on a population basis. However, it is well recognized that on an individual level, the effect of medication can differ substantially from one patient to another, owing to many treatment failures. Interindividual variability in medication responses can be attributed to a variety of factors, including, but not limited to, the patient's clinical presentation, past medical history, family history, and concomitant treatments. Genetic variability is also major factor that can influence the safety, tolerance, and efficacy of medications, accounting for 20 to 95 percent of interindividual variability in drug effect.[1]
Genetic variations can affect the response to medications by modulating their pharmacokinetics or pharmacodynamics properties.

Pharmacokinetic genes encode proteins that influence drug absorption, distribution, **metabolism,** and excretion. The PGx2 report detects variants that affect drug metabolism and **distribution,** notifying the prescriber if any dose adjustments should be considered for adequate exposure to medication. These notifications are found in the **EXPOSURE** sections of the report.

Pharmacodynamic genes encode proteins that can affect the **efficacy** of drug treatments or the risk of particular **adverse drug reactions**. The PGx2 detects variants associated with drug pharmacodynamics, informing the prescriber when these variants are present. These notifications are found in the **EFFICACY** and **ADVERSE DRUG REACTIONS** sections of the report.

Peer-Reviewed Pharmacogenomic Guidelines

The accrual evidence supporting the effects of genetics on drug response has prompted clinical experts in pharmacogenomics to publish guidelines aimed at guiding clinicians when genotyping results are made available. In addition, certain drug monographs also include dosing recommendations based on a patient's genetic results. It is important to note that these recommendations are based on genetic tests only; drug interactions and other clinical factors can have a significant impact on prescribing choices and should be taken into consideration prior to initiating pharmacological therapy. The two most recognized groups that regularly publish and update pharmacogenomic clinical guidelines are the Clinical Pharmacogenetics Implementation Consortium and the Dutch Pharmacogenomic Working Group. Biron's pharmacogenomic test ensures that these peer-reviewed recommendations are integrated, prioritised, and referenced in the report.

Clinical Pharmacogenetics Implementation Consortium (CPIC)
Stemming from the National Institutes of Health's Pharmacogenomics Research Network (http://www.pgrn.org) and the Pharmacogenomics Knowledge Base (PharmGKB, http://www.pharmgkb.org), the Clinical Pharmacogenetics Implementation Consortium (CPIC, http://cpicpgx.org) was formed to provide peer-reviewed, updated, evidence-based, freely accessible guidelines for gene/drug pairs. As of August 2022, there are 26 published guidelines covering 95 medications across many different therapeutic areas (Table 1).

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Table 1. CPIC Guidelines for Psychiatry and Pain Management (2022)

CPIC Guidelines	Medications		Genes (Alleles)	Specialty
CYP2C9 and NSAIDs[2]	aceclofenac aspirin celecoxib diclofenac flurbiprofen ibuprofen indomethacin lornoxicam	lumiracoxib meloxicam metamizole nabumetone naproxen piroxicam tenoxicam	CYP2C9	Pain Management
CYP2C9, HLA-B and Phenytoin[3]	fosphenytoin	phenytoin	CYP2C9 HLA-B (*15:02)	Psychiatry
CYP2D6 and Atomoxetine[4]	atomoxetine		CYP2D6	Psychiatry
CYP2D6, CYP2C19 and SSRIs[5]	citalopram escitalopram fluvoxamine	paroxetine sertraline	CYP2C19 CYP2D6	Psychiatry
CYP2D6, CYP2C19 and Tricyclic Antidepressants[6]	amitriptyline clomipramine desipramine doxepin	imipramine nortriptyline trimipramine	CYP2C19 CYP2D6	Psychiatry
CYP2D6, OPRM1, COMT, and Opioids[7]	alfentanil buprenorphine codeine fentanyl hydrocodone hydromorphone levomethadone	methadone morphine naltrexone oxycodone remifentanil sufentanil tramadol	COMT CYP2D6 OPRM1	Pain Management
HLA-A, HLA-B and Carbamazepine and Oxcarbazepine[8]	carbamazepine	oxcarbazepine	HLA-A (*31:01) HLA-B (*15:02)	Psychiatry

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Royal Dutch Association for the Advancement of Pharmacy Pharmacogenetics Working Group (DPWG)

Much like the CPIC, the Dutch Pharmacogenetics Working Group aims to facilitate PGx implementation by developing evidence-based pharmacogenetic guidelines to optimize pharmacotherapy. These initiatives have given academics and interested physicians access to valuable resources, but they do not offer a complete and practical solution applicable to clinical settings. In addition to providing the pharmacogenomic recommendations found in the CPIC, DPWG and drug monographs, Biron's pharmacogenomic test provides up-to-date evidence-based notifications for all of the medications and complementary treatments that can be considered by clinicians in psychiatric and pain management settings.

Data Curation and Levels of Evidence

The Biron PGx test detects genetic variants that influence the effects of drugs used in psychiatry and pain management, which have been carefully selected using a systematic literature review and data curation methodology. This process ensures that the information shared with the clinician is supported by up-to-date scientific literature and translated into straight forward clinical notifications.
The level of evidence is a term used to score the strength of scientific data supporting the association between a genetic variant and a medication. This association can impact plasma concentrations, efficacy and/or the susceptibility to particular side effects. Scientific evidence may support a gene-drug association if it is described in a peer-reviewed study with statistical significance, involves a gene known as a Very Important Pharmacogene (established by PharmGKB, http://www.pharmgkb.org), found in a drug monograph stating that a drug is metabolized by or interacts with a specific protein/enzyme (and therefore gene) or multiple drug-drug interaction and/or in vitro studies confirm the involvement of the gene in the drug metabolism. On the other hand, evidence that opposes a gene-drug association will be found in peer-reviewed studies with nonsignificant p-value or studies showing significant but contradictory results.
Biron's PGx test classifies gene-drug association on a scale of 1 to 4, wherein "1" indicates a strong scientific support for the association, and "4" indicates insufficient scientific support for the association. As such, all association with a level of evidence of "4" are excluded from the final report (Table 2).

Table 2. Biron's classification scheme for levels of evidence

Level 1	Level 2
Association recognized by a clinical guideline (CPIC, PharmGKB or medical society-endorsed) or specific drug dosing guidance found within drug product monograph (HCSC, FDA, EMA, Swissmedic, PMDA)	Association replicated in multiple studies, in independent cohorts with significant p-values.
When guidelines differ, the most cautious recommendation is provided.	Associated genes known as a Very Important Pharmacogenes (VIP) based on pharmGKB classification (https://www.pharmvar.org/).
When a gene-drug association is included in a clinical guideline and/or drug label, the recommendations is prioritized and takes precedent over other gene-drug association of level 2 or 3.	

Level 3	Level 4 (exclusion from report):
Association based on single study (not replicated), OR	Nonsignificant association found in study.
Case report, OR	Contradictory results but with more results opposing the association.
In vitro, molecular or functional assay evidence only, OR	
Metabolizing enzyme listed in drug label.	

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Clinical Utility

Pharmacogenomic testing is a cost-effective way to evaluate multiple genetic variants from which the results can be applied in multiple clinical contexts. For example, the commonly tested CYP2D6 gene, informs clinicians on the level of activity of the important CYP2D6 enzyme. Since CYP2D6 metabolises a wide range of medications, this result allows prescribers to personalize their prescribing decisions for medications across many fields (e.g. cardiology, oncology, psychiatry, etc) and patients can benefit from the information for future treatments. As such, evaluating the clinical utility of pharmacogenomics should ideally be done over a patient lifetime as the information gathered from testing does not change over time. However, current evidence stems from more feasible approaches of evaluating the impact of pharmacogenomics on patient outcomes with specific diagnoses over limited time periods. To date in psychiatry, the clinical utility of pharmacogenomics has been mainly studied in patients with major depressive disorder.

Major Depressive Disorder.

In patients with major depressive disorder, the clinical utility of pharmacogenomics has been evaluated through randomized controlled trials (RCTs) of commercial tests currently available on the market. Two meta-analyses of these RCTs were subsequently done and showed that patients receiving pharmacogenomic-guided decision support tool therapy were 1.7 times more likely to achieve symptom remission relative to individuals who received treatment as usual.[9] Compared to the content of the tests evaluated in these studies, the Biron PGx test analyses the vast majority of the genes that were covered and expands to include additional genes and alleles based on current evidence. As such, the Biron PGx test is expected to perform at least as well, if not better than the tests evaluated to date through RCTs.

Another class of medications that has gathered a large amount of evidence for the use of pharmacogenomics are the two antipsychotics, aripiprazole and risperidone.

Aripiprazole and Risperidone.

A large retrospective study was performed to measure the effect of CYP2D6 genotype on exposure and efficacy of risperidone and aripiprazole in 1,615 patients.11 The study provided substantial support for earlier assertions that, in order to prevent overdose and dose-dependent side effects, lower doses should be given to CYP2D6 poor metabolizers. It was also shown that poor and ultrarapid CYP2D6 metabolisers had an increased chance of risperidone therapeutic failure. Authors concluded that CYP2D6 genotyping would be a valuable tool for individualising dosing of these two antipsychotics.

Analytical Testing

When ordering a pharmacogenomic test, it is important to consider which genes and alleles are being tested to ensure accurate and reliable results that are relevant for the patient being tested. To this end, Bousman et al. (2019) published a “Minimum, evidence-based genetic testing panel” for psychiatry.[12] In addition, the Association for Molecular Pathology (AMP) has also developed a list of allele sets for important pharmacogenes: CYP2C9, CYP2C19 and CYP2D6.[13-15] Table 3 shows the Biron pharmacogenomic test includes all of the recommended alleles.

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Table 3. Alleles Recommended by AMP and for Psychiatric Pharmacogenomic Testing

Genes	Alleles	Minimum, evidence-based genetic testing panel for psychiatry	AMP Tier 1	Tested by Biron
CYP2C9	*2	x	x	yes
	*3	x	x	yes
	*5		x	yes
	*6		x	yes
	*8		x	yes
	*11		x	yes
CYP2C19	*2		x	yes
	*3		x	yes
	*17		x	yes
CYP2D6	*2		x	yes
	*3	x	x	yes
	*4	x	x	yes
	*5	x	x	yes
	*6	x	x	yes
	*9		x	yes
	*10	x	x	yes
	*17	x	x	yes
	*29		x	yes
	*41	x	x	yes
	CNV	x	x	yes
HLA-A	*31:01	x		yes
HLA-B	*15:02	x		yes

Reporting

The PGx2 report was designed as a clinical decision support tool that is intuitive and straightforward to use.
While individual genetic variants have been significantly associated with variability in drug effect, current data is often lacking on the combined effect of multiple genetic variants. This is especially relevant when looking at both pharmacokinetic and pharmacodynamic variants, the results from which can point towards contradictory treatment decisions. At the moment, data is still lacking that would allow to consolidate multiple genetic results into a single recommendation (i.e. polygenic risk scoring).To circumvent these situations, Biron's pharmacogenomic report divides the different gene-drug associations into three main categories: exposure, efficacy and adverse drug reactions. This feature ensures that the prescriber is aware of all the pharmacogenomic factors that may influence plasma concentrations, response and tolerance, when deciding on which medication to prescribe and which dose to use.

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Conclusion

Current evidence shows that while drug response is multifactorial, genetics can play a determining role in patient outcomes. The paucity of tools available to prescribers often results in a process of trial and error that can hinder patient care. With Biron's genetic test, you obtain valuable information on your patients' individual genetic profile based on peer-reviewed evidence, which can significantly influence the effects of medications used in psychiatry and pain management. With this tool, clinicians can take genetically informed treatment decisions that personalise and improve patient care.

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