

# Landmarks of pharmacogenomics and some considerations for clinical practice

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**Abstract:** Since the completion of the Human Genome Project 28 years ago, myriad genomics applications have risen in areas such as agriculture, livestock, infectious agents, forensics, bioenergy, ancestry, health, disease, and medicine. This was driven partly by the US government's ability to use a unique program to facilitate genome sequencing to the point where the cost of sequencing a whole human genome is not prohibitive. However, application of this knowledge of the double helix twisted DNA at the bedside in psychiatric clinical practice has little to report, despite US Food and Drug Administration (FDA) approval of nearly 40 psychotropic drugs, as well as specific guidelines for their application. Patients with treatment-resistant mental illness, history of unresponsiveness to psychotropic medications, and history or family history of serious adverse effects to psychotropic drugs may qualify for pharmacogenomics (PGx) testing with insurance reimbursement, or a low, out-of-pocket, payment of not greater than US \$300. Psychiatric mental health nurse practitioners and providers who utilize PGx will not only improve patient care outcomes, but also contribute to the acceleration of the potential diagnostic and preventive capabilities of PGx testing.

**Keywords:** pharmacogenetics, pharmacogenomics, phenoconversion, prodrug, substrate, inhibitors, inducers, methylenetetrahydrofolate, biomarkers, cytochrome P450

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## Introduction

Most patients (60–70%) diagnosed with psychiatric disorders (e.g. bipolar disorder, major depressive disorder, schizophrenia, and anxiety disorders) exhibit partial or complete treatment resistance, or do not adhere to their medication therapy due to adverse effects.<sup>1–4</sup> The burden of untreatable psychiatric disorders can be unbearable, not only for the patient and their family, but also for a community that strives to understand and invest in the care of those living with mental illness. The patient in the case example presented here would have been regarded as a hopeless case 50 years ago, left to the mercy of the proponents of willpower and behavioral hypotheses. The advent of pharmacogenomics (PGx) testing has revealed that psychiatric disorders can be treated with fewer adverse side effects, less trial and error, and improved treatment outcomes. Nonetheless, PGx for the treatment of psychiatric disorders has been poorly implemented, with little uptake among psychiatric providers.

## Case presentation

A 21-year-old white man with a history of refractory attention-deficit/hyperactivity disorder (ADHD) and insomnia presented to a psychiatry practice. He was diagnosed with ADHD at the age of 12 years and struggled with the disorder throughout his childhood. Since his diagnosis, he has tried numerous stimulant medications as prescribed by various psychiatrists. Some of these stimulants caused allergic reactions and other side effects that necessitated a change of medication. Consequently, identifying the right medication for the patient was ultimately a matter of trial and error. The patient's condition eventually worsened to the point that he had to drop out of high school. He worried about losing his job because of difficulties in focusing, completing assignments, and frequent impulsivity. A psychiatrist recently recommended PGx testing for this patient, which led to the identification of the most effective and accurate medication dosage for him. PGx testing revealed that the patient was a poor metabolizer (PM) of CYP2D6, but an

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essential metabolizer (EM) of CYP2C19 and CYP2C9. This led to the discontinuation of all antipsychotic medication, and a reduction in the 60-mg methylphenidate extended-release daily capsule to a 20-mg dose. The patient responded well, without the adverse effects of insomnia and loss of appetite.

## Discussion

### *PGx history*

The history of PGx can be traced back to 500 BCE, when Pythagoras discovered that eating fava beans was fatal for some individuals but nourishing for others, and that the beans could be used to treat constipation.<sup>5</sup> The next major discovery in the advent of PGx was by Archibald Garrod, who hypothesized that the ingestion of substances affects genes at the molecular level, and that specific enzymes are required for detoxification. According to Garrod, the lack of these enzymes led to metabolic disorders and potential fatality.<sup>6</sup> By the 1940s and 1950s, scientists had begun to observe and report a range of atypical responses to medications. During World War II, some soldiers, after being administered antimalarial drugs, developed a range of adverse side effects, including anemia. It was later found that these soldiers were deficient in the enzyme glucose 6-dehydrogenase.<sup>5,6</sup> Within the same period, the anesthesia drug succinylcholine was found to prolong paralysis and induce fatal reactions in some individuals with a mutated genetic variant linked to the absence of the enzyme butyrylcholinesterase.<sup>6</sup> Nevertheless, it was not until the late 1950s that Friedrich Vogel coined the term 'pharmacogenetics.'<sup>7</sup> During this period, the single most important contribution that propelled genetic studies in the 20th century was the discovery of the double helical structure of DNA by James Watson and Francis Crick. Later, the term 'pharmacogenomics' became official during the launch of the Human Genome Project in 1990, and, once human DNA mapping was completed in 2003, the field of PGx began to grow.<sup>7,8</sup>

### *PGx and modern medicine*

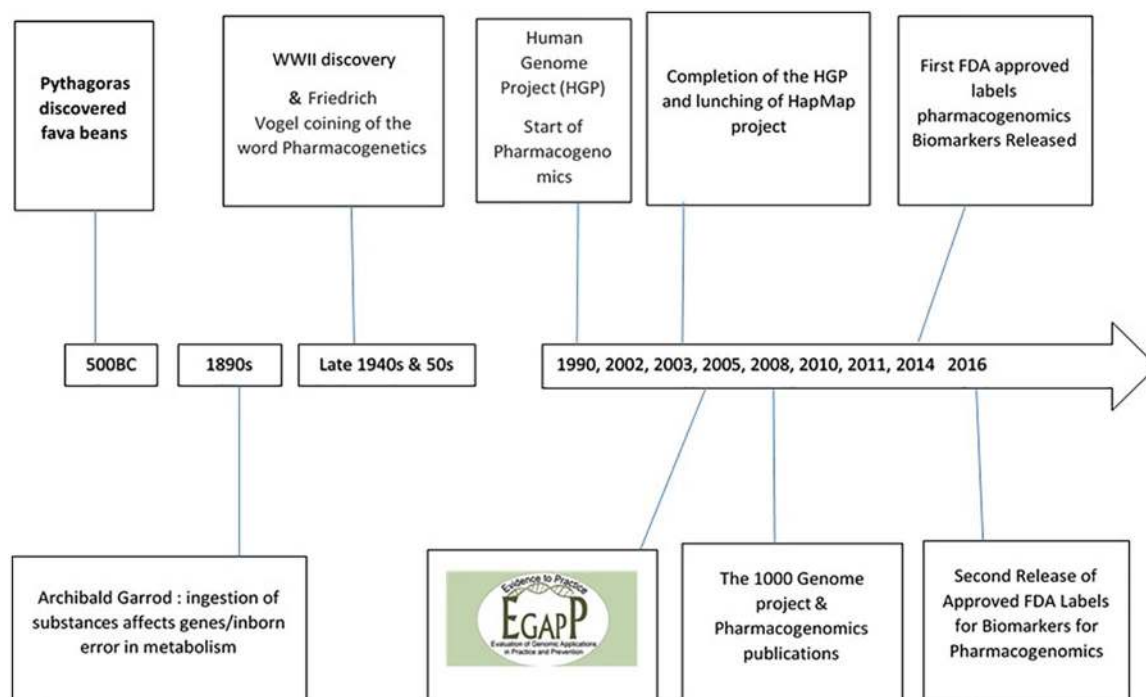
The study of PGx led to the birth of a booming biotechnology industry that continues to identify new cures and therapeutic treatments for diseases. Nonetheless, pharmaceutical companies face high costs in producing and marketing these drugs.<sup>9</sup> Collaboration between pharmaceutical

companies and other biotechnology entities has become a necessity in the search for affordable and effective treatments. This research has resulted in considerable advancement in the fields of medicine and nursing, and has helped elucidate how genes interact with medications to open new pathways in identifying genotypes and phenotypes suitable for specific medications. Research has broadened practitioners' understanding of psychotropic medications and how to minimize adverse drug reactions, negating the need for traditional trial-and-error in psychiatric care. Figure 1 provides a mind map of the development of PGx.

PGx has affected several fields of medicine. Although we are witnessing a resistance to the adoption of PGx in psychiatric medicine, the United States Food and Drug Administration (FDA) has approved roughly 40 psychotropic biomarkers, along with guidelines for the improvement of patient care. Health care providers' major concerns were risks and insurance reimbursement. Public and private insurance companies currently reimburse for PGx testing. The out-of-pocket cost of the PGx panel test is currently US \$300 without insurance.<sup>10</sup> The quantity of biomarkers per PGx test order is not standardized; however, many genetic agencies offer PGx testing beyond the scope approved by the FDA. Some genetic companies cover only the biomarkers approved by the FDA (mostly pharmacokinetic biomarkers), while others cover pharmacokinetic and pharmacodynamic biomarkers.

It is also equally important for providers and consumers to be wary of genetic companies marketing PGx testing without FDA approval. Interested parties are encouraged to research the authenticity of the genetics laboratory agency, and its approval by the FDA, before subscribing to its services. In the world of health care, consumers are dying to find the best antidote for their problems on the market. Companies like Theranos, and executives like Elizabeth Holmes, will continue to emerge, so providers should thoroughly examine company claims and verify their authenticity with regulating authorities. The FDA's recent warning letter to Inova Genomics Laboratory for claims of PGx testing that have not been verified is a reminder that providers cannot be naïve about PGx marketing claims.<sup>11</sup>

Prior to ordering PGx testing, consider the following questions: Have previous psychotropic drugs



**Figure 1.** History and development of pharmacogenomics.

failed to stabilize the patient's condition? Has the patient become noncompliant with therapeutic treatment due to the adverse side effects of psychotropic drugs? Have the patient's symptoms failed to respond to the approved class of psychotropic drugs for the condition after 6 months of treatment? Does the patient's family history show serious adverse responses, such as serotonin syndrome or neuroleptic malignant syndrome, to psychotropic drugs? A positive answer to these questions justifies ordering PGx testing for insurance reimbursement. Health care professionals should also consider using FDA-approved label biomarkers and guidelines (Table 1) to justify whether the medications fall into certain categories.<sup>12</sup>

Physicians should educate patients on PGx testing, and allow patients to make informed decisions. Brochures on the importance of PGx testing for treatment-resistant depression, ADHD, bipolar disorder, and other mood disorders are useful educational resources. Educational tools can also focus on the ability to prevent harm. Having a panel of PGx test results from a patient is the most effective way to stop trial and error, thereby avoiding harm beforehand. When the patient agrees to PGx testing for his or her condition, physicians or their staff should call to verify the patient's insurance coverage for the testing, and inform the

patient of costs if the patient's insurance does not cover the test. By calling, or getting verification from insurance company websites, physicians will avoid undue financial burden on patients. For example, a review of the Tricare website shows that the agency covers specific genetic testing deemed medically necessary, but it does not indicate whether PGx testing for psychotropic drugs is covered.<sup>10</sup> Lastly, physicians should consider inviting a PGx testing company to their practice setting to provide education on PGx.

#### *Practical PGx resources*

In addition to the FDA-approved biomarkers and guidelines, the following resources may be relevant to any provider who intends to incorporate PGx testing into his or her practice. None of these resources provide a guide on whether to order a test or not, but two of the sites have information about current genetic testing and how to use them to improve the outcome of medication treatment.

The Clinical Pharmacogenetics Implementation Consortium (CPIC) is used by many medical professionals.<sup>14</sup> CPIC substantiates its guidelines with published clinical studies, and uses graded levels of evidence to show how phenotypes are assigned to genotypes. CPIC has more robust and

**Table 1.** FDA approved label of pharmacogenomic biomarkers in clinical psychiatry.

Drug	Biomarker	Precautions
Amitriptyline	CYP2D6	About 7–10% of Caucasians are PMs, reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available. PMs have higher than expected plasma concentrations of TCAs when given usual doses.
Aripiprazole	CYP2D6	Dosage adjustments for CYP considerations. Dosage adjustments are recommended in patients who are known CYP2D6 PMs, and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers. When the coadministered drug is withdrawn from the combination therapy, ABILIFY dosage should then be adjusted to its original level. When the coadministered CYP3A4 inducer is withdrawn, ABILIFY dosage should be reduced to the original level over 1–2 weeks. In patients who may be receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g. a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor, or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially, and then adjusted to achieve a favorable clinical response.
Aripiprazole Lauroxil	CYP2D6	Dose adjustments for CYP. For the first 21 days, the patient takes oral aripiprazole concomitantly with the first dose of ARISTADA. Once stabilized on ARISTADA, refer to the dosing recommendations below for patients taking CYP2D6 inhibitors, CYP3A4 inhibitors, or CYP3A4 inducers: No dosage changes recommended for ARISTADA, if CYP modulators are added for <2 weeks. Make dose changes to ARISTADA if CYP modulators are added for >2 weeks. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as PMs. Elimination of aripiprazole is mainly through hepatic metabolism involving CYP3A4 and CYP2D6. Dosage adjustments are recommended in CYP2D6 PMs due to high aripiprazole concentrations.
Atomoxetine	CYP2D6	Approximately 7% of a Caucasian population are PMs. Laboratory tests are available to identify CYP2D6 PMs. The blood levels in PMs are similar to those attained by taking strong inhibitors of CYP2D6.
Brexpiprazole	CYP2D6	Dosage modifications for CYP2D6 PMs, and for concomitant use with CYP inhibitors or inducers. Dosage adjustments are recommended in patients who are known CYP2D6 PMs, and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers.
Brivaracetam	CYP2C19	PMs required dose reduction.
Carbamazepine	HLA-B*15:02 HLA-A*31:01	Serious dermatologic reactions and HLA-B*1502 allele. Serious, sometimes fatal, dermatologic reactions, including TEN and SJS, have been reported during treatment with Tegretol. Hypersensitivity reactions and HLA-A*3101 allele. SJS/TEN, maculopapular eruptions, and drug reaction with eosinophilia and systemic symptoms.
Citalopram	CYP2C19 CYP2D6	20mg/day is the maximum recommended dose for patients >60 years of age, patients with hepatic impairment, and for CYP2C19 PM or those patients taking cimetidine or another CYP2C19 inhibitor. QT-prolongation and Torsade de Pointes: citalopram dose should be limited in certain populations. CYP2D6 PMs: citalopram steady-state levels were not significantly different in PMs and EMs of CYP2D6. Drug–drug interactions: coadministration of a drug that inhibits CYP2D6 with Celexa is unlikely to have clinically significant effects on citalopram metabolism, based on study results in CYP2D6 PMs.
Clobazam	CYP2C19	Dosage adjustments in CYP2C19 PM. In patients known to be CYP2C19 PMs, the starting dose should be 5mg/day, and dose titration should proceed slowly according to weight and tolerable level. If necessary, and based on clinical response, an additional titration to the maximum dose (20mg/day or 40mg/day, depending on the weight group) may be started on day 21.
Clomipramine	CYP2D6	About 7–10% of Caucasians are PMs; reliable estimates of the prevalence of reduced CYP2D6 isozyme activity among Asian, African, and other populations are not yet available
Clozapine	CYP2D6	Renal or hepatic impairment or CYP2D6 noted in PMs. It may be necessary to reduce the CLOZARIL dose in patients with significant renal or hepatic impairment, or in CYP2D6 PMs. Dose reduction may be necessary for patients who are CYP2D6 PMs. Clozapine concentrations may be increased in these patients because clozapine is almost completely metabolized and then excreted. A subset (3–10%) of the population has reduced activity of CYP2D6; i.e. PMs.

(Continued)

Table 1. (Continued)

Drug	Biomarker	Precautions
Desipramine	CYP2D6	About 7–10% of Caucasians are PM. Reliable estimates of the prevalence of reduced P450 2D6 isozyme activity among Asian, African, and other populations are not yet available.
Dextromethorphan and quinidine	CYP2D6	The quinidine in NUDEXTA inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or its activity otherwise pharmacologically inhibited. Because of this effect on CYP2D6, accumulation of parent drug or failure of active metabolite formation may decrease the safety and efficacy of drugs used concomitantly with NUDEXTA that are metabolized by CYP2D6.
Diazepam	CYP2C19	About 3–5% of Caucasians have little or no activity and are PMs, and have CYP3A4
Doxepin	CYP2D6 CYP2C19	PMs of CYPs and CYP2D6 may have higher doxepin plasma levels than normal subjects. PMs of CYP2C19 and CYP2D6 may have higher doxepin plasma levels than normal subjects.
Duloxetine	CYP2D6	Dual inhibition of CYP1A2 and CYP2D6. Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 PM subjects ( $n = 14$ ) resulted in a 6-fold increase in duloxetine AUC and Cmax.
Escitalopram	CYP2D6 D CYP2C19	<i>In vitro</i> studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady-state levels of racemic citalopram were not significantly different in PMs and CYP2D6 EMs after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. Based on the established exposure–response relationship, the predicted QTcF change from placebo arm (95% CI) under the Cmax for the dose of 20 mg is 6.6 [7.9] msec. Escitalopram 30 mg given once daily resulted in a mean Cmax of 1.7-fold higher than the mean Cmax for the maximum recommended therapeutic dose at steady state (20 mg). The exposure under supratherapeutic 30 mg dose is similar to the steady-state concentrations expected in CYP2C19 PMs following a therapeutic dose of 20 mg.
Eteplirsen	DMD	EXONDYS 51 is indicated for the treatment of DMD in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51.
Fluoxetine	CYP2D6	Drugs metabolized by CYP2D6. Fluoxetine inhibits the activity of CYP2D6 and may make individuals with normal CYP2D6 metabolic activity resemble a PM. Coadministration of fluoxetine with other drugs that are metabolized by CYP2D6, including certain antidepressants (e.g. TCAs), antipsychotics (e.g. phenothiazines and most atypicals), and antiarrhythmics (e.g. propafenone, flecainide, and others) should be approached with caution. If fluoxetine is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need for a decreased dose of the original medication should be considered. Drugs with a narrow therapeutic index represent the greatest concern (e.g. flecainide, propafenone, vinblastine, and TCAs). Due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, thioridazine should not be administered with fluoxetine, or within a minimum of 5 weeks after fluoxetine has been discontinued.
Fluvoxamine	CYP2D6	Approximately 7% of the normal population are PMs. Caution is indicated in a patient known to have reduced levels of CYP2D6 activity and those receiving concomitant drugs (e.g. quinidine) known to inhibit this CYP isoenzyme.
Galantamine	CYP2D6	Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of CYP2D6 isozyme.
Iloperidone	CYP2D6	Dosage adjustment for patients taking FANAPT who are PMs of CYP2D6. FANAPT dose should be reduced by one-half for PMs.

(Continued)



Table 1. (Continued)

Drug	Biomarker	Precautions
Imipramine	CYP2D6	About 7–10% of Caucasians are PMs. Reliable estimates of the prevalence of reduced CYP2D6 isozyme activity among Asian, African, and other populations are not yet available.
Lacosamide	CYP2C19	There are no clinically relevant differences in the pharmacokinetics of lacosamide between CYP2C19 PMs and EMs. Results from a trial in poor metabolizers (PM) ( $n=4$ ) and extensive metabolizers (EM) ( $n=8$ ) of cytochrome P450 (CYP) 2C19 showed that lacosamide plasma concentrations were similar in PMs and EMs, but plasma concentrations, and the amount excreted into urine, of the O-desmethyl metabolite were about 70% reduced in PMs compared with EMs.
Modafinil	CYP2C19	CYP2C19 also provides an ancillary pathway for the metabolism of certain TCAs (e.g. clomipramine and desipramine) and selective serotonin reuptake inhibitors that are metabolized primarily by CYP2D6. In tricyclic-treated patients deficient in CYP2D6 (i.e. those who are PMs of debrisoquine; 7–10% of the Caucasian population; similar or lower in other populations), the amount of metabolism by CYP2C19 may be substantially increased. PROVIGIL may cause elevation of tricyclics levels in this subset of patients.
Nefazodone	CYP2D6	No change in the initial dose of either drug is necessary, and dose adjustments should be made on the basis of clinical response. CYP2D6 isozyme A subset (3–10%) of the population has reduced activity of the drug-metabolizing enzyme CYP2D6. The pharmacokinetics of nefazodone and its major metabolites are not altered in these PMs. Plasma concentrations of one minor metabolite (mCPP) are increased in this population; the adjustment of nefazodone dosage is not required when administered to PMs.
Nortriptyline	CYP2D6	About 7–10% of Caucasians are PMs; reliable estimates of the prevalence of reduced CYP2D6 isozyme activity among Asian, African, and other populations are not yet available. Poor metabolizers have higher than expected plasma concentrations of TCAs when given usual doses. Depending on the fraction of the drug metabolized by CYP2D6, the increase in plasma concentration may be small or quite large (8-fold increase in plasma AUC of the TCA).
Oxcarbazepine	HLA-B*15:02	Association with HLA-B*1502. Patients carrying the HLA-B*1502 allele may be at increased risk for SJS/TEN with Oxtellar XR treatment.
Paroxetine	CYP2D6	In healthy volunteers who were EMs of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 h. This resulted in increases in steady-state atomoxetine AUC values that were 6- to 8-fold greater, and in atomoxetine C <sub>max</sub> values that were 3- to 4-fold greater, than when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary, and it is recommended that atomoxetine be initiated at a reduced dose when it is given with paroxetine.
Perphenazine	CYP2D6	Metabolism of a number of medications, including antipsychotics, antidepressants, beta-blockers, and antiarrhythmics, occurs through the CYP2D6 isoenzyme (debrisoquine hydroxylase). Approximately 10% of the Caucasian population has reduced activity of this enzyme, so-called PMs. Prospective phenotyping of elderly patients prior to antipsychotic treatment may identify those at risk for adverse events.
Phenytoin	CYP2C9 CYP2C19	Unusually high levels result from liver disease, variant CYP2C9, and CYP2C19 alleles, or drug interactions that result in metabolic interference. The patient with large variations in phenytoin plasma levels, despite standard doses, presents a difficult clinical problem. Serum level determinations in such patients may be particularly helpful.
	HLA-B*15:02	Consideration should be given to avoiding phenytoin as an alternative for carbamazepine in patients positive for HLA-B*1502.
Pimozide	CYP2D6	Approximately 5–10% of the population exhibit higher pimozide concentrations than CYP2D6 EMs. The concentrations observed in poor CYP2D6 metabolizers are similar to those seen with strong CYP2D6 inhibitors such as paroxetine. The time to achieve steady-state pimozide concentrations is expected to be longer (approximately 2 weeks) in CYP2D6 PMs because of the prolonged half life. Alternative dosing strategies are recommended in patients who are genetically poor CYP2D6 metabolizers.
Protriptyline	CYP2D6	Drugs metabolized by CYP2D6. The biochemical activity of the drug-metabolizing isozyme cytochrome P450 2D6 (debrisoquine hydroxylase) is reduced in a subset of the Caucasian population. About 7–10% of Caucasians are PMs, reliable estimates of the prevalence of reduced CYP2D6 isozyme activity among Asian, African, and other populations are not yet available.

(Continued)

Table 1. (Continued)

Drug	Biomarker	Precautions
Risperidone	CYP2D6	Risperidone is metabolized to 9-hydroxyrisperidone by CYP2D6, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs. CYP2D6 is subject to genetic polymorphism. About 6–8% of Caucasians, and a very low percentage of Asians, have little or no activity and are PMs, prone to inhibition by a variety of substrates and some nonsubstrates, notably quinidine.
Tetrabenazine	CYP2D6	Before prescribing a daily dose of XENAZINE that is greater than 50 mg per day, patients should be genotyped to determine if they express the drug-metabolizing enzyme, CYP2D6. CYP2D6 testing is necessary to determine whether patients are PMs, EMs, or IMs of XENAZINE.
Thioridazine	CYP2D6	Not electronically available.
Tramadol	CYP2D6	Approximately 7% of the population has reduced activity of the CYP2D6 isoenzyme of CYP. These individuals are PMs of debrisoquine, dextromethorphan, and TCAs, among other drugs. Based on a population PK analysis of phase I studies in healthy subjects, concentrations of tramadol were approximately 20% higher in PMs versus EMs, while M1 concentrations were 40% lower.
Trimipramine	CYP2D6	About 7–10% of Caucasians are PMs; reliable estimates of the prevalence of reduced CYP2D6 isozyme activity among Asian, African, and other populations are not yet available.
Valproic acid	POLG	Depakene is contraindicated in patients known to have mitochondrial disorders caused by POLG mutations and children under 2 years of age who are clinically suspected of having a mitochondrial disorder. Valproate-induced acute liver failure and liver-related deaths have been reported in patients with hereditary neurometabolic syndromes caused by mutations in the gene for mitochondrial DNA POLG (e.g. Alpers-Huttenlocher Syndrome) at a higher rate than those without these syndromes. Most of the reported cases of liver failure in patients with these syndromes have been identified in children and adolescents.
	ABL2, ASL, ASS1, CPS1, NAGS, OTC	Valproic acid is contraindicated in patients with known UCD. Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of valproate therapy in patients with UCDs, a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of valproate therapy, evaluation for UCD should be considered in the following patients: <ul style="list-style-type: none"> <li>(1) those with a history of unexplained mental retardation, or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma ammonia or glutamine;</li> <li>(2) those with cyclical vomiting and lethargy, extreme episodic irritability, ataxia, low BUN, or protein avoidance;</li> <li>(3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males);</li> <li>(4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving valproate therapy should receive prompt treatment (including discontinuation of valproate therapy) and be evaluated for underlying UCDs.</li> </ul>
Venlafaxine	CYP2D6	Imipramine partially inhibited the CYP2D6-mediated metabolism of venlafaxine, resulting in higher plasma concentrations of venlafaxine, and lower plasma concentrations of ODV; the total concentration of active compounds (venlafaxine plus ODV) was not affected. No dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.
Vortioxetine	CYP2D6	The maximum recommended dose of TRINTELLIX is 10 mg/day in known CYP2D6 PMs. Reduce the dose of TRINTELLIX by one-half when patients are receiving a CYP2D6 strong inhibitor (e.g. bupropion, fluoxetine, paroxetine, or quinidine) concomitantly. The dose should be increased to the original level when the CYP2D6 inhibitor is discontinued.
Compiled from the FDA table of pharmacogenomics biomarkers in drug labeling. <sup>13</sup> AUC, area under the plasma concentration time curve; BUN, blood nitrogen urea; CI, confidence interval; Cmax, maximum plasma concentration; CYP, cytochrome P450; DMD, Duchenne muscular dystrophy; EM, extensive metabolizer; FDA, food and drug administration; IM, intermediate metabolizer; mCPP, meta-chlorophenylpiperazine; ODV, o-desmethylvenlafaxine; PK, pharmacokinetics; PM, poor metabolizer; POLG, polymerase gamma; SJS, Stevens-Johnson syndrome; TCA, tricyclic antidepressant; TEN, toxic epidermal necrolysis; UCD, urea cycle disorders; UM, ultra-rapid metabolizer.		

relevant information for the clinical application of psychotropic drugs than the FDA guidelines. For instance, CPIC includes the consideration of CYP2D6 and CYP2C19, whereas the FDA guidelines focus on only CYP2D6 for amitriptyline. The CPIC website provides information on drug biomarkers for novice providers to evaluate evidence for themselves. PharmGKB is a subsidiary website of CPIC.<sup>15</sup> PharmGKB publishes clinical guidelines for each drug, and provides recommendations for genotype dosing. The Pharmacogenomics Research Network (PGRN) is a website with open membership for providers, researchers, graduates, and postdoctoral students, and offers interested individuals the opportunity to learn about, and contribute to, PGx research.<sup>13</sup>

#### *Considerations for PGx clinical use*

The FDA has approved roughly 40 psychotropic medications for biomarker labeling. The caveat regarding these approved labels is that few psychiatric practitioners use them to make clinical decisions for patients. A nationwide survey of their awareness and utilization of FDA-approved labels among 10,303 physicians revealed that approximately 41% of physicians use FDA-approved biomarkers labels to inform PGx test decision-making and improve medication management. The field of oncology, with the highest rate of early adopters, has more FDA-approved biomarkers for PGx testing than any other field. However, psychiatrists (with the second largest number of approved FDA biomarkers) have not fully embraced PGx testing in clinical practice.<sup>16,17</sup>

In addition, consistent with Parker and Satkoske,<sup>18</sup> the FDA acknowledges that one key limitation of these labels is that the efficacy of PGx has not been established with minority populations.<sup>12</sup> Moreover, due to the history of the United States government conducting unethical medical experimentation under the guise of clinical trials and treatment with these populations,<sup>18</sup> such efficacy testing is likely to be a sensitive issue. This will undoubtedly contribute to the slow adoption of PGx among minority groups. Although this assertion is controversial, it is a platform from which the medical community can design education that focuses on the benefits of genetic testing for minority populations. The provision of appropriate educational programs highlighting the safety of PGx testing, and its utilization in minority communities, is essential to bridging this gap. The Perera laboratory, along

with other scientists, aim to bring precision medicine to underserved populations.<sup>19</sup> Already, some inroads are leading to an increase in data and the accurate dosing of medications such as warfarin and tacrolimus for underserved populations.<sup>19,20</sup> These discoveries attest to the different alleles in minority populations, which makes it significant for providers to learn about and utilize PGx-guided treatment, and move away from a one-size-fits-all medical approach.

FDA-approved biomarkers require providers to understand certain basic concepts in pharmacology in order to utilize PGx-guided treatment. Phenoconversion is a genotypic conversion of an EM to a phenotypic PM. Phenoconversion occurs as a result of substrates, inhibitors, and inducers changing the expected outcome of a drug prescribed based on PGx testing.<sup>21</sup> Some of these FDA-approved drugs for PGx biomarkers are more susceptible to phenoconversion than others. In addition, interference from other drugs or illicit substances, such as cigarettes, may elicit phenoconversion.<sup>22</sup> Usually, substances that function as inhibitors or substrates can facilitate the therapeutic or adverse effects of another drug metabolized by that isozyme, but inducers decrease the function of that drug's metabolism. These factors pose a major challenge to providers in the application of PGx-guided treatment. Table 2 shows a compilation of some common cytochrome P450 enzymes with their substrates, inducers, and inhibitors.<sup>22,23</sup>

PGx-guided treatment could be used to minimize the opioid epidemic; however, it would be imperative for providers to understand the mechanisms of prodrugs such as tramadol and codeine if the patient is identified as a PM. In most cases, PMs accumulate metabolites of the medication, and in the case of prodrugs, the accumulation of metabolites may be 80% of the inactive drug, while the remaining drug is rendered ineffective.<sup>21</sup> A typical example of this type of phenomenon is seen in codeine, which has a complex biological activity. The prodrugs morphine and metabolite 6-glucuronide become ineffective in PMs. For instance, Koren and colleagues provides several examples of the importance of understanding prodrug mechanisms in PMs.<sup>24</sup> The report a baby who died from breastfeeding because the mother was prescribed codeine postpartum to treat episiotomy pain. A 2-year-old boy underwent an adenotonsillectomy to treat sleep apnea and was prescribed codeine and acetaminophen to reduce the pain,



**Table 2.** Cytochrome P450 psychotropic drug interactions.<sup>21-23</sup>

Cytochrome P450 enzymes	Common substrates	Inhibitors	Inducers
CYP1A2	Amitriptyline clomipramine clozapine cyclobenzaprine imipramine mirtazapine olanzapine caffeine	cimetidine ciprofloxacin enoxacin erythromycin fluvoxamine grepafloxacin isoniazid mexiletine norfloxacin tacrine zileuton	barbiturates carbamazepine lansoprazole omeprazole phenytoin rifampin smoking
CYP2C9	fluvastatin phenytoin warfarin ibuprofen phenobarbital Antabuse glimepiride glipizide glyburide	amiodarone cimetidine cotrimoxazole fluconazole fluvoxamine isoniazid ketoconazole metronidazole zafirlukast	barbiturates carbamazepine rifampin rifapentine St. John's wort
CYP2C19	amitriptyline citalopram clomipramine diazepam imipramine	felbamate fluoxetine fluvoxamine modafinil omeprazole oxcarbazepine	Unknown
CYP2D6	amitriptyline chlorpromazine clomipramine clozapine codeine desipramine	amiodarone cimetidine clomipramine diphenhydramine fluoxetine fluphenazine	Unknown
CYP2D6	dextromethorphan donepezil fluoxetine haloperidol hydrocodone imipramine methamphetamine metoprolol mirtazapine nortriptyline paroxetine perphenazine propranolol risperidone ritonavir thioridazine tramadol trazodone venlafaxine	haloperidol paroxetine perphenazine propafenone propoxyphene quinacrine quinidine ritonavir sertraline terbinafine thioridazine	

*(Continued)*

**Table 2.** (Continued)

Cytochrome P450 enzymes	Common substrates	Inhibitors	Inducers
CYP3A4	citalopram methadone mirtazapine nefazodone nicardipine	amiodarone clarithromycin cyclosporine diltiazem erythromycin	barbiturates carbamazepine dexamethasone efavirenz ethosuximide
CYP3A4	nifedipine nimodipine nisoldipine quetiapine sertraline verapamil zaleplon zileuton zolpidem buspirone carbamazepine citalopram imipramine donepezil	ethinylestradiol fluconazole fluvoxamine grapefruit juice indinavir nefazodone nelfinavir quinine ritonavir verapamil zafirlukast	griseofulvin modafinil nafcillin nevirapine oxcarbazepine phenytoin primidone rifabutin rifampin rifapentine St. John's wort
Compiled from scientific literature from 2012 to 2019. <sup>21-23</sup>			

but he died on the second evening. A 5-year-old boy underwent a bilateral myringotomy tube placement and an adenotonsillectomy and was prescribed codeine/acetaminophen, and he died the following day.<sup>24</sup> This is a significant series of anecdotal cases in which PGx-guided treatment could have prevented the sudden death due to morphine overdose in each case.

A review of codeine-related deaths from 1965 to 2015 revealed the deaths of approximately 21 children, all below the age of 12, and 64 severe respiratory distress cases. The reports relate only to cases submitted to the FDA, leaving room for concern.<sup>25</sup> The FDA and the American Academy of Pediatrics cautioned against the use of codeine and tramadol, but a recent study shows that roughly 1 in 20 children is still prescribed codeine after surgery. The understanding and utilization of PGx-guided treatment will identify ultra-rapid metabolizers and PMs of codeine and tramadol.

Although tramadol and eteplirsen are not psychotropic drugs, these medications were selected as among the approved FDA biomarker drugs because they represent some of the most common medications for patients diagnosed with a mental illness and other medical comorbidities. These medications, and others, present the potential to

inhibit or induce CYP450, even for patients who may be prescribed drugs they can normally metabolize through PGx-guided treatment. Another basic concept and emerging area in the field of psychiatric clinical practice is methylenetetrahydrofolate reductase (MTHFR) polymorphisms and homocysteine. Numerous studies associate the MTHFR variant and abnormal homocysteine levels to neurocognitive disorders and the exacerbation of other mental illnesses.<sup>26-28</sup> Folate and other B vitamins are essential elements in the modulation of neurotransmitters. A patient with MTHFR polymorphism may not respond to psychotropic drugs, even though the patient may be an EM of that drug. Ensuring that the patient is not folate-deficient will positively impact the patient's response to the drug in the brain. For patients with MTHFR, serum folate levels may be within reference range, and may reduce vitamin B12. Based on current literature, these patients might benefit from the ingestion of methylcobalamin and methylfolate.<sup>27</sup> The promotion of adequate vegetable consumption is essential for the therapeutic effect of psychotropic drugs for most patients, but for some, methylcobalamin and methylfolate may be needed for their psychotropic drugs to work.<sup>27</sup>

The hypotheses and theories of genetic interaction with the ingestion of substances span centuries of

anecdotal evidence, from individuals to small communities of scientists. At 28 years after completion of the Human Genome Project, the ability to exploit a double helix at the bedside of medicine is still not realized in practice in several other specialties. Psychiatric mental health nurse practitioners must embrace the opportunity to utilize this new tool beyond prescribing for diagnostic and preventative measures. A late-adopter attitude toward the use of PGx testing is safe but does not innovate or advance genomics for diagnostic, preventive, and treatment of mental illness.

### Conclusion

As the patient case illustrates, PGx testing is important not only in terms of the dose adjustment of psychotropic drugs but also in preventing harm prior to the treatment of patients. In addition to the online resources provided, a summary of the current FDA-approved psychotropic drug biomarkers and precautions could be a guide for any novice provider who intends to use PGx testing to improve patient response to psychotropic medications. It is equally important for a novice provider to comprehend the basic concepts of pharmacology in order to utilize the FDA biomarkers accurately and facilitate better patient outcomes. The use of PGx testing does not rule out holistic care for patients. Appropriate use of PGx testing focuses not only on predictive treatment but also on preventive care and specific lifestyle changes, as many biomarkers become available for pharmacodynamics purposes.

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