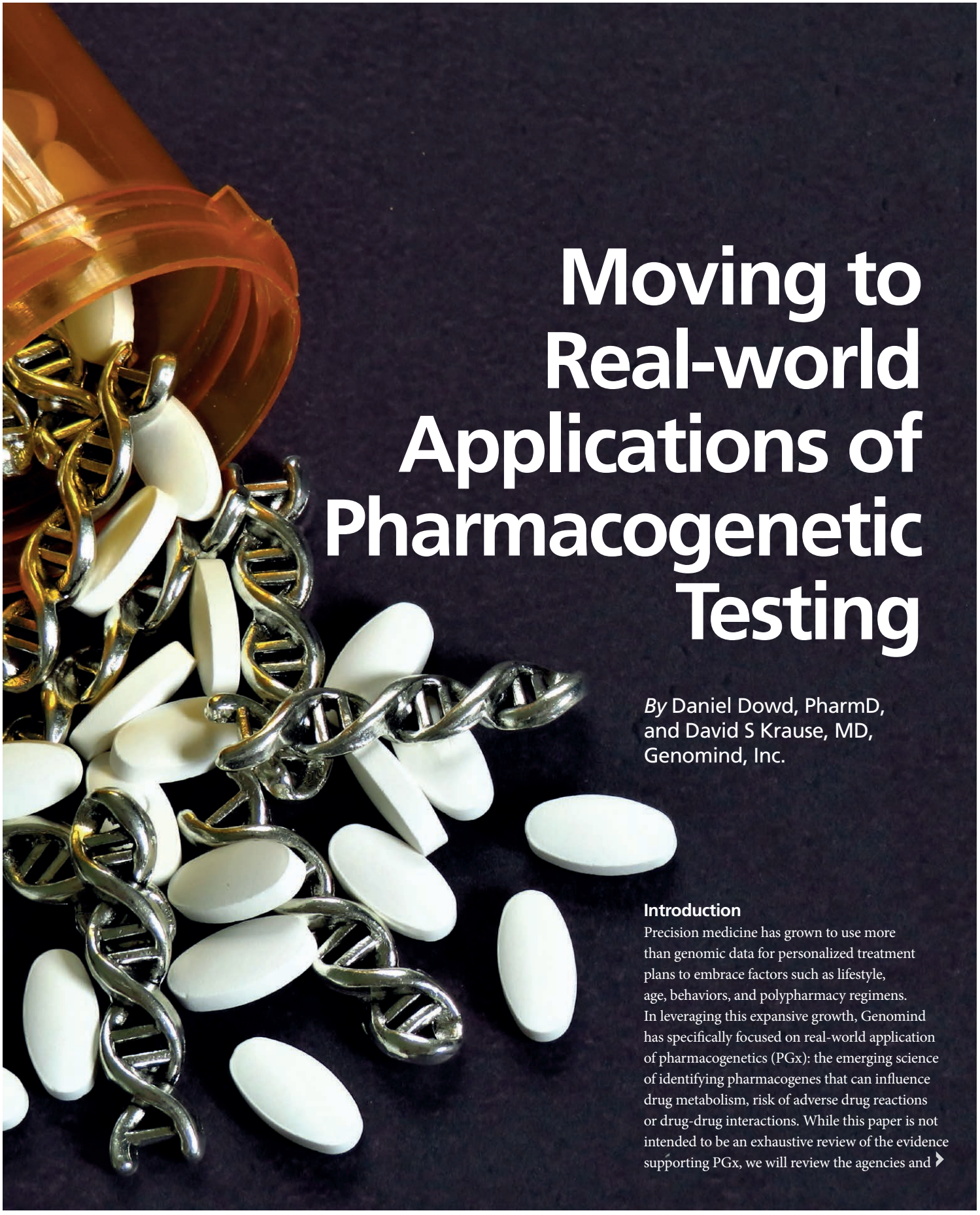

Moving to Real-world Applications of Pharmacogenetic Testing

By Daniel Dowd, PharmD, and David S Krause, MD, Genomind, Inc.

Introduction

Precision medicine has grown to use more than genomic data for personalized treatment plans to embrace factors such as lifestyle, age, behaviors, and polypharmacy regimens. In leveraging this expansive growth, Genomind has specifically focused on real-world application of pharmacogenetics (PGx): the emerging science of identifying pharmacogenes that can influence drug metabolism, risk of adverse drug reactions or drug-drug interactions. While this paper is not intended to be an exhaustive review of the evidence supporting PGx, we will review the agencies and ›

scientific consortiums that support PGx testing, the clinical trials and economic evidence surrounding PGx and the real-world application of PGx.

An important component of personalized medicine is identifying genes that can influence drug metabolism or side effect risk, so-called pharmacogenes. Well-documented variants of certain genes, such as those coding for the cytochrome P450 enzyme superfamily, have been shown to affect drug exposure and in many cases, increase the risk of side effects. Some individuals have genetic substitutions or deletions that result in low, high, or null activity of certain enzymes, resulting in variable metabolism of certain drugs. To complicate this genetic influence, drug-drug interactions can mimic a null activity phenotype through the phenomenon of phenoconversion in which e.g., a genotypic high metabolizer is converted into a phenotypic low metabolizer of drugs via pharmacologic inhibition of the relevant enzyme.

While the use of PGx in therapeutic areas such as psychiatry, cardiology, pain management and others has been increasing, obstacles to broader implementation include poor reimbursement from third party payers, lack of clinician familiarity with PGx, inadequate workflow integration and a lack of standardization in reporting. Payers and providers justifiably have asked for sufficient published data to support the clinical utility of PGx, while healthcare administrators have a need for EMR integration, provider education and a consistent genotype/phenotype reporting structure. The goal of this article is to highlight some solutions to these barriers and demonstrate how real-world implementation of a complete PGx program can succeed.

Polypharmacy Medication Management

Most chronic health conditions are typically addressed through pharmacological intervention, often requiring multiple medications. According to data published by the National Center for Health Statistics, approximately 50% of individuals in the United States report taking at least one prescribed medication.[1] Furthermore, 24% of individuals are prescribed three or more prescription medications and approximately 13% report the use of five or more prescription medications within the past 30 days.[2] In total, approximately 3.8 billion prescriptions were filled at pharmacies in the United States in 2019.[3] Unfortunately, many patients will experience negative effects of medication usage, either in the form of adverse drug events (ADEs) or medication inefficacy, requiring provider diligence in medication management.[4]

With limited time and resources, a clinician must merge multiple factors into a medication plan-proper diagnosis, standard treatment protocols, drug-drug interactions, prior medications, cost, etc. It is possible now for prescribers to have access to patients' genomic data. This additional information will need to be incorporated to ensure safe prescribing.

The safe and effective use of pharmaceuticals is also challenged by the fractured nature of health care delivery in the United States. For example, individuals may see several different providers for different problems. Thus polypharmacy, commonly defined as 5 or more concurrent medications, has become more common, especially as the population ages.[5,6] The most likely group to experience polypharmacy are those over 65 years old. Approximately 44% of men and 57% of women older than 65 take five or more medications per week, while 12% in this age group take 10 or more medications per week. In long-term care facilities, it is estimated that up to 91% of residents take 5 or more medications and 65% take 10 or more medications.[7,8] The growing need for complex medication regimens often leads to ADEs, accounting for an estimated 3.2 million hospital and emergency room visits per year.[9] These statistics make the clear case that our current system of medication management has need for improvement, which we propose can be achieved with adoption of PGx in clinical practice.

"The field of pharmacogenomics (PGx) is growing rapidly and is increasingly being implemented at the point of care"

Creating A PGx World

The goal of a complete PGx program is to enhance medication management via three pillars:

1) Identify and manage patient-specific adverse drug reaction risk
2) Evaluate and if clinically appropriate, implement patient specific dosing
3) Provide guidance on how to manage drug-drug interactions and drug-gene interactions

Much of our knowledge of drug-gene interactions comes from pharmaceutical new drug applications (NDAs), which require new chemical entities (NCEs) to be evaluated for absorption, distribution, metabolism, and elimination (ADME) as well as drug-drug interactions. The U.S. Food and Drug Administration's (FDA) Table of Pharmacogenomic Biomarkers in Drug Labeling is a valuable resource that lists hundreds of drugs with genetic biomarker information, including boxed warnings, precautions, genotype-specific dosing and risk of ADEs. The Agency notes that "Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose."[10]

Whereas the FDA is probably the best-known governmental agency providing information for use of pharmaceuticals, a less well-known group is a non-governmental consortium known as the Clinical Pharmacogenetics Implementation Consortium (CPIC). They have arisen with the mission of "address(ing) this barrier to clinical implementation of pharmacogenetic tests by creating, curating, and posting freely available, peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines."[11] This group of mostly academic clinicians, pharmacologists, pharmacists and volunteers is widely respected as one of the most authoritative sources of evidence-based PGx knowledge. As of this writing, CPIC has published 26 gene-drug guidelines, which grade the strength of evidence for such associations and identify how to use such knowledge. In addition to the curation of gene-drug associations, they also have created nomenclature standardization and recommended universal genotype to phenotype translation tables.

In Europe, the Dutch Pharmacogenomics Working Group (DPWG) occupies a similar niche. The DPWG was established in 2005 to develop pharmacogenetics-based therapeutic (dose) recommendations and to assist drug prescribers and pharmacists by integrating the recommendations into computerized systems for drug prescription and automated medication surveillance (e.g., electronic health records).[12] Like CPIC, the DPWG examines peer-reviewed scientific literature for gene-drug associations, assigns levels of evidence and authors guidelines for the use of this information.

For readers interested in "one stop shopping" for these research groups and their work, visit the NIH sponsored Pharmacogenomics Knowledge Base (PharmGKB), an excellent source of curated drug-gene pairings, levels of evidence and summaries of recommendations from the FDA, CPIC DPWG, and other international consortia.[13] This database has become essential to manage the increasing volume of PGx publications, which has accelerated dramatically since the late 1990s. (**Figure 1**)

PGx In The Clinical Setting

Clinical trial design

While ample scientific evidence exists for individual gene-drug associations, the demonstration of the clinical utility of PGx in prospective, randomized

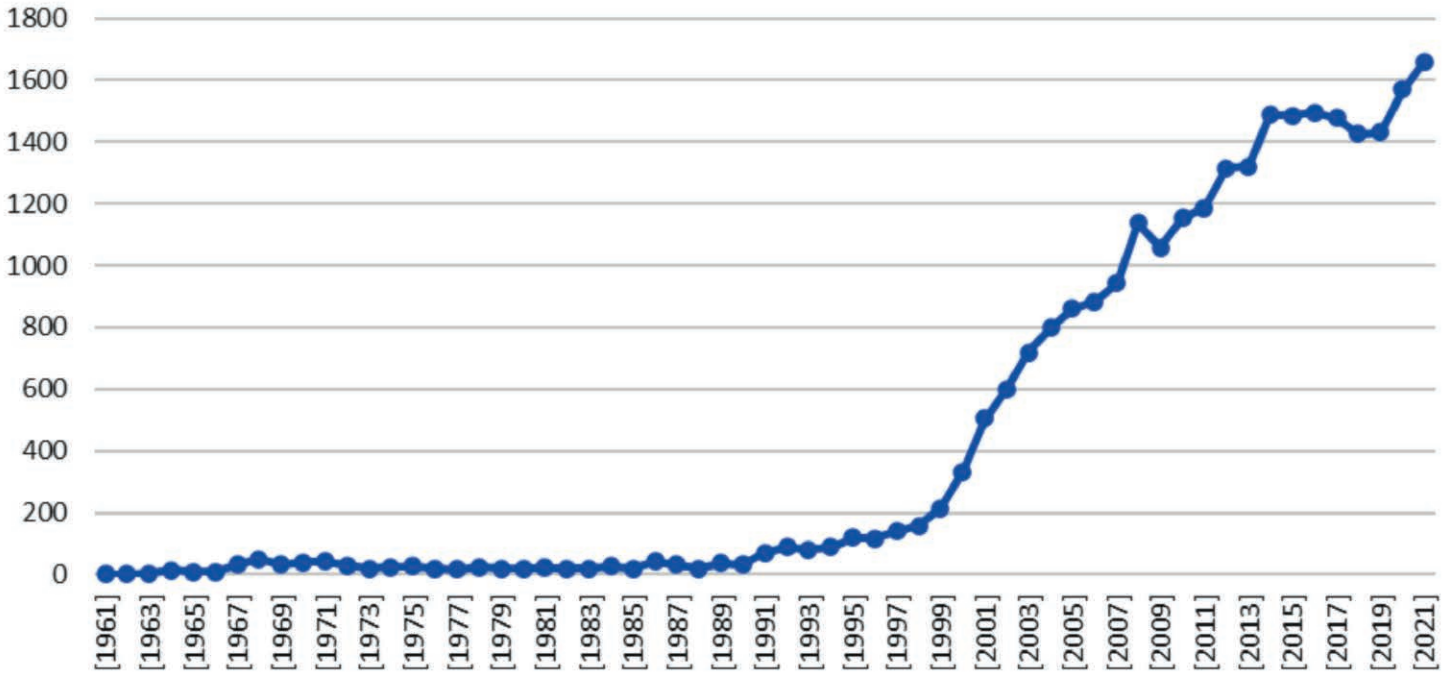

Figure 1: # PubMed Publications by Year (Keyword Pharmacogenetics) 1961 through 2021

clinical trials (RCTs) has proven more challenging. Such individual trials typically have compared PGx-guided treatment to treatment as usual (TAU).[14–16] These designs are constrained by several factors: for example, these trials cannot be truly triple blinded (clinician, patient, rater) and a sham report cannot ethically be generated for TAU-randomized subjects. In addition, these study designs are effectively active control trials, in which patients randomized to TAU receive an active agent deemed safe and effective by the U.S. FDA. Such trials differ dramatically from a typical industry sponsored drug trial in, for example, depression, in which superiority must be demonstrated to placebo.

Finally, the clinician-investigators in PGx trials are not usually obligated to follow the treatment regimen defined by the PGx assay. Thus, it is not surprising that such RCTs have been underpowered or have shown marginal improvement in outcomes.

Outcomes research

Recently however, meta-analyses of such trials have described favorable outcome in depression.[17–19] For example, Bousman et al examined five RCTs of PGx as a decision support tool (DST) in patients with major depressive disorder. Individuals receiving pharmacogenetic-guided therapy (n = 887) were 1.71 (95% CI: 1.17-2.48; p = 0.005) times more likely to achieve symptom remission relative to individuals who received treatment as usual (n = 850).

A remarkable feature of PGx research is that pharmacoeconomic outcomes data have consistently shown benefits in resource utilization and overall costs. Such savings have been demonstrated in retrospective case-control studies of mood disorders, real world medication-management programs and meta-analyses in a variety of clinical settings. In one such paper hospitalizations were consistently reduced, regardless of therapeutic milieux, by approximately 50%.[20–22]

"Sources of PGx information and guidance include the FDA labels and biomarker tables, the Clinical Pharmacogenetics Implementation Consortium (CPIC), the Dutch Pharmacogenetics Working Group (DPWG) and the Pharmacogenomics Knowledge Base (PharmGKB)"

Organizations such as the International Society of Psychiatric Genetics and the American Society of Health-System Pharmacists have also arisen to support limited evidence-based use of PGx, but practice guidelines from authorities such as the American Academy of Family Practice are lacking.[23] Other societies, such as the American Psychiatric Association (APA) have provided mixed messages. A 2019 APA Task Force proclaimed, "there is not sufficient information to support widespread use of pharmacogenetic testing in clinical practice." In contrast, the APA's CEO and Medical Director's response during the Medicare Local Coverage Determination open comments period, was "In general, we view several indications as appropriate for pharmacogenetic testing. With some medications, pharmacogenetic testing prior to treatment initiation is important to identify whether a patient is at heightened risk of developing a serious complication. In this context, knowledge of the patient's genetic status can contribute to a decision to avoid use of a specific medication when several possibilities are under consideration. With other medications, such as those metabolized through cytochrome P450 enzymes, pharmacogenetic testing may be less relevant to initial medication selection but may be important for optimizing medication doses to limit toxicity or enhance outcomes based on principles of pharmacokinetics and known metabolic pathways."[24]

Recently, perhaps the most positive and forward-looking statement supporting universal PGx use came from the UK's National Health Service: "Implementation of pharmacogenomics into the NHS would be the first example in the world of integration into a whole healthcare system, again highlighting the leadership of the UK in genomics… It is now mainstream, it is the future, it can now help us to deliver a new, modern personalised healthcare system fit for 2022, not 1948."[25]

Addressing The Remaining Challenges

Obstacles to PGX implementation remain, including provider education, authoritative clinical

guidelines, cost, and payer implementation and acceptance. Awareness of PGx is growing and in 2020, the U.S. Food and Drug Administration (FDA) announced a collaborative review of the science supporting PGx testing. As the field continues to mature, even payers have taken notice. Medicare, the largest payer in the United States, deemed PGx to be "considered reasonable and necessary when the result of that test is necessary for the physician's decision-making process regarding safely administering or dosing the drug." CMS thus issued a local coverage determination for pharmacogenetic testing in some circumstances, which may represent a sea change in the reimbursement arena.[26] Also United HealthCare, the nation's largest private insurer, has issued criteria for PGx testing in some circumstances.[27]

"Clinical validity and utility of PGx is supported by several meta-analyses, pharmacoeconomic studies and reimbursement coverage policies"

Even with these obstacles, there are many institutions and commercial laboratories that have successfully implemented PGx testing, mostly for those drug-gene pairings with the highest strength of evidence or with FDA/CPIC guidelines. The IGNITE consortium is a group of academic centers that incorporate pharmacogenomic information in diverse clinical settings.[28] Participants include Vanderbilt, the University of Florida, Indiana University, Icahn School of Medicine at Mount Sinai, Duke Medicine, the U.S. Air Force and others. In most cases, PGx alerts are incorporated into the EMR systems of these institutions to aid in genetic risk identification and management. Many of these institutions have had PGx programs implemented for years and serve as models for others. A common feature of these programs is a collaborative team approach with clinical pharmacists providing PGx consults at the point of care.

Dozens of commercial laboratories have also begun to offer multi-gene PGx testing over the last few years. Unfortunately, we still see tremendous variability in analytic and clinical validity of many laboratories and test reports. An evaluation of four reports from prominent PGx companies identified significant discordance between genotypes, phenotypes and drug-gene recommendations.[29] These reports highlight the need for continued standardization in this burgeoning space.

Most private labs have learned similar lessons during their commercialization process. Tools to overcome these obstacles include extensive PGx educational programs, economic data, EMR integration or point of care software solutions. Educational programs include sponsored CME credits and certificate programs from various pharmacy schools, along with internally created webinars and grand rounds. Several companies offer clinical consult services to review individual patient cases. Genomind has recently published a review of its clinical consult program.[30]

To streamline this abundance of new information, many commercial entities have developed software to assist with clinical decision support. Some examples include GenMedPro™ (Genomind), YouScript (Invitae) and Translational Software. These systems are designed to identify drug-gene interactions, assign a severity level and provide precision medicine guidance when warranted. Most also address the issue of phenoconversion by assessing drug-drug interactions at the same time as drug-gene interactions.

Genomind Case Study

To illustrate the real-world implementation of PGx, we present this pediatric case study of a 12-year-old boy who failed multiple medications which prompted PGx testing.[31] His diagnoses were anxiety, obsessive compulsive disorder and ADHD including significant oppositional and impulsive behaviors. These symptoms were quite distressing to the child and parents, and they spent many years working through different combinations of medicines with several psychiatrists.
The authors state, "Many different psychotropic medications had been prescribed, many of which were not tolerated or helpful."[31] Some failed medications included fluoxetine, fluvoxamine, dextroamphetamine, atomoxetine, aripiprazole and risperidone. A common thread among these medications is that they are all metabolized through the CYP2D6 enzyme. Pharmacogenetic testing revealed that this child had a CYP2D6 *4/*5 genotype, which results in poor metabolizer (PM) status, i.e., he did not have the genetic machinery to produce the enzyme required to metabolize these medications. This would result in increased blood levels of these medications and often increased side effects. In fact, several of these medications have published PGx guidelines for CYP2D6 PM. The FDA label for aripiprazole recommends a 50% dose decrease and the atomoxetine label has pediatric gene guided dosing as well.[32–34] Fluvoxamine has a CPIC guideline recommending a 25-50% reduction in starting dose and risperidone has a DPWG guideline recommending 67% of the standard dose.[35–37] (**Table 1**) All of these medications were prescribed prior to PGx testing. Armed with this additional information identifying the patient as a CYP2D6 PM, a trial of escitalopram was started since it is a substrate of the CYP2C19 enzyme and largely bypasses CYP2D6 metabolism. This ended up being a successful treatment with the authors declaring, "Ultimately, escitalopram, which was prescribed, was found to be the most effective medication to date for treating his behavioral problems and supported by his pharmacogenetic testing results." Had PGx testing been performed earlier in treatment, they may have very well arrived at this medication sooner.

"Real world implementation of PGx usually requires accessory elements, including clinical decision support software, EMR integration and provision of clinical education and consultation"

Table 1

Medicine	Source	Guideline
Aripiprazole	FDA	Administer 50% of usual dose[32]
	DPWG	Administer no more than 10 mg/day or 300 mg/month (67-75% of the standard maximum dose of aripiprazole)[36]
Risperidone	DPWG	Use 67% of the standard dose If problematic side effects originating in the central nervous system occur despite this reduced dose, then reduce the dose further to 50% of the standard dose[37]
Atomoxetine	FDA	In patients who are known to be CYP2D6 PMs, atomoxetine should be initiated at 0.5 mg/kg/day and only increased to the usual target dose of 1.2 mg/kg/day if symptoms fail to improve after 4 weeks and the initial dose is well tolerated[33]
	CPIC	Initiate with a dose of 0.5 mg/kg/day and if no clinical response and in the absence of adverse events after 2 weeks, consider obtaining a plasma concentration 4 h after dosing[34]
Fluvoxamine	CPIC	Consider a 25-50% reduction of recommended starting dose and titrate to response or use an alternative drug not metabolized by CYP2D6[35]

On To The Future

In the near future, PGx will likely be more frequently used for two reasons. First, the data will compel regulatory agencies, payers, and medical associations to adopt this approach. Second, and as important, new generations of physicians and allied health care providers will become more educated about the individual, economic, health, and societal implications of PGx. Furthermore, as physicians take up PGx in their practices, pharmacists will in turn need to play a central role in PGx utilization and interpretation.[38] Newer and less expensive genetic technologies will improve the cost-benefit ratio for the use of PGx. Finally, more payers will recognize the economic benefits of PGx and will reimburse for its use. JoPM

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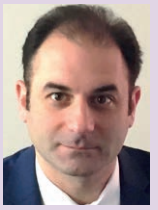

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About Genomind

Genomind is a leading precision medicine company located in King of Prussia PA, with a presence in 18 countries worldwide. Our mission is to optimize the treatment experience for individuals and healthcare providers by unlocking the value of precision medicine through actionable genetic insights and innovative health technology. Founded by a psychiatrist in 2011, Genomind has utilized its pharmacogenetics testing platform, including proprietary state-of-the-art clinical decision support software, GenMedPro™, to assist thousands of prescribing health care providers and their patients. Our flagship product, Genomind® Professional PGx™, is a comprehensive pharmacogenetic testing service helping medical professionals personalize patients' mental health treatment.