Primary Care Reports
The Practical CME Journal for Primary Care and Family Physicians
Volume 20, Number 10 / October 2014
www.ahcmedia.com

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Statement of Financial Disclosure

To reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, Dr. Hocum (author) reports he is a stockholder and clinical pharmacist at Genelex Corporation. Dr. Kitzmiller (peer reviewer) reports he receives grant/research support from the National Institutes of Health and is a retained consultant for Ohio Clinical Trials. Dr. Elizabeth Black (author), Mr. Kevin Black (author), Dr. Wise (editor), Ms. Coplin (executive editor), and Ms. Kimball (managing editor) report no financial relationships relevant to this field of study.

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The Future: Pharmacogenetics in Primary Care

Advancing technology has always challenged physicians in their practice of medicine. New research, techniques, and treatments can improve the prevention and management of disease, but not without confusion and occasional controversy. The addition of pharmacogenetic testing to the armamentarium of primary care providers (PCPs) presents just such a challenge.

Introduction

Pharmacogenetics and pharmacogenomics are very similar terms that often are used interchangeably. Authors tend to use pharmacogenomics when discussing broader research about the relationship between the genome and pharmacotherapy, such as in genome wide association studies (GWAS). Pharmacogenomics usually applies to a population. On the other hand, pharmacogenetics more often is used when talking about specific genes and their influence on specific drugs. An example of this would be the study of how cytochrome P450 2C9 (CYP2C9) and VKORC1 polymorphisms affect warfarin pharmacokinetics and pharmacodynamics.[1] Pharmacogenetics deals with individuals. This article will distinguish the two terms and will focus on pharmacogenetics, which will hereafter be abbreviated, PGx.

Pharmaceutical management is becoming the standard of care for many medical conditions. Many evidence-based standards for quality in the treatment of certain disease states support the introduction of particular drug therapies in the presence of known diagnoses. Even if specific medications or classes of medications are not defined by quality standards, defined management goals may not be achieved without medication.

The rationale for promoting evidence-based standards is clear to most physicians, although the benefit of such programs is debated. Research presents convincing evidence that the risks of many disease states are significantly reduced by the introduction of pharmaceutical agents and adherence to treatment goals. However, these drugs do not come without their own risks.

Many management recommendations are drawn from well-designed studies, but these focus on results in broad populations rather than individuals. Medications shown to be effective in these studies may be less effective in a particular patient, resulting in failure to reach desired treatment goals. Medications can also cause unintended effects. While most often inconvenient or uncomfortable, adverse drug reactions (ADRs) can be very dangerous.

ADRs and/or treatment failure may erode patient confidence in their physician, or perhaps in the validity of the evidence used as a basis for their recommendation. This can lead to mistrust of pharmaceutical treatment as a whole and can reduce patient motivation to meet health management goals. This fear may contribute to the preference of some individuals for alternative therapies. Although many of these therapies have poor evidence of effectiveness, they often are embraced as an alternative to the anecdotal failures of recommended medications.

Executive Summary

With the rapidly increasing number of drugs available to the primary care physician's armamentarium, the rational and judicious use of pharmacogenetics (PGx) can improve drug selection by increasing the likelihood of effectiveness and reduce harmful side effects.

- Adverse drug events contributed to 13.5 million outpatient and ED visits over a recent 3-year period, with the elderly particularly vulnerable.
- The increased utilization of health care resources may be contributing up to 13% of the total spending on healthcare in the United States.
- The FDA refers to alleles that influence drug effectiveness and toxicity as "pharmacogenetic biomarkers." PGx biomarkers are further classified as either pharmacokinetic (PK) or pharmacodynamic (PD). PK biomarkers affect how the body absorbs, distributes, metabolizes, and excretes drugs. PD biomarkers are less well understood. These biomarkers affect the action of drugs at the molecular level.
- Clinical scenarios commonly targeted for pharmacogenomic investigation include statin, warfarin anticoagulation, clopidogrel, pain management, and a host of psychotropic medications.

The emergence of PGx testing offers promise in mitigating some risks associated with medication therapy. Testing for known genetic variants that affect drug metabolism can potentially enhance therapeutic response to medication, reduce ADRs, and optimize treatment of disease. While this can positively affect both disease-specific outcomes and patient satisfaction, PGx testing has its own complications. Testing may indicate that a commonly available medication is less advisable for a particular patient, but alternatives may not be readily accessible. Also, the novelty of the technology may lead to patient uncertainty regarding the significance and implications of genetic testing results. Most health care professionals also feel uncertain about the utility of PGx testing and discussing it with their patients.[2]

Case Vignette

Consider the following hypothetical case:

History of Present Illness: GS is a 46-year-old female office administrator who presents for follow-up on type 2 diabetes, depression, hypertension, and hyperlipidemia. Recent fasting lab work is available for review. She is taking all medications as prescribed. She reports that her depression has recently worsened in conjunction with some stress at home and at work. She is taking citalopram, and her symptoms were previously well-controlled on that medication, but over the last few months, she has had increased dysphoria, anxiety, and anhedonia. She is interested in an antidepressant dose increase to help control her symptoms. She is having some trouble affording Crestor as it is tier 3 on her insurance. She asks if a lower-cost generic would be appropriate for her.

Past Medical History: hypertension, diabetes, hyperlipidemia, major depression, anxiety

Medications:

- *Lisinopril 20 mg daily*
- *HCTZ 25 mg daily*
- *Metformin 500 mg BID*
- *Rosuvastatin 10 mg daily*
- *Citalopram 20 mg daily*
- *Lorazepam 2 mg TID prn*

Recent Lab Results:

- *TSH and CBC WNL*
- *CMP WNL except fasting glucose 127*
- *LDL: 110 mg/dL*
- *CrCl: 80 ml/min*

Framingham's Risk Score: 20%

In the absence of additional information, a PCP might simply try an alternative statin and see if it was tolerated at a sufficient dose to achieve the desired result. The dosage of citalopram could be increased to see if she achieves better results. However, the potential for both tolerance and effectiveness will not be known until after therapy is changed.

Introduction

Bridging the gap in provider understanding of PGx is essential to the future of primary care. PCPs are ideally positioned to counsel patients in a manner that will make this technology most clinically meaningful. Not only are the vast majority of prescriptions written in the primary care setting,[3] but an estimated 60% of office visits related to adverse drug events (ADEs) take place in the primary care setting.[4] Patients are also more likely to report ADEs in that environment.[4] Further, patients have indicated a preference for discussing PGx test results with their PCP.[5]

GS presents with a common constellation of issues. Cost concerns conflict with efforts to reach therapeutic goals and reduce associated risks from known chronic conditions. She also presents with a psychological complaint common to primary care. The very familiarity of this scenario illustrates how PCPs are in an ideal position to use additional information from PGx testing to guide decision making to facilitate positive results, or avoid potential hazards. One of those hazards is the risk of adverse drug reaction to medication.

ADEs and ADRs

ADEs may be classified as any injury resulting from drug use. They contributed to an estimated 13.5 million outpatient visits between 2005 and 2007, including emergency department (ED) and physician office visits.[4] The elderly are particularly vulnerable in this regard. An estimated 100,000 ED visits

related to ADEs among Americans 65 and older resulted in hospital admissions between 2007 and 2009.[6] Polypharmacy also increases the risk of ADEs. Older Americans have the highest rate of health care resource utilization in relation to ADEs, but the highest absolute number of such visits occurred among 45- to 64-year-old patients. In fact, once data are adjusted for comorbidities and number of medications, the effect of age on the rate of visits related to ADEs is greatly reduced.[4] This indicates that the problems of medication management are not exclusive to the geriatric population. The increased utilization of health care resources associated with ADEs may contribute to up to 13% of the total spending on health care in the United States.[7] ADRs are a special type of ADE that occur at commonly prescribed doses, making them of particular interest in pharmacogenomics and PGx.[8]

Reducing the incidence of ADRs may reduce burden on the health care system overall and produce cost savings by preventing a portion of drug-related hospitalizations. Achieving this result will rely on PCPs' understanding of pharmacogenomics and applied PGx.

Tables 1 and 3 show that three of GS's medications are associated with genetic variants that may affect the outcome of therapeutic changes. One of these, citalopram, is associated with a variant that carries an FDA-recommended dosage limitation for patients with a known genetic variant. This genetic variant is associated with increased risk of QTc prolongation and Torsades de Pointes, a potentially severe complication. Information like this is currently widely available and an understanding of how to use it will help PCPs make therapeutic decisions that are more likely to avoid ADRs and improve therapeutic outcomes.

Knowledge, Confidence, and Attitudes Toward PGx

PGx is an area where PCPs report a low index of confidence. In one national survey, the majority of PCPs reported that they do not feel well informed about PGx testing. Although more than half indicated that they received genetics training in medical school, most felt that the training was inadequate to prepare them to use PGx testing in their clinical decision-making. The lack of confidence in using PGx test results may be a reason why many PCPs responding to the survey reported that they have never ordered PGx testing.[2] A multi-specialty survey of U.S. physicians shows that primary care is not unique in this regard. With the sole exception of oncology specialists, the vast majority of physicians surveyed did not regularly order genetic testing, citing lack of information.[9]

While PCPs indicate uncertainty about how to use PGx testing in clinical practice, there is broad acknowledgement of its potential utility. In the multi-specialty survey, 97.6% of respondents believed that genetics may influence a patient's response to drug therapies.[9] In the PCP survey, almost two-thirds of respondents agreed that PGx testing represents a valuable potential tool to predict risk of ADRs or likelihood of efficacy. Among physicians who have utilized PGx testing, reducing drug toxicity and improving effectiveness were cited as significant observed benefits to patients.[2]

PCPs envision a strong role in the future of using PGx information in clinical practice. Most of the PCPs surveyed felt that informing patients of PGx testing availability and recording PGx testing results in patient records should be a responsibility of the PCP. More than half felt that PCPs should also be responsible for informing their patients of PGx testing results. Beyond that point, however, uncertainty again emerges, as less than half of surveyed PCPs felt that they should be primarily responsible for determining how PGx results should be used in medication management.[9]

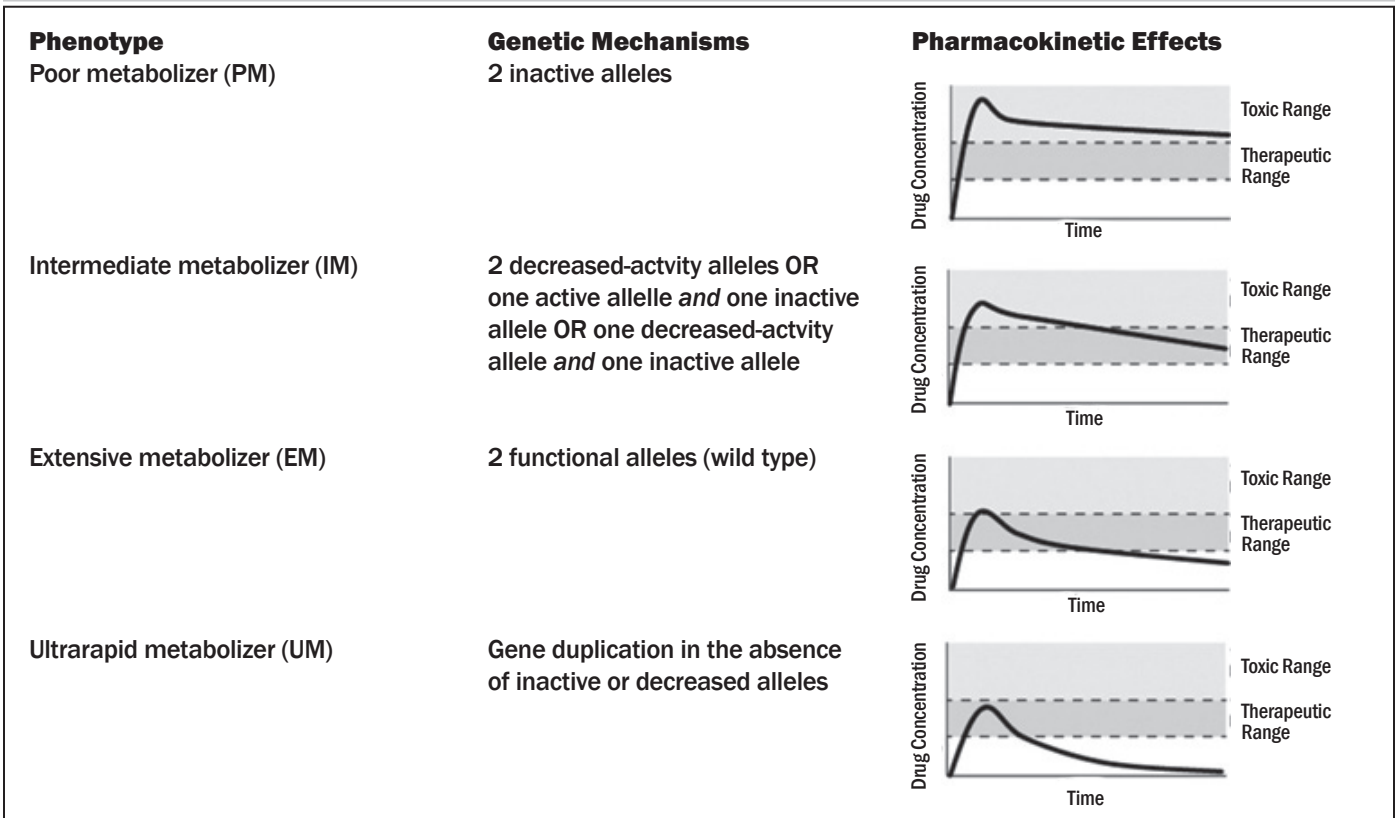
Principles of PGx

SNPs, Alleles, Genotypes and Phenotypes. Different forms of genes that are passed on from parent to child are called alleles. The combination of alleles an individual inherits determines his or her genotype, and the expression of these alleles determines his or her phenotype. Genetic variation arises from the introduction of mutations, or alterations in the DNA sequence, in these alleles. The most commonly identified mutations are single nucleotide polymorphisms, also called SNPs. A particular SNP may or may not result in changes in protein regulation, expression, or activity.

When an identified SNP negatively affects protein function it is termed a loss-of-function allele. Someone with one (heterozygote) or two (homozygote) loss-of-function alleles will have less overall protein expression and/or activity compared to someone with two normal-function alleles. When an SNP is identified that positively affects protein function, it is termed a gain-of-function allele. The presence of a gain-of-function allele, or duplication of a normal function allele, may result in increased protein expression and/or enhanced activity. These genotypes can have a direct impact on numerous metabolic functions, including how individuals respond to certain drugs at a cellular level.

The effect that genetic variations have on drug metabolism is characterized by well-established phenotypes. A poor metabolizer is an individual with two inactive or loss-of-function alleles. In patients with this phenotype, drugs may not be metabolized efficiently. This can result in increased drug concentrations that can reach toxic levels. Ultrarapid metabolizers have gene duplicates and therefore increased drug metabolism. This can result in subtherapeutic drug levels at doses that would likely be effective in normal metabolizers. Figure 1 illustrates the consequences that these genetic variations can have on drug metabolism and therefore effectiveness and toxicity. Loss- and gain-of-function alleles may also result in altered response to medications due to abnormal binding at its site of action or receptor.

Figure 1: Consequences of Genetic Variations on Drug Metabolism, Effectiveness, and Toxicity[35]



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Genetic testing for GS yields the following information:

- *CYP2D6 (*1/*1) Normal Metabolizer*
- *CYP2C9 (*1/*1) Normal Metabolizer*
- *CYP2C19 (*2/*2) Poor Metabolizer*
- *CYP3A4 (*1/*1) Normal Metabolizer*
- *CYP3A5 (*3/*3) Non-expressor*
- *SLCO1B1/OAT1B1 (*1/*1) Normal Transporter*
- *VKORC1 (A/A) High Sensitivity to Warfarin*

Types of PGx Biomarkers. The FDA refers to alleles that influence drug effectiveness and toxicity as "pharmacogenetic biomarkers."[10] PGx biomarkers are further classified as either pharmacokinetic (PK) or pharmacodynamic (PD). PK biomarkers affect how the body absorbs, distributes, metabolizes, and excretes drugs. Their effects on drug bioavailability, blood concentrations, and distribution into tissues are easy to measure[11] and therefore they are well understood and studied. This class of biomarkers includes genes that code for drug-metabolizing enzymes such as CYP2D6, CYP2C9, and CYP2C19. Also included are genes that code for transporter proteins like OAT1B1 and P-glycoprotein. Drug-metabolizing enzymes like the cytochrome P450s biotransform drugs into metabolites more readily eliminated by the body or modified by other enzymes.[12] Transporters function to move drugs in and out of cells and across barriers like the small intestine, liver, kidney, and brain. For this reason they are sometimes referred to as "gatekeepers."[13] They are also involved in directly eliminating drugs via biliary and urinary excretion. Two important biomarkers involved in drug transport include SLCO1B1, which codes for the OAT1B1 transporter, and ABCB1, sometimes called the "multidrug resistance gene," which codes for p-glycoprotein.[14] OAT1B1 is an influx transporter meaning it moves drugs into cells and p-glycoprotein is an efflux transporter meaning it moves drugs out of cells and into the intestinal tract, bile, blood, or urine.[15]

PD biomarkers are less well understood. These biomarkers affect the action of drugs at the molecular level. Their effects are harder to isolate and measure, and uncertainty of the exact mechanism of action for many drugs further limits research in this area. Just as there are different subtypes of PK biomarkers, there are also subtypes of PD biomarkers. Some impact drug response directly whereas others may play a more indirect role as a result of a genetic variance that affects the underlying disease process. Indirect PD biomarkers may still significantly influence the efficacy, toxicity, and/

or laboratory values of treatment. An example of a direct effect would be opioid binding to the mu-opioid receptor. Genetic variations of the OPRM1 gene, which codes for the mu-opioid receptor, may affect the amount of pain attenuation achieved with opioids.[11] An example of an indirect PD biomarker would be HLA-B*1502, which is strongly associated with carbamazepine use and the risk of Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN), despite it not being involved in the drug's known mechanism of action.[16,17] APOE is an example of a PD biomarker that is associated with laboratory values. Certain variations in APOE are associated with greater LDL reductions in patients being treated for high cholesterol.[18]

While PGx biomarkers can increase physician knowledge of how patients will potentially respond to medications, some PK biomarkers may affect the metabolism of a drug in a manner that does not result in a PD difference, either good or bad. A list of significant PGx biomarkers may be found on the FDA website.[10] Tables 1 and 2 describe some of the important PK and PD biomarkers.

GS Treatment plan:
Plan: #1 Prescribe simvastatin 40 mg daily, #2 Diet and exercise recommendations, #3 Change citalopram to paroxetine, #4 Increased psychologist sessions.

GS's PGx results reveal important aspects with regard to current and future medication management. CYP2D6, CYP2C9, and CYP2C19 are all highly polymorphic. Together they metabolize approximately 75% of all hepatically metabolized medications. Currently, citalopram is the only medication GS is receiving that goes through one of these pathways, namely CYP2C19. Being normal at the CYP2D6 and CYP2C9 pathways means that choosing medications that go through these pathways can be administered at standard doses. Being a CYP2C19 poor metabolizer limits the dose or therapeutic option of medications that are substrates for this pathway. At 20 mg daily, citalopram was at a maximum daily dose per the product insert. Therefore, choosing paroxetine, an SSRI metabolized by the CYP2D6 pathway, creates therapeutic options for management of this patient's depression.

CYP3A4 has many substrates, including several of the statins. Individuals with decreased expression/activity of CYP3A4 may require decreased doses to achieve similar therapeutic effects and acceptable risk compared to normal metabolizers. Because GS is a CYP3A4 normal metabolizer, standard doses of a statin metabolized by this pathway may be appropriate. SLCO1B1 is an influx transporter involved in the transport of many medications including many statins. GS's normal SLCO1B1 results allow for the prescriber to more confidently initiate therapy with a SLCO1B1 transported statin that might otherwise result in statin intolerance due to inadvertent increased exposure of the drug. This information leads to the use of simvastatin 40 mg daily for cholesterol management.

Applied PGx. To illustrate how PGx information can affect pharmaceutical management in clinical practice, an illustration drawn from a class of medications that are both commonly used and significantly affected by known biomarkers may be useful. HMG-coenzyme A reductase inhibitors (statins) are an excellent class of drugs to illustrate the value and limitations of PGx in everyday primary care.

Cholesterol management is a pillar in primary care and statins are the most commonly prescribed pharmaceutical therapy in the United States.[19] They also display extensive interpatient variation in blood levels.[20] Although generally safe, this variation undoubtedly leads to toxicity in some individuals or decreased efficacy in others.[21] Table 3 shows some of the PGx biomarkers associated with variances in statin therapy.

The significance of PK biomarkers is similar to PK drug interactions. For example, coadministration of grapefruit and statins is known to increase the blood levels of some statins and increase the risk of ADRs including myalgia and rhabdomyolysis.[22] Coadministration of atorvastatin and grapefruit has resulted in up to a 50% increase in atorvastatin area under the curve (AUC).[23]

The mechanism for this interaction is intestinal inhibition of CYP3A4 by grapefruit. CYP3A4 is one of the enzymes that metabolizes atorvastatin into metabolites. The impaired metabolism of atorvastatin as a result of this inhibition results in increased bioavailability of the drug, therefore increasing the risk of ADRs. A loss-of-function allele for CYP3A4 may have similar effects. Indeed a clinical study observed a 78% decrease in atorvastatin dose requirements in CYP3A4*22 allele carriers compared to non-carriers (*see Table 3*).

In these two scenarios, the clinician faces a similar mechanism potentially affecting the therapeutic outcome of their prescribing decision. The obvious distinction is that while a patient can be advised not to consume grapefruit when atorvastatin is prescribed, a patient's CYP3A4 loss-of-function allele is inherent. However, the clinician may either opt to decrease the atorvastatin dose or choose an alternative statin that does not undergo significant metabolism by CYP3A4 such as rosuvastatin, pitavastatin, pravastatin, or fluvastatin (*see Table 4*).

PD biomarkers can be more challenging to use clinically.[11] When evidence is sufficient, however, they can help to understand an individual's overall sensitivity to a medication. For example, one study found patients' response to atorvastatin 20 mg daily × 14 days varied based on their HMG coenzyme A reductase (HMGCR) genotype. HMGCR expresses phenotypically as the protein that serves as a receptor for statins. Results showed a 15-23% greater LDL reduction in HMGCR rs3846662 AA homozygotes compared to GG homozygotes (*see Table 3*).[24] While this information identifies patients who are most likely to respond to statin therapy, it does not strictly predict efficacy of treatment. Perhaps an alternative statin would work better, but due to the limited

Table 1: Example PK Biomarkers

Biomarker	Phenotype	Affected Drug	Effects and Considerations
CYP2D6	Poor metabolizer	Atomoxetine	AUC (area under the curve) increased up to 900% compared to normal metabolizers. Product insert specifies a more conservative dosing regimen for this phenotype.[36]
		Metoprolol	Plasma concentrations increased up to 390% and heart rate and blood pressure significantly decreased compared to other phenotypes.[37]
	Ultrarapid metabolizer	Nortriptyline	AUC decreased by 35% in patients with three active alleles and 80% in patients with 13 active alleles compared to normal metabolizers.[39] A dose increase of up to 150% has been recommended.[39]
CYP2C9	Poor metabolizer	Celecoxib	AUC increased up to 600% compared to normal metabolizers.[40] Product insert recommends a 50% decreased maintenance dose and to avoid in individuals with juvenile rheumatoid arthritis.[41]
CYP2C19	Poor metabolizer	Clopidogrel	AUC of active metabolite decreased 65% compared to normal metabolizers.[42] A meta-analysis showed a 55% increase in cardiovascular events, MI, or stroke in individuals with this phenotype compared to normal metabolizers undergoing percutaneous coronary intervention for ACS.[43] Product insert recommends using an alternative platelet inhibitor.[44]
		Citalopram	AUC increased 107% compared to normal metabolizers. Product insert recommends 20 mg maximum daily dose in individuals with this phenotype.[45]
	Ultrarapid metabolizer	Omeprazole	AUC decreased 52% compared to normal metabolizers.[46] Dose increases up to 300% have been recommended.[39]
UGT1A1	Poor metabolizer	Ezetimibe	AUC increased 177% compared to normal metabolizers.[47]
UGT2B15	Poor metabolizer	Lorazepam	AUC increased 72% compared to normal metabolizers.[48]
ABCB1 (P-glycoprotein)	2677TT/3435TT	Amlodipine	AUC decreased 33% in 2677TT/3435TT homozygotes compared to 2677GG/3435CC homozygotes.[49]
SLCO1B1 (OAT1B1)	Poor transporter (c.521CC genotype)	Atorvastatin	AUC increased 145% compared to c.521TT homozygotes.[50] Similar results have been observed in other studies.[51,52] The maximum recommended dose is 20 mg daily in individuals with this phenotype.[53]

Disclaimer: Evidence may exist that conflict with the examples used in this table

amount of evidence it is still up to the prescriber to undergo a process of trial and error to determine the optimal treatment strategy.

As these brief examples illustrate, the clinical utility of PK biomarkers is much more straightforward since the routes of metabolism and transport of drugs are often well mapped. Simply adjusting dosage to compensate for the known effects or choosing a medication that utilizes an alternative pathway for metabolism and/or transport may avoid interactions.

PGx testing may in turn help a physician achieve optimal pharmacotherapy more efficiently and with

Table 2: Example PD Biomarkers

Biomarkers	Effects
Beta-1 adrenergic receptor (ADRB1)	Metoprolol-induced decrease in diastolic blood pressure was significantly greater in individuals with the 389Arg/Arg genotype compared to those with the Arg/Gly and Gly/Gly genotype.[54]
Beta-2 adrenergic receptor (ADRB2)	Albuterol resistance was more likely in GLY allele carriers.[55]
Factor II	Factor II 20210A allele carriers taking estrogen-containing oral contraceptive (OC) have been found to have a 400-800% increased risk of venous thromboembolism (VTE).[56-58]
Factor V Leiden	Odds ratios ranging from 11-41 have been reported for combination of Factor V Leiden allele and OC use.[59]
HLA-B*1502	HLA-B*1502 is associated with increased risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in Asians taking carbamazepine.[16,17]
Opioid Receptor Mu-1 (OPRM1)	Oxycodone induced pain attenuation was decreased in OPRM1 118G allele carriers. These individuals required increased oxycodone doses compared to 118AA homozygotes.[60]
Platelet endothelial aggregation receptor-1 (PEAR1)	rs12041331 A allele carriers receiving aspirin had significantly increased risk of MI compared with GG homozygotes.[61]
Potassium voltage-gated channel (KCNH2, hERG)	QTc interval is prolonged 14 ms per KCNH2 897Lys allele in patients receiving steady state methadone compared to non-allele carriers.[62]
Serotonin transporter (5HTT/SLC6A4)	Caucasians with the 5HTT L/L or L/S genotypes had increased response to SSRI therapy compared to individuals with the S/S genotype.[63]
VKORC1	VKORC1 AA and GG homozygotes may have up to a 100% difference in warfarin dose requirements.[64]

Disclaimer: Evidence may exist that conflict with the examples used in this table

less risk of ADRs.[25] As physician knowledge expands, protocols may be developed that will enable PGx testing to become standard of care.

PCP Role in PGx

Getting Educated. To begin incorporating PGx testing into practice, the first step is education for physicians and the health care team. Medical schools in the United States and Canada are beginning to incorporate pharmacogenomics into their curriculum, but do not sufficiently prepare students to confidently utilize PGx in practice. A recent study determined that 82% of U.S. and Canadian medical schools incorporated pharmacogenomics into their curriculum, yet only 28% had more than 4 hours of didactic coursework on the subject and only 29% had plans to expand the curriculum within the next 3 years. Students feel that this is not adequate to prepare them; 57% considered pharmacogenomics instruction at their own school as "poor" or "not at all adequate" while 76% considered it "poor" or "not at all adequate" at most medical schools.[26]

There is more pharmacogenomics training available in schools of pharmacology. A study from 2010 determined that approximately 90% of schools included pharmacogenomics in their PharmD curricula compared to 39% as reported in 2005. Topic coverage was < 10 hours for 40.6%, 10-30 hours for 42.0%, and 31-60 hours for 14.5% of colleges and schools of pharmacy. Fewer than half were planning to increase course work over the next 3 years. [27]

Although the need for ongoing education for future PCPs in pharmacogenomics is significant, PCPs already in practice must rely on resources outside of the classroom for information. Again, the need for suitable sources of professional education is largely unmet. While some physicians report learning of PGx testing and its clinical implications

Table 3: Biomarkers Specific to Statins

Pharmacokinetic		
Biomarker	**Function**	**Example Effect of Polymorphisms**
CYP3A4	Metabolism	Dose requirements of atorvastatin, simvastatin, and lovastatin were decreased 73% in CYP3A4*22 allele carriers compared to normal metabolizers. When analyzed alone, the simvastatin and atorvastatin dose requirements were decreased 40% and 78%, respectively.[65]
CYP2C9	Metabolism	The AUC of fluvastatin increased 200% in poor metabolizers. However, no differences were observed in LDL or total cholesterol levels.[38]
ABCB1 (P-glycoprotein)	Transport	Total cholesterol decreased 29% in 1236T allele carriers receiving simvastatin and only 24% in 1236CC homozygotes. Likewise, LDL decreased 40% in 1236T allele carriers compared to 34% in 1236CC homozygotes.[66]
SLCO1B1 (OAT1B1)	Transport	In poor transporters (c.521CC homozygotes), the AUC of simvastatin acid increased 221%, pitavastatin 162-191%, atorvastatin 144%, pravastatin 57-130%, rosuvastatin 62-117%, and fluvastatin 19%.[67] For every c.521C allele present the odds of myopathy increase 4.5%.[68]
Pharmacodynamic		
Biomarker	**Function**	**Example Effect of Polymorphisms**
Apolipoprotein E (APOE)	Hepatic uptake of lipoproteins	Epsilon-2 allele carriers had greater reduction in LDL and a larger proportion achieved an LDL goal of < 70 mg/dL when treated with atorvastatin or pravastatin compared to epsilon-4 carriers.[18]
Cholesterol ester transfer protein (CETP)	Lipid transfer	Atorvastatin-induced LDL reduction and HDL elevation was greater in CC homozygotes compared to A allele carriers. LDL levels decreased 43.5% in CC homozygotes, 25.5% in CA heterozygotes, and 11.7% in AA homozygotes. However, there was no difference in long-term clinical prognosis.[69]
CYP7A1	Bile acid synthesis	Atorvastatin-induced LDL reduction was 35% in rs8192870 AA homozygotes and 28% in G allele carriers.[70,71]
HMG CoA reductase (HMGCR)	Statin receptor	Atorvastatin-induced LDL reduction was 15-23% greater in HMGCR rs3846662 AA homozygotes compared to GG homozygotes.[24]
Kinesin-like protein 6 (KIF6)	Intracellular transport	Carriers of the KIF6 719Arg allele who received high-dose atorvastatin had a 41% decreased risk of death or major cardiovascular events compared to individuals who received standard-dose pravastatin. This difference was not seen in non-carriers of the 719Arg allele.[70,72]
Parahydroxy-benzoate-polyprenyl-transferase (COQ2)	Synthesis of ubiquinone (Coenzyme Q10)	Homozygotes for SNP1, SNP2 and the 2-SNP haplotype had significantly increased risk of statin intolerance defined as muscle weakness, tenderness, and/or pain with at least one of the following: 1) medically advised discontinuation of statin medication on at least two occasions; 2) serum CK elevated to > 3-fold of the upper limit of normal while on a statin on at least one occasion; and 3) medically diagnosed rhabdomyolysis.[73]

Disclaimer: Evidence may exist that conflict with the examples used in this table

Table 4: Clinically Significant Statin Metabolism and Transport Pathways[74,75]

Statin	CYP3A4	CYP2C9	SLCO1B1 (OAT1B1)	ABCB1 (P-glycoprotein)
Atorvastatin	✓		✓	
Fluvastatin		✓		
Lovastatin	✓			✓
Pitavastatin			✓	
Pravastatin			✓	
Rosuvastatin			✓	
Simvastatin	✓		✓	✓

Disclaimer: Evidence may exist that conflict with the information presented in this table. Does not list all enzyme or transport pathways. Minor or clinically insignificant pathways excluded.

through organized CME such as professional meetings, grand rounds, and professional journals,[2] some physicians also report less formal educational resources such as drug labeling information, communication with professional colleagues, and the Internet as primary sources of information.[9]

Implementation Considerations. Even with increased education, providers and clinical groups will have to carefully consider strategies for the assimilation of PGx into clinical practice. While specialty providers like oncologists may deal with PGx routinely in their practice, there is debate over how PGx testing should be implemented in the primary care setting.

The utilization of resources outside of the primary care setting may be beneficial in this regard. Clearly, pharmacology programs offer more education in the field, and pharmacists are well positioned to partner in the clinical integration of PGx by assisting with pharmaceutical management. Models of PGx testing and information delivery have been proposed that center around pharmacists and genetic counselors,[28] but this may not meet the needs of patients who would prefer working with their PCPs in assimilating PGx testing results.[5] Some PCPs feel that pharmacists should take primary responsibility for determining appropriate medication and dosing for patients dealing with significant PGx results. A collaborative approach, however, may be the most beneficial for the patient and serve to provide support for PCPs as they become more familiar with PGx testing and its implications in primary care. Previous studies have shown improved outcomes as the result of coordinated care between providers and pharmacists.[29,30] This may suggest an ideally partnered approach to applied PGx.

PCPs may want to consider developing streamlined communication with a cooperative, multispecialty care team that includes pharmacists as an integral, rather than incidental, part of care delivery. Genetic counselors can be consulted where they are available. Emerging models of care, such as patient-centered medical homes (PCMHs) and accountable care organizations (ACOs), may be well suited to this kind of collaborative and personalized approach. PCPs can then ensure that testing done either through the primary care office or ordered by another provider is entered into the electronic health record (EHR) and that the patient is appropriately counseled about available testing, his/her individual results, and the implications those results may have for health and treatment.

Developing Protocols. Determining which patient populations to select as candidates for PGx testing will also be an important consideration. There are many proposed strategies with regard to this. Identifying risk due to factors like age, high-risk comorbid medical conditions and polypharmacy, or the presence of medications that are likely to be influenced by varying genotypes are all potential approaches. The association of both age and polypharmacy with ADRs is well established.[4] Many medications have been proposed as high-priority for the potential application of PGx testing. Examples include statins, opioids, and anticoagulants. These medications are high priority because of the prevalence of use and their importance as a class in the management of common high-risk conditions. The known high frequency for ADRs, intolerance, and dependency are also important factors.

The targeting of individual patients on the basis of known risk factors may be more reactive than truly proactive. Trials are underway to develop and test broader approaches to PGx testing. These studies seek to identify potential genetic factors that may impact future care, well before known risk factors are present. Some of these models may have a significant impact on the use of PGx testing in primary care, as they take a truly preventive approach to the use of this technology.[31]

Identifying and utilizing patients' individual genotyping for the purpose of collaborative communication with other members of the health care team will not be possible without consideration of how this information will be documented and shared. Consistent protocols will be of utmost importance in this

Table 5: Biomarker Disease Association Examples

Biomarker(s)	Disease Association(s)
OPRM1, CYP2D6	Addiction[76,77]
CYP2D6	Alzheimer's disease[78]
CYP3A4, ABCB1 (P-glycoprotein)	Cancer risk[79,80]
Factor V Leiden and Factor II	DVT[57]
CYP2C19	Endometriosis susceptibility[81]
FMO3	Fish odor syndrome[82]
UGT1A1	Gilbert's and Crigler-Najjar syndrome[83]
CYP2C8, CYP2C9, CYP2C19	Inflammatory-related diseases such as coronary artery disease[84]
CYP3A4, CYP3A5	Salt-sensitive hypertension[85]
CYP1A2, SULT4A1	Schizophrenia[86-88]

Evidence may exist that conflict with the information presented in this table.

effort. It would be preferable for genetic results to be integrated into the EHR as structured data. This would allow EHR systems to cross-reference other information in the medical record such as medication and problem lists. Tools within the EHR system, such as computerized decision support (CDS), would then be able to flag certain medications or disease states that might be affected by particular genotypes. Indeed, development and testing of such CDS support tools for PGx information is already being done.[32] Furthermore, this structured data could then be shared with members of the health care team. If PGx information were to become standard of care, we may even begin to see it incorporated into the continuity of care document (CCD) standards that currently form part of the interoperability criteria for the CMS meaningful use incentive program.

Much of this could be accomplished by documenting testing through the use of ICD codes. These could be added to the patient record to reflect that genetic testing and counseling is being done, and then added to the problem list if genetic variants potentially effecting medication management are identified. In current ICD-9 nomenclature, v82.79 codes for "genetic screening NEC" and can be used during initial counseling and testing. This will transition to ICD-10 Z13.79, which is "encounter for other screening for genetic and chromosomal anomalies." If a mutation or clinically significant variant is identified through testing, the ICD-9 code V83.89 "genetic carrier status" can be added, which will transition to Z14.8 "genetic carrier of other disease." The implementation of ICD-10 may allow for more specific information to be directly coded into the patient record according to the needs of their care.

This ubiquity and ease of access to clinically significant PGx information may prevent patients from experiencing ADRs through the use of previously obtained genetic information. Also, as new information on pharmacologically significant genotypes becomes available, or if a patient develops a new condition that is affected by a known genetic factor, further testing could be performed and new information could be added into the patient's individual record as needed.

Several years later GS developed atrial fibrillation requiring anticoagulation. Warfarin was chosen as the anticoagulant and the previously obtained PGx results, specifically CYP2C9 and VKORC1, were utilized to assist with dose optimization. Together these results indicated that a maintenance dose of approximately 3.5 mg daily may be sufficient to achieve an INR of 2.5. This helped both the prescriber and patient treat with more confidence.

While there is certainly debate about ordering pharmacogenetic testing specifically for dose optimization of warfarin, there is also considerable evidence that CYP2C9 and VKORC1 can help to reduce ADRs related to warfarin. This case demonstrates and supports the ongoing utility of PGx results in the medical record. A positive value may not be obtained with the use of PGx results for one drug (e.g., warfarin), but over the lifetime of treatment with multiple drugs, the continued use of these results can contribute to improved efficiency, efficacy, and cost effectiveness in applied pharmacotherapy.

Pitfalls. Open access to genetic information is directly opposed to the majority of patient opinion when it comes to how they want their genetic information recorded and used. Most patients currently want their genetic information very closely held and shared only with express consent.[33] Current legislation in the form of the Genetic Information Nondisclosure Act reflects this concern, and limits how such information can be shared. It may be some time before PGx information may be freely used to benefit patient care.

The association between genetic variation and the potential for phenotypic expression in known disease

states is another concern. Indeed, some PGx variations are also associated with increased risk for certain disease states, as illustrated in Table 5. This association presents an ideal opportunity to discuss the ethics of PGx testing with regard to informed consent. While the risks of many disease states as well the benefits of meeting treatment goals are well defined, the significance of some genetic variants are less clear. Informed consent becomes problematic when a patient is asked to make health care decisions weighing a known risk/benefit ratio against an unknown risk/benefit ratio. Patients may already be inclined to fear medication because of personal anxiety, somatization, anecdotal perception of personal or familial susceptibility to ADRs, and/or frightening reports through media sources and peer interactions regarding the risk of pharmaceuticals. Conflicting information might sway patients in favor of declining treatment for known high-risk conditions based on the theoretical genetic risk of ADR. This may result in an ethical violation of non-maleficence ("do no harm").

While information regarding individual genotype should ideally provide patients with reassurance about which medications are safer and more efficacious for them, they have expressed reluctance to discuss information that did not result in clear and predictable advice.[34] Developing a process for obtaining informed consent, preferably in writing, is highly advisable to optimally manage patient expectations, address potential concerns, and engage them in the use of PGx.

Patient engagement will be crucial as patients will need to participate actively in maintaining the most accurate information in their primary care setting as well as in other locations of care. Providing patients with a summary of their PGx results may be helpful if a patient is seeing providers not actively involved in cooperative health care teams. Surveys have indicated that patients may be willing to consider carrying results on a health alert card or some other device.[33] This may provide a way to bypass patient concerns regarding the privacy of their genetic information, but relies on the patient to actively participate in their own care management.

A strong informed consent process would also provide an opportunity for PCPs to be clear on the specific testing options, costs, reimbursement, and procedures for testing in their area when designing protocols for PGx testing and counseling patients. The economics of health care raise significant concerns with regard to accurate and consistent use of genetic information in primary care. As a relatively new technology, PGx testing may not be covered by all insurance. This may create financial barriers to care. Of additional concern is the potential for increased cost of medications if it is discovered that a person's genotype is not suitable for lower cost medications. It is not clear how responsive insurance carriers will be to authorizing preferred, but more costly, medications to patients based on genomic data.

The issue of insurance coverage raises a more direct concern in the management of PGx in primary care. Offices get communication throughout the course of the day from insurance carriers, pharmacies, and patients with requests for medication changes based on cost and formulary coverage. The PCP often manages these requests without adequate time for in-depth consideration or access to the full patient record. Physicians may be able to make the decision if one medication can be substituted for a lower cost medication of the same class, but they cannot be expected to know if the alternative medications will be suitable for the patient's genotype, unless the data are available and they are educated as to how to use it. Furthermore, changes to medications made outside the office visit, either by primary care or by other providers, are not always consistently noted in the patient chart so that the new medications become part of their health record and can be considered in context of the patient's genotype. This may result in patients being asked to return to the office to discuss any changes to their medication, which could in turn erode any potential savings to the health care system from reduced ADRs.

Summary

Increased knowledge in the area of genomic sciences is likely to have an expanding impact on medical care in the near future. PGx is already heavily influencing medication management in primary care, but much of this information is presented to physicians without an organized and proactive framework for applying it.

It is critical that physicians, particularly PCPs, seek to assume a leadership role in the implementation of genomic science in patient care. Ongoing education will help them use this information to manage medications and high-risk conditions optimally. The development of coordinated care models like ACOs and PCMH will also leverage the skill sets of a broader segment of the health care team and greatly benefit the implementation of this technology.

Despite significant barriers and pitfalls, creating solid protocols for implementation will yield optimal results for physicians and patients as genetic information takes a more prominent place in patient care. PCPs must become part of the development of these protocols for this technology to yield the greatest potential benefits.

This article is dedicated to Dr. Brian Robert Hocum, MD (June 18, 1949–July 27, 2014).

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2. Evaluate the credibility of published data and recommendations related to primary care medicine;
3. Discuss the advantages and disadvantages of new diagnostic and therapeutic procedures in the primary care setting.

CME Instructions

To earn credit for this activity, please follow these instructions.

1. Read and study the activity, using the provided references for further research.
2. Scan the QR code to the right, or log on to www.cmecity.com to take a post-test. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
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CME Questions

1. Which of the following best describes a pharmacokinetic biomarker?
   a. A pharmacokinetic biomarker is a gene that codes for an enzyme that affects the metabolism of a drug.
   b. A pharmacokinetic biomarker is a gene that codes for a drug receptor.
   c. Examples of a pharmacokinetic biomarker include OPRM1 and ADRB2.
   d. Pharmacodynamic biomarkers are better understood than pharmacokinetic biomarkers.
2. Which of the following best describes a pharmacodynamic biomarker?
   a. Examples of pharmacodynamic biomarkers include CYP3A4 and SLCO1B1.
   b. A pharmacodynamic biomarker is a gene that codes for an enzyme that affects the metabolism of a drug and therefore the sensitivity to a medication.
   c. A pharmacodynamic biomarker is a gene that codes for a transporter and therefore the sensitivity to a medication.
   d. Pharmacodynamic biomarkers include direct and indirect genetic variances that affect drug sensitivity.
3. Which choice best describes a poor metabolizer?
   a. An individual with two normal functioning alleles
   b. An individual with duplicate copies of an allele
   c. An individual with two loss-of-function alleles
   d. An individual with one loss-of-function allele
4. Which choice best describes a rapid metabolizer?
   a. An individual with two normal functioning alleles
   b. An individual with two loss-of-function alleles
   c. An individual with one loss-of-function allele
   d. An individual with duplicate copies of an allele
5. What best describes the affect on serum drug levels in a poor metabolizer versus a rapid metabolizer?
   a. Drug levels will be significantly increased
   b. Drug levels will be significantly decreased
   c. Drug sensitivity will be significantly decreased
   d. Drug sensitivity will be significantly increased
6. Which statin would most likely avoid an interaction in a patient with the SLCO1B1 poor transporter phenotype?
   a. Lovastatin
   b. Simvastatin
   c. Atorvastatin
   d. Pitavastatin
7. What statin would be the best choice in carriers of the CYP3A4*22 allele or individuals who frequently consume large amounts of grapefruit?
   a. Atorvastatin
   b. Lovastatin
   c. Simvastatin
   d. Rosuvastatin

In Future Issues: Probiotics

Primary Care Reports™ (ISSN 1040-2497) is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326. Telephone: (800) 688-2421 or (404) 262-7436.

Executive Editor: Leslie Coplin
Managing Editor: Neill Kimball
Editorial Director: Lee Landenberger

GST Registration No.: R128870672

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to Primary Care Reports, P.O. Box 550669, Atlanta, GA 30355.

Back issues: $26. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Multiple copy prices: One to nine additional copies, $314 each; 10 or more additional copies, $279 each.

Subscriber Information

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Subscription Prices

1 year *with* free AMA Category 1/Prescribed credits: $379

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