ABSTRACT  Pharmacists must consider all factors when dosing medication for a patient. Until recently, however, one key piece to this puzzle was missing—genetics. This invisible piece of the puzzle can now be utilized with pharmacogenetic testing. By using pharmacogenetic testing, the compounding pharmacist will be able to better predict disease risk as well as the pharmacodynamic and pharmacokinetic actions of the prescriptions their patients are taking. Pharmacogenetics is poised to become the standard of care that not only physicians are embracing, but pharmacists can utilize to better personalize their patient’s needs.
As a health sciences discipline, pharmacists provide patient care that optimizes medication therapy and promotes health, wellness, and disease prevention. Pharmacists have an obligation to contribute to the generation and utilization of state-of-the-art knowledge that advances health and quality of life. The clinical application of pharmacogenetics is one example of such an advancement of innovative knowledge. Pharmacogenetics refers to genetic differences in metabolic pathways that can affect an individual’s response to drugs in terms of therapeutic effect as well as adverse effects. Although the terms pharmacogenomics and pharmacogenetics tend to be used interchangeably, pharmacogenetics is regarded as the clinical testing of genetic variations that gives rise to differing responses to drugs, whereas pharmacogenomics is the broader application of genomic technology associated with drug discovery. Despite the fact that pharmacogenetic and pharmacogenomic concepts have been around for hundreds of years, it is only in recent years that we have seen a rapid increase in the mainstream application of these sciences.

Genes, the units of heredity present on DNA strands inherited from one’s parents, are the blueprints for all individual traits. They code for everything from obvious characteristics such as hair color and height to less obvious characteristics such as blood type. Within every person’s genes lie small differences in the DNA code, with each unique version of the gene referred to as an allele. One common type of difference, called a single nucleotide polymorphism (SNP; pronounced “snip”), occurs when one base in the DNA code is changed. Sometimes SNPs are neutral, meaning they have no effect on the body and the resulting characteristic is unchanged. In other cases, this single change in the DNA code can alter the genetic blueprints such that it results in everything from small alterations to dramatic effects on the characteristics.

Genes also code for enzymes, the chemical workhorses of the body, including all liver enzymes that are responsible for metabolizing drugs and other xenobiotics. Many of these liver enzymes are highly affected by individual SNP variations in the DNA. Since genes come in pairs, one from each parent, a patient can have two normal genes (no variants), one variant (heterozygous), or two variant genes (homozygous). Patients with no variants have normal enzyme function, but patients with one or two variants can have enzymes that function more or less than normal enzymes. This affects how the body metabolizes drugs, which in turn affects the plasma levels of a drug in the blood. Levels that are too high can cause adverse drug reactions (ADRs), and levels that are too low can make treatment ineffective. With more than 4 billion prescriptions being dispensed every year, millions of patients are either under- or over-treated, and there are over two million serious ADRs yearly. Due to this, genotyping to guide pharmacological treatment is becoming the gold standard in patient care and an important step in the personalized medicine revolution. Compounding pharmacists are highly qualified specialists in personalized medicine and are uniquely positioned to offer pharmacogenetic testing as part of their practice. Within the context of this article, we will discuss three clinical applications of pharmacogenetic testing, all of which have valuable relevance to the practice of compounding pharmacy.

**BREAST CANCER RISK PREDICTION**

One important aspect of compounding pharmacy is hormone replacement therapy (HRT). HRT has been used for
decades by post-menopausal and peri-menopausal women to help curb many of the symptoms of menopause such as sweating and hot flashes. As many as two million women in the U.S. use customized hormones for menopause symptoms.\(^5\) Compounding pharmacy provides the service of customizing these individualized medications, a service that industry cannot and will not meet.\(^5\) Customization allows pharmacists to tailor treatment to an individual woman’s needs, an important application of personalized medicine. Notably, these hormones are bioidentical hormones and, as the name suggests, are, therefore, molecularly identical to the hormones a woman produces in her body. This makes HRT more natural. To even further personalize patient experience with HRT, many compounding pharmacists also monitor hormone levels with saliva-based testing.

Although HRT is prescribed for millions of women, the complications of HRT, including risk of breast cancer development, are not insignificant. Studies show estrogens are a prime risk factor for the development of breast cancer.\(^6\)\(^-\)\(^9\) and breast cancer risk is higher in women with early menarche and late menopause because of a longer exposure to estrogens. Experiments on estrogen metabolism,\(^10\)\(^-\)\(^12\) formation of DNA adducts,\(^13\)\(^,\)\(^14\) mutagenicity,\(^15\)\(^,\)\(^16\) cell transformation,\(^17\)\(^,\)\(^18\) and carcinogenicity\(^19\)\(^,\)\(^20\) have implicated certain estrogen metabolites, especially the catechol estrogen 4-hydroxysteradiol (4-OHE\(_2\)) metabolite, to react with DNA via their quinone, causing mutations and initiating cancer.

Genetics and gene variants have also been known to play a role in breast cancer development. The most notorious of these mutations are in the \(BRCA1\) and \(BRCA2\) tumor suppressor genes, which play a key role in repairing DNA damage. Harmful DNA variants cause these enzymes to work more poorly and allow for more DNA damage to accumulate. Over time, this can lead to cancer, and women with \(BRCA\) mutations are at a much higher risk for development of ovarian and breast cancers. Although genetic testing for these genes has gained media attention as of late because of high-profile celebrities testing positive, in actuality, mutations in \(BRCA1\) or \(BRCA2\) only account for about 5% to 10% of all breast cancer cases.\(^21\) Thus, most women that develop breast cancer have risk factors other than mutations in the \(BRCA\) genes.

Since estrogen exposure has been deemed so important to breast cancer development, current models of risk prediction are based mainly on surrogates of cumulative estrogen exposure such as age, age at menarche, and age at first live birth.\(^22\)\(^-\)\(^26\) These tests, however, don’t directly reflect mammary estrogen metabolism and exposure to carcinogenic estrogen metabolites. Researchers at Vanderbilt University recognized this pitfall in current prediction models and developed a superior combined genotypic and phenotypic algorithm to estimate breast cancer risk. This advanced algorithm takes into account cumulative estrogen exposure over a woman’s lifetime, but additionally looks at variants in three genes important in estrogen metabolism, \(COMT\), \(CYP1A1\), and \(CYP1B1\).\(^27\) Depending on which variants in these three genes a woman has, she can potentially skew her estrogen metabolism to produce more DNA damaging (cancer causing) or more DNA protective (anti-cancer) metabolites. This cash-pay buccal swab test, called the Emetab Estrogen Panel Breast Cancer Risk Estimate (Iverson Genetics), therefore offers a combined calculated risk of developing breast cancer. Since certain variants can also be protective, the test can also identify patients who are less likely to develop breast cancer.

Knowing this information is important for any woman considering HRT. Having a high risk for the development of breast cancer may make some women more cautious of taking HRT, whereas other women might opt for HRT formulations with lower estrogen profiles with increased breast cancer screening. Knowing this information is important for any woman considering HRT. Having a high risk for the development of breast cancer may make some women more cautious of taking HRT, whereas other women might opt for HRT formulations with lower estrogen profiles with increased breast cancer screening. Either way, high-risk women may moreover want to implement lifestyle modifications such as smoking cessation and weight loss, additional services that can be offered by the compounding pharmacist. Thus, the role of the compounding pharmacist in providing this service can be twofold 1) to offer the Emetab test to their patients as a service and 2) to provide personalized experiences in helping women make lifestyle changes and decisions regarding their test results.

**DRUG METABOLIZING ENZYME TESTING**

The Emetab test is just one example of the ever-expanding world of pharmacogenetics. Compounding pharmacists are famil-
As compounding pharmacy services have expanded to meet the growing need for specific and personalized medications and dosages, awareness of individual genetic differences has increased in importance in many areas, including anticoagulation therapy. Despite the introduction of new anticoagulant medications, warfarin is still widely prescribed with over 20 million prescriptions written in the U.S. in 2010 and is utilized for a variety of indications. Although uncommon, there may be an occasion to compound warfarin for a patient including a patient’s inability to swallow tablets or allergy to the dye used in some warfarin dosages.

Numerous studies have identified significant associations of the CYP2C9 and VKORC1 polymorphisms and individual variability with warfarin. Individual variations in the cytochrome P450 2C9 gene (CYP2C9) and in the vitamin K epoxide reductase (VKOR) C1 gene (VKORC1) have been shown to be associated with the rate at which warfarin is metabolized and level of sensitivity to warfarin therapy. While the U.S. Food and Drug Administration (FDA) has required changes to warfarin labeling due to study data, the protocol for incorporating genetic testing into warfarin dosing remains unclear.

In an effort to quantify the impact of incorporating pharmacogenetic information in warfarin dosing and how it affects patient outcomes, Iverson Genetics is conducting a prospective, multicentered, double-blinded, randomized, parallel-group study to investigate if using warfarin with the triad approach of one patient, one doctor, one pharmacist. With the vast expanse of information coming out every day on drugs and drug-drug interactions, it is important that the pharmacist support this triad with medication management knowledge. One tool to aid in this is pharmacogenetic testing of the cytochrome P450 enzyme (CYP) family. The CYP are a class of liver enzymes that metabolize 70% to 80% of the prescribed medications used clinically. Many SNPs have been identified in the CYP enzymes, although as mentioned previously, not all SNPs have the same effect. Some SNPs have no clinical significance and are, therefore, of little value when genotyped. Other SNPs may only be important in the metabolism of one or a few drugs. Although many companies now offer genetic testing of enzymes involved in drug metabolism, it is important that pharmacists use due diligence in investigating which companies test SNPs whose information can be of clinical use. Iverson Genetics offers a panel of CYP enzymes called the Drug Metabolizing Enzyme Extended panel (DMEX) that only tests for clinically actionable variants. This means the results of this test can be utilized to make decisions regarding if a medication will work for a particular patient, and if not, if dosage adjustments or alternative medications could be beneficial. Such information is additionally useful to avoid ADRs. Overall, pharmacogenetic testing is a service that is not only valuable to the pharmacist, but also a benefit to the patient.
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By using pharmacogenetic testing, the compounding pharmacist will be able to better predict disease risk as well as the pharmacodynamic and pharmacokinetic actions of the prescriptions their patients are taking.

CONCLUSION

Pharmacists must consider all factors when dosing medication for a patient including age, liver disease, kidney function, and weight. Until recently, however, one key piece to this puzzle was missing—genetics. This invisible piece of the puzzle can now be utilized with pharmacogenetic testing. By using pharmacogenetic testing, the compounding pharmacist will be able to better predict disease risk as well as the pharmacodynamic and pharmacokinetic actions of the prescriptions their patients are taking. By targeting SNPs in the CYP450 family, pharmacists are able to practice proactive versus reactive medicine. Overall, pharmacogenetic testing aims to save money due to the avoidance of ADRs, but ultimately it is most advantageous due to the long-term health benefits for patients.

The ultimate goal, however, is not just to look at how a patient’s genetics will generally guide medication management, but to move towards an even more personalized approach. As pharmacogenetic testing is being used more frequently in clinical settings, testing modalities are moving away from simple genotyping platforms towards more predictive models of personalized medicine. The Emetab Estrogen Panel is such an example that combines a woman’s genotypic information with specific phenotypic information into a predictive model for breast cancer risk. This information can then be utilized to help women considering HRT make more informed decisions. The algorithm used by the WARFARIN Study [31] (www.warfarindosing.org) is another example of such a prediction platform that uses genetic testing combined with patient information to predict starting dosages of a medication that has historically been hard to control. In summary, pharmacogenetics is poised to become the standard of care that not only physicians are embracing, but pharmacists can utilize to better personalize their patient’s needs.

REFERENCES


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