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What you need to know about pharmacogenomics

By Dennis J. Cheek, PhD, RN, FAHA

*MRS. C, 62, IS ADMITTED to the hospital after experiencing an acute myocardial infarction. Her management includes percutaneous coronary intervention (PCI) and a prescription for clopidogrel. She tolerates the procedure well and is admitted to the ICU for close observation. Over the next 48 hours, she has an uneventful course in the ICU with complete resolution of symptoms, stable vital signs, and no further ECG changes. Before Mrs. C is discharged home, the cardiologist prescribes genetic testing. A buccal swab is obtained from Mrs. C, placed into a premixed tube, and sent to the lab for analysis. The results: "positive for CYP2C19*2 variant." Why did the cardiologist prescribe this test, and what do the results mean for Mrs. C?*

Recent studies have shown that a patient's response to drug therapy, including adverse drug reactions, can be strongly influenced by the patient's genetic makeup. *Pharmacogenomics*, or tailoring medications to a patient's



genomic information, is a significant and growing area of research with the potential to improve patient outcomes. This article focuses on how pharmacogenomics can help nurses provide better care for patients. (See *Genetic glossary* for a list of terms related to pharmacogenomics.)

Pharmacogenomic implications

Clinical applications for pharmacogenomics include antiplatelet therapy, mental health, HIV therapy, and oncology.

Antiplatelet therapy. Clopidogrel is a platelet adenosine disphosphate (ADP) receptor antagonist that's indicated for specific atherothrombotic events and therapies, such as stroke, acute coronary syndromes (ACS), peripheral arterial disease, and post-PCI. It's a prodrug with no antiplatelet activity. A two-step metabolizing process involves the cytochrome P450 (CYP450) enzyme, specifically the CYP2C19*1 wild-type enzyme, or the normal enzyme, which converts clopidogrel to an active metabolite with antiplatelet activity.¹

Recent genetic data have shown that people who carry a certain loss-of-function allele produce a variant enzyme known as CYP2C19*2. Those with this CYP2C19*2 variant can't metabolize clopidogrel to the active metabolite that exerts antiplatelet activity.² Consequently, they respond poorly to clopidogrel therapy.

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Genetic testing can identify this variant with DNA sequencing or genome-wide association studies (GWAS). The GWAS method involves scanning the genomes from many different people and looking for genetic markers that can be used to predict the presence of genetic variants that would impact drug metabolism. These genetic tests, however, are costly and labor intensive. A point-of-care system is available in Europe, but not yet in the United States. It comes with a swab, prepackaged substrates, tube, and measurement device. Results are available in 60 minutes. If a patient has the variant, like Mrs. C in the case study above, the healthcare provider may decide to prescribe alternative antiplatelet therapy.

Anticoagulation. Another drug with pharmacogenomic implications is warfarin, a vitamin K antagonist used to manage thromboembolic disorders such as deep vein thrombosis; prevent strokes and other thromboembolic complications in patients with atrial fibrillation; and prevent venous thromboembolism (VTE) in patients who've undergone

major orthopedic surgery. Warfarin has a narrow therapeutic range and a wide variation in dosing requirements. One of the major adverse drug reactions encountered by 10% to 16% of patients is life-threatening bleeding.³

Dosing adjustments are necessary to maintain therapeutic anticoagulation without triggering bleeding. Adjustments are based on the patient's prothrombin time (PT), which measures coagulation inhibition. PT results can vary from lab to lab depending on the specific reagents used, so the results are converted to a standardized international normalized ratio (INR). A normal individual who isn't taking warfarin has an INR of 1. For patients taking warfarin, the goal is to maintain an INR between 2 and 3 (a target of 2.5). Factors that influence warfarin's therapeutic and adverse effects include not only non-genetic factors such as gender, age, and body weight, but also significant genetic variants—specifically, alterations in CYP2C9 and vitamin K epoxide reductase (VKOR).

CYP2C9*1 is the hepatic enzyme responsible for metabolizing

S-warfarin, which is three to five times more potent than R-warfarin (S-warfarin and R-warfarin are enantiomers, or mirror images, of the warfarin molecule). The genetic polymorphisms (variations) CYP2C9*2 and CYP2C9*3, which are common in the general population, result in decreased clearance and increased blood levels of S-warfarin.⁴

Warfarin inhibits VKOR, which is encoded by the VKORC1 gene. Variations within this gene also impact the patient's response to warfarin. The major variation in the VKORC1 gene is 1639GA genotype, which decreases the expression of VKOR. It's more susceptible to inhibition by warfarin so the warfarin dosage should be reduced.⁵

In January 2010, warfarin labeling was updated to include a dosing table for initial dosing based specifically on CYP2C9 and VKORC1 genotypes. Genetic testing can identify patients who are at greater risk for adverse drug reactions so doses can be appropriately adjusted.

Mental health. Many drugs used to treat mental health disorders, such as selective serotonin reuptake inhibitors and tricyclic antidepressants, are metabolized via the hepatic enzyme CYP2D6. The variant CYP2D6*1 allele is responsible for extensive (primary) metabolism of many drugs.⁶ This hepatic metabolizing enzyme has 90 known variants that slow drug metabolism, increasing serum drug concentrations. Several variants of CYP2D6*2 increase enzyme activity, decreasing serum drug levels. With CYP2D6*4, the expressed protein is inactive, so serum drug levels increase, causing adverse reactions. The variant CYP2D6*5 has no expressed enzyme. In CYP2D6*10, the expressed enzyme is unstable and serum drug levels will fluctuate. CYP2D6*17 lessens the affinity of the enzyme for its selective substrate.⁷

Genetic glossary¹⁵

Allele: one of the variant forms of a gene at a particular locus, or location, on a chromosome

Carrier: an individual who possesses one copy of a mutant allele that causes disease only when two copies are present

Gene: a unit of hereditary information located on a specific part of a chromosome

Genetics: the study of inheritance

Genome: the complete genetic information of an organism

Genotype: the genetic identity of an individual that doesn't show as outward characteristics

Pharmacogenetics: the field of study dealing with the variability of responses to medications due to variation in single genes

Pharmacogenomics: this field of study is similar to pharmacogenetics, except it typically involves the search for variations in multiple genes that are associated with variability in drug response

Polymorphism: involves one of two or more variants of a particular DNA sequence

HIV. The FDA strongly recommends genetic testing for HIV-positive patients before they're prescribed abacavir, an antiretroviral agent. This drug should be prescribed only for HIV-positive patients who *don't* have the HLA-B*5701 allele because patients with this allele are at a significantly higher risk for a hypersensitivity reaction to abacavir.⁸ A hypersensitivity reaction can occur within the first 6 weeks of beginning treatment with abacavir. Signs and symptoms include rash, fever, nausea, vomiting, and dyspnea.

Oncology. When breast cancer is diagnosed, a breast cancer tumor marker test should be done as recommended by the American Society of Clinical Oncology, the College of American Pathologists, and the National Comprehensive Cancer Network.^{9,10} The specific marker of interest is the human epidermal growth factor receptor 2 (HER2), which plays an important role in cell growth.^{9,10} Overexpression of HER2 can lead to malignant cell transformation. The assessment of HER2 status is needed to determine if the HER2–targeted medicine trastuzumab is appropriate.

Trastuzumab is a humanized monoclonal antibody targeted against the HER2 receptor.¹¹ Its mechanism of action is the continuous suppression of HER2 activity.¹¹ Use of trastuzumab in the management of all metastatic breast cancer with HER2 overexpression has been shown to increase survival rates and reduce the risk of recurrence.¹²

On June 8, 2012, pertuzumab was approved by the FDA for the treatment of breast cancer in combination with trastuzumab. Pertuzumab inhibits the HER2 receptor from undergoing dimerization (receptor pairing), or prevents the HER2 receptor from becoming functional.¹²

Genetic testing concerns

Although genetic testing can help patients get the individualized



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therapy they need, many patients are concerned about submitting to genetic testing for fear of retribution from their employer or insurer. In May 2008, the Genetic Information Nondiscrimination Act (GINA) was signed into law.¹³ This federal law prohibits discrimination in health coverage and employment based on genetic information.¹³ GINA, in conjunction with the already existing Health Insurance Portability and Accountability Act, prohibits health insurers or health plan administrators from requesting or requiring genetic information on an individual or family member or using it for decisions regarding coverage, rates, or preexisting conditions. GINA also prohibits most employers from using genetic information for hiring, firing, or promotion decisions or for any decision regarding terms of employment.¹³

Unfortunately, GINA's nondiscriminatory protection doesn't extend to life insurance, disability insurance, and long-term-care insurance. GINA's employment provision generally doesn't apply to employers with fewer than 15 employees, nor does it apply to members of the military or

the Tricare military health system, veterans' healthcare administered by the U.S. Department of Veterans Affairs, the Federal Employees Health Benefit Plan, or the Indian Health Service.¹³

Nursing considerations

To determine if pharmacogenomics can help a patient, begin with the nursing admission assessment. Collect information about the patient's family history, looking for genomic influences such as adverse drug reactions or treatment failure.¹⁴ For example, ask a patient if anyone in the family is taking the anticoagulant warfarin. If so, ask if he or she is experiencing bleeding problems, which could be the result of two genetic variants. If a patient has a relative who's had difficulty with anesthesia, he or she could be susceptible to malignant hyperthermia.

Assess the patient's knowledge and perception of genetics or genomics, and explore concerns about genetic testing.¹⁴ Identify any patient who may benefit from referral to a specialized genetic counselor. Provide specific genetic or genomic information or referrals to services that may be needed in conjunction with pharmacologic therapy to improve patient outcomes and reduce adverse reactions.¹⁴ Continually evaluate both the impact and effectiveness of genetic and genomic technology, information, interventions, and treatment on patient outcomes.¹⁴

Better outcomes

*Because Mrs. C's test was positive for the CYP2C19*2 variant, the cardiologist may reduce the clopidogrel dose or order prasugrel, a newer platelet ADP receptor antagonist, to reduce the risk of bleeding. The test has provided a better outcome for Mrs. C, reducing her risk of adverse reactions.*

Advances in pharmacogenomics can improve outcomes in individual

patients. The goal of pharmacogenomics is to develop strategies that optimize therapeutic effects and reduce the potential for adverse reactions. Keeping on top of the latest advances in pharmacogenomics can help you care for the patients of tomorrow. ■

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RESOURCE

The Pharmacogenomics Knowledgebase. <http://www.pharmgkb.org>.

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