Pharmacogenomic Testing and the Prospect of Individualized Treatment

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Pharmacogenomics offers the hope of greater individualization of treatment. Therapies that exemplify the promise of pharmacogenomics include anticoagulation with warfarin and the use of antiplatelet medications (eg, clopidogrel) for secondary prevention after acute coronary syndrome. Good evidence of clinical utility must be obtained before pharmacogenomic testing is widely implemented.

The hope of pharmacogenomics lies in the possibility that we may be able to better individualize medical treatments—prescribing medications to those most likely to benefit and avoiding the use of certain medications in those most likely to be harmed by them [1]. In addition, when several medication options are available, pharmacogenomics could help us choose the one most appropriate for a particular individual.

Scientific advances in genome sequencing have resulted in a number of predictive genetic tests that are potentially useful for health care decision making. Such tests may predict risk for or susceptibility to future diseases in asymptomatic people (for instance, mutations in the BRCA1 and BRCA2 genes indicate a heightened risk of developing breast and ovarian cancer), or they may provide prognostic information for patients with a particular condition (for example, the Oncotype Dx test predicts the risk that breast cancer will recur). Genetic tests may also predict a person’s response to medications (ie, pharmacogenomics) or to environmental factors (for example, nutrigenomics predicts responses to dietary factors).

For many practicing clinicians, the field of genomics is a “black box” plagued by uncertainty, hype, direct-to-consumer marketing, and little evidence of clinical utility. Many clinicians do not have the time or the tools to evaluate pharmacogenomic tests, and these tests are challenging to evaluate even for those who have a relatively detailed knowledge of genetics and related concepts [2].

Two types of drug therapy that exemplify the promise of pharmacogenomics are anticoagulation with warfarin and the use of antiplatelet medications for secondary prevention after acute coronary syndrome. Both types of therapy have large implications for population health. Warfarin is widely used to treat people with atrial fibrillation, deep venous thrombosis, pulmonary emboli, or artificial heart valves. Clopidogrel and other oral P2Y12 inhibitors (eg, ticagrelor and prasugrel) are commonly used for secondary prevention after acute coronary syndrome.

Warfarin

In the United States, more than 30 million prescriptions are written for warfarin each year [3, 4], and of all the drugs in the modern medical formulary, warfarin remains one of the most challenging to manage. It is consistently one of the leading causes of adverse drug reactions leading to emergency department visits and hospitalizations, both in the United States and worldwide [5], and there are an estimated 7.6 adverse bleeding events for every 100 patient-years of treatment [6]. Warfarin has a narrow therapeutic window: Doses that are slightly too high can result in catastrophic hemorrhagic complications, whereas doses that are too low can result in thrombotic complications. As a result, specialized warfarin clinics are devoted solely to monitoring patients on this medication, and frequent monitoring of the patient’s international normalized ratio (INR) is required; on average, such management requires 15 visits per year [7]. Further, individuals’ response to warfarin and their dose requirements vary considerably.

Many genetic and clinical factors are associated with variation in warfarin dose requirements, including age, race, weight, height, smoking status, the use of other medications, and polymorphisms of the CYP2C9, VKORC1, and CYP4F2 genes [8]. The CYP2C9 and VKORC1 genes, which encode for enzymes important for warfarin’s site of action and metabolism (Figure 1), account for approximately 15% and 25% of the variation in warfarin dose requirements, respectively [8]. This finding has been replicated in observational studies of populations around the world [9, 10].

Several dose-calculation algorithms that combine clinical factors and genotypic information have been shown to accurately predict warfarin doses. In retrospective studies of patients receiving long-term therapy with stable doses
Cystic Fibrosis: A Model for Personalized Genetic Medicine

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Cystic fibrosis is the most common fatal autosomal recessive disease among whites, affecting approximately 30,000 people in the United States. It is a multisystem disease with morbidity and mortality resulting primarily from progressive pulmonary disease. Cystic fibrosis results from mutations in CFTR, a gene on chromosome 7 that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This protein is an ion channel that regulates the movement of chloride and bicarbonate, and abnormalities in this protein can lead to problems with the secretion of salt and water in a variety of tissues. To date there is no cure for cystic fibrosis.

Because cystic fibrosis is genetic in nature, researchers have been able to focus on specific CFTR mutations that lead to specific changes in the CFTR protein. These genetic mutations can be separated into 5 categories, referred to as classes [1, 2]. Class 1 mutations result in premature termination of messenger ribonucleic acid (mRNA) and complete absence of the CFTR protein. Class 2 mutations result in defective processing of the CFTR protein; mutations in this class include the most common mutation, F508del. The defective protein produced by class 2 mutations is recognized as misfolded and is quickly degraded; thus it never reaches the cell membrane. Class 3 mutations cause defective protein regulation, often by means of reduced chloride channel activity. Such defects result in normal CFTR protein production but abnormal chloride channel transport. Class 4 mutations also involve defective conductance through the CFTR protein, which reduces the rate of ion flow and the duration of channel opening. Finally, Class 5 mutations result in appropriately folded CFTR proteins on the cell surface, but these proteins are significantly reduced in number. With these separate classes of genetic mutations, multiple opportunities have arisen to target the specific disease process.

Using high-throughput screening libraries, pharmaceutical companies have been able to identify numerous candidate compounds that can target specific mutations. Depending on which CFTR function they modulate, these compounds are referred to as correctors or potentiators. Potentiators promote effective chloride transport and can prolong opening of chloride channels. Correctors, however, improve CFTR processing and maturation in the cell, thus allowing the protein to be folded correctly and transported to the cell surface. Potentiators do not correct protein folding or transcription; rather, they target mutations that impair the function of a protein product that is already on the cell surface (Class 3, 4, or 5 mutations); in contrast, correctors are used to address mutations that result in protein products being trapped within the cell (Class 1 or 2).

The first potentiator to be successfully tested and to receive US Food and Drug Administration approval was ivacaftor. This molecule was found to be most effective in patients with the mutation G551D. In phase III clinical trials of subjects who had at least 1 G551D mutation [3, 4], ivacaftor significantly improved lung function as measured by forced expiratory volume in 1 second (FEV1); this measure improved by at least 10.6% over a 48-week period. Subjects receiving ivacaftor were 55% less likely to have pulmonary exacerbations than those receiving placebo [3], and those receiving ivacaftor also gained more weight [3, 4].

Two other molecules that have been under study also fall into the category of correctors. One of these, VX-809,
has been shown to correct the folding and processing of F508del-CFTR proteins in cells and to increase chloride secretion in bronchial cells by 14% [5]. In human trials, VX-809 when given alone has only been shown to result in a clinically significant decrease in sweat chloride but has not been effective for improving lung function or quality of life [6]. Due to this, phase III studies are now enrolling subjects with 2 copies of the F508del mutation to assess the combination of VX-809 and ivacaftor in terms of overall effectiveness on lung function and other endpoints.

The other corrector compound under study, ataluren, allows ribosomes to read through mRNA premature stop codons, resulting in the production of functional CFTR proteins in patients with specific class 1 CFTR mutations. Phase II studies of this drug showed promise, with ataluren increasing chloride conductance and FEV₁. However, phase III studies showed no significant improvement in any tested outcome, including FEV₁, [7, 8]. On later investigation, researchers found that aminoglycosides such as tobramycin, a medication that is commonly prescribed for cystic fibrosis, can interfere with ataluren at the ribosome [9]. These results will need to be investigated further.

In summary, cystic fibrosis is providing proof of concept that personalized medicine can be used to correct the base pathophysiology of a disease. Ivacaftor is the first drug of its kind to directly target the specific protein misfolding that leads to reduced activity of a protein. In the near future, physicians who treat patients with cystic fibrosis hope to add other medications to their arsenals that can directly combat the underlying defect of the disease. Thus, for any given mutation carried by a cystic fibrosis patient, we will have a drug aimed at that specific mutation. This therapy will reverse the dehydration in the lung and pancreas, in effect slowing the progression of disease. This type of therapeutic development provides promise for multiple other genetic diseases caused by protein defects, and it offers significant hope for the future of medicine. NCMJ

dosing concluded that, although such dosing is unlikely to be cost-effective for typical patients with nonvalvular atrial fibrillation, it may be cost-effective in patients at high risk for hemorrhage who are starting warfarin therapy [19]. Of note, the analysis was based on input from existing trials (which have inherent limitations, as noted above) and on outdated testing costs. The forthcoming results of the COAG trial and rapidly decreasing costs could change this cost-effectiveness balance.

Clopidogrel

In 2011 clopidogrel ranked seventh among the most prescribed medications in the United States, with a total of more than 28 million prescriptions [20]. This drug is commonly prescribed for secondary prevention after acute coronary syndrome. In 2012 the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) released guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction; these guidelines recommend dual antiplatelet therapy with aspirin and an oral P2Y₁₂ inhibitor—clopidogrel, ticagrelor, or prasugrel—for up to 12 months [21]. Until recently, only clopidogrel was available; ticagrelor and prasugrel were just approved by the US Food and Drug Administration (FDA) in 2011 and 2012, respectively. Another recent change is that generic clopidogrel became available in 2012, substantially reducing its cost, so it is now the preferred choice from a public health and cost perspective.

Clopidogrel is a prodrug that is transformed into its active form by several cytochrome P450 (CYP450) enzymes in the liver, one of which is CYP2C19. Variants of the CYP2C19 gene have been associated with differences in the bioavailability of clopidogrel: CYP2C19*2 is the most common vari-
Individuals who carry 1 or 2 copies of these variant alleles may be intermediate or poor metabolizers of clopidogrel and may produce a smaller amount of the active form of the drug (Figure 2) [22-25]. In 5 of 7 cohort studies conducted in 2008 and 2009, the CYP2C19*2 variant was associated with an increased risk of cardiovascular events [26-33], leading to the conclusion that variant alleles may result in nonresponsiveness to clopidogrel and a subsequent increase in the risk of adverse outcomes.

Awareness of how genetic polymorphisms of CYP2C19 can reduce clopidogrel’s efficacy led to product label changes in 2009 and 2010 [34]. The current product label for clopidogrel [35] includes a boxed warning describing the increased risks of cardiovascular events among poor metabolizers; this label also notes that a genetic test is available to identify CYP2C19 polymorphisms. However, there is no recommendation that prescribers pursue genetic testing of their patients. No rigorous studies have established a connection between use of a genotype-guided strategy and improved outcomes, and the ACCF/AHA guidelines explain that the clinical utility of genotypic testing has not been established [21]. Further, alternative hypotheses exist that may explain the link between CYP2C19 variants and adverse outcomes; for example, the variant alleles may directly confer an increased risk of adverse outcomes, unrelated to clopidogrel metabolism.

As with genotype-guided warfarin dosing, pharmacogenomic testing to inform selection of a P2Y₁₂ inhibitor should have good evidence of clinical utility before it is widely implemented. We need randomized trials that compare clinical outcomes for patients who receive genotype-guided medi-
Estimates suggest that about 80% of breast cancers and 90% of ovarian cancers are sporadic [1]; only 5% to 10% of breast cancers are hereditary. Hereditary mutations of the BRCA1 and BRCA2 genes account for 60% of inherited breast and ovarian cancers [1]. According to data from the National Cancer Institute [2], the risk of a BRCA2 mutation carrier developing breast cancer by age 70 years is 45%, and her risk of developing ovarian cancer is 11%–17%; BRCA1 mutation carriers have a slightly higher risk of breast cancer (55%–65%) and a higher risk of ovarian cancer (39%).

Until recently, the management of breast cancers resulting from a BRCA mutation did not differ from management of sporadic tumors. However, genetic information is now important in planning surgeries and adjuvant therapies, and genetic testing for BRCA mutations is increasingly being used for risk assessment. This article will examine the pros and cons of such testing and discuss how it can affect patient care.

Genetic Consultation
In multidisciplinary breast centers, genetic counselors play a vital role by identifying and evaluating women who are at high risk for hereditary breast cancer syndromes. The US Preventive Services Task Force guideline on genetic risk assessment and BRCA testing strongly recommends that high-risk individuals be referred for genetic counseling and possible testing [3]. Genetic counseling and testing provide many benefits to the patient and to the health care team [1]. First, counseling and testing help to identify high-risk individuals who do not have cancer; these women will benefit from early screening and consultation. For a woman with a known cancer, counseling and testing may help her decide whether to undergo a bilateral mastectomy at the time of her cancer surgery, or whether to opt for careful surveillance of the remaining breast tissue. Finally, testing can alleviate the anxiety of not knowing one’s carrier status.

The risks of genetic testing include the inability of such testing to detect all mutations, the unclear efficacy of some interventions, and the possibility of psychosocial or financial harm [1]. Genetic counselors can inform patients about Title I of the Genetic Information Nondiscrimination Act of 2008 [4], which provides protection against discrimination based on genetic information in health insurance underwriting decisions. However, that protection covers only group and individual health insurance; it does not apply to life insurance, disability insurance, or long-term care insurance [4].

Management
Women who test positive for a BRCA mutation have several options for reducing their risk of developing cancer. These include surveillance, chemoprevention, and surgical risk reduction.

For BRCA mutation carriers, early detection strategies include annual or semiannual clinical breast examination by a physician or allied health professional, annual mammography beginning at age 25 years, and/or annual breast magnetic resonance imaging (MRI) [5]; if both breast MRI and mammography are being performed, the breast MRI should be performed 6 months after the yearly mammogram. The benefit of a clinical breast examination is under debate, as such exams have not been shown to improve the rate of cancer detection. Nonetheless, patients say that they find the exam reassuring, and it gives the provider an opportunity to discuss the patient’s care [6].

Mammography has been shown to decrease the breast cancer mortality rate; however, its sensitivity is estimated to be only about 36% in BRCA1 or BRCA2 mutation carriers [7]. In contrast, the sensitivity of MRI screening in women with a familial or genetic predisposition is nearly 80% [7, 8]. The pros of breast cancer surveillance with MRI are that it is noninvasive and it has no long-term side effects. The cons are that it has not been shown to reduce the risk of breast cancer–related death in BRCA mutation carriers, and it carries an increased risk of false-positive results, which can lead to additional imaging or biopsies.

Breast cancer chemoprevention is offered in the form of tamoxifen and raloxifene, with the latter being used for postmenopausal women. The Study of Tamoxifen and Raloxifene (STAR) [9] showed that these selective estrogen receptor modulators (SERMs) lowered the risk of developing invasive breast cancer by about 50%. However, SERMs...
do not completely eliminate the risk of developing breast cancer, and data regarding their effectiveness in BRCA mutation carriers are limited.

Bilateral prophylactic mastectomy has been shown to reduce breast cancer risk in women with a family history of breast cancer. The risk reduction in BRCA mutation carriers has been shown to be 90% in women with intact ovaries and 95% in those who have undergone prophylactic oophorectomy [10]. Many women who choose bilateral mastectomy also opt for immediate breast reconstruction with implants or autologous tissue. The advantage of prophylactic mastectomy is that it greatly reduces the risk of developing breast cancer. The disadvantages include the need for extra surgeries with breast reconstruction, possible surgical complications (eg, bleeding and infections), and psychosexual concerns. However, studies have shown that most women are satisfied with their surgical choice and do not experience poor body image after surgery [11, 12].

In addition to prophylactic mastectomy, BRCA mutation carriers may consider prophylactic oophorectomy. Bilateral prophylactic salpingo-oophorectomy is associated with an 85% reduction in the risk of developing gynecologic cancer among BRCA1 mutation carriers [13].

Breast specialists and genetic counselors play an important role in guiding patients with an increased risk for developing breast cancer through genetic testing and treatment options. There are pros and cons to each risk-reduction strategy, but the more informed a patient is, the better her outcome and overall satisfaction will be. NCMJ

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No longer isolated specialties, genetics and genomics now span all fields of medicine. However, efforts to improve the genomic literacy of health care providers have struggled to keep pace with this change [1]. Canonical approaches to teaching genetics are not necessarily appropriate for the next generation of providers, who will be expected to implement genomic approaches in the clinic [2]. At the same time, patients increasingly have access to personal genomic information that has the potential to empower them to engage with clinicians and to collaborate on improving their health. Given this situation, how can we equip the provider workforce to meaningfully respond to patients’ needs?

A cross-disciplinary team of faculty and staff members of the Duke University School of Nursing and the Duke Center for Personalized and Precision Medicine developed a formal genomics and personalized medicine curriculum for providers, which consists of 2 specialty electives designed for entry-level and advanced students in nursing and other health professionals. These interdisciplinary courses foster professional development and applied learning in key content areas. The focus of the courses is on clinical applications of genomics for the prevention, prognosis, and treatment of complex disease states; optional personal genome testing is made available through an online provider as an experiential learning tool. Overarching themes include ethical and social considerations relating to genome-based information and implications for personal health, public health, and public policy. The courses, which address all core competencies in genomics and genetics for nurses [3] and medical professionals [4] (eg, risk assessment, genetic testing and counseling, clinical management, and ethical implications), focus on underlying genomics concepts, communication with patients, and resources for evaluating technologies and calculating risk [1].

Rather than offering a traditional review of technologies within disease states (eg, cardiovascular risk, cancer, diabetes), the courses take a concept-based approach, discussing topics such as heterogeneity, oligogenicity, and gene-environment interactions. The courses also provide relevant examples from current literature. Classroom exercises build skills in evaluating the clinical validity and utility of genomic applications. Students emerge armed with real-world skills in using genomic applications and personalized medicine approaches, as well as an understanding of the implications of genomic technologies for society.

Students are given an opportunity to evaluate their own genomes and to gain personal experience with genomic testing through optional, subsidized personal genome testing integrated into the curriculum. Similar approaches have been used to educate graduate and medical students [5-9] and have led to improved learning outcomes [9]. Duke learners also are provided with mock genome profiles that they can substitute for, or use to supplement, their own profile. The personal genome platform serves as a touchstone throughout the courses as students explore different contexts of genomic information, from risk perception to ethical concerns.

To address concerns regarding the inclusion of students’ personal genomes as an educational component [6, 10], the following measures were taken and reviewed with an external advisory board: confidentiality of participation; discussion of ethical, legal, and social considerations of direct-to-consumer genetic tests; a requirement that all instructors and students sign confidentiality statements; institutional review board assessment of social science research on the utility of personal genomes in the classroom; establishment of an external advisory board to handle unexpected stress or troubling outcomes; and provision of subsidized telephonic genetic counseling through a third party. The curriculum also establishes foundational principles before students receive their personal genome reports.

In the pilot offering, students unanimously reported that the experiential learning approach enhanced the lessons, noting the advantage of self-reflection within the classroom and acknowledging that both scientific and ethical concepts were reinforced with the personal context.


The challenges of translating genomic technologies into health care practice require novel approaches to educate existing and future health care providers. The future provider workforce must be armed with core principles of genomics, the ability to critically evaluate applications, and familiarity with the implications of genomic information in social and personal contexts. Experiential learning via a personal genome analysis can reinforce these concepts. Pedagogical approaches using personal genome testing of health care providers are likely to be beneficial when the focus of the course is on critical evaluation of dynamic concepts in human genomics. NCMJ

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