Medication Selection by Genotype

By Cynthia A. Prows, MSN, RN, and Daniel R. Prows, PhD

How genetics is changing drug prescribing and efficacy.

Genetic testing has been used in some settings to take the guesswork out of predicting how a person will respond to a medication, and such screening will become more common in the coming decade. This will be especially useful with regard to drugs that are expensive or highly toxic or have a narrow therapeutic range. And as medication prescribing based on genetics becomes a clinical reality, nurses will help patients understand the benefits, limitations, and risks involved.

Currently, most medications are prescribed without assurance of efficacy in a given individual. Often, several drugs must be tried to find one that works. Adverse drug reactions are prevalent and account for hospital expenditures estimated at up to $5.6 billion annually. Thus, there has been strong interest in research in this area, not only in medicine, science, and academia, but also within the pharmaceutical and health insurance industries. An increasing number of academic centers are receiving federal grants for such research. Major pharmaceutical companies have developed research programs as well, having clear financial incentives for taking genetics into account in drug development, as well as for resurrecting medications previously recalled because a few patients experienced rare but severe adverse reactions. And third-party payers are studying the cost-savings potential of genetic testing before drug selection.

REVIEW OF TERMS AND CONCEPTS

If you’re very familiar with the terminology of genetics, you may not need to read this section. If not, here is a brief overview.

The nucleus of every human cell contains 23 pairs of chromosomes: 22 pairs of autosomes (non–sex chromosomes) and one pair of sex chromosomes. Each chromosome consists of a double-stranded helix molecule of DNA tightly coiled around specific proteins. DNA is made up of chemical subunits called nucleotides, the building blocks of genetic material. Each nucleotide consists of a chemical base—adenine (A), thymine (T), cytosine (C), or guanine (G)—attached to a sugar and phosphate molecule. Each strand of nucleotides within a DNA molecule is arranged in a sequence that’s unique to each chromosome pair. A gene is a segment of DNA, at a specific position on a chromosome, that encodes (directs production of) a specific protein or regulates the function of other genes. Each pair of autosomes contains the same genes, although the sequence of them can vary. All of the genetic information contained in any organism is referred to as its genome. In April 2003 the National Human Genome Research Institute (www.genome.gov) announced that one of the Human Genome Project’s goals had been achieved: to determine the exact sequence of the more than 3 billion nucleotides contained within the human genome.

The most common form, or allele, of a gene found within a population is known as the wild-type allele. Alternate forms result from a change in the gene’s chemistry or structure. Genotype refers to

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a person’s specific allelic composition. Phenotype refers to the observable or measurable manifestation of a person’s genotype, either by itself or in coordination with environmental factors. Note that genotype can also refer to a pair of alleles at a specific location (locus) on the chromosome pair in a person’s DNA; phenotype then refers to the resulting expression.

It’s estimated that 99.9% of the human genome sequence is identical in all individuals, despite observable differences. Differences in the human genome, or DNA alterations, are called mutations if they are rarely found within a population and polymorphisms if they are more common (that is, found in 1% or more of a population). In the mainstream media, a gene alteration is often called a mutation if it’s associated with a disease or disorder and a polymorphism if it has no observable or measurable effect. But strictly speaking, both mutations and polymorphisms can have no effect, a beneficial effect, or cause a disease. A single-nucleotide polymorphism (SNP; pronounced “snip”) involves a replacement of one nucleotide base (A, T, C, or G) with any one of the other three. SNPs are common, albeit slight, variations in human DNA, occurring at a rate of about one in every 300 to 1,000 bases. A collection of all significant SNPs for a given individual is called a SNP profile. These profiles are being heralded as a way to scrutinize the genetic bases for various diseases and conditions and to help clinicians predict a patient’s response to a drug.

In this article, three aspects of medication selection by genotype are discussed: medications targeting “gene products,” medication selection by allele, and medication selection by SNP profile.

**MEDICATIONS TARGETING GENE PRODUCTS**

It takes years of intensive research to screen existing drugs or identify new drugs that target specific gene products—biochemical materials, such as proteins, that result from gene expression. First, researchers must locate the wild-type allele of a gene associated with a specific disorder and determine its nucleotide sequence. (Researchers are looking at genetic associations for all types of diseases: those that are known to be inherited, single-gene disorders, such as cystic fibrosis and sickle cell anemia, as well as adult-onset disorders, such as diabetes, hypertension, and asthma, associated with more complex genetics.) In locating and sequencing the wild-type allele for a particular disorder, researchers often detect specific mutations of this allele in people with the disorder. Once mutations have been identified, development of a test to detect these mutations is possible, although it may be available only on a research basis.

Most drugs are used to treat the clinical signs and symptoms of a disease (that is, according to phenotype). The availability of drug prescription on the basis of genotype lags well behind that of genetic testing. It can take more years of research to identify the protein resulting from the expression of a particular wild-type allele and to determine its function. Once a normal protein and its function have been identified, the altered form of that protein can be investigated. Disease-causing alleles usually result in altered protein structure, function, produc-
tion, stability, or a combination of these. How a specific mutation affects the protein depends on the nature of the mutation and where in the gene sequence it occurs. And only after the consequences of the mutation have been determined can researchers identify or develop therapies that modify, inhibit, or replace the abnormal protein.

Consider the following two diseases, chronic myeloid leukemia and cystic fibrosis, and the standard treatments—drugs prescribed according to phenotype—and the newer ones—drugs prescribed according to genotype.

**Chronic myeloid leukemia (CML),** a blood disorder, is characterized by the presence of large numbers of mature myeloid cells in the peripheral blood and bone marrow. In 1960 a unique chromosomal structure, called the Philadelphia chromosome after its place of discovery, was associated with the malignant granulocytes found in most cases of CML. The Philadelphia chromosome, which can be detected through a now-routine test known as a karyotype (chromosome study), occurs as a result of an exchange of DNA segments on chromosomes 9 and 22. Specifically, the transfer of the ABL gene sequence found on the chromosome 9 segment to the BCR gene on the chromosome 22 segment creates a BCR-ABL fusion gene (see Figure 1, page 63). This gene encodes a BCR-ABL protein; cells containing this abnormal protein continue to divide even after exposure to multiple genotoxic drugs. Eventually, these leukemic clones lose the ability to differentiate, and the disease progresses to an acute stage known as blast crisis. The blast crisis is highly resistant to standard treatment, which may include administration of interferon alfa with or without cytarabine (Cytosar-U), allogeneic stem-cell transplantation, or both. In patients in blast crisis, the rate of complete remission with standard chemotherapy is less than 10%, and the five-year survival rate is only 6% with allogeneic stem cell transplantation. These treatments target the phenotype—the large numbers of myeloid cells.

Once researchers had identified the disease-associated BCR-ABL gene, the BCR-ABL protein (the gene product), and the protein's mode of dysfunction, it was possible to develop a drug that targeted that dysfunction. In searching for a treatment specific to genotype, researchers found that a previously manufactured chemical compound known as ST1571 inhibited cell division in the CML clones that express the BCR-ABL protein but did not affect growth of normal cells. ST1571, now called imatinib (Gleevec), has been approved for clinical use. As with many other genotoxic anticancer drugs, cellular resistance to imatinib may develop.

The treatment of CML has provided a benchmark for other genotype-directed cancer therapies that are in various phases of clinical trials.

**Cystic fibrosis** is another condition for which current treatment focuses on managing recognizable manifestations (phenotype). An autosomal recessive disorder, cystic fibrosis is characterized by hypersecretion of thick, sticky mucus from exocrine glands. The organs most affected are the lungs and the pancreas. The mucus provides an ideal medium for bacterial colonization, resulting in chronic pulmonary infection. Inhaled mucus thinners, bronchodilators, and recombinant human deoxyribonuclease, a bioengineered enzyme that has been shown to reduce mucosal viscosity, are used to help clear sputum. Antiinflammatory medications are prescribed to decrease inflammation that, if left uncontrolled, can lead to airway damage and infection. Intravenous and aerosolized antibiotics are given to treat pulmonary infections. Pancreatic insufficiency is treated with nutritional supplementation, including oral fat-soluble vitamins and oral pancreatic enzyme replacement therapy.

In 1989 the cystic fibrosis transmembrane conductance regulator (CFTR) gene was identified. The wild-type CFTR protein was found to function as a chloride channel in the membrane of epithelial cells. The investigators found that people with cystic fibrosis have two altered CFTR alleles (one inherited from each parent). Subsequently, researchers determined that the most common CFTR mutation, ∆F508 (read as “delta-F508”), results in a protein that cannot be properly folded in the endoplasmic reticulum. Despite this abnormality, studies indicate that the protein can still function as a chloride channel; however, the cell's natural “quality control” mechanisms recognize the protein as abnormal and destroy it before it ever reaches the cell membrane.

Clinical studies indicate that a new class of drugs known as small-molecule “chaperones” may provide genotype-directed treatment of cystic fibrosis. Although the exact mechanism varies by specific molecule, these chaperones can stabilize misfolded proteins, correct the folding defect, guide the proteins to the cell membrane, or perform a combination of these. Most studies of small-molecule chaperones have focused on targeting the ∆F508 protein. At the time of this writing, clinical trials were recruiting patients with cystic fibrosis for various studies involving small-molecule chaperones.

Two differences between CML and cystic fibrosis are worth noting. First, in Philadelphia chromosome–positive (Ph+) CML, the disease is linked to a specific chromosomal alteration that creates a gene not normally found in the body, whereas more than 1,000 CFTR gene mutations have been associated with cystic fibrosis. Pharmacologic studies have primarily focused on the ∆F508 protein because about 67% of patients with cystic fibrosis are homozygous for ∆F508 (both CFTR alleles have...
Pharmacogenetics is the study of genetic differences in the alleles associated with individual variability in drug response. Patients with the same diagnosis respond differently because of allelic difference: in this example, the normal gene sequence is GCCCAGCTC but the mutation gene sequence is GCCCAGGTC. The AGC in the sequence of the normal gene codes for serine, but the AGG in the mutation gene’s sequence codes for arginine. The substitution of arginine for serine in the drug-metabolizing enzyme molecule will cause the enzyme to be less effective or ineffective; this person is considered a “poor drug responder.” The practice of pharmacogenetics involves genotyping patients and treating those who would be “poor drug responders” with a drug other than the conventional drug or with a different dosage.

And second, CML results from a genetic alteration that occurs after conception, whereas CFTR mutations are inherited. Sometime after conception, the translocation that creates a Philadelphia chromosome occurs spontaneously during cell division of a myeloid stem cell and is subsequently perpetuated in all of that cell’s clones. Because imatinib specifically targets cells with the BCR-ABL gene, treatment can eradicate only those cells from the patient with CML. If the presence of BCR-ABL genes drops to nondetectable levels, this treatment may be discontinued. In contrast, patients with cystic fibrosis have inherited disease-associated CFTR alleles from both parents; all of the cells contain the mutations. The small-molecule chaperones used to treat cystic fibrosis target the proteins of specific genotypes but do not change the genotype. Consequently, treatment for cystic fibrosis that’s based on genotype will likely be administered throughout a patient’s life.

Nursing implications. You may be asked to obtain a DNA sample from a patient for analysis before medication is prescribed. DNA can be obtained from blood or from a buccal swab.
These two pages highlight the three possible metabolic outcomes (A, B, and C) of medications given as active drugs (this page) or as prodrugs (facing page); the therapeutic effect depends on the activity level (based on the patient’s genotype) of the relevant drug-metabolizing enzyme.
The metabolism of prodrugs also depends on the patient’s enzyme activity level, but the therapeutic effects in the three metabolic outcomes differ from those of active drugs because prodrugs must first be metabolized to their active forms.
Resources for Locating Genetics Professionals

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Although buccal swabbing is less painful for patients than drawing blood is, laboratories prefer blood because the quality and quantity of the extracted DNA are often better. Preferences and details for packaging and sending a DNA sample will need to be obtained directly from the laboratory you will be using. GeneTests (www.genetests.org), a publicly funded resource, provides a directory of laboratories that provide clinical or research-based genetic testing or both.

Education is crucial. Understanding the difference between phenotype and genotype will allow a nurse to describe why two patients with the same condition may present differently. A patient may ask why a genetic test is being done before therapy begins and after diagnosis is made, or why a new medication is being given to some, but not all, patients with a particular condition. For example, to the above questions, your response might be, “The drug is only effective in people whose illness is caused by certain genetic changes. Your physician has ordered the test, and the results will show us whether you can benefit from this drug.” Patients may also ask about potential side effects. Cancer therapies based on genotype are directed at cells that contain specific, disease-associated genetic alterations, whereas standard chemotherapies affect all dividing cells. Experience with imatinib indicates that adverse effects are not as severe as with interferon therapy. The type and severity of possible adverse effects for small-molecule chaperones is unclear; clinical trials are in the early stages.

The National Coalition for Health Professional Education in Genetics (www.nchpeg.org) notes that it’s important for all health care professionals “to recognize the limitations of their own genetics expertise.” When you find you can’t answer patients’ questions, refer them and, if appropriate, their family members to genetics specialists.

**MEDICATION SELECTION BY ALLELE**

**Drug metabolism and therapeutic effect.** Several factors determine the therapeutic effect of a medication. After a drug is administered, it must be absorbed; the drug’s physical properties, as well as the patient’s age, diet, health, and use of other drugs can influence absorption. The drug must then be distributed throughout the body, which requires the coordinated functioning of various proteins, including metabolic enzymes, trafficking proteins, receptor proteins, and others.

Medications can enter the body as either active drugs or inactive prodrugs. Most drugs are metabolized in the liver to make them more water soluble for subsequent elimination through the kidneys or intestines. Prodrugs require metabolic conversion, or biotransformation, to liberate the active compound. Complete biotransformation of any one drug typically requires several different enzymes. Pharmacogenetics is the study of allelic differences associated with individual variability in drug response. The ultimate goal is to determine, through genetic testing, what drug and drug dosage will be most effective in a patient, so that the drug can be prescribed safely from the outset of treatment. Thus far, most research in pharmacogenetics has focused on alleles that produce proteins (usually enzymes) involved in drug metabolism.

A mutation or polymorphism in a gene that encodes such an enzyme can affect drug metabolism. The patient may metabolize certain drugs inefficiently and may show little or no measurable effects (such patients are sometimes referred to as “poor metabolizers”), or the patient may metabolize certain drugs too rapidly and may show toxic effects (such patients are sometimes called “ultrarapid metabolizers”). The actual clinical effect of a given genetic alteration depends on which enzyme has been affected and whether it’s a major metabolizer of the drug given to the patient. A person can be a poor metabolizer of drugs transformed by enzyme A, an extensive (normal) metabolizer of drugs transformed by enzyme B, and an ultrarapid metabolizer of drugs transformed by enzyme C.

Moreover, with either poor or ultrarapid drug metabolism, very different pharmacologic outcomes are possible, depending on the activity status of the drug administered (that is, whether the medication given is a prodrug or is active). For example, consider the variable clinical effects seen with medications containing codeine, a prodrug. Once absorbed, codeine is broken down in the liver into several products including morphine, which is thought to produce the pain-relieving effect. The main liver enzyme involved in converting codeine to morphine is known to be highly polymorphic. Mutant alleles for this enzyme can produce excessive enzyme, deficient enzyme, or none at all. Patients who are ultrarapid metabolizers have multiple copies of an allele at one locus, which results in excess enzyme production and activity. Such a patient who receives a typi-
nal dose of codeine may experience symptoms of narcotic overdose (such as severe abdominal cramp-
ing, constipation, and respiratory depression) as the drug converts rapidly to morphine. Patients who have a pair of alleles resulting in deficient or absent enzyme have a decreased ability to convert codeine to morphine. Such patients will get little to no relief from a normal dose of codeine, although they should benefit from morphine and other morphine-derived pain medications.

Other drugs, metabolized by the same enzyme that breaks down codeine, may have different clinical effects when given in active form. With these drugs (which include many antidepressants and antihypertensives), patients who are ultrarapid metabolizers may show little benefit, because the active drugs are metabolized to their inactive components before they can have a therapeutic effect. Yet given these same drugs, patients who are poor metabolizers may experience adverse effects at normal dosages and even at low dosages because the active drugs accumulate.

Examples of much-studied classes of drug-metabolizing enzymes include the cytochrome P-450s (CYPs), the N-acetyltransferases (NATs), and thiopurine methyltransferase (TPMT). CYPs mainly catalyze oxidative reactions that transform most lipophilic drugs into metabolites, which in turn often require further biotransformation by other enzymes. A patient’s response to a given medication depends on which CYP enzyme is altered and what that enzyme’s role is with regard to that medication. The prevalence of poor metabolizer and ultrarapid metabolizer phenotypes varies by race and ethnicity. One or more CYP enzymes are responsible for metabolism of up to 50% of all medications.

Genetic tests for some CYP enzymes are commercially available in various laboratories and, in a few instances, are being marketed directly to consumers on the Internet. Warfarin is a good example of a CYP-metabolized medication for which genetic testing may have significant utility; it has a narrow therapeutic range and serious adverse effects can result from overdosing. However, it’s critical that patients understand that genetic testing is not comprehensive. Laboratories are not seeking to identify all possible polymorphisms or mutations in a specific CYP gene; the process for doing so is still too labor intensive and costly. Rather, they are testing only for the most common gene alterations associated with either poor or ultrarapid metabolism. Thus a negative test result simply means that the alterations for which the test was done are not present. It’s possible that the gene contains unidentified polymorphisms or mutations that affect drug metabolism.

NATs catalyze the transfer of an acetyl group to particular drugs, thus increasing their water solubility and enhancing renal excretion. Two functional NAT proteins, NAT-1 and NAT-2, are known: NAT-1 metabolizes p-aminosalicylate and p-aminobenzoic acid, and NAT-2 metabolizes isoniazid and other antiinfectives, some cardiovascular agents, caffeine, and numerous miscellaneous drugs. Patients with mutations or polymorphisms in NAT genes that result in slower acetylation can experience high serum concentrations of a drug and related toxic effects. The prevalence of variant NAT alleles varies by race and ethnicity. Although genetic tests for the NAT genes exist, these are still being studied and are rarely used in clinical practice.

TPMT is involved in the metabolism of thiopurine agents, including azathioprine, used to treat rheumatoid arthritis or to prevent rejection of transplanted organs, and mercaptopurine, used to treat pediatric acute lymphoblastic leukemia or steroid-resistant inflammatory bowel disease. Thiopurines, which are inactive prodrugs, are first catalyzed by the enzyme hypoxanthine phosphoribosyl transferase to thioguanine nucleotides, which then exert the desired cytotoxicity. TPMT then catalyzes the transfer (addition) of a methyl group to these nucleotides, thus inactivating their cytotoxic effects. Of the eight variant TPMT alleles that have been identified, three account for nearly 95% of cases of intermediate or low enzyme activity. A recent literature review noted that intermediate TPMT activity occurs in 10% of the white and African American populations in the United States, and low or undetectable TPMT activity occurs in just one in 300 (0.3%). Genetic testing for variant TPMT alleles is clinically available and is being used in select clinical settings.

In some clinical settings, prospective determination of functional TPMT status is preferred to using body weight in calculating dosages of routinely used thiopurine drugs, which are highly toxic and have a narrow therapeutic range. It has been recommended that patients who are heterozygous for a low enzyme–activity allele begin thiopurine-based therapy at 65% of standard dosage. Patients who have inherited two altered TPMT alleles, which encode nonfunctional TPMT enzyme, will accumulate excessive cellular concentrations of thioguanine nucleotides. This accumulation predisposes them to life-threatening toxicity. It’s recommended that these patients start therapy on 6% to 10% of the standard thiopurine dosage.

Nursing implications. When patients fail to reach therapeutic levels of a drug at the recommended dosage, they may erroneously be labeled noncompliant. If the drug is a morphine derivative, they may be labeled “narcotic seekers” when they complain of needing more medication for pain relief. Although such behaviors can influence the therapeutic or toxic effects of a drug, they must not
be the only possibilities considered when a patient’s response to pharmacotherapy is unexpected. Nurses need to learn which of the drugs commonly administered in their practice are metabolized by CYP, NAT, or TPMT enzymes and to consider genetic factors when an unusual patient response to medication occurs.

Nurses should make sure their patients understand that genetic test results don’t fluctuate. Whatever genetic alterations exist will remain present for a lifetime, as will their ramifications. And because alleles are inherited, the patient’s test results may have consequences for descendants as well.

A nurse should determine whether a patient has had any genetic tests done for the purpose of predicting medication response. If so, the nurse will check the documentation, which specifies which alleles were tested and what the results imply regarding the drug now being considered, ordered, or prescribed for this patient.

MEDICATION SELECTION BY SNP PROFILE

SNP profiling, a new technology, may resolve some of the technical limitations of single-gene testing used in pharmacogenetics. SNPs are the most basic and common type of DNA polymorphism in the human genome. As of February, the SNP Consortium, a public–private collaboration among some 15 biotechnology and pharmaceutical companies and the Wellcome Trust (see http://snp.cshl.org), had discovered and characterized nearly 1.8 million SNPs. Many SNPs have no effect on cell function, but others may predispose one to disease or influence drug response.

SNPs are dispersed throughout the human genome—gene and nongene regions alike. Those within genes are more likely to affect protein function. Because the gene regions containing SNPs close to an altered gene will tend to travel together during cell division, all SNPs within and near the gene of interest are valuable as genetic markers for mapping and screening purposes.

One of the most important uses of SNP data will be in screening a patient to determine the effectiveness of specific medications and their potential for causing adverse reactions in that patient. Pharmacogenomics is an area of research that focuses on patterns of genome variations, such as SNPs, that occur within or near genes associated with drug response. Based on one blood or buccal sample, a patient’s SNP profile will permit analysis of how multiple genes are involved in a patient’s response to a particular medication. Understanding how drug response (phenotype) and SNP profile (genotype) are associated can be expected to benefit patients; but as Rioux noted recently, “pharmacogenomics cannot improve the efficacy of a given drug; it simply helps in selecting patients who are likely to respond well.” Pharmacogenomics can also be used to identify groups of patients most likely to experience drug efficacy in clinical trials. SNP data will also help to identify disease-associated genetic alterations and thus yield new targets for drug development, to refine the drug development process, and in the discovery of new diagnostic tools and methods.

To accommodate the expected rise in use of SNP profiles, automated instruments capable of processing many samples simultaneously have been developed. Computer programs and database systems have been revised and expanded to support the collection, organization, and analysis of large amounts of genetic and other biologic data (the discipline is known as bioinformatics).

Microarray technology, named for its use of DNA microarrays, or “chips,” can provide high-output, accurate screening of SNP profiles across the entire genome. This field of research is extremely competitive, and advances are occurring rapidly. DNA microarrays for use in SNP detection are commonly formed by fixing single-stranded DNA fragments, called probes, to a glass slide. The probes, which are designed from target DNA sequences that contain known SNPs, include the complementary sequences for all possible variations of each known enzyme polymorphism. A patient’s DNA sample is then processed into target-sequence segments; these are labeled fluorescently to render them visible. The microarray chip is incubated with the patient’s processed DNA, and the sample target-sequence segments bind to the complementary, fixed probes on the chip. A scanning microscope assesses the fluorescence of the bound DNA. The fluorescent patterns (colors and brightness) of each dot are analyzed and statistically associated with a disease state, a particular drug response, or another phenotype.

Technologic advances in SNP profiling have occurred rapidly. But further improvements must be made before SNP profiling can become clinically useful. Achieving consistently high quality and test–retest reliability of the microarrays has proved difficult. Higher output capability is needed to handle the 60,000 to 600,000 SNPs required to profile the entire genome of a single patient. And the use of microarrays in whole-genome SNP profiling is still expensive. Identification of each SNP in a profile costs about $0.35 to $1; for the test to be affordable, the cost should be significantly less than a penny per SNP in a patient’s genome profile.

Nursing implications. Although medication selection by genotype holds much promise, it also presents new challenges for nurses. First, as new treatments for CML and cystic fibrosis exemplify, medications selected on the basis of genotype will be offered only to patients who have that genotype. This is quite different from the standard approach
to medication, in which newly developed drugs are made available and marketed for all patients with the same clinical diagnosis. A patient may have difficulty accepting that a drug isn’t being offered because a genetic test indicates it will be ineffective or unsafe for him—especially if he knows that others with the same diagnosis and similar symptoms are benefiting from the drug or if few effective alternatives exist. Without an understanding of how a genetic alteration can affect drug metabolism, the patient might claim discrimination. The nurse will need to explain how pharmacotherapy based on genotype differs from that based on phenotype, and to be ready to offer considerable support.

The language of genetics presents challenges for clinicians. For example, the categories “responder” and “nonresponder” are often used to describe patients according to pharmacogenetic or SNP profile results. Will patients labeled nonresponders be considered deficient? Will nonresponsiveness be thought of as akin to a disease state? If SNP profiling becomes affordable and clinical utility is established, testing an individual’s entire genome early in life may be proposed as part of a preventive strategy. The results might also be used to determine a patient’s responsiveness (or lack thereof) to certain types of drugs before a need arises.

Will being labeled a nonresponder affect a patient’s insurability by influencing risk calculations made by insurance actuaries? Although such information will be valuable to clinicians, a patient whose SNP profile suggests he’ll be nonresponsive to numerous medications may be reluctant to have employers or insurers to know this. Yet insurers may seek to make pharmacogenetic testing or SNP profiling a requirement before they agree to cover a drug that’s expensive, significantly toxic, or known to be ineffective in a population subset.

Patients must participate in decisions about genetic testing,10,41 which is just emerging as an adjunct to standard considerations (such as weight, age, and kidney function) in the selection and prescription of medications. Although commercially available, pharmacogenetic testing for alleles associated with drug metabolism is not yet standard practice, and pharmacogenomic testing using SNP profiles is still being developed in research laboratories. Research into the genetic basis of various adult-onset diseases (such as Alzheimer disease, Parkinson disease, diabetes, and cardiovascular disease) is ongoing. It’s conceivable that genetic alterations associated with drug response may also be found to play a role in the development of one or more such diseases. Test results will be documented in the patient’s medical record. If a known gene alteration is later linked to increased risk of developing a given disease, will the patient want to know? This possibility should be discussed with patients when they are deciding whether to undergo genetic testing. It’s important to ask the patient, “Do you want to be contacted if your genotype is found at a later time to be associated with a condition for which you weren’t originally tested?” If so, whose responsibility will it be to discuss this with him? Will he need referral to a genetics professional? Questions for clinicians include: How can we ensure that a patient’s genetic test results remain private but accessible, in the event that new information about a genotype warrants contacting him? And who will be responsible for contacting such patients?

It’s not too early to start looking for answers.▼

REFERENCES


