7

PHARMACOGENOMICS AND MOLECULAR TESTING

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OBJECTIVES

After completing this chapter, the reader should be able to

- Define pharmacogenetics
- Differentiate germline and somatic mutations
- Understand the use of molecular testing in pharmacogenetics/genomics as tools for personalizing therapy
- Describe the difference between empirical pharmacotherapy and genotype-enhanced pharmacotherapy
- Understand how pharmacogenetics can enhance therapeutic drug monitoring
- Assess the utility of genotype in addition to other patient-specific factors for specific medications in the provision of pharmaceutical care
- Discuss the role of laboratory medicine in pharmacogenetics in terms of turnaround time, interpretative reporting, and assay performance

PHARMACOGENETICS

As early as the 1950s, the heritable nature of drug response was noted for agents such as succinylcholine, isoniazid, and primaquine.[1-3] Later, twin studies confirmed this heritability by showing that the half-lives of some drugs were tightly correlated in monozygotic twins and had little correlation in dizygotic twins.[4] Since that time, the fields of pharmacogenetics and pharmacogenomics have taken off, and the genetic basis for variability in drug metabolism, transport, and pharmacodynamic effect is increasingly being appreciated. In fact, pharmacogenetic and molecular tests are routinely used in therapeutic areas such as hematology/oncology, and their usefulness is being explored in every major therapeutic drug class.[5]

Pharmacogenetics/pharmacogenomics is the translational science of correlating interindividual genetic variation with variability in drug response. Historically and practically, the terms *pharmacogenetics* and *pharmacogenomics* have been used interchangeably (as in this chapter). However, definitions may vary depending on the context. For example, pharmacogenetics can be seen as the study of variants in a handful of candidate genes. Contrarily, because of our expanding technological ability to simultaneously investigate millions of variants across the human genome using genome-wide genotyping arrays or high-throughput sequencing, pharmacogenomics may refer to genome-wide investigation of drug response variability.

Pharmacogenetics seeks to avoid adverse drug reactions and improve clinical efficacy, providing personalized medicine to patients, much the same way therapeutic drug monitoring by serum drug concentrations customizes certain medication regimens for individual patients. One goal of pharmacogenetics is to refine the current empirical approach to drug therapy management so that it is less "trial-and-error" in nature. There are often many drug classes available to treat a given condition, and several drugs within each of those classes that a clinician may opt to use. This large armamentarium of drug therapy choices can lead to an inefficient, time-consuming management strategy in which the therapeutic decision is based on little more than clinician preference. Another goal of pharmacogenetics is to provide the appropriate dose to individual patients so that the "one dose fits all" strategy is avoided. Incorporating the results of genetic tests along with nongenetic factors (e.g., age, sex, smoking status, interacting drugs, and others) into pharmacotherapy decision making may help streamline this process such that the likelihood for response is maximized while the chance of toxicity is minimized.[6]

Understanding the results of molecular tests that are used in the application of pharmacogenetics is of critical importance to healthcare providers if this form of personalized medicine is going to improve patient care. Many institutions are attempting to implement preemptive genotyping so that results will be in the electronic medical record before a particular drug with a useful genetic test is prescribed. Furthermore, direct-to-consumer genetic tests are already available to patients, regardless of whether or not they have been proven to improve care. Despite the

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great promise of personalized medicine, the field is changing very rapidly and exactly how and when tests should be applied clinically is still very much a work in progress. Therefore, this chapter will focus on pharmacogenetic laboratory tests that are FDA-approved, used commonly in clinical practice, or are most likely to be incorporated into clinical practice in the near future.

Presently, organizations such as the National Academy of Clinical Biochemistry (NACB) have established practice guidelines for the application of pharmacogenetics in the practice of laboratory medicine.[7] Coordinately, clinical pharmacology groups such as the Clinical Pharmacogenetics Implementation Consortium (CPIC) have published practice guidelines for specific drug/gene pairs with clinical importance as data become available.[8] Taken together, guidelines from these organizations and others will likely be useful in bringing together the fields of laboratory medicine and clinical pharmacology in the application of pharmacogenetics. An overview of such guidelines and their implications will be discussed.

Pharmacogenetic Testing Versus Disease Genetic Testing

Although laboratory testing for pharmacogenetic and genetic polymorphisms/mutations will yield the same general types of results, the target populations and how the test results are used may be in principle quite different. Clinically used pharmacogenetic tests provide information that may aid in selection or dosing of medications. Therefore, individuals receiving pharmacogenetic tests will typically be candidates for a particular therapeutic agent. Individuals receiving disease genetic tests, on the other hand, will usually be those who are healthy (e.g., for screening purposes), or at risk of developing or are suspected of having a particular disease or condition.

Historically, pharmacogenetic testing has been considered to have fewer ethical issues surrounding it than disease genetic testing.[9] However, while this is still generally considered to be the case, the risks of pharmacogenetic testing also have been outlined and a framework created to ensure appropriate delivery of pharmacogenetic information in the healthcare system.[10] This framework outlines three major considerations regarding whether a particular pharmacogenetic test raises ethical issues: whether the genetic variant is inherited or acquired, whether the goal of testing is to address a specific clinical question or to provide information for future clinical care, and whether the test reveals ancillary clinical information (e.g., disease risk).[10]

Pharmacogenetics and Personalized/ Precision Medicine

Pharmacogenetics offers one piece to the puzzle of personalized or precision medicine. Personalized medicine seeks to tailor medical therapy to individual characteristics of patients. It can include genetics information, as in pharmacogenetics, or any other molecular analyses (such as metabolomics, proteomics, etc.). This chapter will focus on pharmacogenetics as a means of providing personalized medicine.

DRUG DISPOSITION-RELATED MOLECULAR TESTS

Pharmacokinetics is concerned with the fate of drugs or other substances once administered and studies the rate and extent of **a**bsorption, **d**istribution, **m**etabolism, and **e**xcretion (ADME). As early as the 1950s, it was noted that a great deal of interpatient variability existed in the pharmacokinetics of many drugs. One common source of interpatient variability occurs in drug metabolism. Drug disposition reactions can be divided into phase I, phase II, and phase III reactions. Phase I reactions typically involve processes such as oxidation, reduction, and hydrolysis of compounds and are typified by hepatic cytochrome P450 (CYP) drug metabolism. Phase II reactions include conjugation or synthetic reactions such as glucuronidation, sulfation, methylation, acetylation, and others. The purpose of phase II metabolism is to make compounds more water-soluble and facilitate excretion. Finally, phase III reactions are characterized by transport protein-mediated cellular efflux of drugs usually at the level of the gut, liver, kidney, and highly sequestered tissues. Genetic variability occurs in each of the above phases of drug disposition (**Figure 7-1**).

Cytochrome P450 System

Although many of the genes encoding CYP enzymes are highly polymorphic, *CYP2D6, CYP2C9,* and *CYP2C19* have genetic variations (polymorphisms), which can describe fairly predictable distributions of drug concentrations, making them clinically relevant for some pharmacogenetic tests. Metabolizer status can be described as extensive (i.e., "normal"), intermediate, poor, or ultrarapid based on the presence or absence of gene variations. This genotype–phenotype relationship could help identify poor metabolizers likely to experience side effects (or therapeutic

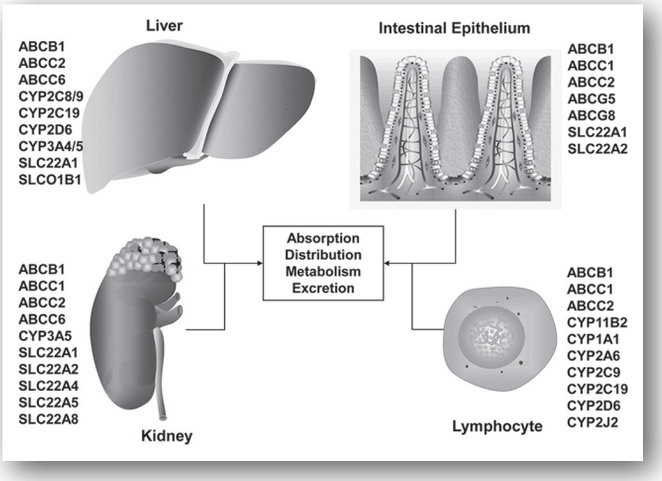

FIGURE 7-1. Sample polymorphic genes involved in drug pharmacokinetics. Polymorphic genes involved in drug pharmacokinetics are listed next to organs involved in drug absorption, distribution, metabolism, and excretion. VisiScience, Inc. software was used in the creation of the image.