

THE ERA OF PERSONALIZED MEDICINE

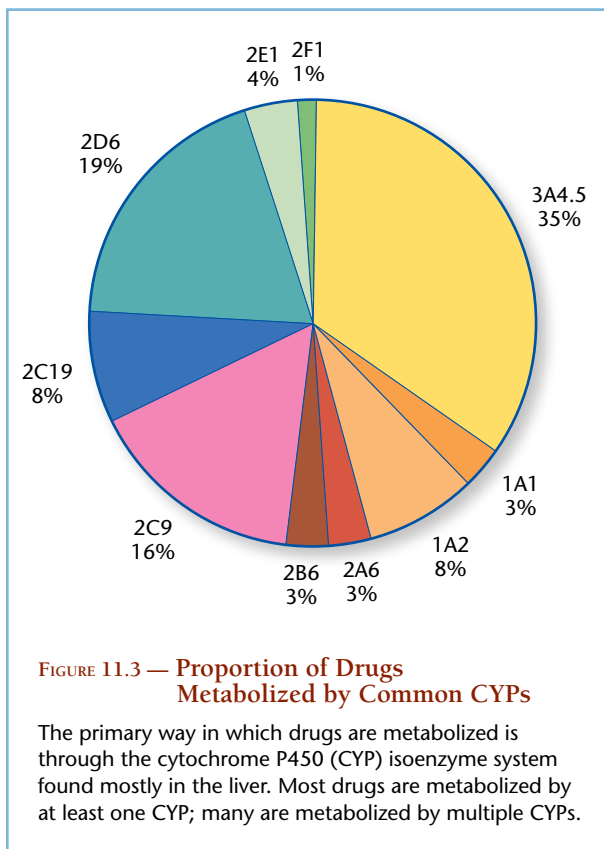
Given the ability of modern science to easily detect and evaluate the effects of these SNPs on human health, an era of what is being referred to as “personalized medicine” is evolving. Two areas where this is happening rapidly are pharmacogenomics and nutrigenomics.

PHARMACOGENOMICS

The conventional approach to pharmacotherapy is for physicians to prescribe drugs for an individual based on population studies and clinical trials. If a particular drug was not effective or had undue side effects, the dosage may be adjusted or another drug used. Finding an effective drug and dosage may, therefore, take several months. Physicians must rely heavily on their clinical experience and population-based studies. Therapeutic drug monitoring in blood has been used for years to guide clinicians in cases where maintaining safe and effective blood levels for the patient were critical and achievable. On the other hand, if clinicians could predict which drug would be effective and at what dose, then pharmacotherapy could be individualized. This is the goal of pharmacogenomics.

Pharmacogenomics testing attempts to predict how an individual will respond to a drug based on their genetic makeup. The two main areas to which pharmacogenomics can be applied are drug metabolism and responsiveness. The primary way in which drugs are metabolized is through the cytochrome P450 (CYP) isoenzyme system found mostly in the liver. Most drugs are metabolized by at least one CYP; many are metabolized by multiple CYPs. Specific dosing guidelines based on pharmacogenetic data are being developed and are beginning to appear in the literature to predict adverse drug reactions (ADR).³ Genotype-based dosage guidelines have been published for a number of drugs.⁴⁻⁷

Current genetic variants of CYPs can be identified through several commercially available assays as well as through clinical laboratory-developed tests. The CYP variant can affect the metabolic phenotype through changes in protein expression, structure, functional stability and/or substrate specificity. The CYP activity is expressed as four major categories: extensive or normal metabolizer (EM), the ultrafast metabolizer (UM), the intermediate metabolizer (IM) and the poor or slow metabolizer (PM). These designations have



been extensively studied for several CYPs, and clinically significant variance can be seen among ethnic groups.^{8,9} Figure 11.3 shows the proportion of drugs metabolized by different CYPs.

The other application of pharmacogenomic testing is in the area of drug responsiveness. Population-based clinical trials for drug efficacy suffer from the same variability of drug response as previously discussed. A recent example is the drug Vercepin, developed by Genentech. In initial clinical trials on a broad population base, the effectiveness of the drug did not reach FDA standards for efficacy and was not approved for human use. However, when patients were evaluated for genetic makeup, a different picture emerged. In women who were epidermal growth factor receptor 2 (HER2)-positive, Vercepin produced significantly better effects on reducing metastatic breast cancer than in women who were HER2-negative. Genentech teamed with Dako Corporation to develop a test for HER2 positivity. Both the drug and the test received FDA approval for this application in 1998. By targeting the population sensitive to the drug, patients with this form of cancer receive a positive