Individualized Medicine:  
What Pharmacogenetics Will Mean to Your Practice

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Medical recommendations driven by a patient’s inborn ability to efficiently utilize specific drugs are quickly becoming mainstream practice. The term “pharmacogenetics” is defined as the study of genetic causes of individual variation in drug response. The knowledge of which genes and their polymorphisms, or variations, adversely affect drug metabolism is proliferating. The clinical utility of CYP2D6 genetic testing to determine a patient’s predicted response to tamoxifen has been demonstrated, which has led some insurance providers to request this testing prior to administration of the drug or renewal of a prescription. This article aims to summarize the current information and application of this technology, primarily using tamoxifen as an example, as well as future directions and implications.

It has been long understood that many genes manufacture enzymes that help to metabolize everything people ingest, from food to medications. Individual variation in drug metabolizing capacity is a complicating factor in the efficacy of cancer treatment regimens. Research has focused on understanding which genes are the most crucial in metabolizing commonly-used drugs and chemotherapeutic agents, as well as which variants within these genes predispose to decreased metabolic potential. For example, if a patient is known to carry a genetic variant that predisposes her to poorly metabolize a particular drug, then the efficacy of that drug in her treatment would also be poor. This information would obviously lead her physician to prescribe a different drug course that would have a higher potential to be helpful.

Genes that encode certain members of the CYP450 family of enzymes are thought to participate in the metabolism of over 75% of prescribed drugs. These enzymes are genetically polymorphic, and these variations can form enzymes that have significantly altered activity. A particular genetic variant can define individuals as poor, intermediate, extensive, or ultra-rapid metabolizers of a given drug. The enzyme’s level of activity is dependent on what the genetic variant dictates.

Within the CYP450 family, CYP2D6 is the best characterized enzyme to date. Multiple studies have shown that CYP2D6 is the key player in the activation of tamoxifen (used in the prevention and treatment of hormone receptor positive breast cancer) to endoxifen. In a study where breast cancer patients receiving adjuvant tamoxifen therapy were found to have genetic variations in CYP2D6 that cause decreased enzyme activity, they were shown to have increased cancer recurrence rates and smaller intervals of time between cancer recurrences. In the same study, no significant effect was found on overall mortality rates. Several other studies have confirmed this data. Many other genetic variations have been discovered within enzymes of the CYP450 family that affect the efficacy of other chemotherapeutic agents, such as docetaxel and imatinib.

Our extensive understanding and continuing discoveries within the CYP450 enzymes is only the beginning. Within the next several years, many more genetic variations and their effect on prescription drug metabolism will be discovered and likely utilized in clinical practice throughout many areas of medicine. It is important to understand that these genetic variations are within the germline; not only do they affect the individual in question, but these traits are inherited from parents.
and passed on to children. The familial effect should be considered when these genetic tests are ordered. If a patient has further questions regarding pharmacogenetic testing, a genetic counselor can be consulted regarding questions and help with result interpretation.

Another consideration is the possibility of insurance providers requesting or requiring this testing prior to determining coverage for medications (chemotherapeutic or otherwise). To provide a current example, Medco Health Solutions, Inc. manages prescription drug benefits for certain health plans. In reference to patients that have filled prescriptions for tamoxifen, Medco sends a “Tamoxifen Personalized Medicine Program” form to the ordering physician. It states that genetic testing is available to determine the patient’s genetic metabolic potential to convert tamoxifen to its active form, and the physician can sign the form to order the test. Medco would then contact the patient to provide information on the test, and have one specific testing laboratory send the buccal swab test kit to the patient if she is agreeable. This practice will likely increase and could become mandatory in the future. While the information gleaned from the testing can be clinically helpful in guiding treatment, ethical implications should be considered. One example is the possible bias in clinical information being provided to the patient by the requesting entity. Another example pertains to individuals that fall into the “intermediate metabolizer” category. Where will the line be drawn for insurance coverage and clinical utility when the result is ambiguous, and who will be making these decisions? These concerns should be thoroughly addressed as these technologies become more commonplace.

References: