Pharmacogenomics: Hope and Hype

Physicians and researchers have expressed great optimism and confidence in pharmacogenetics merging into medical practice. As the science progresses, it may become feasible that, rather than treating a patient with therapies that may not work for them – or could be toxic – doctors armed with pharmacogenetic know-how will tailor treatments. This approach has the potential to reduce health care costs by avoiding therapies with little chance of success, and to reduce the number of adverse drug reactions (about two million per year in the United States, 100,000 of them fatal). With the completed human genome sequence to draw on, researchers rapidly are identifying genetic variants that may be associated with health conditions or that affect how the body processes drugs and nutrients. Thus far, however, there has been only modest pay-off, and significant scientific, economic, policy, and practical challenges must be faced before the field's potential can be realized.

To understand the challenges of implementing pharmacogenetics into health care, it is instructive to consider examples of drugs for which pharmacogenetic tests are already being used in clinical practice. Perhaps the best known example is the drug trastuzumab (Herceptin®). This drug targets a specific type of breast cancer tumor; an estimated 25-30 percent of primary breast cancer tumors are susceptible to Herceptin. Before treating breast cancer, physicians use a genetic test to determine whether the tumor is likely to respond to the Herceptin, and to another medication, lapatinib (Tyker®).

Pharmacogenetic tests also can be used to avoid prescribing a drug that will cause dangerous side effects. For example, abacavir (Ziagen®) is an antiretroviral drug prescribed to HIV-1 patients. While the drug is effective in slowing HIV-1 progression, it was found during clinical trials that a small percentage of patients had a fatal hypersensitivity to the medication. Further studies found that this hypersensitivity was predicted by a specific variant in a gene related to immune response, *HLA-B*. Approximately five percent of Caucasians have at least one copy of this variant, and half of them are hypersensitive to the drug. Health care providers can test for the variant before prescribing abacavir, and select an alternate medication for those at risk.

Pharmacogenetic tests also could help doctors figure out the appropriate dosage of medication for an individual patient. For example, warfarin (Coumadin®), a blood thinner that prevents clots, is prescribed to millions of patients each year and is associated with significant risk of bleeding-related adverse events. The dosage is carefully tailored to the individual patient through careful monitoring of whether a patient's blood clotting time is within normal range, but establishing the right dosage can take months. For this reason, there has been considerable interest in identifying genetic variants associated with warfarin response, and variants in two genes (*CYP2C9* and *VKORC1*) appear to influence patient response. Individuals with the relevant variants appear to have varying clotting times, but it is unclear whether testing for these variants prior to administering warfarin will improve patient outcomes better than the existing trial-and-error methods. However, it has not yet been demonstrated that testing patients for variants within these genes before initiating

warfarin therapy reduces the number of adverse reactions. Studies are underway to evaluate whether such testing improves patient outcomes.

For drugs currently in development, the Food and Drug Administration (FDA) encourages the collection of genetic information, and has issued several guidance documents on the subject. Particularly when a drug is already on the market, collecting pharmacogenetic information can be challenging, since genetic information likely was not collected from study participants at the time of the drug's clinical trials. A drug company may have incentive to explore pharmacogenetic predictors of adverse effects in order to mitigate liability, or indeed it may be compelled to do so by FDA. However, drug companies may have little incentive to investigate the pharmacogenetic causes for lack of response to a medication, since predicting non-response could limit the population of patients using the drug and therefore negatively affect sales.

Once pharmacogenetic research has been completed, the results need to be communicated to health care providers so they can incorporate them into clinical practice. FDA relies on the drug label (the printed information accompanying prescription drugs) to communicate relevant safety information to doctors, and approves the label information as part of the drug approval process. Changing the label after drug approval typically involves negotiation between FDA and the drug's sponsor, and can be a lengthy process. FDA relies on expert advisory panels to make recommendations on when changes are needed. To date, FDA has approved changes to 58 drug labels to include pharmacogenetic information. The majority of the labels reference a particular gene, gene product, or genetic factor and its potential importance in prescribing or dosing the named drug; only four drug labels (for warfarin, trastuzumab, mercaptopurine and irinotecan) describe specific genetic variants and how they affect dosage or prescription. As of September 2008 the label for abacavir has not been updated to incorporate the *HLA-B* testing despite evidence that testing leads to improved patient outcomes.

Another challenge relates to the lack of validated pharmacogenetic tests. FDA has a clearly defined role in determining the efficacy and safety of drugs on the market, but not a clear role in the regulation of genetic tests. Most genetic tests are developed by laboratories and not reviewed by FDA or any other third party to ensure their clinical validity. FDA's lack of involvement makes it difficult for anyone to ensure that pharmacogenetic claims being made by those offering genetic tests are accurate.

Several questions remain to be answered before pharmacogenetic applications become commonplace: 1) Who is responsible for providing evidence for a pharmacogenetic application? 2) What level of evidence should be required before a pharmacogenetic application is brought to the public? 3) How should evidence of the validity and utility of a pharmacogenetic test be gathered and evaluated? 4) When should pharmacogenetic tests be included on a drug label or package insert, and what information should be provided? How these questions are answered will help determine whether pharmacogenetics ultimately will bring about improvements in medical treatment.

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