



**ADVANCING
DRUG DEVELOPMENT
THROUGH PHARMACOGENOMICS**

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One size does not necessarily fit all when it comes to medicine. Two patients may respond differently to the same drug. In one patient, the drug may work as expected; in the other, it may have no result, or possibly cause side effects. This is because small genetic variations in individuals determine how a drug is metabolized in the body. Pharmacogenomics (PGx) is the study of how such genetic differences influence drug therapy. The goal is to use a person's DNA profile to predict how the individual will respond to a medicine. The ability to predict drug response holds enormous promise to advance the drug development process and to improve drug safety and effectiveness in medical practice.

» PGx looks at the 0.1 percent of gene sequence variation to account for the different ways individuals experience diseases.

HOW PGx WORKS

As humans, 99.9 percent of our gene sequences are the same. PGx looks at the 0.1 percent of gene sequence variation differences among people to try to account for the different ways individuals experience diseases – such as cancer, diabetes or asthma – and different reactions to medicines.

PGx research focuses on linking genetic variations to specific disease patterns or drug treatment outcomes (side effects, for example). When a link is confirmed, the genetic variation or set of genetic variations serve as a “biomarker” and can be used to predict an individual's response to drug treatment. DNA diagnostic tests determine whether an individual has a particular genetic variation that will affect drug response or disease progression. Physicians can use these biomarkers to select the drug corresponding to the patient characteristics or to tailor their drug dosage. Clinical researchers can use biomarkers to select patients for clinical trials and to interpret study results.

» PGx holds great promise to improve treatment efficacy and to reduce treatment costs and risks for adverse drug reactions.

PREDICTING DRUG RESPONSE

Among the most important biomarkers for predicting drug response are genetic variations that affect a special group of liver enzymes. These enzymes metabolize most drugs used in clinical practice today, from cancer treatments to analgesics.

Genetic variations can result in over- or under-activity of these enzymes. Too much enzyme breaks down the drug before it can be effective; too little allows the drug to remain too long in the body and results in side effects. This gives rise to three general “responder” types that can be identified by PGx testing:

- » *Efficient metabolizers* (or “responders”) have sufficient enzyme levels to metabolize a given drug; the drug is effective at recommended doses.
- » *Poor metabolizers* have insufficient enzyme levels and are likely to experience side effects or exaggerated drug response; they may be able to tolerate the drug at lower doses.
- » *Ultra-rapid metabolizers* (or “non-responders”) have excess enzyme levels and are likely not to respond to a drug; they may require higher doses for the drug to have therapeutic effect.

PGx IN MEDICAL PRACTICE

PGx has inspired the concept of “personalized medicine” in which disease prevention and treatment are designed for subgroups of patients sharing the same characteristics of their DNA profile. Although this is still a vision for the future, the beginnings of genetics-based medical practice can be seen now in cancer therapy.

Thiopurine drugs used to treat leukemia can cause fatal toxicity at normal doses in children who have a certain inherited enzyme deficiency. PGx diagnostics identify this genetic variation, and children can be successfully treated with much smaller doses. The breast cancer treatment Herceptin[®] also relies on PGx diagnostics. About 25 percent of patients have a genetic variation that causes over-expression of a certain receptor gene. Herceptin is effective only in these women, who are identified using a PGx test.

Experts believe some form of genetics-based medical practice will evolve as our knowledge of biomarkers grows and PGx diagnostics become available. PGx holds great promise to reduce treatment costs and risks for adverse drug reactions.

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PGx IN CLINICAL TRIALS

PGx also promises great advances for the clinical trial and the drug development process. Genetics data and biomarkers can be used as additional information to deepen the understanding of study findings and to guide next steps in developing a new medicine as well as to design smaller and therefore faster trials. Clinical trials must enroll large numbers of patients because only about a third of people in the general population are likely to experience a drug's therapeutic effect. If new drugs could be tested in subgroups of patients with increased likelihood of being responders, trials aimed at proving drug effectiveness could be smaller and faster. In theory, researchers would use PGx diagnostic tests to identify patients with relevant genetic variations, then study the drug in patients most likely to respond. This application of "patient profiling" is still in the future for most diseases, but applications are currently performed in today's oncology clinical trials for example.

Phase I trials routinely collect DNA samples to gather data on possible biomarkers and interpret findings in Phase II studies. About half of Quintiles' Phase I trials use genetic profiling.

Phase II: Reliable biomarkers are being used to measure drug effects and to provide "end points" in clinical trials to improve research efficiencies.

Rescue Trials: When a drug fails to show efficacy in a trial, a biomarker may identify a subgroup of patients who benefited. The drug could be tested again in this identified responder population.

POTENTIAL FOR DRAMATIC CHANGE

The ability to predict drug response based on a person's genetic profile holds great promise for both patient treatment and pharmaceutical development, although this process is not suitable for all therapeutic areas or drugs. PGx is advancing, with increasing knowledge about genetic links to disease and drug response; regulatory standards to guide use of PGx data in clinical trials; and advances in PGx diagnostics to promote wider use in medical practice. Whatever form genetics-based medicine may take, PGx is certain to shape this new frontier.