Pharmacogenomics and Pharmacogenetics: Future Role of Molecular Diagnostics in the Clinical Diagnostic Laboratory

Over the past 50 years, the clinical laboratory has evolved into a complex, technology-driven enterprise with the principal tasks of diagnosing and screening for disease, monitoring health and therapeutic response, and gauging deviations from normal physiology in humans and animals. Advances in diagnostic medicine, on the other hand, have come through the application of science and technology as a result of a coordinated effort among academia, industry, government, and private institutions. We are now entering the era of Molecular Diagnostics and Pathology, which is bringing forth the newest and most powerful science and technology available for the modern-day practice of diagnostic laboratory medicine. Among the numerous important areas to consider with molecular diagnostics are the emerging issues concerning the development of genetic assays and their use for testing individual patient responses or suitability for pharmaceutical drugs.

The definitions of pharmacogenomics (PGo) and pharmacogenetics (PGe) to be used in this context are as follows:

- Pharmacogenomics refers to the general study of the many different genes that determine drug behavior.
- Pharmacogenetics refers to the study of inherited differences (variation) in drug metabolism and response.

The distinction between the two terms has become somewhat arbitrary in the literature, and they have been used interchangeably (1); however, we wish to apply them in their proper context in the following discussion.

Recently, the US Food and Drug Administration (FDA) made recommendations to pharmaceutical companies to evaluate the PGo of their drugs. These recommendations eventually evolved into a draft guidance document (2, 3), and as a result, many pharmaceutical and biotechnology companies developed internal PGo committees to handle this aspect of drug behavior. The role of some of these committees was to review the data from internal research, clinical trials, literature, and similar drug compounds to help predict drug “responder” vs “non-responder” patients and those who may have adverse drug reactions (ADRs). The task was to identify biomarkers, mutations, single-nucleotide polymorphisms (SNPs), and/or specific genes and then develop clinical screening assays to differentiate between patients. This activity encompassed two important central purposes: (a) to select responders for clinical trials, which would greatly improve the potential efficacy of a drug; and (b) to exclude patients who may be prone to ADRs. Both of these benefits would greatly enhance the FDA approval process and potentially improve patient care.

Despite these goals, PGo committees found that these assigned tasks were nearly impossible to accomplish for a new drug entering clinical trials. Clinical assays developed by pharmaceutical companies for this purpose must be validated for phase III trials, and the time frame for this process is ~8 to 12 weeks for assays involving pharmacokineti and pharmacodynamic assessment alone. This time compression does not allow for sufficient development and evaluation of the clinical utility of PGo assays or their use in large populations of patients. Nonetheless, the initiation of clinical trials serves as an excellent starting point for PGo and PGe clinical assays.

PGo and PGe assays are a form of genetic testing and thus raise complex problems or issues that are difficult for the pharmaceutical and biotechnology industries to resolve. Answers to many genetic testing issues are not clear at this early stage of development and need to be resolved by expert representatives from the federal government, academia, and industry, along with representatives from the public and private sectors. Some of the fundamental and ethical questions being asked are the following:

Should pharmaceutical companies influence the development of tests used to screen potential patients for their own drug therapy?

Pharmaceutical companies frequently develop their own clinical assays for pharmacokinetic and pharmacodynamic studies. They are required to have assays validated for human clinical phase III trials that comply with current Good Clinical Practice guidelines for FDA submission purposes. PGo and PGe testing, however, is another issue. This involves testing patients as potential recipients of a drug before the administration of the drug. This difference poses an ethical dilemma for pharmaceutical companies, especially if inadequate testing excludes some patients who might benefit from receiving the drug or, conversely, long-term dosing continues with a drug that does not have good clinical efficacy.

We believe the answer to this question is yes. Pharmaceutical companies should be involved with the initial development of PGo assays because they have the primary data and information necessary for this stage of assay development. However, this assay development activity should be transferred to outside reference laboratories, clinical core laboratories in academic health centers, or established Clinical Research Organizations when research and development transitions into clinical application because these independent external sites are able to handle this function.

Do the pharmaceutical companies have the knowledge/capabilities required to develop complex screening tests?

Pharmaceutical and biotechnology companies do not place assay development or clinical laboratory testing among their primary goals, although many have first-rate clinical laboratories for drug toxicity studies. Pharmaceutical companies are primarily structured to discover and develop drugs, to determine their efficacy in test animals and humans by use of preclinical and clinical phase I–III studies, and to manufacture and supply high-quality,
reliable formulations of a drug. In contrast, the performance of screening assays and therapeutic drug monitoring is common in many clinical laboratories and performed on a large scale in many commercial reference laboratories. A good example is cytochrome P450 screening (2D6 mutation genotyping), which can prevent ADRs by identifying poor drug metabolizers or accelerated drug metabolism in rapid metabolizers. Developing and performing PGo and PGe assays for screening patients as potential recipients of a drug is a logical next step for the clinical laboratory.

Who protects patient/physician medical confidentiality for PGo/PGe testing?

Drug selection based on genetic assessment may be considered confidential information. Both pharmaceutical and clinical diagnostic industries have in place appropriate measures to protect confidentiality of information. However, the clinical laboratory has established a proven structure for testing patient samples and a system to provide confidential information to the patient’s physician. In the future, PGo and PGe testing may provide detailed genetic information necessary for physicians and genetic counselors to prescribe the correct drug and dose. This structure already exists with the clinical laboratories and is the most proficient means to protect patient/physician confidentiality.

How will PGo/PGe testing be provided?

The clinical diagnostic laboratory performs testing of patient samples, provides guidelines for standardizing test development and utilization, and is the site most likely to standardize PGo and PGe testing. As a result, the hospital-based clinical laboratory is the logical site to perform routine PGo and PGe testing. However, if not embraced properly by clinical laboratories, the development and performance of PGo and PGe testing may well become the purview of reference laboratories, university-based core laboratories, or Clinical Research Organizations in collaboration with pharmaceutical companies and university-based research laboratories.

Who will pay for PGo/PGe tests?

Reimbursement or payment for genetic testing is another topic of considerable consequence that is already creating controversy among health maintenance organizations, healthcare providers, and the patients themselves. One can predict, however, that health insurance companies will be very interested in patient PGo and PGe testing to document the proper dosing of expensive prescription drugs and hence reduce the incidence or risks of ADRs. Health insurers typically pay the costs for the drug prescription as well as the potential medical costs if ADRs ensue. ADRs are an important consideration, however, and cannot be minimized. In 1994, 2.2 million severe ADRs occurred in the United States, and 106,000 of these were fatal (4). Fatal ADRs rank from fourth to sixth as the leading cause of death, with an estimated cost of up to $4 billion annually (5). It will be interesting to see whether insurers will consider PGo and PGe testing to be a cost-effective alternative to the current trial-and-error approaches to dosage regulation.

The clinical laboratory has a long history of developing, managing, and providing assays and test results for diagnosing disease. A good example of this was the development of immunoassays and the enhancements made to this technology with the introduction of monoclonal antibodies. The rapidly growing area of molecular diagnostics is ideally suited to clinical laboratories. Molecular diagnostics show great promise in making personalized medicine the next major advance in the delivery of healthcare. PGo and PGe testing is a necessary and critical step to move personalized medicine into practice. What are required to fulfill this promise are the same needs fulfilled by the clinical diagnostic industry for immunoassays: assay development, standardization, reference databases, novel automation platforms, training and education, sample procurement and processing guidelines, and so forth. These are concepts that are all too familiar to the clinical laboratory scientist. It is important and quite timely for the clinical diagnostic industry to step up, assume these new responsibilities, and advance the application of PGo and PGe testing as well as other segments of molecular diagnostics.

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References


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