Fine-Tuning Pharmacogenetics: Paradigm for Linking Laboratory Results to Clinical Action

Pharmacogenetics (PGx) is the study of the relationship between gene-based markers and pharmacology as it relates to the processing and/or function of drugs. The clinical utility of PGx is embodied principally in the ability to predict either the most appropriate dosing of a medicine or the selection of a particular medicine for a given individual. This expectation has led to the concept of “personalized medicine”. Although the science and clinical application of PGx seem to be rapidly converging, the horizon remains a bit fuzzy, partly because the evidence needed to establish its clinical application to patient care is just now beginning to surface.

The clinical laboratory is the principal vehicle for providing PGx testing services to the medical community (1). These services include providing access to the testing, selecting appropriate testing profiles, and among other responsibilities, providing the evidence required to formulate decisions on medical applications (2). From this perspective, advances in laboratory medicine, as with most medical disciplines, are typically achieved in incremental steps. Each step provides a basis on which to build consensus for accepting a standard for the practice. Often however, new information gets substantially ahead of the commonly accepted medical practice and an element of confusion, perhaps driven by high expectations, sets in. To avoid this dilemma, a reasonable strategy must be developed to establish pathways for translating basic findings such as those using PGx information into appropriate clinical practice.

The power of this relatively new discipline in laboratory medicine lies in its perceived ability to predict. Initially, the most likely application is in optimizing the dosing of medications to avoid excessive or suboptimal concentrations of medicines. The use of gene-based information to stratify patients, preferably before they are prescribed medication, is perceived as having substantial merit. One prerequisite to this approach lies in establishing a quantitative link between phenotype (ability to metabolize a drug) and genotype (associated with variation in production or type of enzymes responsible for metabolism). On the basis of observed phenotyping data, such as metabolic ratios of drug components in blood and urine, a reasonable separation can be demonstrated between rapid metabolizers (generally referred to as ultra-rapid) and slow metabolizers in their ability to biotransform specific medications. However, the distinction between groups having a more common or normal metabolic profile (extensive metabolizers) and those having a slower metabolic profile (intermediate metabolizers) has been more difficult (3–6). Until recently, tools were not available to tease out this important group or to establish a quantitative approach for calculating dosing requirements. For PGx to find its way into general clinical practice, methods must be established for translating the genetic information provided by the marker (usually detection of single-nucleotide polymorphism variants associated with key cytochrome P450 enzymes) into a quantifiable and reliable altered dosing scheme.

The report by Steimer et al. (7) in this issue of the Journal is important because it describes and validates a process for grading the information obtained through cytochrome P4502D6 genotyping. In this report, Steimer et al. focus on a group of individuals who would conventionally be grouped within the extensive metabolizer phenotype. Using unique CYP2D6 genotypes within this heterogeneous group, the authors derive corrections to standard dosing of amitriptyline. This was accomplished by expressing the CYP2D6 genotype in terms of semiquantitative CYP2D6 gene dose. These investigators applied a process they termed “allele-specific change of concentration on identical background” (ASCOC). In this context, the “identical background” is the other CYP2D6 allele (i.e., second allele) of the genotype for each individual within the groups being compared. In a way, one establishes something akin to an internal standard for each individual and thus allows for the contribution of individual alleles to the observed phenotype to be sorted out in the context of a variety of allele combinations (genotypes).

Functional gene dosages were calculated, based on measured ASCOC values for individual alleles, by defining the reference gene dose as having a value of 2 (Table 1). For each allele for which there was a measured difference in the resulting plasma concentration at steady state, the reference gene dose of 2 was divided by the percentage change in concentration attributed to that allele. For example, steady-state plasma drug concentrations of individuals with the CYP2D6*10 allele were ~63% higher than those of individuals with the *1 or *2 alleles and the same second (or “background”) allele. Thus, the functional gene dose for an individual with the CYP2D6*1/CYP2D6*10 genotype equals 2 divided by (1 + 0.63), or 1.23. This functional gene dose was then expressed in terms of a semiquantitative gene dose of 1.5.

The concept of semiquantitative gene dosing was validated by demonstrating that semiquantitative gene doses of 0.5, 1.0, and 1.5 corresponded to significantly different plasma drug concentrations at steady state under stan-

<table>
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<tr>
<th>Genotypes traditionally associated with the extensive metabolizer phenotype.</th>
<th>Representative genotype</th>
<th>Measured functional gene dose</th>
<th>Semiquantitative gene dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active/Active</td>
<td>*1/*1</td>
<td>Reference point</td>
<td>2.0</td>
</tr>
<tr>
<td>Active/Intermediate</td>
<td>*1/*41</td>
<td>1.43</td>
<td>1.5</td>
</tr>
<tr>
<td>Active/Inactive</td>
<td>*1/*4</td>
<td>1.02</td>
<td>1.0</td>
</tr>
<tr>
<td>Intermediate/Inactive</td>
<td>*41/*4</td>
<td>0.73</td>
<td>0.5</td>
</tr>
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* EM, extensive metabolizer.
standardized dosing conditions. In essence, this approach sets the stage for expressing a link between genotype and phenotype (i.e., older model) and introduces a model for expressing genotype as an allele-specific change in function (i.e., newer model).

The power of this approach is that now the clinical relevance of heterozygous and rare genotypes can be measured without the necessity of large population studies required to make direct genotype comparisons. This may be an important step forward in terms of providing meaningful interpretations of pharmacogenetic assays and should be considered a means for evaluating data from future pharmacogenetic studies. It is likely that this approach will need to be extended to deal with individual nucleotide polymorphisms and haplotypes. Although this seems to be a promising model for analyzing the data, the prospective reliability of this approach needs to be further validated. Validation can lead to guidelines for practice that adjust the doses of medications known to be processed by specific CYP450 enzymes.

The pathway needed to advance PGx testing into clinical practice begins with studies like that of Steimer et al. (7). Importantly, the evolution of the discipline into routine practice will require establishing guidelines spanning from the clinical laboratory to the patient bedside. The National Academy of Clinical Biochemistry (NACB) has undertaken establishing a Laboratory Medicine Practice Guideline document with a focus on transitioning PGx into a laboratory-based clinical practice. It is anticipated that the first working document open for public comment will shortly be available for input from all interested parties. The draft document will be posted at the Academy’s web site (8), and approved guidelines will appear in this Journal. The evolution of transitioning PGx into the practice of laboratory medicine is just now beginning, and the clinical laboratory is anticipated to play a central role in this process.

References

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