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Telling It Like It Is: A Call for Accurate Pharmacogenetic Labeling

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Individual differences in response to medications are an important challenge in clinical practice. Drugs that work well for some patients are ineffective for others, and individuals vary markedly in their experience of adverse drug reactions. Much of this variation is due to individual differences in the genes involved in drug uptake, distribution, metabolism, target engagement and action. Some variants show striking effects. For example, individuals with the *HLA-B*5701* variant have an approximately 50% risk of a hypersensitivity reaction when exposed to the drug abacavir, used to treat human immunodeficiency virus (HIV) infection; use of an alternative drug in these individuals prevents virtually all such adverse events (1). The drug ivacaftor, used to treat cystic fibrosis (CF), illustrates a different effect. This drug has genetically targeted efficacy; it was designed to enhance the function of the defective trans-membrane chloride channel in a subset of CF patients who have a particular *CFTR* gene mutation (G551D) (2). As these examples illustrate, pharmacogenetic testing offers great promise for improving the safety and efficacy of drug treatment.

However, gene variants associated with drug response do not always provide clinically useful information. Variants may have small physiological effects, or alternative metabolic pathways may blunt their effect. In the case of venlafaxine for depression, for example, differences in metabolism associated with *CYP2D6* variants do not have sufficient effect on therapeutic levels to merit clinical testing (3). For many variants, the clinical value of testing is simply unknown because the available evidence consists of a single case report, laboratory-based studies, or other limited observations. In these cases, further study is necessary to determine clinical benefit.

As a result, clinicians need guidance to help them determine which pharmacogenetic variants have sufficient clinical utility to merit testing. Drug labels approved by the US Food and Drug Administration (FDA) offer an important mechanism for accomplishing this goal. The labels are produced by drug manufacturers in negotiation with the FDA, and must comply with standards defined by the agency. These require that information about genetic

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contributors to drug metabolism, transport and response be included in the drug label as appropriate, in particular when pharmacogenetic information “has important implications for safe and effective use and the consequences of the genetic differences result in recommendations for restricted use, dosage adjustments, contraindications, or warning” (4).

In a study in this issue, Wang and colleagues ask how well drug labels communicate information about pharmacogenetic testing, and whether this information is helpful to clinicians (3). The results are sobering. Only 36% of the labels reviewed provided convincing evidence for the clinical validity of the pharmacogenetic test, that is, an established association between the pharmacogenetic variant and drug response; and only 15% provided convincing evidence of clinical utility, that is, one or more controlled studies demonstrating improved clinical outcomes with test use. The study also found considerable heterogeneity in the extent and quality of the pharmacogenetic information conveyed. Labels varied in their descriptions of study data and prescribing recommendations, often had incomplete citations, and were inconsistent in their use of black box warnings (3).

It is possible, of course, that evidence of benefit was not adequately captured in all drug labels. However, the paucity of evidence about most genetic tests is well documented (5), suggesting that the limitations in drug label information reflect in significant part our current state of knowledge about pharmacogenetics. Further, the data provided by Wang and colleagues indicate that current drug labels are an unreliable source for what is known about pharmacogenetic tests.

This problem could and should be remedied. Drug labels are readily available to clinicians and patients in electronic formats, and offer a time-efficient mechanism for delivering point of service information. They generally offer reliable information about dosage and other aspects of prescribing. They should also provide accurate and trustworthy information about pharmacogenetics. To accomplish this goal, the FDA should provide clear and specific direction, extending beyond its current guidance (4), to establish a standardized “Pharmacogenomics” section for all drug labels. This section should inform clinicians about pharmacogenetic tests with established clinical validity and clinical utility. When such tests are available, summaries of the evidence and relevant practice guidelines should be provided, with appropriate citations. If there is no pharmacogenetic test meeting these standards, the label should say so. A black box label should be reserved for the minority of drug-test combinations with convincing evidence that test use prevents serious patient harm, making it easy for clinicians to discern the tests with highest impact.

The evidence required to justify inclusion of the pharmacogenetic test on a drug label is likely to be debated. Wang and colleagues used a stringent standard: a randomized controlled trial was required to establish convincing evidence of clinical utility (3). Yet high quality observational data have been used to establish clinical benefit for some pharmacogenetic tests, notably testing for *TPMT* variants to assure appropriate dosing and prevention of serious hematological complication in thiopurine treatment for acute lymphoblastic leukemia (6). For this reason, we propose that evidence for both clinical validity and clinical utility should be included in the pharmacogenomics section of drug labels. However, further consensus development is needed to define the evidence required to

establish clinical validity and utility, as well as the evidence threshold for a black box warning concerning a pharmacogenetic test.

Because knowledge about drug-gene interactions is rapidly accumulating, and additional effective pharmacogenetic tests are likely to emerge, regular updating of the pharmacogenomics section will be needed, as is the case for other drug label information. This can be challenging, because drug labels are the product of negotiated agreement between the drug sponsor and the regulatory agency. Thus, other efforts to provide clinicians with information may also be merited. For example, the FDA should publicize more broadly its web-based listing of Pharmacogenomic Biomarkers in Drug Labeling and add to the listing a summary of evidence on clinical validity and utility for those tests and drugs that it highlights, including publication citations. Pharmacogenetic tests that currently lack such evidence could be provided on a separate “watch” list for interested clinicians. FDA could further benefit the field by hosting stakeholder discussions to define appropriate evidence thresholds for establishing clinical validity and utility and for generating black box warnings.

Effective pharmacogenetic tests are likely to prove one of the most beneficial products of genomic research. As Wang and colleagues document, a small number of tests have been shown to improve patient outcomes (3). Current research is likely to yield additional effective tests over time, with the corollary benefit of reductions in the costs of adverse drug outcomes and ineffective therapy. It is unrealistic, however, to suppose that all gene variants associated with drug disposition or response can offer these benefits. To promote testing that offers proven benefit, and avoid testing that lacks adequate evidence, clinicians need ready access to accurate information. Drug labels unfortunately add confusion rather than clarity to this new area of practice. With a systematic and rigorous approach, however, they could become the linchpin of a new approach to safe and effective prescribing.

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