Pharmacogenomic and pharmacogenetic tests are increasingly being used during drug development. Such tests are employed to improve or "personalize" drug dosage, identify those at risk for atypical adverse drug reactions, and determine who will respond to the drug. As such, there is particular interest in refining the ability to select the optimal dosage for a specific patient.

The terms "pharmacogenetics" and "pharmacogenomics" are often used interchangeably. Other terms include "theranostics" and, more recently, "onocogenomics." The European Committee for Proprietary Medicinal Products, the European Union's equivalent of our FDA, defined pharmacogenetics as the "study of interindividual variations in DNA sequencing relating to drug response." Pharmacogenomics is defined as the "study of the variability of the expression of individual genes relevant to disease susceptibility as well as to the drug response at the cellular, tissue, individual, or population level." In this article, the term "pharmacogenomics" is used.

COMPANION DIAGNOSTICS
Pharmacogenomic tests play an important role in identifying which patients will respond to a medicine. One of the best-known examples is the HER-2 receptor (human epidermal growth factor receptor 2) testing used to select women most likely to respond to the drug trastuzumab (Herceptin) for the treatment of breast cancer.

The approval of this breast cancer drug, along with the availability of a diagnostic test that would identify those patients most likely to respond, was assumed by many to mark the start of a new era of companion diagnostics in the pharmaceutical industry. Experts believed this era would yield a consistent development of drug/diagnostic combinations to improve patient outcomes. However, the much anticipated pipeline of companion diagnostics ushering in an era of personalized medicine has been slower to develop than expected. Two key reasons are the complexity of the technology involved in bringing such products to market and the time companies need to implement such processes. Also, many of the drugs now reaching the marketplace were already on a specific development track before the benefit of companion diagnostics was fully understood. The drug and diagnostic industries have very different development paths, different selling models, and different tracks for FDA approval. Nevertheless, there are some similarities. Both industries develop regulated products that require objective clinical data for widespread adoption and reimbursement. As a result, there is potential for the drug and diagnostic industries to follow a carefully coordinated codevelopment path.

PHARMACOGENOMICS AND HIV
The remainder of this column discusses some companion diagnostics relevant to HIV care: abacavir/HLA B*5701, maraviroc/tropism testing, and psychoactive drugs/cytochrome P-450 (CYP450) testing.

Abacavir Hypersensitivity
Mallal and colleagues described the possible use of HLA screening to identify patients at significantly increased risk for serious life-threatening hypersensitivity reactions to the antiretroviral drug abacavir. More recently, in the large, prospective, double-blind PREDICT-1 trial, the utility of HLA typing was tested using skin-patch results as confirmation of an abacavir hypersensitivity reaction (HSR). In this trial of 1956 HIV-infected patients who were scheduled to start regimens containing abacavir, half the patients were randomized to undergo HLA screening at baseline and half were not. Those who underwent screening started abacavir therapy only if they tested negative for HLA B*5701; those who did not undergo screening started abacavir therapy immediately and provided blood samples for later HLA typing. All patients who developed clinical signs of HSR underwent skin-patch testing.
The results showed that HLA screening significantly reduced the incidence of both clinically suspected HSR (from 7.8% to 3.4%) and immunologically confirmed HSR (from 2.7% to 0%). Sensitivity of B*5701 testing for immunologically confirmed HSR (positive skin test) was 100%, and perhaps more important, the negative predictive value was also 100%. In other words, based on these study results, B*5701 appears to be effective at screening out patients at risk for an abacavir HSR, allowing for more appropriate use of this drug.

The HLA screening test used in these studies is currently offered by commercial reference laboratories at a cost of $150 to $200 and is also available in some hospital laboratories. As a genetic test, the results indicate either presence or absence of B*5701, so the test needs to be done only once.

Already used extensively in some countries (notably Australia, United Kingdom, and Ireland), HLA testing has the potential to decrease or even eliminate both the true and "false call" cases of abacavir HSR. The overall cost-effectiveness of HLA testing is unknown, as is the question of whether to use the test in racial and ethnic groups that tend to have low rates of B*5701 carriage.

In the case of abacavir and its companion diagnostic, there was a lag from the time abacavir was approved in the United States (1998) and the approval of B*5701 as an in vitro diagnostic (2004); furthermore, validation studies were reported years later (2007).[8]

**Maraviroc and Tropism**

The recently approved antiretroviral agent maraviroc is the first in its class of drugs—the CCR5 (chemokine C-C motif receptor 5) coreceptor antagonists—to be clinically available. Maraviroc is designed to interfere with the so-called R5 variants, or quasi-species, of HIV, which use the host cell CCR5 coreceptor to infect cells.[9] Although several chemokine receptors can function as viral coreceptors, the CCR5 coreceptor is likely the most physiologically important during natural infection, and at least 50% to 60% of treatment-experienced patients harbor CCR5-using viruses, or quasi-species.

Another HIV quasi-species, the R4 stains of HIV, utilize the CXCR4 coreceptor to gain cell entry and are not blocked by CCR5 coreceptor antagonists. In other words, the R4 strains, because of their different path of cell entry, do not use CCR5 coreceptors to infect cells and presumably will be resistant to the effects of CCR5 antagonists such as maraviroc. Therefore, FDA product labeling for maraviroc recommends determining the tropism status of HIV-infected patients before initiating CCR5 antagonist therapy.[10]

There are several different assays available to assess coreceptor tropism,[11] but the specific test or technology is not specified in the product labeling for maraviroc. However, a cell-based assay (Trofile, Monogram Biosciences) was used for patient selection in the pivotal clinical trials of maraviroc that led to FDA approval. Another assay uses nucleic acid sequencing of the V3 envelope genes derived from a patient's HIV strains; however, in a recent study comparing this assay with the cell-based technology mentioned above, nucleic acid sequencing of the HIV V3 envelope genes was found to be "technically hampered" by the sequence diversity and heterogeneous length of the V3 region.[12] This study also demonstrated that the current state-of-the-art interpretation algorithms used with sequencing technology significantly underreport the presence of viruses that use the CXCR4 coreceptor—strains that are highly unlikely to respond to maraviroc. Health care providers should check with their laboratory on the availability of tests for tropism and the specific technology being used for the test.

Unlike the development of the companion diagnostic HLA B*5701 for abacavir, maraviroc and its cell-based tropism diagnostic test were introduced into clinical practice at the same time. The retail cost of the cell-based tropism test can be as high as $2000, so providers need to check with their laboratories regarding reimbursement status. Also, while the recommendation for tropism testing before maraviroc use is clear, it is not certain if and when the test would need to be repeated during the course of therapy.[10,11]

This tropism assay is the result of a unique drug/diagnostic collaboration that identifies persons with HIV/AIDS for maraviroc treatment. This companion drug/diagnostic development approach is in keeping with an FDA initiative that encourages this type of collaboration in an effort to improve patient safety through more appropriate drug selection. By supplying a companion diagnostic to a pharmaceutical company as a part of a drug's development process, diagnostic test firms establish a new business strategy that relies on the use of the drug to drive sales of its diagnostic product.

**CYP450 AND PSYCHOACTIVE DRUGS**
Pharmacogenomics also has arrived in clinical psychiatric practice with the FDA approval of the CYP450 test to determine genotypes for key CYP450 genes that control metabolism of certain psychotropic drugs and warfarin. At present, there is still a fairly steep learning curve in order to link this test to clinical decision making.

The most recently approved in vitro diagnostic test is an assay of two CYP450 genes: 2D6 (CYP2D6) and 2C19 (CYP2C19) (AmpliChip, Roche Diagnostics). Other pharmacogenomic P450 technologies (CodeLink Human P450, GE Healthcare; Drug Met Genotyping Test, Jurlab; Tag-It Mutation Detection Kit, Tm Bioscience) measure different P450 genes that may also be associated with adverse drug reactions as a result of suboptimal metabolism.

These diagnostics have some application in HIV medicine, because many persons with HIV/AIDS take psychotropic drugs. CYP2D6 is important for the metabolism of many antidepressants and antipsychotics, and CYP2C19 is important for the metabolism of some antidepressants. A poor metabolizer phenotype that lacks the CYP2D6 enzyme is present in up to 7% of whites and the phenotype that lacks the CYP2C19 enzyme is present in up to 25% of East Asians. Patients who have 3 or more active CYP2D6 alleles (up to 29% in persons originating from North Africa and the Middle East) are considered CYP2D6 ultra-rapid metabolizers. CYP2D6 phenotypes are probably important in patients taking tricyclic antidepressants, venlafaxine, typical antipsychotics, or risperidone—particularly in those who are poor metabolizers. The CYP2C19 poor-metabolizer phenotype is probably important in patients taking tricyclic antidepressants and perhaps those taking citalopram, escitalopram, or sertraline.13

The test report includes 2 kinds of results: a detailed genotype and a predictive, or "virtual," phenotype, similar to some resistance assays used in HIV medicine. The 4 possible phenotypes are poor metabolizers, extensive metabolizers, intermediate metabolizers, and ultra-rapid metabolizers. Extensive metabolizers have a normal predicted phenotype based on a genotypic analysis of the CYP2D6 and CYP2C19 genes. Clinically, patients with this phenotype demonstrate the expected response to standard doses of most drugs. Ultra-rapid metabolizers, on the other hand, may have a suboptimal response to certain drugs.13

Currently, there are no algorithms for dosage adjustments based on the patient's phenotype for various drugs, although de Leon and colleagues13 have made some recommendations based on broad clinical experience using the test to guide drug dosing. In tandem with this advancing technology, studies are now looking at the clinical utility of pharmacogenomic genotyping. For example, de Leon and colleagues found that the CYP2D6 poor-metabolizer phenotype may be associated with adverse drug reactions to risperidone and drug discontinuation.14 Using risperidone as an example, until we have more experience with dosing adjustments with various phenotypes, it is prudent to use this diagnostic test for drug selection and avoid risperidone in patients with the poor or ultra-rapid metabolizer phenotypes.

REIMBURSEMENT ISSUES: THE LAST WORD

Companion diagnostic tests are gaining momentum in health care in general and in HIV care specifically. The FDA endorsement of the collaborative approach to drug/diagnostic development helps move this agenda forward. However, reimbursement for these companion diagnostics has been uneven at best, and this will likely limit their use for the short term. Even though these diagnostic tests are available through reference or hospital laboratories, reimbursement approvals take a different path, and approval depends on the payer's approach and whether or not they decide to include these new technologies on their lists of approved diagnostics.

Major third-party payers, including Medicare, Medicaid, and different states' Ryan White AIDS Drug Assistance Programs (ADAPs), all take a different approach and timeline to reimbursement. Key drivers of reimbursement decision making for companion diagnostics include evidence to support their use, cost-effectiveness and outcomes, cost of the test, and the current reimbursement limitations for diagnostic testing in general.15

The report from the Secretary of Health and Human Services on genetic testing offers some insight into the issues and the agenda for the future of reimbursement of diagnostic testing similar to that discussed here.16 In the meantime, although reimbursement methods are a "black hole" from the provider perspective, even a rudimentary knowledge of reimbursement issues for specific diagnostics should be helpful when making decisions about diagnostics (Box). In the end, it's all about patients and outcomes.
References:


Links: