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Clinically Available Pharmacogenomics Tests

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Abstract

The development of robust and clinically valuable pharmacogenomic tests has been anticipated to be one of the first tangible results of the Human Genome Project. Despite both obvious and unanticipated obstacles, a number of tests have now become available in various practice settings. Lessons can be learned from examination of these tests, the evidence that has catalyzed their use, their value to prescribers, and their merit as tools for personalizing therapeutics.

The use of genetic tests to optimize a patient's chance of significant benefit from drug treatment has been anticipated since 1931, when Archibald Garrod proposed the concept of genetic influence on individualized drug responses. This idea has persisted through the recent dramatic technical advances in human genomics.[1] Indeed, one of the first questions asked when the full genomic sequences of James Watson and Craig Venter were made available concerned which drugs they might respond to.[2]

The contrast between this widespread anticipation and the lack of widely available tests has frustrated many. Emphasis has been placed on the formidable barriers that block the development and implementation of pharmacogenetic tests. These include scientific, economic, commercial, political,[3] and educational barriers to effective communication of clinically useful information to practitioners and patients. In addition, the field suffers from a lack of evidence of benefits accruing from such testing, in particular, benefits of the broad and inclusive kind that insurers and reimbursement agencies find persuasive.[4]

A number of recently developed tests for somatic mutations in tumors and for tumor expression of specific markers are now in widespread use. These include testing for the HER2 receptor for trastuzumab (Herceptin), BCR-ABL testing for imatinib (Gleevec), and epidermal growth factor receptor testing for getfitinib and erlotinib (Iressa and Tarceva). In addition to these, an increasing number of pharmacogenetic tests are being carried out by national diagnostic laboratories (Table 1), and the US Food and Drug Administration (FDA) has approved modifications to 58 drug labels that now contain pharmacogenetics information (http://www.dnapolicy.org/images/issuebriefpdfs/PGx%20IB.pdf). Although establishing evidence of clinical benefit in terms of outcomes remains a considerable challenge in many cases,[3,4] it is now reasonable to examine commercially available tests to identify the contexts in which they are most valuable and the limitations of their applicability. This information should help us identify elements that allow widespread clinical utility as well as help identify

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areas of research needed to generate new tests of value to determine which "dead ends" we should not pursue or fund.

Two recurrent themes will be seen within these scenarios. First, it is not sufficient that any new clinical test simply show a significant association with outcomes. A new test should provide predictive capability that augments our existing ability to predict outcome. Second, pharmacogenomic tests are designed to predict the necessity of a change in dose (e.g., warfarin) or in drug (e.g., tamoxifen). If no other drug is available, or no alternative dose has been studied, then the test is unlikely to be useful.

There is a clear need for clinically robust testing. Reimbursement decisions for expensive drugs are starting to depend on demonstration of efficacy. In 2007, the National Institute for Health and Clinical Excellence published a guidance recommending a response-rebate scheme for bortezomib (Velcade) (http://www.nice.org.uk/nicemedia/pdf/TA129Guidance.pdf). This was designed to allow patients who showed a response to continue with this expensive therapy treatment (funded by the National Health Service) and for patients who showed little response to stop it and have the cost reimbursed by the manufacturer.[4] This precedent, the underlying widespread realization that lack of efficacy is quite as costly as toxicity, and the fact that the FDA now (since March 2008) has the power to require a genetic test as part of a plan to optimize safety or efficacy (since March 2008) (Public Law No. 110-85, 121 Stat. 823) all contribute to a widespread need for clinically and commercially viable testing. President Obama has recognized the need for commercially and clinically feasible approaches to achieving personalized therapeutics (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_bills&docid=f:s976is.txt.pdf).[5] A small number of such tests are now commercially available, allowing us to examine their value within the rigors of a busy clinical environment.

WARFARIN AND CYP2C9/VKCOR

Warfarin is the most widely used medicine for which a pharmacogenetic test has been proposed. The use of such testing as standard of care has had to overcome three very significant hurdles: (i) the presence of an alternative biomarker: the international normalized ratio, which is widely used and trusted by the practice community, (ii) the need for specific dosing guidelines resulting from testing, and (iii) the need to demonstrate improvements not only in short-term toxicity but in long-term efficacy. This has been challenging for a drug that is used for multiple indications in multiple practice environments. Several dosing algorithms have been proposed, and an international group of investigators, organized by the PharmGKB (Pharmacogenomics Knowledge Base), has established a clear dosing algorithm that appears generalizable. A genome-wide association study that examined approximately 550,000 polymorphisms identified only the *VKORC1* ($P = 6.2 \times 10^{-13}$) and *CYP2C9* ($P = 5 \times 10^{-4}$) polymorphisms as significant, suggesting that large and expensive trials would be required in order to identify other important genetic variants.[6] FDA labeling has changed to include genetic data, recognizing the strength of the association of *CYP2C9* genotype with the risk of severe bleeding episodes and with some surrogates of efficacy (http://www.fda.gov/cder/foi/label/2007/009218s105lblv2.pdf).[7] Research that convincingly addresses the specificity and sensitivity of testing for both efficacy and toxicity will likely be required before current practice guidelines[8] are updated to incorporate *CYP2C9*9 and *VKORC1* testing as clinical recommendations. Of note, one health insurance provider, CIGNA, has already approved reimbursement for warfarin pharmacogenetics testing (http://www.cigna.com/customer_care/healthcare_professional/coverage_positions/medical/mm_0484_coveragepositioncriteria_pharmacogenetic_testing_for_warfarin_metabolism.pdf).

TAMOXIFEN AND CYP2D6

Tests for germline variation in the *CYP2D6* gene are widely available, but no indication for use of the test has reached guideline status. Tamoxifen has perhaps come closest. Since the Consortium on Breast Cancer Pharmacogenomics demonstrated a robust association between concentrations of the active metabolite, endoxifen, and the *CYP2D6* genotype,[10,11] many investigators around the world have tested for associations between genotype and clinical outcome. Although more than 10 studies addressing this question have been published, they are all relatively small, and none of the large prospective trials comparing tamoxifen with aromatase inhibitors has been opened for analysis.[12,13] This is important because the publication of relatively small studies risks underpowering and selection bias from a myriad of causes. Given that it is now possible to determine complex *CYP* genotypes from paraffin sections,[14] it should soon be possible to determine the answer to the association question, and these data should be key to the long-term clinical utility of *CYP2D6* testing for tamoxifen efficacy in the many practice settings in which it is used.

ABACAVIR AND *HLA*B5701*

The use of abacavir in the treatment of HIV/AIDS is associated with a debilitating skin sensitivity that has markedly limited its use. Fortunately, serious skin reactions are tightly associated with a germline *HLA* variant, and testing for *HLA*B5701* has been widely used all over the world to avert these reactions. This has led to more effective use of the drug and to germline testing as the standard of care when abacavir is prescribed. This success rests, in part, on the publication of pivotal prospective clinical trials indicating reductions in the incidence of skin sensitivity reactions with clinically acceptable specificity and sensitivity.[15,16] These trials were associated with large increases in the use of testing, whereas FDA labeling had relatively little influence.[16] That said, abacavir is not widely used in all practice environments, and a single pharmacoeconomic analysis suggested that *HLA-B*5701* testing remained the preferred strategy only if abacavir-based treatment had equal efficacy and cost less per month than tenofovir-based treatment.[17]

CARBAMAZEPINE AND *HLA-B*1502*

As is the case with abacavir, dangerous skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, can be caused by carbamazepine. These adverse events have been associated with a particular *HLA* allele, *HLA-B*1502*,[18] which occurs almost exclusively in individuals of Asian ancestry. Genetic tests for *HLA-B*1502* are available, and the FDA has concluded that Asian patients should be screened before starting treatment with carbamazepine (http://www.fda.gov/cder/foi/label/2007/016608s098lbl.pdf). If they test positive, carbamazepine should not be started unless the expected benefit clearly outweighs the increased risk of serious skin reactions. The case of carbamazepine makes clear that fast FDA action is possible when the association is compelling and a clinical change can be made, even if a pharmacogenetic effect is confined to a single ethnic group. Of note, the same genetic variant has recently been associated with hypersensitivity reactions seen with phenytoin.

CLOZAPINE AND *HLA-DQB1*

The *HLA* locus has also been implicated in the principal dangerous side effect of clozapine, agranulocytosis, which limits the use of this important and effective medication. In this case, an association has been described between the occurrence of clozapine-related agranulocytosis and *HLA-DQB1*0201* in patients with schizophrenia.[19] The association is based on relatively small studies of fewer than 50 patients each, and therefore it is less robust, with less specificity than that seen in the cases of abacavir and carbamazepine. As a result, the test is less widely accepted and guidelines have not yet been generated.

5-FLUROURACIL AND DIHYDROPYRIMIDINE DEHYDROGENASE DEFICINCY-THYMIDYLATE SYNTHASE-METHYLENETETRAHYDROFOLATE REDUCTASE

5-Fluorouracil is a chemotherapy drug widely used in the treatment of solid tumors, but its variable efficacy is compounded by equally variable and often severe mucocutaneous toxicity. A large number of functional genetic variants in the principal metabolic enzyme, dihydropyrimidine dehydrogenase;[20] in the target of 5-fluorouracil, thymidylate synthase; and in methylenetetrahydrofolate reductase have been described. Not all cases of toxicity can be identified using tests for these variants, thereby resulting in low specificity and sensitivity.[21] This may be attributable to contributions from genetic variants[22] that have not yet been identified or from nongenetic factors such as age and gender, which have been well documented as exerting an influence on 5-fluorouracil clearance[23] and toxicity.[24] In this context, there may well be value to genome-wide association studies and to the development of predictive scoring combining clinical and genomic predictors.

IRINOTECAN AND UGT1A1

The use of irinotecan as an effective agent in the treatment of colorectal and lung cancer is compromised by variable efficacy and potentially life-threatening toxicity.[25] Irinotecan is converted to an active metabolite, SN-38, which is then cleared by phase II glucuronidation, catalyzed by UGT1A1.[26] It was quickly appreciated that this enzyme is also the proximate cause of the benign, congenital hyperbilirubinemia seen in Gilbert's syndrome.[27] Subsequent trials showed that *UGT1A1* polymorphisms are also predictive of irinotecan pharmacokinetics and treatment outcomes.[28,29] The FDA-approved label for irinotecan has been changed to include reference to *UGT1A1* genetic testing, but it does not include specific dosing recommendations (http://www.fda.gov/MedWatch/safety/2005/Jun_PI/Camptosar_PI.pdf). This has limited use of the test, as has evidence indicating that *UGT1A1* testing may not be predictive for all irinotecan dosing regimens. As is the case with abacavir, FDA labeling has not resulted in widespread use of this test. This may be attributable to the consequences of testing being unclear, i.e., to the lack of clearly defined alternative therapeutic strategies for patients with specific *UGT1A1* genotypes.

AZATHIOPRINE 6-MERCAPTOPURINE, AND THIOPURINE METHYLTRANSFERASE

Rare but life-threatening granulocytopenia is associated with the administration of normal doses of azathioprine or 6-mercaptopurine to individuals carrying homozygous variants of the thiopurine methyltransferase gene (*TPMT*).[30] Although these drugs are indicated in the treatment of leukemia in children, most of their clinical use is in the treatment of inflammatory bowel disease in adults, a setting in which fewer studies of their utility have been conducted. The perception that other biomarkers, such as the simple measurement of white blood cell count, can serve as substitutes has limited the use of the genetic test. In addition, the availability of an equally predictive alternative—the test for phenotypic activity of the enzyme—has resulted in greater use of this phenotypic test in some settings.[31] The FDA labeling of the drugs involved now includes reference to the *TPMT* genotype test, but it does not specify either the criteria for testing or the consequences of the outcome of the test. Overall, the widespread utility of testing for *TPMT* genotype is limited by the rarity of the variant phenotype, the availability of alternative predictors, and an FDA label that is neither specific nor proscriptive (http://www.fda.gov/cder/foi/label/2004/09053s024lbl.pdf).

SUMMARY

Several broad lessons emerge from an evaluation of the current commercially available tests. Whatever the strength of an association between any variant and a therapeutic effect, data obtained in the intended clinical setting are critical. Although FDA approval requires some level of evidence, it does not inevitably lead to widespread use. The evidence required for reimbursement decisions, both commercial and governmental, will probably be greater than that required for simple FDA labeling. The publication of strong association data demonstrating high sensitivity and specificity, from either prospective or retrospective data, appears to be critical. It is evident from the precedents of trastuzumab and the Oncotype Dx test that these data can reasonably be derived from the retrospective examination of two adequately powered, prospective randomized trials, but this need not inevitably be the case. Ultimately, such reimbursement decisions hinge on simple return on investment, and this in turn depends on patient volume, test pricing, and acceptance by practitioners.

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Table 1

Drugs with available pharmacogenetic tests

Drug name	Pharmacogenetic test	Test name[a]	Pharmacogenetic information in drug label (drug label URL[b])
Abacavir	HLA-B*5701	HLA-B5701 test	"Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction." (Ziagen (abacavir) label: http://www.fda.gov/cder/foi/label/2008/020977s019,020978s022lbl.pdf)
5-FU	DPYD	TheraGuide 5-FU	"Efudex should not be used in patients with dihydropyrimidine dehydrogenase (DPD) deficiency." (Efudex (fluorouracil) label: http://www.fda.gov/cder/foi/label/2005/016831s049lbl.pdf)
Irinotecan	UGT1A1*28	Invader UGT1A1 Molecular Assay	"When administered in combination with other agents, or as a single-agent, a reduction in the starting dose by at least one level of CAMPOSTAR should be considered for patients known to be homozygous for the UGT1A1*28 allele." (Camptosar (irinotecan) label: http://www.fda.gov/cder/foi/label/2006/020571s030lbl.pdf)
Azathioprine 6-Mercaptopurine	TPMT	Prometheus TPMT Genetics	"It is recommended that consideration be given to either genotype or phenotype patients for TPMT."(Imuran (azathioprine) label: http://www.fda.gov/cder/foi/label/2008/016324s031,017391s014lbl.pdf)
Warfarin	CYP2C9 VKORC1	Cytochrome P450 2C9 and VKORC1 warfarin genotyping	"The lower initiation doses should be considered for patients with certain genetic variations in CYP2C9 andVKORC1 enzymes." (Coumadin (warfarin) label: http://www.fda.gov/cder/foi/label/2007/009218s105lblv2.pdf)
Tamoxifen	CYP2D6	Tamoxifen response	No information on CYP2D6 genotype and response to tamoxifen on drug label. (Tamoxifen label: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=4262)
Carbamazepine Phenytoin	HLA-B*1502	HLA B*1502 carbamazepine sensitivity	"Patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with Tegretol. Patients testing positive for the allele should not be treated with Tegretol unless the benefit clearly outweighs the risk." (Tegretol (carbamazepine) label: http://www.fda.gov/cder/foi/label/2007/016608s098lbl.pdf)
Clozapine	HLA-DQB1	Clozapine	No information on HLA-DQB1 genotype and response to clozapine on drug label. (Clozaril (clozapine) label: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=8631)
Trastuzumab	HER2	PathVysion HER2 DNA Probe Kit	"Detection of HER2 protein overexpression is necessary for selection of patients appropriate for Herceptin therapy because these are the only patients studied for whom

Drug name	Pharmacogenetic test	Test name[a]	Pharmacogenetic information in drug label (drug label URL[b])
			benefit has been shown. Assessment for HER2 overexpression and of HER2 gene amplification should be performed by laboratories with demonstrated proficiency in the specific technology being utilized." (Herceptin (trastuzumab) label: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=8221)
Dasatinib Imatinib	BCR-ABL (BCR and ABL1 translocation)	BCR-ABL quantitation in CML; BCR-ABL mutations in CML	"SPRYCEL is also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy." (Sprycel (dasatinib) label: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=8592)
Tetrabenazine	CYP2D6	AmpliChipCYP450Test	"Patients should be genotyped for CYP2D6 prior to treatment with daily doses of tetrabenazine over 50 mg. Patients who are poor metabolizers should not be given daily doses greater than 50 mg." (Xenazine (tetrabenazine) label: http://www.fda.gov/cder/foi/label/2008/021894lbl.pdf)

5-FU, 5-fluorouracil; CML, chronic myelogenous leukemia; HER2, human epidermal growth factor receptor 2;TPMT, thiopurine methyltransferase.

[a] The names of specific pharmacogenetic tests are provided for information purposes only as examples of available tests and do not constitute an endorsement of any particular test or vendor.

[b] All URLs were retrieved on 3 March 2009. Pharmacogenetic tests and vendors of these tests were identified through Internet searches using the Google search engine (http://www.google.com) and by searching the Food and Drug Administration (FDA) website (http://www.fda.gov) and the Pharmacogenomics Reporter website (http://www.genomeweb.com/newsletter/pharmacogenomics-reporter) using gene names, variant names, and/or drug names as query terms. For each drug, the most recent drug label was retrieved from the FDA website (http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/index.cfm); if the most recent drug label version was unavailable from the FDA but was available at DailyMed, the label was retrieved from DailyMed (http://dailymed.nlm.nih.gov/dailymed/about.cfm).