

POLICY

Pharmacy Benefit Managers, Pharmacies, and Pharmacogenomic Testing: Prescription for Progress?

Eric J. Topol

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Few would argue that the ability to match individual patients with the safest and most effective drugs and doses would be a major advance for clinical medicine. But while clinicians have been reluctant to routinely use pharmacogenomic analyses to guide their prescribing practices, pharmacy benefit managers and drugstores are proceeding with major pharmacogenetic initiatives.

FUTURE PERFECT

For decades, researchers and clinicians alike have been intrigued by the possibility of using genetic markers to match the right drug, at the right dose, with the right patient. Although there are a few accepted absolute indications for genotyping an individual before administering a particular medication, this is the rare exception in clinical care. But that may soon change, as a result of an unanticipated and unprecedented movement by pharmacy benefit managers (PBMs). Two of the largest firms—Medco, which provides pharmacy benefit coverage for 65 million Americans, and CVS/Caremark, handling prescriptions for over 35 million Americans—have announced that they are proceeding with major pharmacogenetic initiatives (1–3).

In leading up to the rollout of their new pharmacogenetic programs, the two PBM enterprises invested in companies with genotyping services or guidance. Medco acquired DNA Direct, a large full-service company with high-throughput genotyping capabilities, in February 2010, and CVS/Caremark gained majority ownership of Generation Health, an advisor for targeted-medicine services, in December 2009. Even before acquiring DNA Direct, Medco established a Personalized Medicine Center, set up its own genotyping facilities, and, in collaboration with the Mayo Clinic, published a large observational study supporting the clinical efficacy of genotyping to guide therapy with warfarin, a drug used to treat aberrant blood clot development in vessels

(4). Medco has a current pharmacogenetic program for 10 million of its members for the genotyping of those who are prescribed warfarin or the breast cancer drug tamoxifen. In July, this program was extended to clopidogrel (Plavix) and two AIDS drugs (abacavir and maraviroc), and later this year the program will be applied to three drugs used for the treatment of chronic myelogenous leukemia (5). CVS/Caremark is starting a similar genotyping program in July 2010, and its president, Larry J. Merlo, has declared that pharmacogenomic tests “are the next frontier” for the improvement of drug benefits (5).

PRESCRIPTION FOR CHANGE

This is certainly a unique trend in the history of U.S. medicine, at a time when prescription drug costs collectively reach \$300 billion per year (Fig. 1A). Whereas one might have anticipated that the medical community would, on its own initiative, have ushered in the era of pharmacogenetics, it has been left to the PBMs to get the ball rolling. What explains this phenomenon, and what are the incentives for PBMs?

The medical profession is unfortunately exceptionally resistant to change, and the demands of physicians for suitable evidence may at times provide cover for its profound lack of plasticity (6). A case in point is the pharmacogenetics story of clopidogrel, the third leading prescription drug in the United States, with over \$9 billion in annual sales

(7). This drug exists in a biologically inactive form and requires metabolism in the liver, predominantly via the P450 cytochrome CYP2C19, which converts the drug to an active antiplatelet agent that inhibits platelet aggregation at sites of damage in the vasculature. To date, via genome-wide association studies on the antiplatelet effect of clopidogrel, only a single locus that contains the *CYP2C19* gene has been demonstrated to explain the variability in platelet response to the drug. Carriers of loss-of-function *CYP2C19* alleles are extremely common, ranging from 30% in those of European ancestry to more than 50% in Asians. Studies in multiple large cohorts of patients who underwent coronary stenting demonstrated an approximately threefold higher rate of death, heart attack, or stroke for individuals with at least one loss-of-function allele. Ac-

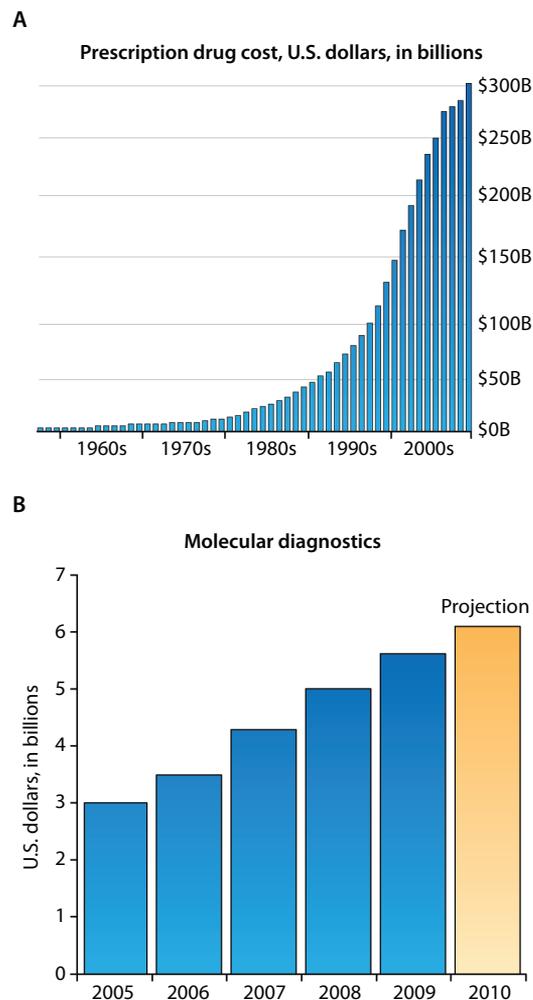


Fig. 1. Cost of living. (A) The rapid rise in prescription drug costs shows an unremitting increase over the past 5 decades. (B) Molecular diagnostics costs have doubled over the past 5 years.

cordingly, the stakes are high for serious adverse outcomes in individuals who are not responsive to this antiplatelet agent (8).

There is a simple way to confirm and quantify the extent of platelet response to clopidogrel, using a variety of point-of-care platelet function tests, each of which has been clinically validated to predict long-term prognosis. Furthermore, the information is highly practical, because patients who do not respond to the antiplatelet drug can have their platelet suppression achieved by using higher doses of clopidogrel or prasugrel (Effient) or by using alternative antiplatelet agents that are expected to be approved in the months ahead. Still, the medical community takes no initiative in routinely genotyping patients who are taking clopidogrel. In March 2010, the U.S. Food and Drug Administration (FDA) put a “black box” warning on clopidogrel that addresses the issue of risk in “poor metabolizers,” as defined by genotyping (8). However, months after this action was taken, it remains exceptionally rare for a patient receiving clopidogrel to undergo genotyping. The lesson here is clear: The medical community is unwilling to change clinical practice and wants more evidence, even in the wake of a significant regulatory body warning.

This reluctance on the part of clinicians has left the door wide open for PBMs. These companies can pitch to their clients—large employers—that they are benefiting their employees by avoiding the use of a drug that won't work or isn't being administered at an effective dose. For the exceptionally common clopidogrel medication, which costs \$4 to \$5 per day, the rationale for more precise use and the avoidance of major adverse outcomes seems attractive. In the next year or two, this medication will become generic, so that routine determination of genotype and, if necessary, platelet responsiveness could provide marked cost savings by avoiding the use of a proprietary drug when unnecessary. Promoting the right drug, the right dose, and the right cost for patients may well improve the competitiveness of PBMs.

But the potential benefits for PBMs go far beyond this pitch. Under the pretext of personalized medicine, these companies potentially may charge patients or insurance companies for genotyping services—for which the market has doubled over the past 5 years (Fig. 1B)—while at the same time also profiting from the drugs prescribed and sold. This may represent a conflict of interest or at least the potential perception

of double- or triple-dipping. It will be important for PBMs that pursue such initiatives to be transparent about their genotyping strategies and drug recommendations.

DIRECT TO CONSUMERS

Walgreens is a large chain of over 7500 drugstores in the United States and operates a PBM service for employers. The Walgreens PBM has not yet initiated a pharmacogenetic strategy. However, in May 2010, it was announced that Pathway Genomics, which markets consumer genomics panels for the determination of disease susceptibility and for pharmacogenetic interactions, would have its kits available in all Walgreens drugstores (9). The Pathways Genomics Drug Response Report panel is illustrated in Fig. 2 (my summary result) and was going to be made available to consumers for \$79. The report provides data for eight different drugs, with either the typical or atypical response noted, and more details and advice for individuals who have gene variants that are associated with an atypical response of reduced efficacy or heightened risk of side effects. For illustrative purposes, my findings indicated slow metabolism of caffeine, such that chronic ingestion of high amounts of caffeine (>4 cups of coffee per day) would be associated with a more than twofold

Pathway Genomics Drug Response Report for Eric Topol

Drug name	Drug response
Abacavir	Hypersensitivity
Caffeine	Metabolism
Carbamazepine	Hypersensitivity
Clopidogrel	Metabolism
Methotrexate	Toxicity
Statins	Protection against myocardial infarction
Statins	Myopathy
Tamoxifen	Metabolism
Warfarin	Sensitivity

□ Atypical response

Fig. 2. Medicine gets personal. The author's pharmacogenetic report from Pathway Genomics.

increased risk of myocardial infarction; marked sensitivity to warfarin, which would require the use of low drug doses; and normal expected responsiveness to clopidogrel with the *CYP2C19*^{+/+} wild-type alleles.

Within 2 days of the announcement, the FDA notified Pathway Genomics that its test

had not been approved, and Walgreens announced that it would postpone selling this consumer genetic panel (10). This comes as quite a surprise, because the genome-wide scanning tests from companies such as 23andMe, Navigenics, and deCODE Genetics are widely available to anyone via the Internet and are not FDA-approved. It appears that somehow wide-scale availability of consumer genomic testing through a large chain of drugstores set a new precedent and “crossed the line” with respect to FDA tolerance. As an added sequel, the House Committee on Energy and Commerce, chaired by Congressman Henry Waxman (D-CA), has subsequently launched an investigation of Pathway Genomics and extended this to 23andMe, deCODE Genetics, Illumina, Knome, and Navigenics (11) and held a hearing on 22 July 2010 with a report from the Government Accountability Office that highlighted significant inconsistencies, misleading test results, and deceptive marketing practices (12).

Nevertheless, the intersection of pharmacogenomics with large PBMs and two of the largest drugstore chains in the world is a sign of the times. Although the medical community continues to be reluctant to accept the utility of genotyping for predicting drug response, PBMs are pursuing strategies that touch over 100 million Americans. Even if lowering cost is not the prime motive for PBMs, more appropriate matching of drugs, doses, and patients may ultimately help to lower the cost of prescription drugs. After the FDA shutdown of the Pathway Genomics testing panel at Walgreens, there has been an outcry by consumers, rallying and declaring “they're my data” (13), and one individual nicely articulated the argument for the democratization of genomic data: “To say that this information has to be routed through your doctor is a little like the Middle Ages, when only priests were allowed (or able) to read the Bible. Gutenberg came along with the printing press even though few people were able to read. This triggered a literacy/literature spiral that had incredible benefits for civilization, even if it reduced the power of the priestly class” (14). At present, we are in a state of disequilibrium regarding the role of pharmacogenomics among the four principal groups concerned: consumers, physicians, regulators, and PBMs.

The lack of alignment will probably be further exacerbated in the next phase of genomic medicine, in which whole-genome

sequencing becomes commonplace. The first clinically annotated sequence, albeit requiring a team of 30 investigators and 600 person-hours, demonstrated 63 pharmacogenomic variants of clinical relevance (15). As more information becomes available from genome-wide association studies that provide actionable data, such as recently reported regarding interferon therapy for hepatitis C (16), the era for routine pharmacogenomics may finally shift into high gear. In the end, we may ultimately view the surprise movement by PBMs and drugstores as having helped catapult genomic medicine forward.

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