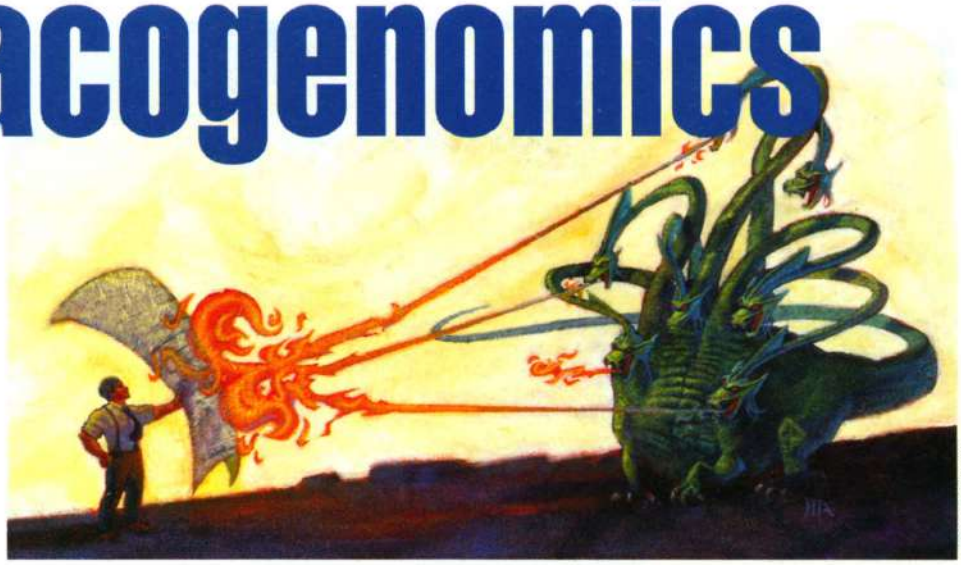
The 5 Myths of Pharmacogenomics



MASTER SERIES

Stan Bernard

PREVAILING NOTIONS ABOUT PGx ARE OFTEN BASED ON MISCONCEPTIONS. BUT IN REALITY, THE TECHNOLOGY PLAYS A VITAL ROLE IN PHARMA'S BUSINESS TODAY.

Stan Bernard, MD, MBA, is president of Bernard Associates, a management consulting firm based in Neshanic Station, NJ. He also teaches Pharmaceutical Management at the Wharton School of Business and can be reached at SBernardMD@aol.com or 908-369-0842.

Since the historic decoding of the human genome, there has been a lot of buzz about pharmacogenomics (PGx), defined simply as how people respond to drugs based on their genes. Within the pharma industry, researchers are excited about PGx's potential to accelerate drug discovery and development by identifying better drug targets, establishing preferred patient populations, and improving safety and efficacy profiles. But there has been much less excitement among industry's business executives, especially marketers, many of whom have concerns about PGx's business impact.

The emerging field has the potential to dramatically change the pharma business, perhaps even more than the way managed care has altered the industry's marketing model. Consequently, executives need to understand the implications and applications of pharmacogenomics today—because they have already begun to influence the use and marketing of pharma products. Unfortunately, many executives have misconceptions, misunderstandings, and misgivings about pharmacogenomics. This article attempts to put the emerging technology into perspective by identifying and debunking five common myths.

1. PGx Is Only a Research Tool

Many industry execs believe that pharmacogenomics is primarily a research and development tool used to identify

Executive's Checklist

- Is pharmacogenomics on your executive agenda and, if so, where?
- What are PGx's implications for your industry and company?
- What is the company's strategy for leveraging PGx in drug commercialization?
- How does the company plan to use PGx for and against competitive differentiation?

Business Development/Licensing

- Is the company continually monitoring PGx technologies and companies for partnerships and competitive exclusivities?

Intellectual Capital/Organization

- Does your company have PGx intellectual capital and expertise?
- Does the company have the staffing and resources to support PGx?
- Has it embedded pharmacogenomics in corporate processes?
- What PGx training is the company providing?

drug targets more quickly and that it has yet to have a role in the success or failure of marketed drugs.

In the broadest sense, PGx has both research and clinical applications: to identify drug targets (research) and to predict the safety and efficacy of drugs in individual patients or groups of patients (clinical). The second application is referred to as pharmaco*genetics*. For the purposes of this article, the term pharmacogenomics encompasses the subgroup of pharmacogenetics.

The first half of the myth is based on experience: Most major pharma companies use PGx to identify new drug targets and to select appropriate study patients. But there are several cases that demonstrate how pharmacogenomic differences have affected products' commercial prospects. For example, in 1998, FDA forced Hoechst Marion Roussel (now Aventis) to withdraw its $600-million-a-year anti-allergy medication Seldane (terfenadine) from the market because of pharmacogenomic differences in a very small segment of patients. Fewer than 0.5 percent of all people have a variant CYP3A gene that makes them unable to metabolize Seldane in the presence of the antibiotic erythromycin, resulting in severe cardiotoxicity. If the company had had a pharmacogenomic test to identify the small population of adverse reactants at the time, Seldane may have remained on the market. Consequently, Aventis was forced to focus its marketing efforts on another anti-allergy medication, Allegra (fexofenadine).

Researchers now believe that many recent drug withdrawals—Bayer's cholesterol agent Baycol, Wyeth's appetite suppressant Redux, and GlaxoSmithKline's oral diabetes agent Rezulin—may have been a direct result of pharmacogenomic differences among small patient subpopulations. Many more potentially useful and lucrative drugs may have never reached the market because poor responders negatively affected the overall safety or efficacy data.

Isolating pharmacogenomic responses can also rescue a drug. Genentech found that its breast cancer drug Herceptin (trastuzumab) was effective only in the 25 percent of women whose tumors generated excess proteins from a HER2 gene.

Consequently, the company saved the "failing" drug by coupling it with a PGx test (HercepTest) to identify potential responders. GSK's Ziagen (abacavir), an important HIV treatment, may precipitate a severe and potentially fatal hypersensitivity reaction in approximately 5 percent of people with a certain genetic marker. To rescue the product's $200 million in annual sales, GSK is currently working with FDA to develop a PGx test to identify patients likely to have the adverse reaction.

2. PGx Is for Tomorrow

The second most common misconception is that pharmacogenomics is a technology that will not be used by doctors in clinical practice for at least five to ten years. The reality is that physicians have been using some pharmacogenomic tests in clinical practice for several years.

GlaxoSmithKline's drug Purinethol (mercaptopurine) is commonly prescribed for leukemia in children. Yet one in 300 children has a gene defect for the enzyme thiopurine methyltransferase (TPMT), which normally inactivates the drug. It is now standard practice to give a TPMT test to screen for kids at risk of developing life-threatening bone marrow toxicity. Oncologists also routinely use HercepTest on metastatic breast cancer patients to identify candidates for Herceptin therapy. Many other pharmacogenomic tests are in development that will identify patient responses to other cancer therapies.

Several companies, including Genelex and Roche Diagnostics, offer a series of PGx screening tests for cytochrome p450 (CYP) enzymes and pathways. Produced in the liver, the enzymes metabolize more than half of all marketed drugs. About 5–10 percent of Caucasians have defects in those pathways that may reduce the effectiveness or increase the toxicity of certain categories of drugs, including analgesics such as morphine and Demerol (meperidine), antiarhythmics, and antidepressants like Prozac (fluoxetine).

One high-profile case involving cytochrome p450 enzymes dramatically demonstrates the promises and pitfalls of pharmacogenomic testing. In 1999, FDA reported the Prozac-related death of Michael Adams-Conroy, a nine-year-old boy with mental illness. The medical examiner concluded that the boy's adoptive parents had administered an intentional Prozac overdose. Indicted for murder, the parents sought a second medical opinion, which found the boy had a CYP 2D6 gene defect, resulting in poor drug metabolism and a toxic accumulation of his prescribed Prozac dose.

The murder charge was dropped, and in a *Fortune* article (10/02), Michael's mother, Jayne Adams-Conroy, stated: "After Michael died, we found out that there were tests to spot enzyme deficiencies that can cause adverse drug reactions. I felt devastated when I heard that. It should be the norm that the tests are used whenever there are concerns about possible side effects." ➤

3. PGx Is Dependent on Technology

Many in the industry also believe that the only major factor driving the adoption of pharmacogenomics in clinical practice is the rate at which PGx technology develops. Despite the highly profiled Adams-Conroy case, CYP tests—unlike the TPMT test and HercepTest—are seldom used in clinical practice, although they are commercially available.

One possible explanation is that the CYP technology is not as accurate or drug-specific as the other two tests. Although it is likely that technology advances will help drive overall adoption, there are several other important and interdependent factors that are driving the adoption of PGx testing in clinical practice.

Regulations. One of the major reasons that HercepTest has become standard clinical practice is that FDA required in the product labeling that it be given before prescribing Herceptin. In a 2002 *Pharmacogenomics Journal* article, FDA regulators said. "It is likely that the FDA would not have approved Herceptin without the accompanying diagnostic [pharmacogenomic] data." The agency is also encouraging pharma companies to conduct PGx research and submit the data to a proposed "Interdisciplinary Pharmacogenomic Review Group" that is separate from the drug approval process. (See *PE*'s Washington Report, June 2003.) Other international regulatory bodies are also developing PGx regulations.

Reimbursement. US reimbursement for diagnostics often follows regulatory or governmental policies. For example, most third-party payers reimburse for HercepTest. In fact, they typically require the test *before* reimbursing for Herceptin. In cases where there is no regulation or government policy, payers often follow "the standard of care." Consequently, the TPMT test is typically covered, while CYP tests usually are not.

Most payers view PGx testing as another medical technology that will ultimately increase their costs. However, a few are conducting studies to ascertain if they can "cherry pick" pharmacogenomic tests to reduce drug costs in carefully selected cases. United Healthcare is conducting a study with Interleukin Genetics to develop a PGx test that could exclude patients who may be non-responsive to certain high-cost rheumatoid arthritis drugs. Payers are thus likely to selectively support and use pharmacogenomic testing and data.

Legalities. Use of the TPMT test has been implicitly driven by the threat of medical liability. Oncologists do not want to risk prescribing Purinethol to a child with leukemia without ensuring that the child is not at risk of bone marrow toxicity from a TPMT gene defect. However, legal liability in the quickly evolving pharmacogenomic area can be ambiguous. The doctor who prescribed Prozac to Michael Adams-Conroy was sued by the boy's parents, despite the fact that the CYP test was not a standard of care at that time.

The case was settled out of court. In a separate lawsuit (Georgia, November 2002) a widower alleged that Lilly, Prozac's maker, failed to publicize research showing that some people are "poor metabolizers of Prozac," referring to patients with CYP2D6 gene defects. Medical and product liability threats will likely hasten PGx's use.

Competition. There are a plethora of pharmacogenomic players who see the field as a lucrative business opportunity. Many small companies, such as Affymetrix, Aureon Biosciences, Dako, and Decode Genetics, are developing and selling PGx tests, information, and supplies. Large diagnostic and laboratory testing companies, including Roche Diagnostics and Quest Diagnostics, are also involved in the field.

Premier hospitals and academic centers have embraced the genomics business as well. Harvard and MIT recently launched a $300 million "genome institute" joint venture. Massachusetts General Hospital, Johns Hopkins, and Columbia all have announced multimillion-dollar genetic initiatives. The quality and quantity of healthcare entities investing in genomics and pharmacogenomics will expedite the technology's adoption.

Stakeholders. Three key groups will significantly influence PGx's adoption rate: physicians, patients, and pharma companies. Physicians will be influenced most notably by patient safety, medical liability, regulations, and reimbursement, especially if they can be reimbursed for conducting or consulting on PGx tests. They will also have to be convinced of PGx's clinical validity and benefit, which suggests that most physicians may take a cautious and somewhat skeptical approach to the technology.

Although consumers and patients may have concerns about insurance and privacy issues, they are likely to support PGx tests that predetermine which drugs are helpful or harmful. That assessment is based on the assumption that consumers will not have to pay much out of their pocket for the tests. The prevailing view in the pharma industry is that most executives and marketers do not want PGx testing and will resist its adoption. ➤

Marketer's Checklist

- What pharmacogenomics education/training has your team received?
- Have you done a PGx assessment as part of your marketing plan?
- What are PGx's implications and applications for marketing products in your specific therapeutic area?
- Are there processes in place to embed PGx into marketing?
- Does PGx help or hurt your efforts to position your products?

Research/Clinical

- From a PGx research/clinical standpoint, what do you know about your products?
- What PGx trials are being conducted by your company to develop differentiation claims?

Competition

- What is your competition doing with PGx to differentiate its products?
- Where is your product vulnerable to PGx differentiation?

4. PGx=Death to Blockbusters

The main reason for that resistance is the myth that pharmacogenomics will fragment and reduce products' market size and, ultimately, kill the blockbuster model. Reporter Geeta Anand summarized that view in a 2001 *Wall Street Journal* story: "The technique threatens to be so disruptive to the business of big pharmaceutical companies—it could limit the market for some of their blockbuster products—that many of them are resisting its widespread use."

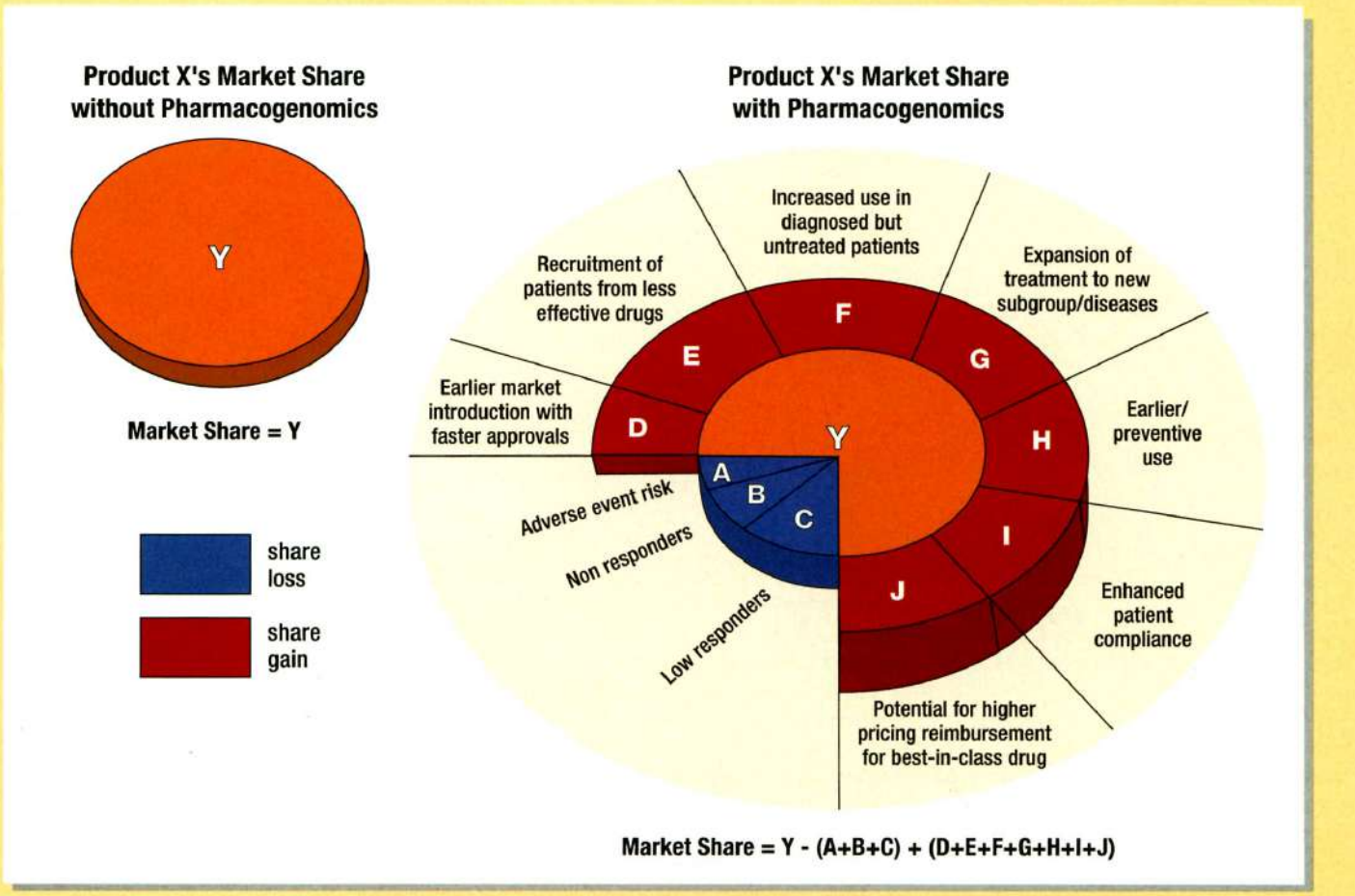
But the reality is that pharmacogenomics has the potential to either reduce or increase market size, depending on a variety of factors specific to the individual product at a certain point in time. Imagine that drug X has market share Y before genetic testing is introduced. Then PGx testing comes into the marketplace. Product X is likely to lose the market share of patients identified to have adverse events (A), no efficacy (B), or low efficacy (C). Consequently, the market share of product X with pharmacogenomics becomes Y-(A+B+C). (See "Win Some, Lose Some.") That is the "glass is half empty" perception shared by many pharma executives and marketers.

However, PGx testing has several benefits, most of which have the potential to increase market share:

- Faster approvals with earlier market introductions (D): PGx testing early during R&D should identify drug targets and responsive patients more quickly.
- Recruitment of patients from less effective drugs (E): Patients who fail PGx testing for competing drugs could become new patients for product X.
- Increased use in diagnosed but untreated patients (F): Patients who have refused treatment because of safety or efficacy concerns would be more likely to try product X if a test confirmed that they would be a good candidate.
- Expansion of treatment to new subgroups/diseases (G): Understanding of the genomic basis of diseases helps researchers identify disease subgroups and new diseases that can be treated with the same drug.
- Preventive use (H): Patients who have been identified as susceptible to certain diseases may elect to take product X to slow the rate of disease progression.
- Enhanced patient compliance (I):

WIN SOME, LOSE SOME

Marketing a genetic test with a product can produce both share loss and gain, potentially resulting in a market share increase.



Source: Bernard Associates

PE Graphic

Patients who know that the drug will work for them will be more likely to comply with the treatment. Moreover, if patients fail to respond appropriately, their doctors are more likely to know the problem is noncompliance.

- Potential for higher pricing/reimbursement (J): Governments and other payers may be willing to pay a premium for drugs that, with PGx tests, can identify the patients who will respond favorably. Or at least those products may have a formulary advantage over products without PGx testing support.

Thus, the net result of pharmacogenomics' effect on product X's market share could be an overall gain.

5. Marketers Need Not Worry

The last misconception is that, because it will be years before pharmacogenomics is applied in clinical practice, it will take even longer to affect marketing. But some pharma marketers have been dealing with, or reacting to, pharmacogenomic issues for several years. Even though there are only a handful of such tests in the marketplace, there is a groundswell of PGx research, reports, and opinions that could influence how physicians and other stakeholders view the efficacy and safety of particular products. There are three primary sources of PGx information: scientific researchers, pharmacogenomic companies, and pharma companies.

Researchers have published numerous scientific articles that have been covered in the lay media. Consider, for example, the many stories about "individualized hormone replacement therapy," based on a 2002 *New England Journal of Medicine* article about women taking estrogen who have a particular genetic variation in the estrogen receptor. Those women therefore obtain higher HDL (good cholesterol) responses and presumably better cardio-protective effects than women without the genetic variation. That information could potentially explain some of the controversy surrounding the differential responses of women taking HRT.

Pharmacogenomic testing companies are also interested in publicizing their data for specific products to demonstrate their capabilities. For example, Genaissance has been conducting a highly publicized trial of the statins Lipitor (atorvastatin), Zocor (simvastatin), and Pravachol (pravastatin). It is no accident that Genaissance selected the lipid-lowering category—it is the chemical class with the highest annual sales.

Executives and strategists need to understand and appreciate PGx's business implications for their industry.

Although the company has distributed press releases announcing that it has "discovered genetic markers associated with responses to individual statin drugs," it has not yet released information about which statin drugs have the greatest cholesterol-reducing effects in patient populations with certain genetic profiles. If Genaissance or another testing company were to publicize the significant differential effects of those drugs, it would likely influence physicians' prescribing behavior long before supporting scientific studies and tests became available.

And pharma companies themselves are conducting or sponsoring PGx studies to differentiate their products. In 2000, Craig Fitzgerald, vice-president of applied genetics for GlaxoSmithKline, wrote about such activities in *Advance Tech Monitor*: "At Glaxo, we intend to generate evidence for pharmacogenetic claims and use them as a novel and unique way to differentiate our products. For example, Glaxo intends to publish its first differentiation study later during the year 2000. This study will use pharmacogenetics to differentiate Glaxo compounds from competing products and make additional claims or superiority claims for the company's products. Hopefully, the FDA will be willing to discuss the results of this study and allow us to use them for marketing purposes."

Clearly, marketers cannot wait until PGx tests become widely available. Nancy Lurker, former group vice-president of Pharmacia's Global Prescription Business, said it best at the 2002 Pharmaceutical Marketing Congress: "If you want to be a leading executive in the industry, then you need to know about pharmacogenomics. It is coming. Marketers need to be aware of these changes as they are going to alter the landscape of marketing."

So what can marketers do to prepare? Initially, they should become better educated about pharmacogenomics, particularly in their therapeutic areas. Next, they should work with their teams and other experts to determine the potential implications and applications for their products. Specifically, marketers need to determine what clinical trials their company initiated or completed for specific products and what the competition is doing or could do to differentiate its products using pharmacogenomics. See "Marketers' Checklist" on page 74 for a more complete list of activities.

Senior executives and strategists have their own list of priorities. (See "Executives' Checklist," page 72) They need to understand and appreciate PGx's business implications for the industry and their company. It is important that they develop an overall corporate pharmacogenomic strategic plan. The company should monitor PGx developments and identify potential partners to assist in research and test development. Executives also need to ensure that their company trains and develops internal staff and embeds PGx in the company's business processes, not just R&D.

Perhaps the most important thing that pharma executives and marketers need to understand is that the prevailing notions about pharmacogenomics are often based on myths. Pharmacogenomics is not a futuristic force. It is a reality of doing business in the pharmaceutical industry today, and its impact is likely to grow dramatically. ▮