

THE BEGINNING OF A NEW ERA IN MEDICINE



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Here, Dr. Bernard argues that the use of genetic and related information to personalize medical care is the culmination of medicine's long quest to provide the right treatments to the right patients. Furthermore, he believes that the unavoidable shift towards personalized medicine should be embraced by the pharmaceutical industry and provides a checklist for executives to monitor their own efforts.

WHLE: People mean different things when they use the term 'personalized medicine.' How do you define personalized medicine?

SB: Personalized medicine is the use of a person's genetic and related information to help understand and manage disease susceptibility, diagnosis, and treatment. Other terms people use to describe personalized medicine and related technologies include 'targeted therapy,' 'individualized medicine,' 'pharmacogenomics,' and 'pharmacogenetics.' The important distinction is that personalized medicine is not limited to personalized medicines; it signifies a broader definition that includes personal disease risk and detection as well as tailored, individualized treatment.

WHLE: So it is not just about drugs, then, and it is not just about diagnostics. How do you differentiate the various components of personalized medicine?

SB: Personalized medicine is a new clinical approach that applies genetic and related information across the spectrum of medical care, from disease

prevention and detection to therapeutic management and monitoring. I classify personalized medicine into two major categories: disease applications and drug (or therapeutic) applications. Among the disease applications, there are two major types: *disease susceptibility* applications and *disease diagnostic* applications. Disease susceptibility applications help determine the likelihood of a person getting a disease. For example, Myriad Genetics' BRCA1/BRCA2 test helps determine the likelihood of a woman getting breast cancer or ovarian cancer. Disease diagnostic applications help to establish or confirm the diagnosis of a disease or condition. For instance, TM Bioscience recently received FDA approval for a genetic test to help diagnose cystic fibrosis.

There are two types of therapeutic applications: *designer* or *targeted drugs* and *pharmacogenetic* or *drug response* tests. These tests help identify how individuals will respond to drugs from an efficacy and safety standpoint. The classic example of a drug response test is HercepTest, a genetic test to predict

the response of women with breast cancer to the cancer drug Herceptin. We have several other examples of drug response applications. Most recently, Roche Diagnostics received FDA approval for its AmpliChip CYP450 test which helps determine patient response to about 25% of marketed drugs.

WHLE: Within drug response tests, two types of tests have received a lot of attention: safety response tests and efficacy response tests. Is one or the other likely to have a more pronounced impact on medicine?

SB: While I am primarily a business consultant, I am also a physician. From a medical perspective, there is no greater initial need than for safety response testing, especially considering that we have over two million severe adverse drug reactions a year causing over 100,000 deaths. A significant portion of these are related to genetic factors. I am very excited about the potential of safety response tests to reduce that death toll.

Two recent cases highlight this issue. GlaxoSmithKline's Ziagen is an AIDS drug that causes a potentially fatal hypersensitivity reaction in about 5% of patients with certain genetic variations. The FDA has been working with GSK to create a test to screen patients needing that particular drug. Similarly, researchers at St. Jude's Hospital in Memphis have developed a TPMT pharmacogenetic test which helps keep Purinethol and related chemotherapeutic agents on the market. Children with cancers treated by those agents take the TPMT Test to identify the 1-2% of individuals who might develop a life-threatening adverse drug reaction because of their genetic profile. Therefore, we have shown that there is the potential, in selected cases, for some drugs to be rescued by the development and use of safety response tests. By preventing those most likely to suffer adverse reactions from taking a medication in the first place, we can adjust our safety predictions for others not at increased genetic risk, thus seeing not only an enhanced safety profile of various medications but also presumably enhanced efficacy as well.

As important as safety is, I believe we are more likely to see some of the efficacy response tests commercialized first, particularly in the area of cancer. There are already some early efficacy tests available

for a few cancer drugs, like Herceptin and Tarceva. However, we have also seen that some efficacy response tests, like the one for the cancer drug Iressa, may not be as accurate and predictive of response as we had initially hoped. It is important to recognize that in many cases, genetic testing will not provide black and white answers: there will be many gray areas where we must consider probabilities, not certainties.

WHLE: Popular opinion is that personalized medicine is very futuristic, but you have cited a number of examples of its use in current medical care. How is it that personalized medicine is available now?

SB: The most important thing people need to know is that the era of personalized medicine has been underway for nearly two decades. It is already being used by health care professionals to benefit patients today. Let me put this in context. Since Hippocrates' time over 2000 years ago, health care practitioners have tried to personalize medicine without the information or tools

to achieve the level of personalization we desire. As we now define it, personalized medicine allows us to enter the newest frontier of medical understanding: the genetic level. Genetic medicine is the ultimate personalized level of intervention because no two human beings have and express genes exactly the same way. If we can manage and treat patients at the genetic level, that is as personal as it can get. We have already begun these sorts of genetic interventions, but the next 10 years will see an exponential increase in the personalized medicine tools in the proverbial black bag.

WHLE: What is the vision of personalized medicine? What value does personalized medicine provide and are we certain of that value?

SB: The vision of personalized medicine is three-fold: to leverage genetic information and applications to better prevent and detect diseases; to develop and tailor treatments for certain diseases and individuals; and to maximize safety and efficacy of treatment options for the individual. Clinically, personalized medicine represents the next era in medicine, the hallmark of the next new frontier in scientific discovery and clinical application. These new genetic technologies have the potential to help health care professionals prevent disease, improve

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diagnoses, and enhance safe and effective treatments, all of which will ultimately result in better patient outcomes at a lower cost. Consequently, individual patients will be the primary beneficiaries of personalized medicine approaches, but businesses will benefit as well.

Many business executives still need convincing that personalized medicine is to their advantage and that they need to address this area now. Many executives have been reluctant to dedicate sufficient resources to personalized medicine, pharmacogenomic research, and related activities because of a misconception that personalized medicine will fragment markets and niche their products, ultimately reducing pharmaceutical sales and destroying the 'blockbuster model.' This is a myth. In fact, personalized medicine applications, including both disease and drug applications, have the potential to increase or decrease product shares and market sizes, depending on a host of important factors.

WHLE: In what ways might personalized medicine affect pharmaceutical business models?

SB: Many pharmaceutical professionals are not aware that personalized medicine can actually increase market size or share for products in several potential ways: by recruiting patients from other less effective or appropriate competitors; by increasing use in diagnosed but untreated patients; by expanding to genetically similar disease states beyond a drug's primary indication; by encouraging earlier, preventive use of drugs; by enhancing patient compliance; and by obtaining higher reimbursement for safer and more effective drugs. In addition, personalized medicine has the potential to rescue drugs that otherwise might be withdrawn from the market. The FDA agreed to approve Herceptin only with the HercepTest.

I believe that progressive pharmaceutical companies will actually create a few 'megablockbusters' by leveraging personalized medicine technologies. If we can identify drugs that are shown to be extremely safe or effective for certain individuals by pharmacogenetic tests, they could potentially capture a larger portion of the market. Imagine if pharmacogenetic tests on Lipitor demonstrated superior efficacy or safety over its competitors, efficacy in other diseases, or that drug susceptibility tests identified more patients that

could benefit from statin therapy. That is actually a possibility.

There are many other myths that I confront in working with pharmaceutical and other business executives. I often hear that 'personalized medicine won't happen for years, so my company doesn't need to worry about it.' Try telling that to the Ziagen marketing team. Try telling that to the Iressa marketing team. On the other side, there are a number of cutting-edge companies, such as Genentech, which are embracing this technology and actively leveraging it. Clearly, personalized medicine is already impacting the pharmaceutical industry - positively and negatively - in selected situations.

WHLE: It seems as if the industry is heading for a tipping point where having a test may be necessary to maintain competitive advantage.

SB: It is clear that personalized medicine and pharmacogenetics will increasingly be used for competitive advantage by companies for their products. For example, a company marketing a late entrant into a therapeutic category may use a pharmacogenetic test to differentiate the product and

take a piece of a sizable market. Herceptin did that. Herceptin started with a small slice of the metastatic breast cancer market and has increasingly taken a bigger wedge, driving nearly \$1 billion in sales.

In the future, I anticipate that some companies will develop pharmacogenetic tests and encourage doctors to use their test first to see if their drug will work. If their patient responds well to that drug, it will be used ahead of competitive agents. There will be gradually increasing competitive pressure within the pharmaceutical industry to leverage personalized medicine, which will speed the adoption of the technology.

Over time, the battleground for pharmaceutical marketers will increasingly move from their products to the pharmacogenetic test that identifies the appropriate use of their products. Consequently, we are seeing some of the more progressive companies forming relationships with diagnostic testing companies and seeking exclusive licensing agreements for diagnostic tests and processes. Gradually, drug response tests in some therapeutic categories will become the key product differentiator, more important than clinical data, marketing activities,

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or sales detailing.

WHLE: Competitive pressure is one way to move this forward, what are some other likely drivers for personalized medicine?

SB: There are a number of other factors that will influence the adoption rate of personalized medicine. Certainly, legal considerations, including product liability and medical malpractice, will be important. Eli Lilly has already been sued by a widower whose husband died taking Prozac. Subsequent information suggested that he was a poor responder to Prozac-like medications based on his genetic profile. The AMA has warned physicians to become more educated about genomics in order to avoid medical malpractice.

Regulations will also influence the rate of adoption of personalized medicine applications. Generally speaking, the FDA and other regulators are very favorably disposed to personalized medicine because these applications could help ensure the safety and efficacy of the drugs they are regulating. In 2005, the FDA issued guidelines encouraging the use of pharmacogenetic and related information in clinical trials.

Reimbursement will be a powerful influencer of personalized medicine. Most payors are concerned that personalized medicine tests will increase their overall costs, and they fear the increased financial burden of new tests and technologies. However, these applications could ultimately limit inappropriate product and service utilization as well as costly consequences of adverse reactions due to inappropriate or ineffective medication choices. Recognizing this, United Healthcare formed a partnership with Interleukin Genetics in 2002 to evaluate genetic testing to help guide the appropriate use of expensive rheumatoid arthritis drugs.

WHLE: In such a complex environment, who is going to be successful?

SB: There are a wide variety of players and categories of players in the personalized medicine arena. It is premature to tell who will ultimately succeed, but there are some early leaders. Among providers, the Mayo Clinic has leveraged their database of a local, genetically-homogenous population. Many genetics companies

have demonstrated early successes, including Myriad Genetics, deCODE Genetics, and Celera Genomics. Platform developers such as Affymetrix, whose platform was used for Roche's recently approved AmpliChip Test; leading diagnostic companies, including Roche and Abbott; and laboratory companies, particularly LabCorp and Quest, are all well-positioned. IT companies like IBM and imaging companies like GE stand to benefit considerably. Roche, Genentech, and GSK are among the early leaders on the biopharmaceutical side.

As with most new medical technologies, some will succeed but many will fail. Companies most likely to succeed will be those whose executives have the vision and leadership to leverage the technology and develop appropriate business models for their companies. Just as the field of personalized medicine is based on individual variation and individual solutions, the business opportunities, strategies, and solutions need to be based on individual company assessments, business plans, and customized solutions. There is no generalized approach to personalized

medicine. Given that, there are several key steps that business executives should take to help ensure success in this field [see Dr. Bernard's "Executive's Checklist" in the box accompanying this article].

WHLE: On a different note, you are a Wharton alumnus. How has your career led you to your current position, consulting to executives on cutting-edge issues like personalized medicine?

SB: As a young boy, I dreamed of becoming a surgeon. This led me to Baylor College of Medicine where I had planned to study general surgery with people like the great heart surgeon Dr. William DeBakey. While there in the early 1980's, I realized that the evolving managed care model would have a major adverse effect on medical practice. So, I decided to transition from clinical medicine to leverage my medical background in the business world.

During my transition, I was fortunate to get advice from a number of leading health care executives. The most influential advice came from Dr. Tommy Frist, Jr., the CEO of Hospital Corporation of America at

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EXECUTIVE'S PERSONALIZED MEDICINE CHECKLIST

Corporate Strategy

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

Intellectual Capital/Organization

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

Business Development / Licensing

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

Marketing

- What are personalized medicine's implications and applications for marketing products in your specific therapeutic area?
- Does personalized medicine help or hurt your efforts to position your products?
- What is your competition doing with personalized medicine to differentiate its products?

Adapted from Bernard, S., "The Five Myths of Pharmacogenomics," Pharmaceutical Executive, October 2003.

that time. He advised me to go get an MBA in health care management, specifically suggesting that I attend what he referred to as 'the best health care management program in the world': The Wharton Health Care MBA Program. I followed his advice and went to Wharton. I began my post-MBA career at Squibb Pharmaceuticals (now Bristol-Myers Squibb) in Worldwide Licensing and Business Development and held several other executive positions within the company during my time there.

In the mid-1990's, I joined A.T. Kearney, a leading global management consulting firm and division of EDS as a principal in their Health Care and Pharmaceutical Consulting Practice. While at A.T. Kearney, I received a number of requests from business executives saying that they wanted to engage me - not a consulting team - to consult for them. Recognizing the business opportunity, I launched Bernard Associates (www.BernardAssociatesLLC.com) in 1999 and created a novel approach to management consulting. I call this 'Executive Consulting.' In this new consulting model, I work directly with business executives and their teams, leading their intra- or interdepartmental teams through the process using my consulting methodologies, facilitation and project management skills, and relevant domain expertise. The internal team then works on the project under my guidance.

There are three major business advantages to the Executive Consulting approach: increased likelihood of project implementation with internal team buy-in, retention of intellectual capital, and dramatically lower costs. I have successfully grown this practice over the past six years and have had the pleasure to work with seven out of the top ten pharmaceutical companies as well as many other health care products companies, including biotech, medical device, diagnostics, and consumer products companies. I have maintained a connection with the Wharton School by teaching in two different courses: the 'Pharmaceutical Management' course starting in 1991 and the 'eHealth' course starting in 1999. I have also had the pleasure of working with several former Wharton students as clients. ■