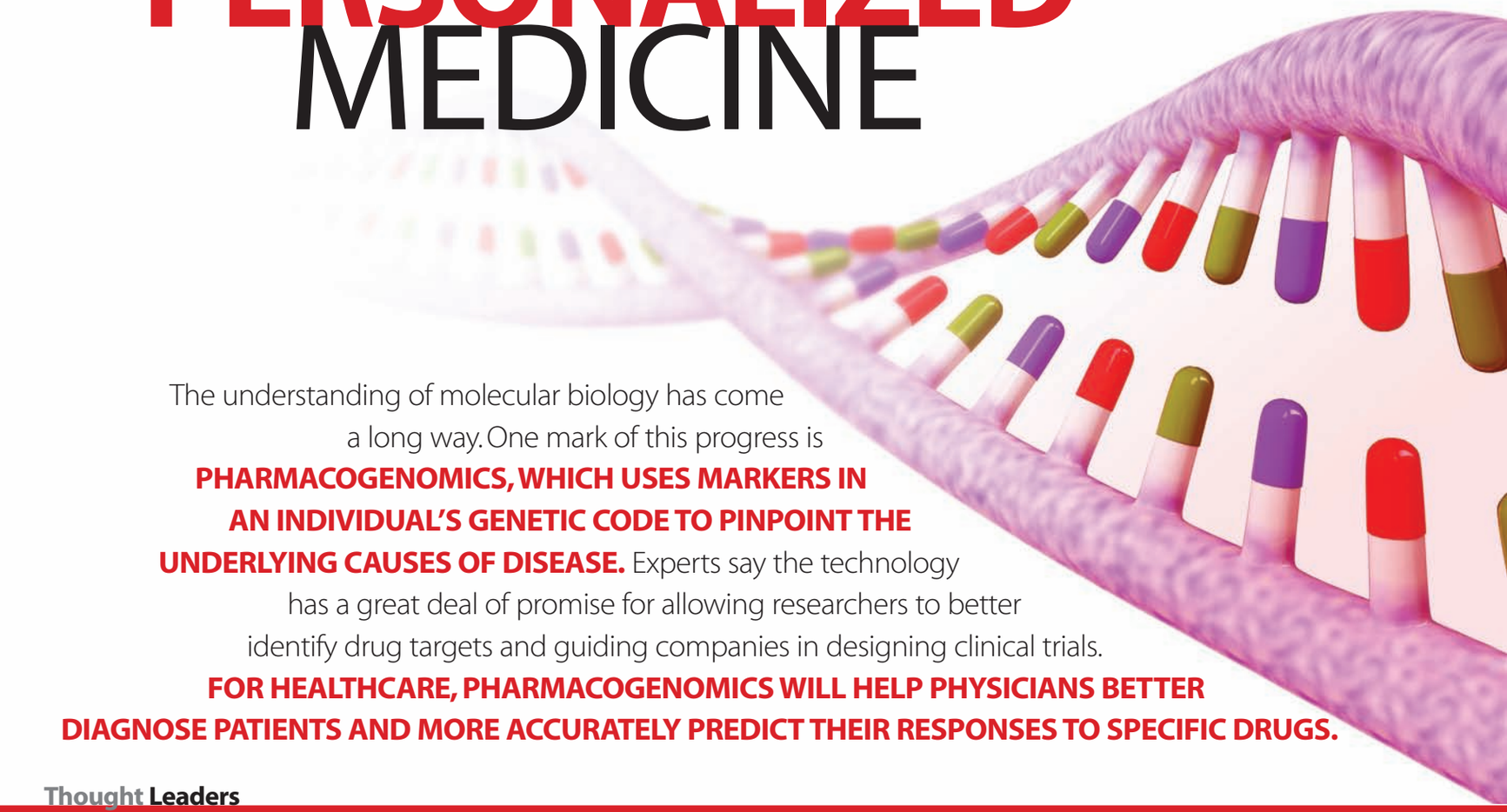
BY DENISE MYSHKO

The Age of PERSONALIZED MEDICINE



The understanding of molecular biology has come a long way. One mark of this progress is **PHARMACOGENOMICS, WHICH USES MARKERS IN AN INDIVIDUAL'S GENETIC CODE TO PINPOINT THE UNDERLYING CAUSES OF DISEASE.** Experts say the technology has a great deal of promise for allowing researchers to better identify drug targets and guiding companies in designing clinical trials. **FOR HEALTHCARE, PHARMACOGENOMICS WILL HELP PHYSICIANS BETTER DIAGNOSE PATIENTS AND MORE ACCURATELY PREDICT THEIR RESPONSES TO SPECIFIC DRUGS.**

Thought Leaders

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Many say pharmacogenomics has the potential to significantly change disease management by enabling the development of targeted therapies that will be administered based upon a patient's genetic make up, not his or her symptoms. The hope is that this will lead to more targeted therapies and personalized medicine — giving the right dose of the right drug to the right patient at the right time.

Although pharmaceutical products based on pharmacogenomics are unlikely to have blockbuster sales, experts at Pricewaterhouse-Coopers predict some products could have sales in the $300 million to $500 million range.

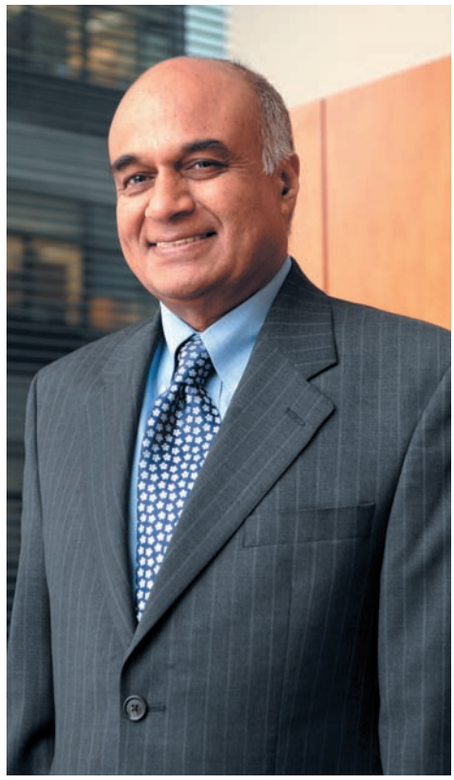
And they say pharmacogenomics could expand markets and revenue by defining new uses or targets for existing drugs, rescuing drugs in development, managing product life cycles, and dominating niche markets. Highlighting a product's pharmacogenomic aspects could help companies differentiate their products and build new demand.

Progress in Genomics

Since the sequencing of the human genome in 2001, much progress has been made in understanding the molecular basis of disease. Going forward, the technologies, as well as the application of genomics, are expected to advance at a rapid pace.

DR. RAJU KUCHERLAPATI
Harvard Partners Center for Genetics and Genomics

We need to think about educating physicians throughout the country about the importance of genetics and pharmacogenetic testing. I ANTICIPATE THAT THERE IS GOING TO BE GREATER AND GREATER UTILIZATION OF GENETIC INFORMATION in making treatment decisions for patients.



SPEAR. ABBOTT. Three major trends have emerged during the past few years in the pharmacogenomics field. First, pharmacogenomics technologies have become a near-standard element of the drug-development process. Early drug development now consistently includes research on how drug response varies from patient to patient. Second, the cost of conducting whole genome scans, which allow us to look at hundreds of thousands of DNA markers for genetic association to a particular response, has gone down to the point where they can be used regularly in exploratory drug development. Cost reductions will have a major effect on our ability to find genes related to drug response. And third, there is growing interest in how genes relate to adverse side effects in patient populations. The NIH, FDA, and most drug companies are taking an active interest in understanding and discovering the molecular mechanisms by which some people have adverse reactions to particular drugs, while most people don't. Research in this area will lead to better opportunities for predicting drug response with regard to adverse events.

GIROUX. SUDLER & HENNESSEY. As pharmacogenomics goes mainstream in the coming decades, it has the promise to radically improve

a global strategy executed locally in almost 150 countries. For more information, visit deloitte.com/lifesciences.

RAJU KUCHERLAPATI, PH.D. Scientific Director, Harvard Partners Center for Genetics and Genomics, Cambridge, Mass.; HPCGG was launched in the fall of 2001 with the mission to promote genetics and genomics in research and clinical medicine. For more information, visit hpcgg.org.

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WILLIAM D. YOUNG. CEO, Monogram Biosciences Inc., South San Francisco, Calif.; Monogram Biosciences is advancing individualized medicine by discovering, developing, and marketing innovative products to guide and improve treatment of serious infectious diseases and cancer. For more information, visit monogrambio.com.

health for the next generation. Even today, remarkable progress is being made in identifying specific proteins — and the genes that code for them — that cause disease and variances in response to therapy. For patients with chronic conditions where tolerance to therapy directly impacts success, pharmacogenomics offers promise. For drug research, we now have a tool for subgrouping patient populations to determine response. For drug discovery, we now have a powerful tool for identifying and validating drug targets.

KUCHERLAPATI. HPCGG. Two of the most widely used examples of pharmacogenomics concern two drugs: Iressa developed by AstraZeneca and Tarceva developed by Genentech. In both of these incidences, we know, with a very high level of certainty, which patients are

SPRYCEL: The Development of a Targeted Therapy

Gleevec's approval in May 2001 for the treatment of a specific form of leukemia was considered a milestone in the development of targeted therapeutics. It was the first oncology drug to be validated as an effective and generally well-tolerated medicine that targets a specific cause of a cancer.

The Food and Drug Administration approved Gleevec within 11 weeks of the application being submitted. Developed by Novartis Pharmaceuticals Corp., Gleevec is indicated for patients with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.

Data marking four and half years of use show that more than 90% of patients taking Gleevec continued to survive and were free from progressing to advanced disease. But almost immediately after approval, some patients began to show resistance to Gleevec.

Researchers at Bristol-Myers Squibb Co. saw a medical need. Aberrant BCR-ABL tyrosine kinase drives CML. Two chromosomes, chromosome 9 and 22, are abnormal in patients with CML. Pieces of the chromosomes, which are broken off in the blood cells, switch with each other. The human ABL gene mutates and then fuses with the remaining part of the BCR gene. This fusion between BCR and ABL leads to an abnormal fused gene, called BCR-ABL.

But this abnormal gene can mutate further, leading to resistance to Gleevec. Mutations have occurred in the protein sequence of the BCR-ABL tyrosine kinase, causing multidrug resistance gene overexpression, and the activation of alternate signaling pathways involving the SRC family kinases.

In June 2006, Bristol-Myers Squibb received FDA approval of Sprycel (dasatinib), which is an oral inhibitor of multiple tyrosine kinases for the treatment of adults in all phases of CML with resistance or intolerance to prior therapy, including Gleevec. The product had received priority review from the regulatory agency, which means the agency had six months from the submission date to take action on the NDA.

"Sprycel is a wonderful example of giving the right drug to the right patient at the right time," says Edwin Clark, M.D., director of clinical discovery at Bristol-Myers Squibb. "It started with understanding the patient population we're going after, then understanding the target, and determining the right molecule. It shows what can be done."

Bristol-Myers Squibb first synthesized Sprycel in 1999 and within two years showed activity against the BCR-ABL mutations. In November 2003, the company began clinical trials designed specifically to determine if it could address Gleevec-resistant CML. In two and half years, the company filed its submission for Sprycel.

Dr. Clark says the company is working to develop a test or diagnostic for all of its oncology therapies, including Sprycel, to help identify those patients who will most benefit from the therapy. The company is working to identify partners to develop those diagnostics.

"In the case of Sprycel, we can test for the mutation by isolating blood from patients, taking the leukemic cells, which are floating around the blood stream of these patients, isolating the DNA from those cells and sequencing the BCR-ABL gene fusion," Dr. Clark says. "We're looking for a change in a given codon; basically one of the pieces of the gene you see has a change or mutation."

Bristol-Myers Squibb is continuing development of Sprycel, including conducting a Phase II study that is a head-to-head comparison in patients who have not been treated with either Sprycel or Gleevec.

"In studies that were just reported at the American Society of Hematology meeting in December 2006, Sprycel compared quite favorably with Gleevec in patients who had not seen either drug before," Dr. Clark says. "In CML, patients who responded to treatment sooner do better than those who eventually respond to therapy. What we've seen with Sprycel is that it's very active very early and so patients get responses early."

Sprycel also is being studied for both hematological and solid tumor malignancies. The product has shown activity in preclinical studies of breast cancers that are triple negative, or negative for estrogen receptor-breast cancer, HER2 negative breast cancer, or both. A Phase I study for this indication began in December 2006.

The company is also about to begin clinical studies of Sprycel in prostate cancer. Clinical studies are being planned to investigate Sprycel's effect on multiple myeloma.

"There has been a lot of interest in the role of SRC family kinases in the bone," Dr. Clark says. "SRC appears to play an important role in osteoclasts, which help in remodeling bone."

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DR. BRIAN SPEAR
Abbott

PHARMACOGENOMICS ALREADY IS IMPACTING THE BASIC INFORMATION we have about new drugs and the patients who take them. This will steadily increase, becoming the background information for every new drug.

most likely to respond to the drug and which patients are least likely to respond to the drug. And that information is based on examining the DNA of tumors from the patients and examining the nature of the changes that might have occurred in the target for the drug.

CARINI. MDS PHARMA. While the practice of medicine still relies heavily on the knowledge and intuition of individual doctors, gradual advances in disease biomarker discovery over the past few decades have boosted their diagnostic ability considerably. Until recently, the search for new biomarkers was excruciatingly slow. Often it took years to associate some measurable parameters of physiology with a risk. Understanding why a particular marker is associated with a particular disease could take decades longer, as clinicians waited for basic science to catch up with medical observations.

ABRAHAMS. PMC. If realized, personalized medicine is extraordinarily promising. What we need to do to advance the paradigm is to determine what's missing. There are a couple of areas that I think are critical. The first is that we need better economic data and better explanations of why linking therapeutics and diagnostics makes economic sense. That includes a better understanding of the business model that would support personalized medicine. The other big area is healthcare provider education.

CARINI. MDS PHARMA. Using genomic and proteomic tools researchers are now engaged in an unprecedented large-scale hunt for new biomarkers. There has been growing recognition within the last decade that the identification of the unique molecular signature, or biomarkers, that readily distinguish human cancer from nonmalignant counterparts could potentially serve as powerful tools in diagnosis and prognosis. A variety of genomic and proteomic methodologies have been developed and dedicated toward the identification of novel cancer biomarkers. Many of these approaches involve the broad screening of nonmalignant and malignant cells and tissues for differences in DNA sequence, gene expression, or protein content. Another experimental strategy for biomarker discovery involves refining the search to only the molecular components that compromise a particular cellular process involved in the disease state. This has an advantage in that it may facilitate the identification of molecules that are in low abundance in cancer cells but that are, nonetheless, important to the maintenance of the disease state.

KUCHERLAPATI. HPCGG. An emerging example is the use of genetic information to make decisions about the right drug and the right dose to give to patients. About 2 million new patients begin using warfarin each year, but with this drug, the dosing is very critical. If a patient isn't given an adequate dose, there is a possibility the patient will get clots and that will result in stroke. If the patient is given too much, there is a potential for intracranial bleeding and hemorrhaging. Even though this drug has been available for a while, the method that physicians use to choose the right dose is still trial and error. But over the past couple of years, additional information has been obtained that looks at the variants in a couple of genes. The examination of these two genes in determining the dose could result in significant benefits.

EPSTEIN. MEDCO. The science has shown that people who are poor metabolizers of Coumadin (warfarin) end up having significant bleeding episodes. We did our own internal research and looked at our database of members to find out what happens with people who have multiple dose adjustments. This is a proxy for people who might have a genetic difference. Within six months of starting on Coumadin, 30% of them end up in the hospital, either with a bleed or another clot, versus 20% of people who don't have adjustments. So there is a big difference in hospitalization rates and morbidity. Our clients would like to see their patients get the right dose of Coumadin sooner so they don't have those outcomes.

WEIDENHAMMER. NANOGEN. Any particular drug is likely to be effective in fewer than 50% of patients. For some indications, especially those for which efficacy can be hard to measure, patients can require months or years of trial and error before an appropriate medication is identified. Adverse events are the fifth leading cause of death in the United States and are associated with costs to the healthcare system that exceed $150 billion annually. Clearly, if a $3,000 hospital stay can be alleviated by performing a $250 test, then the healthcare system will benefit. Even for those patients suffering milder adverse events, noncompliance is an issue, and costs related to noncompliance can be significant.

BERNARD. BERNARD ASSOCIATES. There certainly is increasing awareness of pharmacogenomics among those in the pharmaceutical industry and other stakeholders. There have been a number of important recent developments. First and foremost, the FDA issued guidelines to pharmaceutical companies regarding pharmacogenetic data. The FDA has also approved a number of new pharmacogenomic tests, including Roche Diagnostics' Cytochrome P-450 Amplichip. And several pharmaceutical companies have publicly announced plans to develop or support the commercialization of pharmacogenomic tests for their products.

YOUNG. MONOGRAM BIOSCIENCES. One of the biggest challenges will be adoption. The promise of personalized medicine means a complete sea change for pretty much the entire industry. Drug makers accustomed to developing big blockbusters need to retool business models to incorporate a more personalized approach. Insurance companies and other payers need to appreciate the value that these new technologies bring to the field and how they can make healthcare delivery better and more efficient. Doctors and patients need

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DR. MITCHELL MARTIN
Roche

PHARMACOGENOMICS WILL HELP US IDENTIFY DRUG TARGETS that matter to our patients, not targets that matter to our rodents.

MATTHEW HUDES
Deloitte Consulting

WE'RE GOING TO NEED MORE CLARITY AROUND REGULATORY ISSUES, AND WE PROBABLY NEED MORE LEGISLATION. There also are likely to be issues around patents, and they will need to be protected to stimulate innovation.

to be fully informed of the benefits personalized medicine will provide in terms of better outcomes with fewer side effects, but at the same time they will need to be educated in how personalized medicine is different from traditional approaches to disease treatment.

LAPIDUS. HELICOS BIOSCIENCES. There is a sense that pharmaceutical companies at one time were resistant to the idea of pharmacogenomics because of the concern about markets being made smaller. Now with the removal of drugs from the market that were expensive to develop but that were quite effective in selected populations, and the recognition that the costs of those incidents are so great, there's no doubt in my mind that pharmacogenomics is being adopted as quickly as it can be.

BERNARD. BERNARD ASSOCIATES. Individual pharmaceutical companies have had a somewhat of a schizophrenic view of pharmacogenomics. Initially, many pharmaceutical researchers were encouraging the use of pharmacogenomics, while many business professionals and marketers were resisting its use. We've moved on, and now we have a variety of individual perspectives on pharmacogenomics within different pharmaceutical companies. But there remain a number of challenges to the widespread adoption and use of pharmacogenomics. First, there are the clinical and technology challenges. The clinical validity, accuracy, and practicality of pharmacogenomic tests are key issues. There are regulatory challenges. While most regulatory bodies are very much in favor of pharmacogenomic tests because they can help ensure the safety and efficacy of drugs, there are hurdles to getting the tests through an underdeveloped regulatory process. There are several legal issues, including intellectual property rights, medical liability, and patient privacy issues.

WEIDENHAMMER. NANOGEN. For pharma companies, tailoring drugs to patients who are most likely to respond and least likely to suffer an adverse event could significantly increase demand. Big savings are anticipated to arise during drug development; by identifying earlier in the development process those drugs likely to work in a particular population, companies can streamline their clinical trials and reduce costs.

HUDES. DELOITTE CONSULTING. There are challenges at the manufacturing level, mainly in terms of the scale. Companies will be manufacturing smaller batch sizes, and there will be smaller production lines. There are also a number of challenges throughout the health economic system that make it difficult to implement personalized medicine. With targeted therapies and personalized medicine, there has to be the promise of saving money. Effective prevention and early treatment of chronic conditions based on an understanding of the genetic basis of disease will need to be demonstrated.

YOUNG. MONOGRAM BIOSCIENCES. In three to five years the changes in personalized medicine that are now occurring in molecular diagnostics, academic and institutional research, and early-stage drug development will begin providing tangible benefits to patients, doctors, payers, and everyone impacted by the healthcare system. This, in turn, will generate greater interest in the field and will hopefully bring about a new era of thinking about how we treat disease.

GIROUX. SUDLER & HENNESSEY. As our understanding of the human genome grows we will begin to be more sophisticated in the application of pharmacogenomics. Identifying the relevance of our genetic make up to disease susceptibility and responsiveness to drugs will evolve rapidly in the coming years. However, the application of this approach will require addressing the concerns of cost, availability, and patient confidentiality. Much as cord blood banking has become a popular birth gift, future generations may choose genotyping and create their own DNA chip so that disease prevention could begin very early in life. This, however, could lead to a crisis of medical ethics.

The Business Model

Experts say concerns about whether pharmacogenomics will end the blockbuster model are unfounded. In fact, pharmacogenomics will present opportunities for expanding markets by defining new uses for products, rescuing drugs in the pipeline, managing product life cycles, and dominating niche markets.

HUDES. DELOITTE CONSULTING. There are many questions in terms of the business model. If companies need to have a diagnostic to link to their therapeutic, do they undertake that development themselves? Do they set up an alliance? Do they share the IT on the diagnostic side? How do they encourage what has been a lower margin business on the diagnostic side to participate in the value that's created on the therapeutic side?

BERNARD. BERNARD ASSOCIATES. Ultimately, pharmaceutical business executives and marketers need to embrace pharmacogenomics. The biggest fear is that pharmacogenomics is going to kill the blockbuster model, fragment markets, and by definition reduce sales and profits. That quite simply is the biggest myth about pharmacogenomics in the pharmaceutical industry. In fact, pharmacogenomics has the potential to decrease and increase market shares and sales of products.

CLARK. BRISTOL-MYERS SQUIBB. The blockbuster model is one that is hard to sustain. Just look at the statin therapies that are making tens of billions of dollars a year. When a therapy like that goes off patent, a company suddenly has a huge hole in its portfolio. It is much easier to sustain a business model in which there are many therapies. On their own none is a blockbuster but combined a company can sustain continued research and development.

HUDES. DELOITTE CONSULTING. The industry is in a situation where the science is getting ahead of the economics. Things are possible but not payable. There is ROI, but it has to be measured in a different way from how we've traditionally measured the return on investment of a therapeutic.

BERNARD. BERNARD ASSOCIATES. In many ways, the biggest challenge we face remains the pharmaceutical industry's stance toward pharmacogenomics. Pharmaceutical executives have to become more aware and educated about the implications and applications of pharmacogenomics. They need to start to analyze how pharmacogenomics and other personalized medicine technologies might impact their particular products and therapeutic areas. There are many marketing and business people who see pharmacogenomics as a threat. There are several ways in which this technology can actually increase product market shares and sales. First, there is the opportunity to increase market share by recruiting patients from less effective competitive drugs. Second, pharmacogenomics can increase product compliance because there is less likelihood of side effects and the perception of side effects, as well as greater product efficacy. Consequently, patients are more likely to start their medications and to stay on them. Emerging genetic disease susceptibility and diagnostic tests may help expand the use of preventive therapeutics. There is also the potential for higher reimbursement for highly effective and targeted agents, particularly for new products coming to market. Moreover, pharmacogenomic tests can "rescue" currently marketed products, as we have seen with the TPMT test for the cancer agent Purinethol, and developmental compounds, as was the case with the HercepTest for the cancer agent Herceptin. These rescue tests can ensure that certain products get to the market and help keep products on the market.

LAPIDUS. HELICOS BIOSCIENCES. Pharmacogenomics that look at toxicology effects won't limit the market. Few patients have had the kind of dramatic side effects that were reported to have occurred with Vioxx. The side effect is infrequent but very dramatic. Losing a fraction of a percent from tox effects doesn't change the economics of selling the drug, but

THE IMPACT OF Pharmacogenomics

- THE BLOCKBUSTER MODEL CURRENTLY PURSUED by the pharmaceutical industry carries high risk and high costs. Because investigators have previously been unable to determine which participants will benefit, trials have had to be large enough to show statistically significant response among all subjects. Blockbuster drugs are typically efficacious in only 40% to 60% of the patient population. If drugs result in severe to fatal adverse events in patient subpopulations, they are removed from the market — at huge financial and public-relations costs.
- THE BLOCKBUSTER MODEL MAY EVENTUALLY DISAPPEAR but its demise is not imminent. The pharmaceutical industry is not prepared or inclined to abandon the blockbuster approach. And in the United States, the regulatory and reimbursement frameworks are currently built around this business model.
- PHARMACOGENOMICS TECHNOLOGY IS COMING OF AGE. The sequencing of the human genome in 2001 brought intense interest in and increased understanding of the tools to decipher DNA. These tools have been streamlined, upgraded, and replicated, and the costs of genomic sequencing and bioinformatics analyses are decreasing.
- STRATIFYING PROSPECTIVE PATIENTS THROUGH PHARMACOGENOMICS can increase rather than contract a product's market share. Pharmacogenomics could expand markets and revenue by defining new uses or targets for existing drugs, rescuing drugs in development, managing product life cycles, and dominating niche markets. Pharmacogenomics could help companies differentiate their products and build new demand.
- THERE ARE CLINICAL DEMANDS FOR PHARMACOGENOMICS PRODUCTS. The promise of pharmacogenomics is that biomarkers can bring clarity to an individual's condition and treatment regimen. Biomarkers can help predict the efficacy of a product and anticipate side effects. Pharmacogenomics can help better define a patient's health picture by diagnosing specific subtypes of diseases within cancer, diabetes, and other conditions.
- THE REGULATORY AND REIMBURSEMENT STRUCTURES pertaining to pharmacogenomics are being engineered.

Source: PricewaterhouseCoopers, New York. For more information, visit pwc.com/healthcare.
Note: Excerpts taken from Personalized Medicine: The Emerging Pharmacogenomics Revolution.

it hugely changes the economics of being overwhelmed by lawsuits.

MARTIN. ROCHE. We've had the benefit of having a sister diagnostic division for several years now, and it's a relationship that has to be very carefully structured. It is important that people within diagnostics and pharma understand each other's business better, and this requires a long-term relationship. The two entities don't necessarily have to be under one roof. That said, working side by side worked well in our case.

BERNARD. BERNARD ASSOCIATES. There will be a mix of different pharmaceutical strategies and approaches. We'll see some pharmaceutical companies that may leverage their own diagnostic divisions for competitive advantage in pharmacogenomic tests. But I believe this will be the minority. The majority of pharmaceutical companies are going to work to identify and develop partnerships with various pharmacogenomic and other testing and diagnostic companies, either to help bring their pharmaceutical products to market or to partner with them for products that are already marketed.

CARINI. MDS PHARMA. It is widely anticipated that during the next five years the molecular diagnostic industry will continue to grow at double-digit pace to meet increasing demand for personalized medicine. An increasingly educated public will demand more information about their predisposition for serious diseases and how potential illnesses can be detected in an early stage when they can be arrested or cured with new therapies custom-designed for their individual clinical status. To respond to this demand, major pharmaceutical companies will partner with service companies or develop their own capabilities that will permit efficient production of more effective and less toxic integrated personalized drugs and test products.

HUDES. DELOITTE CONSULTING. In general, there are incentives for biopharma and life-sciences companies to develop diagnostics with partners. Traditionally, diagnostics are a lower margin business. But if a therapeutic is going to require a diagnostic there is a shared value that's created. That's probably going to transform some of the diagnostic companies. We're going to see various forms of deals and more alliances.

LAPIDUS. HELICOS BIOSCIENCES. It seems to me that the pharma interest is not necessarily in owning a diagnostic test; it's making sure that the test is out there and in capable hands, whether it's a diagnostics company or testing laboratory or both. One might well envision a licensing strategy that makes pharmacogenomic insights available only on a nonexclusive basis to assure that testing is broadly available.

BERNARD. BERNARD ASSOCIATES. It is important to recognize that pharmaceutical companies will — in many cases — not be the drivers of pharmacogenomic tests or information that may dramatically impact their products. For example, there will be pharmacogenomic testing companies that come to market with their own tests that may or may not be specific to a particular drug, and pharmaceutical companies will have to address and deal with those situations. There are research labs and academic researchers who are regularly publishing pharmacogenomic information in the professional and lay media that influence the thinking and prescribing patterns of physicians, long before actual pharmacogenomic tests come to market. And managed care companies and pharmacy benefit management companies have already demonstrated that they will try to bring some of these pharmacogenomic tests to market to control the use of certain high-priced or high-utilization products.

Discovery and Development

Industry experts say pharmacogenomics will lead to better drug target selection and faster clinical development by making it acceptable to enroll fewer patients in clinical trials — the patients who are most likely to respond to therapy.

CARINI. MDS PHARMA. Pharmacogenetic approaches might be expected to both raise efficacy and avoid adverse events by stratifying patient eligibility for a drug according to appropriate markers. In both cases, clinical decisions must be supported by data that have undergone rigorous biostatistical scrutiny. On the basis of the substantially different opportunities, we expect the use of pharmacogenetics for enhanced efficacy to be considerably more likely than for the avoidance of adverse events.

LAPIDUS. HELICOS BIOSCIENCES. Pharmacogenomics will dramatically reduce the cost of drug development and that hasn't been factored into the debate. Candidates that are not likely to be effective can be taken out of the pipeline earlier. If candidates that are likely to work on targeted populations can be brought forward earlier, trials become smaller, they become better directed, and studies can be powered with a smaller number of patients. With well-selected patients, one can envision the day when there

THE FDA'S THINKING on Pharmacogenomics

In November 2006, the Food and Drug Administration released a preliminary concept paper on pharmacogenomic data submissions. The paper expands on the agency's March 2005 guidance and is based on the agency's experience over the past two years with voluntary genomic data submissions, various clinical-trial protocols, and data submitted under investigational new drug applications, new drug applications, and biologics license applications.

The agency plans to develop a guidance document based on these recommendations. Areas covered in the new document are: gene expression data from microarrays, including sections on RNA isolation, handling and characterization, labeling reactions, RNA labeling situations to be avoided, proficiency testing to avoid procedural failures, hybridizations and fluorescence reader settings for microarrays, and differentially expressed genes and their biological interpretation, genotyping methods and reporting, as well as DNA isolation, handling, and characterization; genomic data in clinical study reports; and genomic data from nonclinical toxicology studies.

Source: Food and Drug Administration, Rockville, Md. For more information, visit fda.gov.

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WILLIAM YOUNG
Monogram Biosciences

ENORMOUS PROGRESS HAS BEEN MADE IN UNDERSTANDING THE MOLECULAR INTERACTIONS between drug, disease, and patient, and we've been able to begin developing sophisticated diagnostics, in cancer for instance, that tap into this new understanding.

are no longer two-armed studies. There will be no need for a placebo arm if a drug works sufficiently well in the one treatment arm.

CARINI. MDS PHARMA. Despite technical and scientific progress, having sequenced the complete human genome has neither translated into understanding of life nor caused the expected surge in novel drugs. The genomic maps are road maps to future discoveries, but these discoveries must come from a hypothesis-driven approach leading to a better understanding of the biology of the disease.

MARTIN. ROCHE. There have been two events that have accelerated the use of pharmacogenomics, at least in an exploratory context. The first is high throughput genotyping technologies. The scale of our studies is no longer limited by the technology, cost aside. The second is the recent publication of the human HapMap, which now means that we have a sense of which SNPs (single nucleotide polymorphisms) in the human genome to focus on

for an association to or correlation with some type of outcome: susceptibility to disease, path of disease progression, and so on. Together, these improvements allow us to start the discovery program with human clinical information rather than relying primarily on information from disease models in, say, rodents. This is going to help us overcome a key stumbling point: picking drug targets that matter to our patients not targets that matter to our rodents.

YOUNG. MONOGRAM BIOSCIENCES. Pharmacogenomics, and molecular diagnostics in particular, already are playing a crucial role in the development of drugs for HIV, for example. New viral entry inhibitors are tailored to very specific patient populations, so advanced molecular diagnostics are helping identify those who will likely respond to the drug, which helps with clinical-trial selection, which in turn can reduce the amount of development time it takes to get new therapeutics to those who most need them.

SPEAR. ABBOTT. The biggest challenge is still connecting specific genes to specific outcomes when someone takes a drug — benefit, lack of benefit, adverse effect. Drug companies must demonstrate the clinical value of a test that might indicate whether patients will be favorable responders. Knowing that a gene is related to a response isn't enough. To introduce a credible diagnostic, we must show how a test will change medical practice appreciably for the better, for instance better patient outcomes, fewer adverse events, or lower cost.

CARINI. MDS PHARMA. The likelihood that adequate data on efficacy in a subgroup can be generated is reasonably high, given the fact that unless the drug is viable for a sizeable number of patients, it will not be developed.

DR. ROBERT EPSTEIN
Medco Health Solutions

PHARMACOGENOMICS IS NOT JUST ABOUT DEVELOPING NEW TARGETS for drug development; it's also about improving the practical side of patient care.

The utility and clinical application of pharmacogenetic approaches to improve safety will meet with considerably greater hurdles, and is therefore less likely to become reality. Thus, it is likely that the practical application of using pharmacogenetics to limit an adverse event will be restricted to diseases with dire prognosis, for which there is a high medical need and the side effects are relatively common and tolerated in favor of the beneficial effect of the drug.

SPEAR. ABBOTT. Predicting whether and when a company may need to develop a diagnostic assay to complement a particular drug is another challenge. The development of a companion diagnostic assay, which would identify a genomically defined population, can have a major effect on how a drug will eventually be registered, labeled, and used, and thus has a huge impact on the clinical/regulatory process. But the need to narrow a patient population through genomics often becomes apparent late in the process, during pivotal trials when the experimental drug is in a larger patient population. Ideally, we'd learn early in the drug-development process that a diagnostic assay will be needed to separate a genomically defined patient subpopulation, and the assay would be developed in parallel.

MARTIN. ROCHE. The FDA is trying to become more familiar with pharmacogenomic data and at the same time is trying to make the industry feel more at ease in terms of using these data to guide drug development. Some companies are beginning to voluntarily submit pharmacogenomic data to the agency on the assurances that the information wouldn't be included in the label. The intention is to get the agency accustomed to looking at the data. The FDA is going about it sensibly, in my view. It's probably the best way to introduce these data into the regulatory process, and this gives us a chance to work with regulators and build our own internal processes to use these data routinely.

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WEIDENHAMMER. NANOGEN. The FDA has been quite proactive, issuing draft guidelines related to (pharmaco)genomic data submission, genotyping of drug metabolizing enzymes, and the development of companion diagnostics, as well as working on relabeling of drugs for which pharmacogenetic testing may help dosing or treatment decisions. These activities have helped to push progress and will continue to do so.

ABRAHAMS. PMC. We'd like to see an easier path in terms of codevelopment and that is something the FDA is still evaluating. We just heard that the agency is going to continue to push forward the white paper on codevelopment, which has not progressed since the draft was first published in March 2005. That's a critical piece of regulation, because this is where the rubber meets the road in personalized medicine. This will encourage codevelopment at the beginning of the process and not codevelopment at the end of the process.

YOUNG. MONOGRAM BIOSCIENCES. Over the next few years, we'll see more drug submissions in which a drug is indicated for a genomically defined subpopulation — defined by a diagnostic test. Herceptin is still the only real example in this category, but we'll certainly see more drug/diagnostic companion products over the next few years. We'll see an incremental — but not meteoric — increase in the use of pharmacogenomics in drug development. We'll see pharmacogenomics data incorporated into drug labels, in all new drug

SELECTED PERSONALIZED MEDICINES on the Market

THERAPY	BIOMARKER/TEST	INDICATION
Anti-retroviral drugs*	**TruGene HIV 1 Genotyping Kit**	Guides selection of therapy based on genetic variations that make the virus resistant to some anti-retroviral drugs.
Cancer treatments	**OncoType DX 21-gene assay**	Quantifies the expression of 21 genes linked to the likelihood of breast cancer recurrence in women and the magnitude of benefit from certain types of chemotherapy and hormonal therapy.
Camptosar (irinotecan)*	**UGT1A1**	Colon cancer: variations in the UGT1A1 can influence a patient's ability to break down irinotecan, which can lead to increased blood levels of the drug and a higher risk of side effects.
Drugs metabolized by cytochrome p450*	**Amplichip CYP2D6/CYP2C19**	FDA classification 21 CFR 862.3360: this device is used as an aid in determining treatment choice and determining treatment dose for therapeutics that are metabolized primarily by the specific enzyme about which the system provides genotypic information.
Gleevec (imatinib mesylate)*	**BCR-ABL**	Chronic myelogenous leukemia (CML): Gleevec is indicated for the treatment of patients with Philadelphia chromosome positive chronic myeloid leukemia in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy.
Gleevec (imatinib mesylate)*	**c-KIT**	Gastrointestinal stromal tumor (GIST): Gleevec also is indicated for the treatment of patients with Kit (CD117) positive unresectable and/or metastatic malignant gastrointestinal stromal tumors.
Herceptin (trastuzumab)*	**HER-2/neureceptor**	Breast cancer: for the treatment of metastatic breast cancer whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease.
Immunosuppressive drugs	**AlloMap gene profile**	Monitors patients' immune response to heart transplant to guide immunosuppressive therapy.
Pharmaceutical and surgical prevention/surveillance	**BRCA 1,2**	Guides surveillance/preventive treatment based on susceptibility risk for breast and ovarian cancers.
Pharmaceutical and lifestyle prevention options	**Familion 5-gene profile**	Guides prevention and drug selection for patients with inherited cardiac channelopathies, such as long QT syndrome, which can lead to cardiac rhythm abnormalities.
Pharmaceutical and surgical treatment/surveillance	**p16/CDKN2A**	Guides surveillance/preventive treatment based on susceptibility risk for melanoma.
Purinethol (mercaptopurine)*	**TPMT**	Guides adjustment of dose in treatment of acute lymphoblastic leukemia: Patients with inherited little or no thiopurine S-methyltransferase (TPMT) activity are at increased risk for severe purinethol toxicity from conventional doses.
Tamoxifen*	**Estrogen receptor**	The estrogen and progesterone receptor values in breast cancer patients may help to predict whether adjuvant tamoxifen citrate therapy is likely to be beneficial.

* These are products in which diagnostic tests received formal FDA approval or drugs that have a reference to pharmacogenomic selection in their label.
Source: Personalized Medicine Coalition, Washington, D.C. For more information, visit personalizedmedicinecoalition.org.

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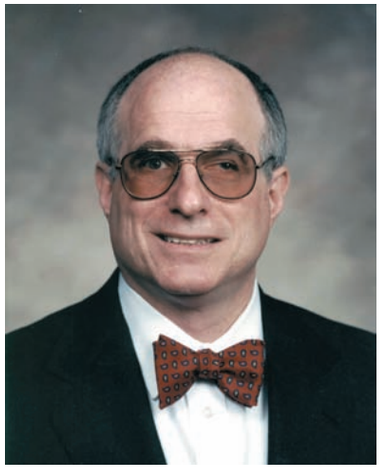
PAUL GIROUX
Sudler & Hennessey

AS PHARMACOGENOMICS GOES MAINSTREAM IN THE COMING DECADES, it has the promise to radically improve health for the next generation.



STANLEY LAPIDUS
Helicos BioSciences

PHARMACOGENOMICS WILL DRAMATICALLY REDUCE THE COST OF DRUG DEVELOPMENT. Trials will become smaller and they will become better directed. With well-selected patients, one can envision the day when there is a one-arm study.

submissions, and in more assays available to guide decision making.

WEIDENHAMMER. NANOGEN. Other entities also have been involved in educating different groups about personalized medicine. Organizations, such as the American Association for Clinical Chemistry, the Association for Molecular Pathology, the American Association of Clinical Pharmacology and Therapeutics, and the International Association of Therapeutic Drug Monitoring and Clinical Toxicology have been including presentations and workshops on personalized medicine in their meetings, providing an opportunity for members to increase their knowledge of advances in the field.

Postmarketing Issues

Pharmaceutical marketers, experts say, have to incorporate genomics into their marketing plans and be able to address the needs of patients, physicians, and payers.

GIROUX. SUDLER & HENNESSEY. In theory, pharmacogenomics is the ultimate diagnostic test that will enable the medical community to predict an individual's response to therapy. Through this we may understand which statin is best for lowering LDL for an individual or perhaps more importantly we can identify who might have side effects. Cancer treatments, which are generally highly toxic, may be selected for individual tolerability. Perhaps success rates could rise because the oncologist is able to increase doses for patients who can better tolerate a drug. Pharmacogenomics has the promise to become a cutting-edge research tool. Patient populations can be objectively subgrouped to determine response. This could be particularly valuable for drugs or disease states where achieving clinical significance is particularly difficult. Simple health economics and testing availability will delay realizing the vision of pharmacogenomics for many years. For today, trial and error with comparatively inexpensive generic products and brands will negate the need for an "expensive" gene screening. Pharmacogenomics holds promise not in today's satisfied high population markets but in life-threatening illnesses where therapy is limited.

BERNARD. BERNARD ASSOCIATES. Pharmaceutical marketing professionals must be educated and trained on the commercial implications and applications of pharmacogenomics. Each company should have a market surveillance program in place to identify pharmacogenomic testing opportunities and threats, including potential partnerships. And I believe that strategic marketing plans for every pharmaceutical product and therapeutic area should include a section on pharmacogenomics. Pharmacogenomics is simply too important and evolving too rapidly to ignore.

ABRAHAMS. PMC. Reimbursement has to encourage preventive methods. The ideal reimbursement environment would not look at proteomic-based products, especially codeveloped products or diagnostic tests, individually and price them based on the archaic methods that payers now use but instead incentivize their development by pricing these diagnostic tests at a premium or at least full value to the medical system.

EPSTEIN. MEDCO. We're at a point in time when the payer community is very interested in the application of these tests, and our clients are those payers. We work with employers and health plans and government plans to help administer the drugs.

WEIDENHAMMER. NANOGEN. One challenge is the lack of knowledge among the ordering physicians and/or the reluctance to include genetic information into patient-management decisions. In some areas, adverse events are considered par for the course, and so adding another test that may mitigate, but not eliminate, the risk of adverse events may not seem worth the incremental costs. From the coverage perspective, unanswered questions remain about whether coverage would be denied for someone of the "wrong" genotype desiring to take a particular therapeutic or whether insurance costs would be higher for someone genetically predisposed to a complex disease with both genetic and environmental influences, and so on.

KUCHERLAPATI. HPCGG. We need to be thinking about the appropriate cost-benefit ratios. In the case of warfarin, which I mentioned earlier, there's a recent Brookings Institution report that states that just testing one of the two genes could save the overall healthcare system as much as $2 billion a year. It's these types of studies that are necessary to show the whole healthcare system that the cost-benefit ratios are favorable.✦

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