

# THE PROMISE OF PHARMACOGENOMICS

BY RANDOLPH FILLMORE

IN THE BRAVE NEW WORLD CREATED BY THE HUMAN GENOME PROJECT—THE AMBITIOUS AND SUCCESSFUL ENDEAVOR TO MAP ALL THE GENES IN THE HUMAN BODY—WHAT SPINOFF HOLDS THE MOST HOPE OF IMPROVING HEALTH CARE IN THE 21ST CENTURY? IT'S THE RISE OF pharmacogenomics, the science of custom-fitting drug treatment to an individual's genetic makeup. Pharmacogenomics, which promises to optimize drug discovery, development, and patient treatment, could be a giant leap from "one size fits all" therapy to a this-drug-is-for-you future.

However, that future is fraught with questions—scientific, economic, legal, and ethical. Here, some of those questions are posed to a panel of experts: Russell J. DiGate, PhD, professor and associate dean for research and graduate education, School of Pharmacy; Paul S. Shapiro, PhD, assistant professor, School of Pharmacy; C. Daniel Mullins, PhD, associate professor, School of Pharmacy; and Karen H. Rothenberg, JD, MPA, dean, School of Law.

## WHAT WAS LEARNED FROM THE HUMAN GENOME PROJECT?

**RUSSELL DIGATE:** One result of the project was the improvement of genetic mapping, which helps make the hunt for specific disease genes faster, cheaper, and more practical. Genetic mapping is a process used in the discovery of DNA markers. DNA markers can tell researchers, roughly, where a gene exists on a given chromosome. The more DNA markers there are on a genetic map, the more likely it is that one will be closely linked to a disease gene and made easier to target. Mapping has already been used successfully to find the single genes for several diseases, such as cystic fibrosis and muscular dystrophy.

## WHAT IS PHARMACOGENOMICS?

**RD:** Pharmacogenomics is the science of applying genetic information to drug design, development, and delivery using our new understanding of how genes respond to stimuli. In the broadest sense, pharmacogenomics applies not only to traditional drugs, but to bioengineered proteins and gene therapy as well. Pharmacogenomics is not new. It's an extension of work we have been doing for some time, but augmented by knowledge gleaned from mapping the human genome.

## WHAT DOES PHARMACOGENOMICS OFFER IN TERMS OF THERAPY?

**RD:** Nearly all diseases have a genetic component. And, we know that drugs are metabolized by enzymes, which are themselves genetic products, distinct in genetic groups as well as in individuals. Some drugs are effective for some people and not for others because of genetic differences among individuals. Once those genetic differences are known, drugs can be matched to the variations. An ability to identify and target specific proteins and

genes can provide better, and perhaps safer, therapy.

In designing targeted drugs to treat cancer, for example, we will likely find a series of genes or receptors—not just one—involved in what we call the oncogenic pathway, the cascade of events that leads to disease. The difficulty will be in determining which genes, or receptors, to target. We may not have the resources to target all of them during research and development. However, by virtue of our knowledge about the pathways, researchers will design systems, or use animal systems, to look at the responses and predict side effects before they happen.

## HOW WILL DRUGS BE DESIGNED TO TARGET SPECIFIC GENES, DISEASES, OR RECEPTORS?

**PAUL SHAPIRO:** Identifying the genes that are involved in a particular disease is the easy part. Understanding the function of the proteins that these genes encode is more difficult. Proteins contain many structural motifs and undergo a variety of post-translational modifications that regulate the proteins' structure and function. Identifying the structure, modifications, and specific function of proteins is non-trivial and is compounded by the fact that many proteins function only through interactions with other proteins in multiprotein complexes. Yet, drug and biotech companies, and academic researchers as well, are spending a lot of resources developing drugs that specifically inhibit proteins involved in human diseases, such as the development of specific inhibitors of growth factors and their receptors for preventing cancer cell proliferation. So, the real importance in the work arising from pharmacogenomics will be in proteomics—the characterization of proteins.

## WILL PHARMACOGENOMICS MAKE DRUG DEVELOPMENT AND TESTING MORE EFFICIENT?

**DANIEL MULLINS:** Given that 80 percent of compounds fail in clinical trials and the industry spends \$500 million to \$700 million for each new drug approval, the benefits of applying pharmacogenomics to drug development may be substantial. Pharmacogenomics could also be used to determine exclusion criteria for participants in clinical trials, thereby saving time and money.

## IS PHARMACOGENOMICS LIKELY TO INCREASE OR DECREASE THE COST OF HEALTH CARE?

**DM:** Pharmacogenomics testing could increase the average cost of treatment. The issue is that clinical trials could become more costly because pretesting will be required to determine which patients should participate. However, the

costs of these tests may be offset by the savings realized when ineffective treatments are avoided. Up to \$80 billion is spent every year in the United States for treatment associated with drug-related adverse events in hospitalized and ambulatory patients. Pretesting patients to determine those who will not respond to a therapy, or those who may have an adverse effect, could present a significant savings in terms of health care costs. Pharmacogenomics will be cost-effective if increased costs associated with genetic testing are less than the value of improved health outcomes.

## WHAT ETHICAL AND LEGAL QUESTIONS WILL ARISE WHEN SCREENING FOR DISEASE USING AN INDIVIDUAL'S GENETIC MAKEUP?

**KAREN ROTHENBERG:** One of the promises of the Human Genome Project is that our genetic susceptibility to common disorders can be better understood, allowing for individualized, preventive, and therapeutic medicine through drugs designed for specific genetic targets. Our enthusiasm for the data coming out of the Human Genome Project has, however, been chilled by the fear that genetic information will make us vulnerable to discrimination. This discrimination could come at the hands of employers or insurance companies, as it is reasonable to assume that health insurers and employees may not fully understand the implications and limitations of genetic test results. Just as with other new technologies, negative consequences can be anticipated.

To date, there is no comprehensive federal legislation that addresses genetic discrimination and privacy in insurance or employment contexts. The sooner we act to protect genetic information and prevent genetic discrimination the better.

## HOW WILL PHARMACOGENOMICS CHANGE THE EDUCATION OF PHARMACISTS AND THEIR PRACTICE?

**RD:** Pharmacy education will become more molecular. Because drugs are the niche of pharmacy, pharmacy needs to keep up with innovations in drug design, development, and delivery. Our department focuses on those three Ds. There will be new technology installed in Health Sciences Facility II to address the three Ds related to the investigation of the structure of genes and proteins involved in disease states and the subsequent development of compounds that will interact with them.

The role pharmacists play will be determined, in part, by the degree to which other health care professionals shape it, what responsibilities pharmacists want to take, and how they embrace the future. ☐



Russell DiGate



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