

## *Virtual Mentor*

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### STATE OF THE ART AND SCIENCE

#### **Pharmacogenomics: Revolution in a Bottle?**

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Pharmacogenomics applies information about the human genome, gene sequencing technology, and molecular biology to drug design. At first glance, the technology seems not to present the same sort of harrowing ethical dilemmas we have come to expect from genetic knowledge and technology, such moral conundrums as parental right to select offspring traits or determining whether it is ethical to fertilize and implant an embryo in hopes of conceiving a tissue donor baby to save an existing child. Instead, like all advances in drug treatment, pharmacogenomics will bring with it higher cost and, thus, concerns about equitable distribution of health care. Like all gene-related technologies, it will reveal more about us and challenge the current procedures to protect the confidentiality of the additional information. The social justice and policy problems embedded in those 2 outcomes are grand in scope and correspondingly difficult to resolve. In the end, pharmacogenomics may be part of a revolution in personal identity as well as in how we pay for medical care in the U.S.

The potential benefits of pharmacogenomics are considerable. Applying knowledge about an individual's inherited response to drugs to the design and development of commercial pharmaceuticals holds the promise that drugs may one day be tailor-made to each person's genetic makeup.<sup>1</sup> The products of this "rational drug design" technology would replace current drugs that are intended to serve the entire patient population. These blockbuster, one-formula-fits-all, drugs, typically work for only 60 percent of the population at best.<sup>2</sup> More worrisome and costly than their ineffectiveness is the instance of serious adverse drug reactions (ADRs) that are responsible for 100,000 deaths a year in the U.S.<sup>2-5</sup> and cost society an estimated \$100 billion a year.<sup>3</sup>

#### **The Promise of Pharmacogenomics**

Pharmacogenomics expands upon a progenitor science, pharmacogenetics, which dates from the 1950s when researchers first noticed an inherited tendency in the way people react to drugs. An individual's reaction to a particular drug depends, in large part, upon whether the drug's target cells have the proper receptors for the chemical compound being delivered and how the individual metabolizes the drug. Ultra-rapid metabolism of a drug can cause it to be ineffective, and slow or non-metabolism can result in the accumulation of toxic amounts of the drug in the body. Genes control both these factors—receptor binding sites and enzymes involved in metabolism.

Before it was possible to isolate the genes involved in the synthesis of given metabolic enzymes, appearance and family relationship were the main clues to the presence of inherited or genetic factor in reaction to drugs. Early pharmacogenetics investigators focused on the broadest and most obvious categories of inheritance and relationship: ethnicity, geography, language, and race. This approach revealed, for example, that 5 to 10 percent of people from Mediterranean and African ancestry lack the glucose-6-phosphate dehydrogenase enzyme and thus risk breakdown of red blood cells from more than 200 drugs. Testing for drug sensitivity was by trial and error. The drug was prescribed, and then the patient's urine was examined to check the rate of the drug's metabolism.

### **SNiPs**

The science of connecting drug reaction to genes took a great leap forward with the discovery and use of SNPs (pronounced snips) in the late 1990s. On their way to sequencing the entire genome of 3 billion base pairs (purine and pyrimidine bases bound together to create the "rungs" across the now-familiar double helix) scientists kept coming upon instances where one member of the base pair differed from the expected. Of the 4 bases that DNA comprises—adenine, cytosine, guanine, and thymine—adenine generally bonds with thymine, and cytosine binds with guanine. About every 1,000 or so base pairs, scientists observed a mistaken pairing: a guanine paired with a thymine, for example, instead of with a cytosine. These single departures are SNPs, "single nucleotide polymorphisms." What makes SNPs helpful is that certain SNPs are found sprinkled throughout the population, so that by looking at the DNA of individuals who share a certain inherited condition, drug reaction, or susceptibility, researchers can sometimes identify a shared SNP. (To be helpful, the polymorphism must be shared by at least 1 percent of the population tested, so the promise that pharmacogenomics will create drugs tailored to each *individual* is a slight exaggeration.)

Enough DNA samples taken from enough people make it possible to connect drug toxicity and ineffectiveness to SNPs, with 2 results. First, genetic tests can identify those who would have serious ADRs before they receive the drug. Second, drugs can be designed to work effectively but non-toxically on those who have ADRs to the one-formula-fits-all blockbuster drugs. Step one has already begun. For example, a set of enzymes called CYP34 metabolizes about 50 percent of all common drug compounds. Searching for SNPs that control these enzymes, pharmacologists at St. Jude Children's Hospital in Memphis discovered 2 SNPs that "quash" production of active enzymes. "People who carry either one of the culprit SNPs metabolize drugs more sluggishly than do people who harbor other versions of the gene".<sup>6</sup> Those in the field predict that testing for most enzyme-related drug reactions and resistance will be available within the next 5 years and that rationally designed drugs will be available in the next 7 to 12 years.<sup>7</sup>

### **Pharmacogenomics: At What Price?**

The question of resource allocation comes up whenever public money is spent for research and development. That question is less an issue in pharmacogenomics

because pharmaceutical companies have, understandably, jumped on the technology, many of them merging with biotech companies that suddenly see a profitable product in the near future for the first time.<sup>8,9</sup> It might seem that drug companies would be less interested in products that work on only a portion, 40 percent, say, of the population; that such products would bring in only 40 percent of the revenues. But a drug guaranteed to work on the 40 percent for whom other drugs are ineffective or cause harmful side effects will return a steady revenue at a premium price.

Chances are good that pharmaceutical companies will also spend less in gaining FDA approval to introduce new pharmacogenomically produced drugs to the market. Clinical trials can currently cost upward of \$250 million per drug, most of it spent on phase III.<sup>2</sup> After phases I and II have demonstrated, respectively, the candidate drug's safety and efficacy on several hundred people, phase III verifies those results on 5,000 to 10,000 people. With pharmacogenomically designed drugs, adverse responders and non-responders will be identified in phases I and II, so that phase III participants can be far fewer in number—only those whose genetic tests show they will respond favorably.<sup>9</sup>

While this advantage will reduce the amount pharmaceutical companies must invest in bringing a new drug to market, the savings may not be passed on to patients. As mentioned, the guarantee of effectiveness will draw top dollar on the market. Adding to overall patient expenses will be physicians' desire to guard against ADRs and lost treatment time due to ineffective drugs by ordering DNA tests. These currently cost about \$500, though that is expected to come down. The topic of DNA testing raises not only patient cost but also the threat of compromised confidentiality of patient information.

The swipe card containing every person's genomic identification is still beyond technology's reach, but it won't be for long. With new correlations continually being made between SNPs and diseases, drug sensitivity, and other susceptibilities, it seems sensible and economic to test individuals just once and keep all the information on file. This presents a nightmarish challenge to patient confidentiality and one that physicians and policy makers will have to solve soon. Physicians will have to determine how to manage the information that DNA tests will reveal to patients about themselves and their family members. Still, they cannot be expected to explain to each patient the basics of genetics, genetic probability, and the prognoses of diseases the patient doesn't yet have, if indeed he or she ever will. Acquiring informed consent for DNA tests and determining what resulting information a patient does and does not want to know will be a daunting task. Perhaps genetic counselors will find a role here. Whoever ends up doing the educating, patients or their insurers will pay.

The second level of confidentiality—who besides the patient has access to the information—should be a matter for policy, to my mind, policy that severely restricts access to patient records. It makes no sense that physicians should be

burdened with the practical hassle (not to mention the dubious ethics) of maintaining isolated or shadow files so that employers and insurers cannot view DNA test results. Instead we must decide, as a society, what any third party—employers, insurers, schools—have a right to know. In my view, the answer should be "almost nothing." The support for my argument entails a restructuring of the way insurers do business and make profits, replacing the individual risk and "actuarial fairness" foundation with one rate for all who are covered. This would amount to a huge upheaval in a large segment of the corporate sector, but one no larger than the change the health care sector has undergone in a mere 2 decades.

While costs to patients will go up, pharmacogenomics could well reduce the economic cost of missed work and low productivity. The reduction will come from fewer ADRs; less lengthy drug treatment periods for patients; greater effectiveness of drugs (reducing the toll of disease on the body), and an increase in the number of illnesses that drugs can treat effectively.<sup>1</sup>

### **Conclusion**

Viewed alongside such attention-getting dilemmas as genetic enhancement of embryos, pharmacogenomics seems like a gentle giant. But it could signal the need for sweeping policy changes. First, it will lead to an explosion in DNA testing, for once drug sensitivity testing is available, it will become a standard against which negligence can be measured in cases of severe or fatal drug reactions. Secondly, physicians will have to work out means for educating patients about genetics and preserving confidentiality of their records. At the same time, the cost of DNA testing (on which physicians will insist for the reason just given) and the high price of more effective, safer drug therapy will drive up expenses. These challenges to confidentiality and affordability should force policy makers to address insurance discrimination (for those have insurance) and the just distribution of health care to all members of society (including those who do not have insurance). If it achieves these ends, pharmacogenomics will be good medicine indeed for the nation.

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