COUTURE CURES: THIS DRUG'S FOR YOU

Doctors may one day sneak a peek at your genes to determine which drugs will cure you and which might kill you. **By Karen Hopkin**

"ONE PILL makes you larger and one pill makes you small. And the ones that Mother gives you don't do anything at all."

Some things were so simple in the '60s. If Grace Slick were to sing of today's pharmacology, her verse would probably sound more like the fine print at the bottom of a glossy drug ad: This pill may make you larger or smaller. It may also cause headaches, vomiting, night blindness, impotence and heart failure.

Of course, pharmaceutical companies want to avoid litigation when they market their medications to the public. But the long list of possible effects—and side effects—that accompanies every drug on the market today also reflects the recognition that individuals differ in the way they respond to medications. And that response depends, in large part, on a person's genes.

Now scientists are beginning to take advantage of new techniques that allow them to collect and compare large volumes of information about gene sequences—and about drug action—to predict how a person will respond to a given drug. These techniques stand to speed up the way drugs are designed and tested and may even change the way doctors diagnose and treat disease in the future.

Researchers have long known that genetic alterations can lead to disease. Mutations in one gene cause cystic fibrosis; in another gene, sickle cell anemia. But it is now becoming clear that genetic differences can also affect how well a person absorbs, breaks down and responds to various drugs. The cholesterol-lowering drug pravastatin, for example, does nothing for people with high cholesterol who have a common variant of an enzyme called cholesteryl transfer protein.

Genetic variations can also render drugs toxic to certain individuals. Isoniazid, a tuberculosis drug, causes tingling, pain and weakness in the limbs of those who are termed slow acetylators. These individuals possess a less active form of the enzyme *N*-acetyltransferase, which normally helps to clear the drug from the body. Thus, the drug can outlive its usefulness and may stick around long enough to get in the way of other, normal biochemical processes. If slow acetylators receive procainamide, a drug commonly given after a heart attack, they stand a good chance of developing an autoimmune disease resembling lupus.

BALM OR BANE?

Enter pharmacogenomics, a new science that aims to use a systematic genome-wide analysis of genetic variation to see which drugs might work for you and which might make you sicker. The clues come in the form of single nucleotide polymorphisms, or SNPs (pronounced "snips")—genetic hot spots scattered along our chromosomes that can vary in DNA sequence from person to person. Researchers are now compiling an extensive catalogue of these SNPs in the hopes that they will be able to link particular genetic fingerprints with differences in drug response.

SNP testing would work something like this: a doctor or technician would extract DNA from a small sample of a person's blood or other body cells. The DNA would then be washed over a SNP chip—a glass slide studded with DNA fragments that represent all the common genetic variations in, say, a gene known to control how well a drug is absorbed. (Some SNPs correlate with good absorption and some with poor absorption.) The DNA from the

TOM MOORE

Drug vending machines that dole out designer doses on demand probably won't be popping up on street corners anytime soon. But scientists envision a day when physicians will prescribe pharmaceuticals tailored to our own specific genetic information, which we might carry around encoded on a credit-card-size plastic plate.

A physician could **biopsy a tumor**, grow the harvested cells on a chip and then test to see **which chemicals** would be most effective at **killing the cells.**

patient would stick to whichever SNP it matched, and a scanner could then look at the chip and determine whether the person would be able to absorb the drug in question.

But beyond improving diagnostics, drug companies hope that pharmacogenomics will help them get more novel drugs to market. Currently 80 percent of drugs are shot down in early clinical trials because they are not effective or are even toxic, according to the Tufts Center for the Study of Drug Development at Tufts University. Pharmaceutical companies would like to boost the success rate of drug approval by testing new drugs only in individuals who are likely to show benefits from them during the clinical trial.

The problem is that people who are deemed genetically unresponsive might then fall through the cracks, observes William A. Haseltine, CEO of Human Genome Sciences in Rockville, Md. As it stands, pharmacogenomics is headed toward splintering the drug market, generating three or four different drugs that each might treat only tens of thousands of individuals with a particular disease—a scenario Haseltine views as "utter folly." Instead he favors using pharmacogenomics to develop new drugs aimed at treating the majority of people.

Using pharmacogenomics to select people who will respond to new drugs, Haseltine notes, "is a route around, not through, a major problem"—the problem being that it is difficult to develop drugs that work. Indeed, many companies are pursuing different methods for stepping up the flow through the pharmaceutical development pipeline. The goal, simply put, is to be able to generate and test the largest number of compounds in the shortest amount of time with the least amount of human effort. So researchers are turning to robots that can simultaneously analyze tiny volumes of thousands of samples—a process dubbed high-throughput screening. Then they use computers to process and keep track of all the results—and, in some cases, to suggest which drugs should be tested.

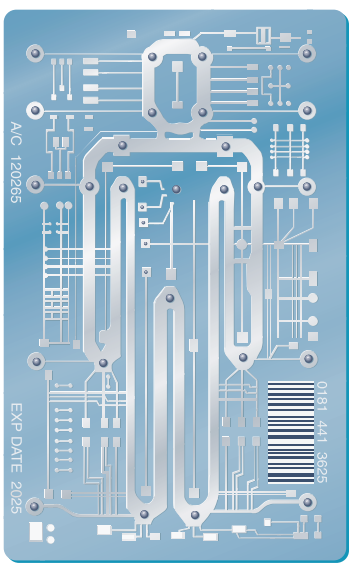
THE PHYSICAL OF THE FUTURE

"I SEE THIS is your first visit," says the doctor, looking up from her notes. "What seems to be the problem?" With a shuddering sigh, you describe your lack of energy, inability to sleep, disinterest in activities you once found pleasurable, and the crying—every day you cry. "Have you ever been treated for depression?" she asks, reaching for what looks like a small plastic tongue depressor. "Uh-uh," you gurgle, mouth agape, as the doctor scrapes a swath of cells from inside your cheek. "Then we'll just do a quick 'snip check,' and you can pick up your prescription this afternoon," she says, dropping the spatula into a vial and sending it off to the laboratory. There technicians will extract and analyze your DNA to determine which of the 837 antidepressants on the market will best chase away your blues.

Will pharmacogenomics usher in such an era of personalized medicine, in which our genetic fingerprints will determine the kind of medical treatment we receive? Will every trip to the clinic involve surrendering some DNA for sequencing? And once our DNA sequences can be easily accessed from a global database, will physicals be replaced by phone-ins?

Well, yes and no. First, it is important to keep in mind that genes aren't everything. "Many factors determine drug response," cautions William A. Haseltine of Human Genome Sciences. Genes are important, but so are the age, sex and general health of the patient, as well as the other drugs he or she might be taking. Still, scientists anticipate that genetic profiling may soon help doctors diagnose diseases and allow them to prescribe medications that will work best for an individual patient. "Most drugs only work on 30 or 40 percent of people," says Daniel Cohen of Genset in Paris. "Only aspirin works on almost everyone."

Genetic testing should help match the right drug at the right dose to the right patient without a lot of time-consuming trial and error. If you were clinically depressed, for example, a quick look at the results of a test called a P450 profile might indicate that you break down drugs so rapidly that you would probably clear certain antidepressants from your bloodstream before they could take effect. Or you might break them down so slowly that normal doses would make you antsy.



IAN WORPOLE

In addition to helping determine drug dosage and minimizing unwanted side effects, genetic screening may soon be used to predict a patient's predispositions to disease. Perhaps when you're 18 years old, you'll automatically be screened for your susceptibility to heart disease, diabetes, Alzheimer's disease, cancer and scores of other disorders. Armed with this knowledge, you might then be able to change the way you live or the foods you eat to boost the odds that you'll stay healthy.

Will we all eventually carry plastic plates the size of credit cards that are digitally encoded with all the genetic secrets stored in our genomes? "No, they'll probably be on chips implanted under our arms," jokes John Tallman, Neurogen's executive vice president. Although both options may someday be technologically possible, they will probably be a ways off. For one, investigators have yet to sequence one complete human genome. So rather than sequencing every one of the six billion nucleotide letters that make up your personal genetic code, for now pharmacogeneticists will very likely focus on the few hundred gene mutations, or SNPs, that have been shown to correlate with drug responsiveness or disease risk, says Francis S. Collins of the National Human Genome Research Institute. Ultimately, researchers hope such tests will cost a few dollars and yield results in an hour.

Genetic testing, of course, raises privacy issues. Will your employer or insurer be able to access your genetic profile? What about telemarketers? With any luck, legislators will pass laws designed to protect your genetic privacy long before the technology makes this future possible. Still, imagine answering the phone during dinner to hear a chirpy electronic voice dispense unwanted medical advice: "Isn't it time you started taking Progenitol?" —*K.H.*

Forget insurance cards. In the future your doctor might be more interested in your SNP chip, which will contain information about your single nucleotide polymorphisms (SNPs). These genetic sequences show how you differ from someone else in traits such as how fast your body is able to break down various drugs.

Researchers at Neurogen, a pharmaceutical company in Branford, Conn., for example, use high-throughput computer modeling methods to select the most promising drugs from a "virtual library," a computer database that contains the molecular structures of billions and billions of chemical compounds not yet made. Say they want to develop a more effective antianxiety medication. The scientists browse through a few hundred million molecules in their virtual library and select a few dozen groups of compounds that might interact with the particular types of satellite-dish-like proteins called receptors on the surfaces of nerve cells in the brain that are specifically associated with anxiety. Drugs that bind to these receptors could prevent panic attacks by interfering with the chemistry that makes some people unnecessarily anxious. The compounds could then be synthesized and tested, and the results could be used to home in on the most promising antianxiety drugs. Combining such rational drug design with powerful computing tools allows investigators to test thousands of compounds in a matter of weeks, says Neurogen's vice president Charles Manly.

But pharmaceutical companies are seeking to do more than just increase the number of drugs they test: they are also looking for better ways to select the best drugs early in the process. One way they are doing this is by making early drug screening richer in information. Instead of just testing whether a compound can bind to a receptor, for instance, researchers are developing high-throughput assays to measure how strong the binding is and how the drug affects the various biochemical processes of a cell. Does it switch on the correct genes and proteins, for example, or does it shut them off? Testing a drug's selectivity, toxicity, metabolism and absorption at the start of the screening process will cut down on efforts wasted on trying ineffective drugs in humans.

LIVING CHIPS

Eventually, scientists will be able to assay compounds on living cells that are growing on silicon chips, says D. Lansing Taylor of Cellomics in Pittsburgh. He and his colleagues are now developing such a cell chip for detecting agents of biological warfare. The device, dubbed a "canary on a chip," is a prepackaged piece of silicon covered with living nerve cells from insects. Many of the bacteria believed to be favored by bioterrorists secrete nerve toxins, so these chips could provide an early warning of a biological attack.

Such cell-chip technology might also allow doctors to determine which kinds of chemotherapies would work best for a cancer patient. A physician could biopsy a tumor, grow the harvested cells on a chip and then test to see which chemicals would be most effective at killing the cells. Testing the cells themselves could save the patient from undergoing a series of unnecessary and ineffective treatments.

For some of these technologies, the future is already here. Affymetrix in Santa Clara, Calif., now offers a SNP chip that can be used to detect 18 variants of the gene that codes for cytochrome P450—a liver enzyme responsible for breaking down nearly one quarter of all commonly prescribed drugs. The company should soon release HuSNP, a DNA chip that will allow researchers or physicians to characterize genetic variations at 1,500 different marker sequences, which will help them link individual variations to different diseases. And in the next few years workers at the National Institutes of Health's National Human Genome Research Institute (NHGRI)—and at the 10 pharmaceutical companies that recently banded with the Wellcome Trust to form the SNP Consortium—expect to generate a map containing some 400,000 SNPs.

And that's when the fun will begin. "We'll have this catalogue of SNPs, but we'll still have to figure out which ones are associated with disease risk or drug response," says Francis S. Collins, director of the NHGRI. Then disease by disease, drug by drug, investigators will need to compare thousands of individuals—people who respond well to a drug and those who respond poorly, for example—and determine how they differ at every one of these 400,000 SNPs. "That's a lot of SNPs," Collins notes. But the potential benefits—to drug companies and to society—are sure to be greater than the considerable challenge.

PILLS OF TOMORROW: PAPER OR PLASTIC?

Sure, one milligram is fine for you. But your mom may need 10, and Grandpa can't get away with taking less than 100. How can pharmacies cater to the full range of needs that will arise once gene screening optimizes drug dosages for particular individuals?

The answer, according to one company, lies in the humble office photocopier. Researchers at Delsys in Princeton, N.J., are using electrostatic charges to deposit precise amounts of drugs onto sheets of gelatinlike polymer or even onto pieces of paper. The charge attracts and holds the dry powder—whether ink or drug—to the backing. "It's using a technology that's nearly 100 years old to address a 21st-century problem," says Martyn Greenacre, CEO of Delsys.

COURTESY OF DELSYS

One prescription for the future predicts that tablets and capsules won't be alone on pharmacy shelves. Dots of drugs sprayed on an edible backing could allow us to take just the amount we need and no more.

Someday medications for controlling abnormal heart rhythms might be shaped like little hearts on a strawberry-flavored polymer that just melts in your mouth. Although the image may call to mind the LSD microdots of the late 1960s, Greenacre hopes to avoid becoming known as the Timothy Leary of medical manufacturing. If the U.S. Food and Drug Administration approves the new method, these drug dots may hit the market by 2003.

Once Delsys gets the production process up to speed—they would like to be able to run off about 3,000 pills per minute—a doctor should be able to tap your prescription into his terminal and have the pharmacist print out your personalized paper pills lickety-split. —*K.H.*

ABOUT THE AUTHOR

KAREN HOPKIN is a freelance science writer who lives in suburban Washington, D.C. If she could carry her genes around on a credit card, she would undoubtedly lose it.