

The "right" drugs kill 100,000 people a year. But genetic breakthroughs are

## Making Medicine SAFE

BY ROB WATERS

SEVERAL MONTHS AGO, 11-year-old Hillary DeSmarais of Fort Worth, Texas, attended a party in her honor. People brought presents, laughed, and gave the healthy girl hugs. It wasn't her birthday; the party was at a hospital. At the age of six, Hillary had been diagnosed with acute lymphoblastic leukemia.

Hillary could easily have lost her battle with cancer. Not because she didn't get good care: Her doctors acted quickly, putting her on a

PHOTOGRAPH BY STEVEN PUMPHREY

115



Hillary DeSmarais and her mother, Araceli, five years after she faced death.

RD INNOVATION | MAY 2004

cocktail of powerful chemotherapy drugs. This treatment helps cure some 80 percent of leukemia patients. But one of the drugs, mercaptopurine, can produce toxic effects.

After a few weeks of treatment, Hillary's white blood cell counts had dropped so low that she had virtually no immune system. Her doctors had to stop treatment to let her immunity recover, and so began a terrible dance for the little girl: Hillary would be on the drugs for two to three weeks, and her white blood cell count would plummet. Then she'd go off for a week to give her immunity a chance to return. "It was scary," says her mother, Araceli, a pediatric nurse. "Every time she went off treatment, she'd get leg pain. I kept thinking it was cancer in her bone marrow."

Three frightening months later, Hillary finally caught a break. Her doctor called William Evans, research di-

rector at St. Jude Children's Hospital in Memphis. Evans had helped uncover a genetic breakthrough: One in ten Americans have a bad version of a gene that produces the enzyme called TPMT. This enzyme helps break down certain drugs, including mercaptopurine. People with bum copies of the gene have virtually no TPMT. "When they take mercaptopurine," explains Evans, "it's as if you're giving them up to ten times too much."

Sure enough, a blood test showed that Hillary had a bad copy of the gene. Her dosage was slashed, and she remained on finely tuned doses of mercaptopurine for two and a half years. Last December at her party, Hillary was celebrating five years of being cancer-free—the official definition of a survivor.

Hillary DeSmarais is among a growing number of people who are reaping the benefits of pharmacogenomics, a new field of personalized medicine. Because of their genes, people like Hillary are uniquely sensitive to certain drugs; for others, those same drugs have little effect. The promise of personalized medicine is that by testing a patient's DNA, doctors will be able to identify these genetic variations. "You can lower the dose of the drug, you can raise it or you can avoid it altogether," says Richard Weinshilbom, a professor of molecular pharmacology at the Mayo Clinic and a leading pharmacogenomic researcher. "This is one of the first places where the genomic revolution is having an impact on medical practice."

### GETTING TESTED

**I**F YOUR DOCTOR prescribes any of the drugs mentioned in this story, discuss the need for a test. A warning: The tests run \$250 to \$500, and insurance may not pay.

- Genelex offers a direct-to-consumer test. You can contact their office at 800-523-3080.
- Prometheus Laboratories offers pharmacogenetic testing through a doctor. To contact, call 888-423-5227.
- Nanogen makes the genetic chip used in Mayo Clinic tests. For other testing sites, call 877-626-6436.

### DEADLY DOSES

An estimated 106,000 Americans die each year due to adverse reactions to medications, according to most recent research. Consider: Nearly half of all drugs on the market—including painkillers such as codeine, cholesterol-lowering statins, and antidepressants such as Prozac and Paxil—are processed by enzymes controlled by a family of genes known as CYP450.

Mutations in these genes can have very different results. Some people have multiple copies of a gene called 2D6. Dubbed "supermetabolizers," these people will, for instance, get no relief from codeine because it's broken down so fast it has no effect. Others—more than 15 million Americans—have two bad copies of 2D6, making them poor metabolizers. This was the case for nine-year-old Michael Adams-Conroy, who suffered from Tourette's syndrome and obsessive-compulsive disorder. He was put on Prozac, but his body was unable to metabolize the drug, which built up toxic levels. He eventually had a seizure and died. His genotype was learned only after his death.

"If you're taking Paxil or Prozac and you're one of the 7 of 100 people, you're going to build up high levels of drug in your system," says David Mrazek, a child psychiatrist who chairs the department of psychiatry and psychology at the Mayo Clinic in Rochester, Minnesota. "If you're an adult, you'll normally stop taking it because you'll have headaches and be sick to

your stomach. But if you're a six-year-old and you've been told to take this drug, it's tougher to say, 'No, I feel lousy. I'm not going to take it.'"

### THE GENE SCREEN

Mrazek's clinic can now test patients who are candidates for Prozac and other antidepressants. Thanks to a device called a genetic chip (see page 118), Mrazek can identify with 99.9 percent certainty the form of the gene people have and thus how well they'll be able to metabolize the drug.

"What we've done in the past is to try to choose a medication that we believe will be helpful and then watch and see what happens. And if there is a bad reaction, we try another," Mrazek says. "There are now 23 different medications that can be used to treat depression—it's a staggering number." Using this trial-and-error process, he says, it could take months to find the right medication.

### STOP THE BLEEDING

Warfarin is one of the 20 most commonly prescribed drugs in the country. Every year, some two million patients take it to prevent blood clotting and stroke. But about 40,000 of them develop major bleeding. "It's an effective drug," says Brian Gage, associate professor of medicine at Washington University in St. Louis. "But if you get too much, it can kill you."

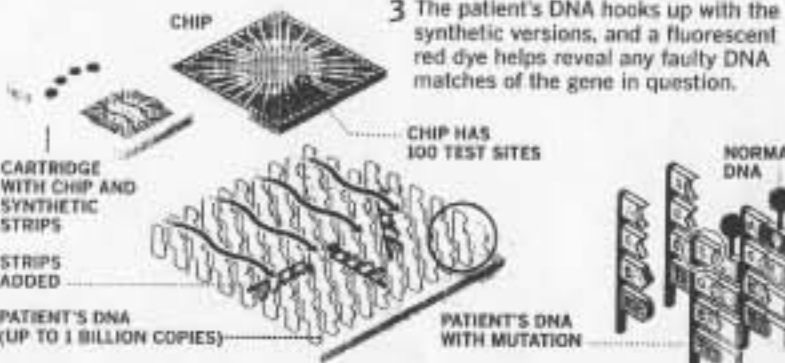
Nearly one-third of Americans have a variation of a gene (known as 2C9)

117

### How the Genetic Chip Works

Specific gene mutations can interfere with—or accelerate—your body's ability to metabolize certain drugs. Here's how doctors look for these mutations.

- 1 Using a blood sample or swab from the patient's cheek, a tester extracts a sample of the patient's DNA.
- 2 The tester places the sample on the postage stamp-sized chip. Synthetic strips of both normal and faulty DNA are then added.
- 3 The patient's DNA hooks up with the synthetic versions, and a fluorescent red dye helps reveal any faulty DNA matches of the gene in question.



that causes them to be poor metabolizers of the drug. According to a 2002 study, these people are nearly two and a half times as likely to suffer serious, life-threatening bleeding.

In another study of 369 warfarin patients published in January, Gage and his colleagues concluded that by testing patients in advance and adjusting their dosage, they could reduce the number of potential overdoses from 16 percent down to 6.5 percent. "There are hundreds to thousands of major bleeds each year attributable to this variation. They could be prevented if patients were genotyped," Gage says.

### PRIME TIME

As pharmacogenomic knowledge advances, regulators at the Food and Drug Administration are wrestling with the type of testing they should

require from drugmakers, and the information they want drug companies to provide to doctors and patients. In 2002, Strattera, a new drug for attention deficit/hyperactivity disorder, became the first drug with a message on its label informing doctors they could test patients to determine their version of the 2D6 gene.

Last year, an advisory committee to the FDA recommended that such information be added to the label for mercaptopurine. This would not only benefit leukemia patients, whose doctors are now generally aware of the genetic issue, but also patients who suffer from Crohn's disease, a much more common ailment that is often treated with a similar drug.

When Randy Adams had a flareup of Crohn's disease in 1999, it caused such crippling stomach pain that he had to go to the emergency room. Doc-

RD INNOVATION | MAY 2004

tors put him on a powerful drug called Imuran, which keeps the body's immune system from attacking healthy tissue. But because Imuran, a cousin of mercaptopurine, can cause severe side effects, doctors use it cautiously, and Adams's doctor was no exception: He set the dose low, then stopped the drug after a couple of months when it seemed not to be working.

As luck would have it, Adams's fiancée, Melanie, had started working at a pharmaceutical firm, Prometheus Laboratories, which performs pharmacogenetic tests. Her colleagues urged Adams to consult a specialist and take a test for the TPMT gene.

The test brought good news: Adams had a version of the gene that would allow him to handle much higher doses of Imuran. His doctor increased his dose sixfold and the pain and inflammation were soon under control, without negative side effects or need for surgery. "I felt great," said Adams. "I had energy, I could run for a mile and I didn't have to have surgery."

Soon, checking patients' gene types and tailoring their dosage may be so routine that patients are unaware of the process. Early this year, a few weeks before he was going to have

hip replacement surgery at Barnes-Jewish Hospital in St. Louis, Hal Regele, 64, was asked if he wanted to participate in a gene study for patients taking warfarin. He agreed, and a few days before his scheduled surgery, he learned his postoperative dosage of warfarin would be cut in half.

Regele has a variation of the 2C9 gene that makes him a poor metabolizer of the drug. His surgery went well, but when it was over and he was home on warfarin, he developed bruises and swelling and had to return to the hospital. Measurements of his blood showed it was excessively thin, despite the reductions in his warfarin dose. Doctors took him off the drug for two or three days, and then lowered his dosage again, allowing his blood to reach safe levels.

Despite the problems, Gage said the gene testing was a success. "Just imagine what could have happened to him if he had gotten a standard dose," he mused. "Instead of having some localized bruising and bleeding, he might have bled somewhere that would have been worse, possibly into his brain. As they say on 'Star Trek,' we took evasive action. It was certainly better than it could have been."