

# THE QUEST FOR CUSTOM CURES

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Boosted by new technology, the burgeoning science of genomics is ushering in an age of personalized medicine.

DARLENE NIPPER GOT ALMOST NOTHING BUT awful news in the early weeks of September 2003. First she learned that the two-centimeter lump in her left breast--the one her gynecologist had responded to by saying, "I'm sure it's nothing, but let's get a biopsy"--was in fact cancer. Worse, the disease had spread to her lymph nodes. At age 39 and in the best shape of her life, Nipper had to undergo immediate surgery to remove the tumor and several lymph nodes. It sapped her strength so severely that she quit her job as the BET Foundation's executive director.

Doctors at the Suburban Outpatient Surgery Center in Bethesda, Md., promised that she would progress smoothly through the ensuing months of chemotherapy. Nipper, not surprisingly, found that impossible to believe. "My impression was that everyone on chemotherapy dies," she says. "I thought, This is it, my death sentence." So when Nipper's doctor told her a diagnostic test showed that her tumor carried multiple copies of the HER2-positive gene, qualifying her to try a new drug, she felt as if she'd hit the DNA lottery.

Nipper's genetic blueprint made her eligible to enter a clinical trial for Herceptin, a metastatic breast cancer drug fashioned exclusively for the 25% of breast cancer sufferers who overproduce the HER2 gene. The drug works by blocking certain genetic signals, thereby preventing the growth of cancerous cells. Though Herceptin is approved only as a late-stage treatment for patients who have already tried other forms of chemotherapy, its maker, Genentech, is seeking ways to get it okayed as an earlier-stage treatment. That's where Nipper and some 2,700 other women across the country come in. As part of Genentech's trials, she received Herceptin as a first line of defense against her disease. Each week for a year she sat down for a 30-minute infusion. Her final dose came this past December. The trials are still underway, and whether Herceptin works as an early cancer medicine remains to be seen. But Nipper has all the proof she needs. "I'm in remission, and my doctor thinks I have a 90% chance of not having a recurrence," she says. "Patients don't realize how random getting medication is. The doctor doesn't really know whether the drug will work for you. This feels like a more civilized way of being treated."

Drugs like Herceptin, specifically tailored for a segment of sufferers who share genetic similarities, are poised to change the world of medicine--and the business of making drugs. The dirty little secret of the pharma industry is that most mass-marketed prescription drugs typically produce the desired effect for only 40% to 60% of the patient population. Genomics promises to vastly improve those odds. Discoveries in the human genome are helping scientists identify the

genetic origins of disease and gain a deeper understanding of how patients of a particular genotype respond to treatments. The payoff? Safer and more effective remedies. "We help patients by soothing symptoms, but rarely can we cure a disease," says Andre Terzic, professor of medicine and pharmacology at the Mayo Clinic. "The real future will go to the foundation of the disease and remove the problem."

The era of truly personalized medicine, when every pill you take will be tailored to your genetic makeup, is still the stuff of science fiction; even the most optimistic medical thinkers don't envision drugs with a market of one. But drugs for groups of people who share a genetic profile are already a reality. Along with Herceptin, approved for sale in 1998, there is Gleevec, from Novartis, which is administered to leukemia patients who have a genetic variation that causes an overproduction of white blood cells. Gleevec essentially turns off the genes that cause those cells to become cancerous. This condition affects only about 5,000 people in the U.S.

More such targeted remedies are on the way. Following the complete sequencing of the human genome in 2003, and with the cost of genomic analysis coming down, researchers have begun to make rapid progress. JSB Intelligence, a British market research firm, predicts that personalized drugs will account for more than three-fourths of Big Pharma's revenues over the next two decades.

Almost every major drug firm has launched a pharmacogenomics division. GlaxoSmithKline researchers recently analyzed genetic information for patients who take the company's Ziagen to learn why some 5% of them experience severe allergic reactions; they identified two genes related to the side effect. Many big firms are also employing biotechs, such as Genaissance Pharmaceuticals of New Haven, to identify patients who will benefit from drugs that failed as remedies for broader populations, a process known as drug rescue. "I think in the next five to ten years you will see the life sciences explode," says Dan Burns, a senior vice president for genetics research at GlaxoSmithKline, "because we now have the ability to do things that we simply couldn't do just a few years ago."

In March the FDA established a framework for reviewing and approving genetically prescribed drugs: It released a long-awaited set of guidelines governing how and when it is appropriate for drug companies to submit genetic data about clinical-trial patients as part of an application for new-drug approval. From 1995 through 2000, only 15 new-drug applications to the FDA contained pharmacogenomic data, such as patient biomarker information or particular genotypes that should be included or excluded from the patient population for safety or efficacy reasons. In the past two years, more than 100 submissions have had such data. With the new guidelines, that number is expected to double this year. "The guidelines remove doubts within the industry about what the FDA wants," says Larry Lesko, who will lead the FDA's new genetic data initiative as director of the agency's Office of Clinical Pharmacology and Biopharmaceutics. But he insists that the FDA will be very selective in granting approvals. "We have to be careful of 'genohyping,'" says Lesko. "As more and more companies are developing drugs that address difficult diseases, there'll be a higher bar for discerning differences between patients, and for personalizing drug choice and drug dosage."

From the industry's standpoint, this new era couldn't have arrived at a better time. Big Pharma's

current mode of operation--churning out mass-marketed blockbusters that garner more than \$1 billion a year--is costly and high risk (though often highly lucrative). Almost 80% of drug candidates in clinical development fail to make it to pharmacy shelves. Medicines that do succeed end up costing nearly \$1 billion to develop and usher to market. And in the aftermath of Merck's Vioxx recall and the FDA's recent request that Pfizer stop selling Bextra, drug safety is under more intense scrutiny too. "Pharmacogenomics could expand markets and revenues by defining new uses for existing drugs, rescuing [failed] drugs in development, managing product life cycles, and dominating niche markets," says Tracy Lefteroff, global managing partner for life sciences at PricewaterhouseCoopers. "Because success in the pharmaceutical business depends so much on marketing and branding, highlighting a product's pharmacogenomic aspects will help companies differentiate their products and build new demand."

Consumer demand is already helping drive pharmacogenomics. As baby-boomers encounter the depredations of old age--especially boomers stricken with cancer and other hard-to-treat ailments like Alzheimer's and heart disease--they are clamoring for innovative treatments. "Patients feel entitled to have personalized medicine," says Susan Desmond-Hellmann, Genentech's president of product development.

Of course, as with any new technology, the promise of miracles can lead to inflated expectations, and even abuse and fraud. Gene science has so infused itself into society's DNA that Target stores now sell at-home genetic profile kits starting at \$29.99. In the world of sport, Olympic officials fret that gene therapy could become the new steroids, helping dishonest athletes reengineer muscle tissue in a way that is virtually undetectable. Dubious "DNA diets," customized eating regimens designed to head off diseases that run in families, are an Internet fad.

Clearly this is an area where fantasies about future possibilities will outstrip reality for some time to come. But here's a look at a few of the ways genomics is already having an impact.

- Rescuing failed drugs.Among the most interesting examples of genomics-aided drug rescue is NitroMed's BiDil. In 1999 the FDA rejected the drug because the agency found it ineffective at treating heart failure. Rather than accept defeat, scientists at NitroMed delved back into their data from the clinical trials. They discovered that the African Americans in the trial had far better outcomes than patients of other races. They immediately asked the FDA for permission to conduct a larger trial, this time using only black patients.

Last summer researchers halted the new experiment: BiDil was proving so effective that it would be unethical to continue withholding it from patients in the control group. According NitroMed, the data showed that black patients with heart failure experienced a 43% improvement in survival after coupling BiDil with a standard heart therapy. The FDA is reviewing the drug and is likely to approve it by the summer. That would make BiDil the first drug ever exclusively produced for and marketed to a racial group. Because race is an inexact indicator of genetic similarities, NitroMed is in the process of reviewing its data to find biomarkers among the patients that will make prescribing more precise. "If we can demonstrate the genetic basis for this, we can expand the number of patients who benefit," says CFO Dr. Lawrence Bloch.

- Finding new uses for old drugs.The breast cancer treatment Tamoxifen protects some women,

but not others, from osteoporosis. A study at the University of Indiana found that women who possess an inherited genetic variant associated with estrogen production received the bone-strengthening benefits. The next step: using those data to develop a test that will screen for women with the genetic variant. Tamoxifen could potentially be marketed to those women as an osteoporosis drug that also protects against cancer.

- Fine-tuning treatment programs. A study at the University of California at San Francisco is examining the genetic factors behind sensitivity to nicotine. Researchers seek to discover how smokers get the habit. In the experiments, 40 patients who have never smoked (20 Asian Americans and 20 of European descent) were dosed with a seven-milligram nicotine skin patch for eight hours--the equivalent of roughly seven cigarettes. Dr. Delia Dempsey, who led the study, concluded that the ease with which some smokers pick up the habit may be determined genetically. Patients carrying genes associated with slower breakdown of nicotine in the liver had more adverse responses to the patch. They became anxious, lightheaded, and nauseous. Interestingly, a higher percentage of them were Asian American. The upshot: A smoker's genotype might influence response to nicotine smoking-cessation treatments. "It's conceivable that we may want to have different smoking-prevention programs for Asians and Caucasians," says Dempsey.

- Staying ahead of AIDS. The HIV virus is constantly mutating to develop resistance to medication, which makes it especially difficult to treat. But physicians have figured out a way to apply genomic testing to determine which variation of the virus a patient has. In this case, drugs are customized for the genetic makeup of the disease rather than the patient. Last winter, when doctors at the Aaron Diamond AIDS Research Center (ADARC) in New York encountered a patient infected with a rare, multidrug-resistant strain of HIV, they analyzed the virus using a genetic test made by ViroLogic, in South San Francisco. The test was invaluable. Says Dr. David Ho, renowned AIDS researcher and CEO of ADARC: "The value of having access to comprehensive drug-resistance testing technologies helped to clarify this patient's best treatment options." Gene-based drugs are certainly the medicines of the future. But as Ho suggests, the future is now.