



WHEN A PATIENT'S GENES EXPRESS THEMSELVES, THEY MIGHT:

Suggest that a certain treatment is almost sure to work // Signal that heart transplant rejection is imminent // Advise against chemotherapy // Issue other messages we don't yet understand.

Medicine Gets Personal

■ BY ANITA SLOMSKI

Genes first cursed, then blessed Michael Santo. When he arrived at the Massachusetts General Hospital in Boston, in 2002, after falling unconscious at home, he had no doubt his diagnosis would be the same one that had doomed his father. “I know why I’m here,” Santo, now 59, interrupted Tracy T. Batchelor, director of neuro-medical oncology, before Batchelor broke the news of Santo’s brain tumor.

Santo’s father was dead two weeks after his tumor was discovered in 1988. But when Batchelor read the biopsy report on Michael Santo’s tumor, he was elated to find that the tumor’s cells were missing chromosomes 1p and 19q. That meant Santo would almost certainly respond to chemotherapy and could expect to live another decade or more—unlike the 30% of patients with the same tumor but with those two chromosomes intact: They usually succumb within two to three years.

That Batchelor could use the genetic profile of a patient’s tumor to select the right treatment (if the chromosomes weren’t missing, Santo would have been treated with radiation) fulfills one promise of personalized medicine. In an ideal world, this genetics-based revolution would provide fully individualized diagnosis and treatment, enabling doctors to predict what diseases you’ll get and when you’ll get them, as well as to know how to treat them. Someday, far down the road, it might even be possible to pluck out faulty genes and replace

them with normal DNA, restoring you to robust health.

In fact, we’re still far from that world. No one can say how long it will take to find the links between variations on some 20,000 human genes and approximately 1,500 diseases. And while genetic and genomic tests are being rushed to market, some predict the onset of diseases for which there’s no effective treatment. Yet, already, remarkable progress has been made, with almost weekly announcements heralding breakthroughs in everything from basic science to immediate applications.

The vision and reality of personalized medicine are separated by 3 billion genetic “letters,” chemical base pairs of DNA that contain instructions for everything a human cell does. The 13-year-long Human Genome Project, completed in 2003, made a monumental contribution, determining the order, in each base pair, of the four chemical bases that make up human DNA. The resulting map provides invaluable information about what makes a human human—rather than a chimpanzee, fruit fly or yeast—and should yield insights into disease patterns and prognoses. Yet, sequencing the genome was only a first step. Rudolph Tanzi, director of the genetics and aging unit at the Massachusetts General Hospital, describes it as providing a phone book of all the genetic suspects that may be implicated in human disease.

“Suppose you’re a detective looking for a serial killer,” Tanzi says. “You now have the book of names of everyone and where

they live, but you still have to do old-fashioned detective work—in our case, testing gene variants, looking at inheritance in families—to zero in on the killer and find the smoking gun, the variants on the genes that cause the problems.”

Detecting those smoking guns has been aided by the International HapMap Project, finished last year, that clusters genetic variants into “city blocks,” to continue Tanzi’s analogy. “Now you know which neighborhoods to look in, and you can implicate multiple suspects”—that is, variations on two or three genes that may also be inherited with the disease-causing gene defect you’re after, says Tanzi.

By dovetailing the HapMap with new technology that allows scientists to put microscopic samples of DNA on a chip and scan thousands of genes at a time, as well as computer programs that can analyze vast amounts of genetic data, Tanzi can test for

under a microscope,” says Randy Scott, president and CEO of Genomic Health, which provides a test that attempts to predict whether estrogen-sensitive breast cancer is likely to recur and whether a woman needs chemotherapy as well as the hormonal treatment tamoxifen.

Genomic Health’s Oncotype DX test measures the amount of RNA expressed by 16 genes in early-stage breast cancer tumors sensitive to estrogen. “Some of the genes are good and some are bad,” says Scott. “The relative amounts that each tumor expresses show how aggressive the tumor is.” A high score, earned by about a fourth of tumors, indicates that the cancer is too aggressive to be tamed by tamoxifen alone and will require chemotherapy as well. Conversely, the test can also identify women who might safely skip chemotherapy, sparing them the trauma and expense of needless treatment.

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a gene variant at average increments of 5,000 DNA base pairs on the 3-billion-base-pair genome—compared with having to screen genes in groups of 50 million base-pair regions before.

Amid this ongoing hunt for individual genes, many practical applications of personalized diagnosis and treatment are flowing from genomics, the study of gene expression. Because the amount of RNA a gene expresses may vary in different tissues and tumors, it can be a very sensitive measure for, among other uses, distinguishing one tumor from another. Genomics tests that gauge those variations have the potential to help physicians determine what treatment is needed and when and how effective it’s likely to be.

Many of these tests, some making their way into clinical practice, involve cancer. “Genomic differences can vary widely among individuals, resulting in variable responses to therapy, even for patients whose cancers seem identical

Other tests can help doctors time a drug for maximum effect—a particular benefit when prescribing potent immunosuppressants and steroids for transplant patients. Working from a blood sample, the genomics test AlloMap measures the RNA expressed by 20 genes in leukocytes (white blood cells) for signs that a heart transplant patient’s immune system is about to launch an attack against the heart. Before this test was developed, the only way to monitor a patient for signs of organ rejection was to snake a catheter into the new heart and snip off several pieces of heart muscle for biopsy—a risky procedure typically repeated 25 times in the first four years after transplant.

In some 30 transplant centers, cardiologists use AlloMap in addition to biopsy to alert them when rejection is imminent. If AlloMap indicates that the patient is not rejecting the heart, physicians may decide to forgo biopsies and continue weaning the patient off antirejection drugs, says Pierre Cassigneul,

president and CEO of XDx Inc., the maker of AlloMap. “The test helps clinicians identify when the immune system is in check. Ultimately, clinicians want to decrease long-term side effects by lowering the immunosuppression without increasing the risk of rejection. But they also want to intervene before rejection—and irreversible damage to the heart—occurs.”

Still other genomics tests could benefit psychiatric patients. Wolfgang Sadee, professor of medicine and pharmacology at Ohio State University, expects that within five years he’ll identify gene variants that alter drug receptor activity and the metabolism of antipsychotic drugs. Finding those 10 to 20 genes should enable him to develop a test that will predict who will respond to a particular treatment, avoiding a trial-and-error approach to gauge whether a particular drug is working. “When you prescribe an ineffective drug, the patient suffers,” Sadee says. “Each episode of psychosis causes lasting damage.”

So do treatments that are toxic for patients, which result in about 1,000 U.S. deaths every year. The AmpliChip CYP450 test, a new diagnostic tool from Roche Diagnostics, looks for variations on two genes that determine how an individual

will metabolize certain prescription drugs. Physicians can use that information to avoid prescribing doses that may be either dangerously high or ineffectively low.

As encouraging as it is to witness the arrival of tests and treatments, the march of medical progress often seems agonizingly slow for those desperate for a cure. Forty years ago, scientists found the first genetic clue to chronic myelogenous leukemia (CML), a cancer of the blood and bone marrow: One chromosome in the white blood cells was shorter than normal. But it wasn’t until 1987 that scientists identified the protein that the two ends of the broken chromosomes express, Bcr-Abl tyrosine kinase, which produces an excess of white blood cells. In the early 1990s, Novartis was trying to make a drug to combat a gene implicated in coronary thrombosis. Though the therapy wasn’t effective for that purpose, it did block the Bcr-Abl protein. Gleevec (imatinib mesylate) entered Phase I clinical trials in 1998 and was granted fast track approval by the FDA in 2001 after the majority of CML patients responded well with no serious side effects. And so, after 35 years, Gleevec became the first therapy to target the expression of a gene abnormality.

Iressa (gefitinib), approved in 2003, also blocks a tyrosine kinase, but in non-small-cell lung tumors. When it works, Iressa reduces tumors by 50% to 90%. Yet only one in 10 U.S. patients responds to the drug. To find out why, Daniel Haber, director of the Massachusetts General Hospital Cancer Center, looked at the gene producing the protein targeted by Iressa—epidermal growth factor receptor—and found that tumors responding to the drug had a genetic mutation at exactly the site where Iressa would bind to them. The mutation causes the protein to bind to Iressa 10 times more tightly than a normal protein does. That finding, confirmed by other researchers in Boston, New York and elsewhere, helped explain the low overall response

Intrigued by a breakthrough cancer drug that helped just one in 10 patients, Daniel Haber discovered that those patients shared a propitious genetic mutation.



PHOTOGRAPH BY MICHAEL EDWARDS



Seeking early warning of transplant rejection, Pierre Cassigneul's AlloMap test measures the RNA expressed by genes in white blood cells.

rate to Iressa, and provided an approach for targeting the drug to those most likely to respond. It also led to a genomics test that examines DNA from lung tumor tissue to predict which patients will benefit from Iressa.

Now Haber and others are seeking to understand another anomaly—that large percentages of some populations with non-small-cell lung cancer, namely women, Asians and non-

smokers, have the mutation that makes the tumor treatable with Iressa. But for aerospace engineer G.M. of San Gabriel, Calif., the reason hardly mattered. G.M., who is Chinese and who spent the first 18 years of his life in Hong Kong, was devastated when doctors discovered a golf ball-size tumor in his right lung. But his oncologist told him how extremely effective Tarceva (a drug related to Iressa, and preferred in the United States) is for nonsmokers, particularly those of Asian descent. Five months after his therapy began, G.M.'s lung tumor disappeared.

Five years from now, Haber predicts, physicians will prescribe therapies based on a tumor's critical genes rather than on where in the body the cancer originated, because many targeted drugs are found to work in multiple types of cancers. "Right now we are looking only at mutations in genes producing kinases because it is possible to make drugs targeting those proteins," says Haber. "As soon as we can make drugs against other types of proteins, researchers will be matching them with genetic abnormalities in those cancer genes as well."

Even better than treating the expression of a defective gene would be replacing the gene with normal DNA. Since 1990, researchers have been trying to correct genetic defects by inserting chemically produced DNA into a vector—typically a virus stripped of its ability to replicate and

Barriers to Treatment //

The shift from broad-based methods of diagnosis and treatment to precise, individualized approaches could be slowed by several hurdles, most related to losing the economies of scale that come with treating large populations. Yet solutions are emerging.

COST // Some analysts have speculated that, because most targeted therapies are aimed at a small slice of the population—Tarceva, for example, has been found most useful in only about one in 10 new cases of lung cancer—the pharmaceutical industry would never see an adequate return on the cost of development. "Five years ago, companies were generally resistant to developing drugs tailored for subsets of patients with a particular disease, fearing that would shrink profit margins," says Edward Abrahams, executive director of the Personalized Medicine Coalition, a consortium of academic institutions, doctors, drug companies and others. "But now most have embraced pharmacogenetics. In the long run,

it will save money because it's very expensive for drug companies as well as patients to keep trying drugs that don't work."

TESTING // The randomized controlled trial is designed to gauge effectiveness among large populations, while a drug such as Iressa may work well only for the small number of people with a particular genetic makeup. One way to get meaningful test results for targeted treatments would be to subclassify patients in a trial to determine who might or might not respond to a particular therapy. Profiling tumors as well as patients in clinical trials could also help. And in March 2005, in what many saw as a government endorsement

of targeted therapies, the FDA released guidelines advising pharmaceutical companies to provide data from genetic tests that may be relevant to a drug's usefulness.

AFFORDABILITY // Will only the wealthy be able to afford targeted therapies? "For an extremely expensive drug, the copay may be 20%, which is prohibitive for most people," notes William J. Gradishar, director of breast oncology at Northwestern Memorial Hospital in Chicago. But that's an issue that affects all kinds of treatments, and if targeted therapies ultimately save drug companies money, insurers and patients might see comparatively lower costs. BY ELIZABETH GEHRMAN

Each new piece of information about genes and their expression reveals another possible pathway for taming disease at its most basic level.

cause illness—and injecting it into cells so that they will follow the inserted DNA's instructions and behave like normal cells. Unfortunately, results have been mixed, even disastrous.

An 18-year-old died in 1999 after a severe immune response to the DNA-bearing virus intended to replace a broken gene that prevented his liver from making an essential enzyme. Since 2002, three “bubble boys” in France have developed leukemia after doctors replaced the faulty genes on their X chromosomes that had left them without immune systems. (As many as seven others have been successfully treated, however, and a similar trial cured several children in England suffering from the same affliction.) And recently, a gene-replacement trial in Germany significantly improved the ability of two men with another rare immune deficiency disorder, chronic granulomatous disease, to fight infections.

The FDA, worried about potential harm to patients, now restricts gene trials to small numbers of individuals and with very low initial doses of DNA. But those requirements have done little to slow research that continues to explore gene therapy as a treatment or cure for many diseases, including muscular dystrophy and Parkinson's disease. In one experiment, a Phase I clinical trial involving 12 patients, William J. Marks Jr., associate professor of neurology at the University of California at San Francisco, and physicians at Rush University Medical Center in Chicago are injecting into the brain a viral vector containing the DNA that codes for a growth factor protein called neurturin. Marks hopes that the DNA's genetic instructions will prompt brain cells to start making neurturin, keeping those cells alive and producing dopamine, the neurotransmitter involved in controlling movement and that is depleted by Parkinson's disease.

Viral vectors packed with DNA may also change how drugs are delivered. Injected DNA could be targeted to the exact site of disease, avoiding toxic side effects that may result from taking a drug systemically. The biotech company GenVec, for example, has used a gene that, when injected into the heart of a patient with severe coronary artery disease, triggers the production of vascular endothelial growth factor, which generates blood-vessel growth in areas of the heart starved for

oxygen. Another GenVec gene promotes a tumor necrosis protein that damages tumor blood vessels.

“You can kill a tumor with a locally produced protein that would be too toxic to give as a drug,” says GenVec president and CEO Paul Fischer. What's more, because vector-delivered DNA isn't incorporated into the cellular DNA, local protein production is temporary, on the order of months rather than years, says Fischer. And for cancer at least, clinical trials have shown that one injection is adequate to shrink tumors in combination with chemotherapy and radiation so they can be surgically removed, increasing the two-year survival rate from 10% to 30%.

Each new piece of information about genes and their expression reveals another possible pathway for taming disease at its most basic level. But progress won't be as rapid as many people outside medicine would like to think. “The success of the Human Genome Project led many to expect an avalanche of approaches, tests and treatments that would revolutionize medicine,” says Bruce Korf, chair of the department of genetics at the University of Alabama at Birmingham. “In fact, though the progress is dramatic, it is gradual. Some findings have made a huge difference, like the discovery of a gene for breast cancer. But the complexity is enormous. The genetic revolution will likely be an evolution. It's like watching the first airplane flight in the beginning of the twentieth century. It took more than 50 years before people were routinely flying across continents.” ■



DOSSIER

1. “Pharmacogenomics: Harbinger for the Era of Personalized Medicine?” by Wolfgang Sadee, *Molecular Interventions*, 2005. Outlines how genetics will affect choice of drug therapy and the changes in drug research that must occur before personalized medicine reaches its full potential.
2. www.personalizedmedicinecoalition.org. Compilation of new reports on the latest genetic discoveries, tests and treatments, as well as in-depth articles on personalized medicine.