

A Better Crystal Ball

personalized medicine promises a new level of clarity with treatments tailored to one's genes but it hinges on development of exacting gene-based tests

BY MAYA PINES
PHOTOGRAPHS BY NOAH WEBB AND PAUL FETTERS

“What’s your genetic subtype?”

This sounds like a futuristic pick-up line, but it is actually the key question for researchers focused on “personalized medicine,” tailored specifically for each patient’s genes. They believe that, within a few years, tests to reveal patient subtypes will become part of the routine evaluation of disease.

Such tests can already show how rapidly or slowly a person metabolizes drugs, for instance, helping doctors prescribe doses that are large enough to be effective, yet not so large as to cause harm in a particular patient with heart disease, depression, or schizophrenia. Other gene-based tests can indicate whether a patient with an early tumor really needs to undergo chemotherapy—with its many side effects—after surgery. One test may soon detect the first signs of a particular cancer in a patient’s blood before any symptoms appear and in time for a definitive cure by surgery.

Some of these tests will save money in the long run. Others will lead to expensive new drugs (some have already) that are targeted to specific subtypes of patients—drugs that not every patient can afford. “This is an enormous and challenging issue,” says Kenneth Offit, chief of the Clinical Genetics Service at Memorial Sloan-Kettering Cancer Center in New York City. He recently took part in an Institute of Medicine conference where, he notes, several speakers emphasized the need for “more evidence-based reviews and more cost-benefit analyses to inform the discussion of access to molecular medicine.”

Offit is one of many optimistic researchers who are convinced that the overall effect of gene-based tests will be to make treatment more

efficient and effective, reducing the instances in which people take drugs that don’t work.

“We now know that certain drugs work only in a particular subset of patients,” says Charles L. Sawyers, an HHMI investigator at the University of California, Los Angeles (UCLA), “but we don’t yet know how to identify subsets in an easy way.” This is why Sawyers and other researchers are busy ferreting out differences in patients’ genes, then using these distinctions to stratify people into smaller and smaller subgroups, each of which responds to drugs in its own particular way. This approach has already changed how certain diseases are treated, at least in leading hospitals and research centers. At the same time, it is inducing drug companies to take account of subtypes as they develop and test new treatments.

The fruits of personalized medicine are most evident in cancer. Sawyers’s own work has helped revolutionize the treatment of chronic myeloid leukemia (CML) by aiming the precisely targeted and highly effective Gleevec (imatinib), and now the recently approved drug Sprycel (dasatinib), at specific genetic mutations in the cancer (see sidebar, pg 37). Research by others has revealed the genetic mutations that make the drug Herceptin (trastuzumab) effective against certain types of breast cancer, and Iressa (gefitinib) effective against a small subset of lung cancers. New tests for these mutations can identify who is most likely to benefit from these costly drugs—and who should try something else, saving valuable time and expense as well as reducing unnecessary toxicities.

While there is growing excitement among researchers about the promise of personalized medicine, only a handful of gene-based tests are in wide use at present. “Why does the community oncologist in middle America generally not use such tests?” asks Todd R. Golub, an HHMI investigator who directs the cancer program at the Broad Institute of Harvard University and the Massachusetts Institute of Technology in Cambridge, Massachusetts. “That’s simply because most of the early molecular genomic tests that are predictive of response to treatment have now gone into the black hole of validation—and have yet to emerge.”

Many of the initial reports of gene-expression profiles that could identify subtypes of cancer

Simplified, Early Diagnostics

The current gold standard for colon cancer detection is colonoscopy, an invasive and unpleasant procedure that many people avoid. The more widely used fecal occult blood test, designed to detect blood in the stool, catches only about 30 percent of colon cancer cases. Malignant tumors do not always bleed. For the past decade, HHMI investigator Bert Vogelstein and his colleagues at the Johns Hopkins University School of Medicine have sought ways to detect specific alterations of DNA in patients with very early colon cancer—first in the patients’ stool cells (one test he developed to detect DNA alterations in stool samples became available in 2003), and now in blood. “In colon cancer, the genetic mutations are well known,” points out Vogelstein, who played a major role in discovering them. So he began the ambitious project of looking for fragments of the cancer-causing gene, *adenomatous polyposis coli* (APC), in samples of blood. With the aid of a technique called BEAMing, in which DNA fragments of a cancer gene are attached to metal beads and amplified, he found tiny samples of APC in blood drawn from patients with colon cancer. He has evidence that such fragments are released into the blood when white cells destroy dead tumor tissue. Pilot studies of Vogelstein’s experimental blood test showed that it easily identified people with advanced colon cancer and could even detect more than half of those whose cancers were in the early stages at which they could be cured by surgery—without the need for chemotherapy. “We could still find fragments of the mutant DNA in their blood, but fewer of them,” says Vogelstein. “They were detectable in more than 60 percent of the early-stage patients.” This could save hundreds of thousands of lives every year among people who do not undergo colonoscopies. He hopes the test will eventually become more sensitive; more advanced versions are being developed. Vogelstein expects patient compliance, once the test becomes available, to be much higher than for other tests, “because most patients routinely have blood drawn when they visit their physicians.” He adds, “This type of blood test might apply to other early cancers, as well. That’s one of the reasons we’re excited about it.”

were based on only tens or perhaps hundreds of patients. “Before routinely implementing them in the clinic, we need to make sure they really hold up in many other patients and many other places,” Golub says. “This takes a lot of time and effort.”

A few tests have gone through more extensive validation, he says, and are available commercially to physicians. Among them are predictive tests for breast cancer recurrence, such as the Oncotype DX test in the United States and MammaPrint in Europe.

INFORMED DECISIONS

The Oncotype DX test focuses on 16 specific genes related to the molecular behavior of breast cancer cells in tumors removed from women with early breast cancers that are fueled by estrogen, giving each patient a score from 0 to 100. The higher the score, the greater the danger the cancer will return. Researchers at Genomic Health, Inc., of Redwood City, California, found these 16 genes to be *least* active in the tumors of patients who survived 10 years without a relapse. The very same genes were *most* active in the tumors of patients who had suffered bad outcomes.

At New York University School of Medicine, oncologist Ruth Oratz uses the test, and it has changed the way she treats some of her patients. Recently, a woman who looked like a good candidate to receive only hormonal treatments after her breast surgery and radiation—she was older, had a very small tumor, and no signs of cancer cells in the lymph nodes under her arm—was, according to the Oncotype DX, at very high risk of having a recurrence. “So she was given chemotherapy in addition to the hormonal treatment,” Oratz recalls. The test has made the pendulum swing the other way as well for some of Oratz’s patients, leading them to forego aggressive chemotherapy when the test score was very low.

About 7,000 Oncotype tests were performed in 2005. Many insurers refused to reimburse the \$3,460 cost because they were not convinced of the test’s merits. The test received so much support from oncologists, however, that early this year Medicare decided to cover the cost for its beneficiaries. Several private insurers have begun covering it too.

Another widely accepted test called AlloMap, devised by XDx, Inc., in South



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San Francisco, recognizes the earliest steps of rejection in heart transplant patients by measuring the activity of 11 immunology-related genes. Thanks to this test, patients can now avoid many of the frequent and unpleasant heart biopsies they had to undergo to look for signs of rejection.

Tests like these may be useful, but they fall short of revealing the cause of a disease, and they don't provide any leads to better treatments. The real bottleneck in personalized medicine, according to Golub, is still a lack of specific knowledge. “We need to know more about the molecular underpinnings of a disease so we know exactly what to measure in a patient,” he says. “We also need a mechanism to actually measure these molecules in a clinical setting before deciding on a treatment.” He calls for “more effort in early discovery.”

Bert Vogelstein, an HHMI investigator at the Johns Hopkins University School of Medicine, agrees. “The first challenge is to discover the inherited or acquired alterations in DNA that are responsible for a disease,” he declares. “In most cancers, these have not yet been discovered. Only a small fraction of the alterations that contribute to breast, prostate, lung, or other common cancers have been identified. So we act like the drunk who looked for his keys, not where he lost them, but under a lamp, where the light was good. Many other places might be better.”

He also complains that, “almost all ‘translational’ research funds now go to find new therapeutics. This is not optimal,” he says. “Our best hope for reducing sickness and death—and health care costs—is through prevention and early detection, rather than therapies.” Vogelstein's own research has focused on early detection of cancer (see sidebar, pg 34). “One difficulty is that if you learn how to detect a cancer at a stage when it can be cured by surgery or something simple, you have to screen 100 or 500 patients to find one that you catch early,” he says. “This is not nearly as dramatic or sexy as taking a sick patient with more advanced disease and putting him or her in remission. But remember that this one patient [whose disease is caught early] will be completely cured of the cancer and won't ever die from it!” By contrast, “drugs put cancer patients in

remission only for a period of time—often a surprisingly short time, and they are surprisingly expensive.”

GOOD FOR BUSINESS

Meanwhile, gene-based tests are becoming a big business. “There are about 1,000 gene-based tests that you could get today,” says Kathy Hudson, director of the Genetics and Public Policy Center at Johns Hopkins. She notes that “only a dozen of them have been reviewed and approved by the U.S. Food and Drug Administration (FDA),” and wishes the government would give more attention to the validity of such tests.

The FDA may be paying more attention. Drug companies are joining the rush to stratify patients according to their genes, and they’re doing it with the blessing of the FDA, says Edward Abrahams, executive director of the Personalized Medicine Coalition, a Washington-based public-interest group. He notes that in March 2005 the FDA started asking drug companies to voluntarily share information on how specific subtypes of patients respond to the drugs submitted for review. Since then, more than 25 companies have submitted such data.

Not surprisingly, “many drug companies have concluded that they must incorporate genetic tests into their drug trials,” says UCLA’s Sawyers. That was his experience with Bristol-Myers Squibb, the maker of dasatinib. There had been a lot of debate about the usefulness of genetic tests in drug development, he says, “but now most parties agree that it’s a good thing. The cost of drug development should go way down when you do clinical trials with the right subgroup of patients. You get faster approval, and you can go on to develop more drugs.”

Insurance companies will have to come along as well, to pay for the new gene-based tests, Sawyers contends, “because these tests will guide the treatment. Insurers could avoid paying treatment costs for all patients, when in fact the treatment might help only a fraction of them.” Abrahams adds that “the growing link between therapy and diagnostics” (in the form of gene-based tests) is the key to the future development of personalized medicine. “The tipping point,” he says, “will come when patients refuse to accept what they often get now—trial-and-error medicine.” ■

Personalized Medicine Made Real

Progress against chronic myeloid leukemia (CML), using Gleevec to halt the cancer where it starts—and now the drug Sprycel (dasatinib) when drug resistance takes hold—is “proof of principle” that personalized medicine can work, according to HHMI investigator Gary Gilliland, a cancer researcher at Brigham and Women’s Hospital in Boston. “Once it is demonstrated that a specific genetic mutation causes a cancer, as for the *BCR-ABL* mutation in CML, you can reliably predict that patients will respond to its inhibitors, such as imatinib – and there are rational strategies to overcome resistance to imatinib if it develops.” In patients with CML, the abnormal fusion gene, *BCR-ABL*, leads to an overactive form of the ABL kinase, an enzyme that regulates cell growth and differentiation. The abnormal kinase makes white blood cells grow out of control; it is fundamental to the cancer itself. Gleevec, a drug pioneered by HHMI investigators Brian J. Druker, at Oregon Health & Science University, and Charles Sawyers, at the University of California, Los Angeles, blocks ABL kinase activity, and was approved by the FDA in 2001 for CML. Far more effective than most other chemotherapy because it is targeted so precisely, “Gleevec puts 80 percent of patients into complete remission,” says Charles Sawyers. That is a huge improvement for a disease that was once uniformly deadly. Gleevec was not the end of the story, however, because patients—about 4 percent a year—eventually develop resistance to the drug and relapse. “Three-fourths of patients are still doing well in their seventh year of therapy,” Sawyers says. “But in 20 years, most of them would be expected to relapse.” Determined to solve this problem, Sawyers teamed up with John Kuriyan, a crystallographer and HHMI investigator at University of California, Berkeley, and showed that patients whose cancer resisted Gleevec had a special subset of genetic mutations that made their kinase too rigid, keeping it in the “on” position at all times (Gleevec binds to ABL kinase only when it’s in the “off” position). They began to search for a “sloppier” drug that might bind with the ABL kinase in any position, and Bristol-Myers Squibb turned out to have a good candidate, called dasatinib. In the June 15 issue of *The New England Journal of Medicine*, Sawyers announced that dasatinib produced excellent responses in a phase 1 study. So far it has been tested only in patients who relapsed after Gleevec, but Sawyers says, “It may prove even better than Gleevec—it is much more potent and has a broader reach.” In late June, the FDA granted accelerated approval for marketing of the drug under the name Sprycel for CML patients who have relapsed from or cannot tolerate Gleevec. It was also approved for certain patients with acute lymphoblastic leukemia. Dosages of the new drug were fine-tuned for each patient based on detailed studies that examined how well the drug inhibited its target—a technique that was pioneered by Sawyers’s group for use in earlier studies in mice. In addition, each patient’s resistance-enhancing mutation was sequenced by Bristol-Myers Squibb scientists. This allowed the researchers to correlate how the drug responded to each type of mutation. “Every single patient who was predicted to be sensitive to dasatinib based on the genotyping studies had a clinical response,” Sawyers says. This shows that all CML patients could be genotyped (have their genes analyzed) to decide whether their condition will respond to these molecularly targeted drugs. Genzyme’s new *BCR-ABL* Mutation Analysis test is already available to physicians, Sawyers notes, and “in leukemia, the tumor is in the blood, so it is easy to test for.”