What the Devil *Is* Personalized Medicine?

Bob Carlson, MHA, Senior Contributing Editor

Robert M. Roy is not the kind of guy who calls in sick. For one thing, he's a self-employed corrosion consultant who teaches and travels the world, inspecting ships, bridges, nuclear power plants, and other infrastructure. He's also ex-Special Forces, with a "high pain threshold," as he puts it.

Roy, who had just turned 50, had been feeling unusually fatigued after he returned from Belgium in 2000, but he figured it was his hectic travel schedule. It wasn't. Doctors at the University of Texas M.D. Anderson Cancer Center, in Houston, told him he had blast phase chronic myelogenous leukemia (CML) and needed to be hospitalized immediately.

Hydroxyurea and chemotherapy were the standard of care back then, and while the hydroxyurea seemed to stabilize his white cell count, Roy developed esophageal and throat ulcers and lost 40 pounds. When the U.S. Food and Drug Administration approved imatinib mesylate (Gleevec) the following year, Roy was switched to that drug.

Imatinib worked for two and a half years, but, as sometimes happens, the disease mutated into a form resistant to it, and Roy was back to square one. Roy's doctor, Jorge Cortes, MD, deputy chair of the department of leukemia at M.D. Anderson, was principal investigator in trials of dasatinib (Sprycel), a potent investigational CML drug. Cortes enrolled Roy in phase 2 trials of dasatinib, and six weeks later, Roy's CML was in remission. Dasatinib was approved in 2006.

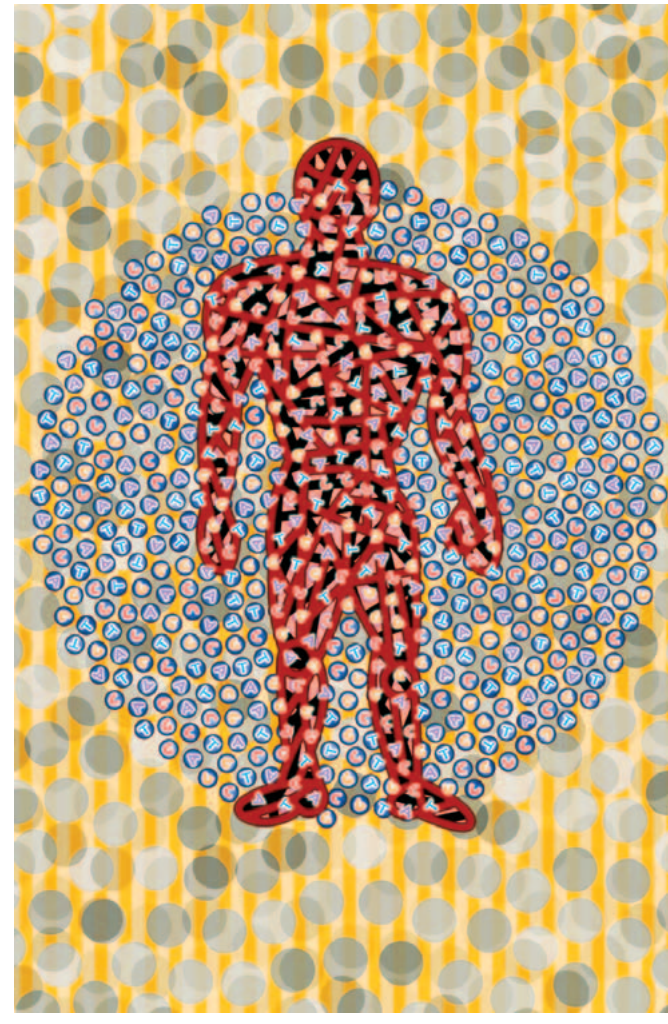
"That was in February of 2005, and I've been on Sprycel ever since," Roy says. "I am traveling the world again, and Sprycel makes it possible for me to do that. I don't know how it works, but I know it works."

WHAT MAKES IT PERSONAL?

Roy is one of thousands saved by imatinib and dasatinib and one of millions who have been helped by a new generation of personalized drugs that have saved lives, enhanced quality of life, and perhaps even reduced the overall cost of care.

The dosage form of imatinib and dasatinib happens to be a tablet, but personalized drugs also can be injected or infused biologics. Together, these kinds of drugs and other interventions are among the first entities in the relatively new category of *personalized medicine*.

What's personalized about imatinib and dasatinib is that they target the root cause of CML and Philadelphia chromosome-positive acute lymphoblastic leukemia by blocking the abnormal activity of a gene that controls cell proliferation. In contrast, most drugs on the market today are "one-size-fits-all" medications that may or may not be effective in certain types of patients, and carry the potential for side effects that outweigh any benefits provided. Roy's experience with hydroxyurea is a good example. Sometimes, the side effects turn out to be an unexpectedly high rate of injury or even death, which often results in the withdrawal of the drug from the market.



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A personalized drug, on the other hand, relies on molecular diagnostic tests, sometimes called *theranostics* (therapy + diagnostics), that predetermine a therapeutic target and the likelihood that a drug will achieve the desired response. In Roy's case, cytogenetic testing confirmed the presence of a *biomarker* —and indicator of a particular disease — in his case, the Philadelphia chromosome in his bone marrow cells.

Ideally, molecular analysis can determine an individual's disease predisposition and suggest prevention strategies. Here's how the Personalized Medicine Coalition describes this scenario in its 2006 paper, "The Case for Personalized Medicine":

> The molecular methods that make personalized medicine possible include testing for variations in genes, gene expression, proteins, and metabolites, as well as new treatments that target molecular mechanisms. … These tests could offer substantially more information about a patient's condition, including disease susceptibility and progression, and likely drug response. Due to their predictive nature, the tests may form the basis of more preventive interventions.

Personalized medicine includes:

- Specialty drugs, including oral products, injectable and infusible agents, and therapeutic vaccines
- Diagnostic tests, such as assays that measure the expression of multiple genes, detect genetic variations, and quantify proteins and other molecules in our bodies
- Molecular imaging such as positron emission tomography, which produces a three-dimensional image of how the body functions

If personalized medicine seems partial to diagnostics, that's because it is. In fact, all those diagnostics may end up turning the pharma industry on its head.

"Let's say you're developing an obesity drug and your drug works only in a small subpopulation of obese people," explains Kenneth I. Kaitin, PhD, director of the Tufts Center for the Study of Drug Development in Boston. "To identify that subpopulation of responders, your diagnostic has to be given to all obese patients. So, you have the potential for a huge market for your diagnostic, but perhaps a small market for your therapeutic."

And as more biomarkers for disease are identified, the reasoning goes, diagnostic tests will come into play not just to verify that an individual will respond to a therapy, but to monitor therapy.

"These diagnostics are going to look more and more like chronic-use products," adds Kaitin. "I wouldn't be surprised if diagnostics become the new blockbuster products of the future."

PERSONALIZED MEDICINE TODAY

People working in personalized medicine rarely say the words "personalized medicine." They are more likely to think in terms of *molecular imaging,* or *companion diagnostics*, the tests that determine if a person will respond to a certain drug. These professionals also may work with gene-expression assays or biomarkers.

But "personalized medicine" remains a convenient buzzphrase. Its early definitions tended to focus on the *genome*, the total genetic information of an individual. *Pharmacogenomics*, the science of determining the probability of drug response based on an individual's genome, was considered synonymous with personalized medicine.

The MSN Encarta online dictionary still defines personalized medicine as "the prevention, detection, and treatment of disease taking into account a person's unique genetic profile."

Technically, one could argue that proteins, metabolic enzymes, and RNA are all determined by one's genome, with due regard given for the influence of environmental factors. But definitions that limit personalized medicine to the genome ignore biomarkers other than genes and genetic variations. Compare the Encarta definition with one from Edwin Clark, PhD, director of oncology biomarkers at Bristol-Myers Squibb, in a 2006 BIOTECHNOLOGY HEALTHCARE article:

> We want to use whatever tools are available to us. My definition of personalized medicine is "the right drug for the right patient at the right time," and it doesn't matter whether it's genomics or proteomics or a test of how far you can spit that tells you that a given drug is going to be good for you. It doesn't have to be some fancy genomic test.

Personalized medicine now includes *proteomics*, *metabolomics,* and *transcriptomics,* in addition to *genomics*. These "omics" represent the study of the proteins, the intermediate and end products of metabolism, and the messenger RNA (mRNA) molecules in the human body. Any of these biomarkers can provide valuable information about an individual's predisposition for disease, enable early diagnosis, predict responsiveness to a drug, and suggest therapeutic targets.

INFINITELY MORE COMPLICATED

In the excitement following the sequencing of the human genome in 2003, a lot of smart people were convinced that disease cures were just around the corner. Find the gene responsible for a disease, "repair" (gene therapy) or "silence" (microRNA or RNA interference) the gene, and *presto!* — disease cured.

It hasn't quite worked out that way. Some disorders, such as sickle cell anemia, cystic fibrosis, and Huntington's disease, correlate with a single defective gene. Most dis-

eases, though, are associated with multiple genes, and each gene implicated in a disease may exhibit one or more variations and may produce one or more proteins — each of which interacts with other proteins, other DNA, or other RNA from the other 24,999 genes in the human genome. The biochemical relationships get very complex, very quickly.

Despite all that, astounding progress is being made in coming up with personalized fixes when something in our complex biological organism goes haywire. They're not yet perfect, but personalized drugs certainly beat what came before. Just ask Rob Roy. At the same time, success stories like imatinib and dasatinib can make for irrational exuberance about personalized medicine.

"There's a misperception that eventually all drugs are going to be personalized drugs, and that we'll have personalized medicines for every disease," says Kaitin. "Actually, it's highly unlikely that we'll have only personalized medicines because, very often, the economics won't support their development or use."

"For certain indications," he continues, "generalized medicines may be the most cost-effective method of treatment. For example, if everybody in the world who has a headache can be adequately treated with either ibuprofen or acetaminophen, then it would make no medical or commercial sense to develop a personalized headache medicine and the accompanying diagnostic screen to identify those individuals who will respond to it."

His point is one of several that payers and employers think about when deciding whether to pay for pricey new personalized medicines. It's a tough call, especially when trying to ascertain long-term benefit for diseases whose natural history can span years. One explanation for the big price tags is the fact that molecular diagnostic tests reduce the market for that drug. Ergo, unit prices have to go up to make up the difference and pay for the additional research and development costs of the companion diagnostic.

Personalized medicine poses other challenges to the status quo, as all disruptive technologies do. For example, if it takes approximately 10 years to develop a drug and 2 years for a companion test, one can imagine that a drug maker might be reluctant to make the R&D investment with no guarantee that a suitable diagnostic will be forthcoming. The diagnostics people may have similar worries about allocating resources before an approved drug is in hand.

Because it starts with specific therapeutic targets and works with patients selected on the basis of some biomarker, personalized medicine promises at least the possibility of a less costly and a faster path from drug discovery to approval. Dasatinib, for instance, was developed in an unheard of 25 months from the start of clinical studies.

WHY IT MATTERS TO YOU

One sign that personalized medicine has attained a certain cachet, at least among early adopters, is the launch in 2007 of three Web-based, direct-to-consumer ventures that will sequence your genome, advise you about your genetic risk for certain diseases, tell you about your genetic ancestry, and provide updates on future discoveries — all for just under $1,000.

The entertainment value of comparing genomes and what they mean seems to be a big part of the sales pitch for these products — maybe because there isn't much else consumers can do with their sequenced genomes right now. In a few years, though, we may be admiring these entrepreneurs for their vision. Perhaps we will all have our genomes sequenced and allow physicians to use it to craft the most effective prevention or treatment strategy for us.

"I don't think these start-ups are indicative of a general acceptance of having your sequences done," says Kaitin. "It's going to take a lot of education and experience for the public to feel comfortable with these products."

That's where BIOTECHNOLOGY HEALTHCARE comes in. The aim of this column is not to sequence your genome or tell you about your ancestors. We want to keep you informed about this still immature — but already real and relevant approach — to achieving optimal health, quality of life, and productivity. And we'll do it for less than $1,000.

Not a week passes without word of a new gene expression test, molecular imaging agent, protein signature, drug, or other advancement that can alert you to diseases to which you may be susceptible, suggest ways to prevent them, zero in on the root cause, ensure response to a drug, and monitor your progress back to wellness.

In this column, we'll look at some of these advances, introduce you to the people who make them happen, and explain why it matters to you. Ultimately, personalized medicine will make a difference in your members, your employees, and your own life. Those who are positioned to take advantage of what personalized medicine has to offer will be ahead of the game.

Bob Carlson, MHA, writes exclusively about healthcare. He lives near Zionsville, Ind.

Looking ahead

Personalized Medicine columns in BIOTECHNOLOGY HEALTHCARE

- Testing for warfarin metabolism
- Direct-to-consumer genetic testing
- Tobacco addiction biomarkers and benefit design issues