



MAKING MEDICINE PERSONAL

Personalized medicine represents a radical departure in the pharma business model. But are the mixed results to date a sign of its future?

Until relatively recently, technologies for personalizing drug treatments—for identifying responders, and individuals likely to experience serious side effects—did not exist. Thanks to advances in biology, particularly genetics, efforts to inject scientific evidence into drug prescribing are beginning to pay off.

Personalized medicine's key hurdle will be overcoming the pharmaceutical industry's prevailing blockbuster economic model. When personalized medicine first became a phenomenon several years ago, drug companies and industry experts rushed to contradict statements to that effect, but the truth is inescapable: Personalized medicine and the blockbuster model are incompatible.

For example Genentech's Avastin cancer treatment, with \$2 billion in annual sales, costs about \$50,000 for treating colon cancer, and twice as much for breast cancer (the dose is doubled). A test to identify individuals most likely to benefit from Avastin treatment cannot but cut the number of doses administered.

Bigger may not be better

Following the blockbuster model means chasing big markets, and skirting huge risk as well. In May, for example, independent analysis of clinical data suggested a 43% increase in heart attack risk among patients taking Avandia, GlaxoSmithKline's \$2.2 billion-a-year diabetes drug. GSK disputed the claim. Only last fall, the company released results from its "DREAM" trial, which GSK claimed demonstrated Avandia's ability to prevent type 2 diabetes in non-symptomatic individuals. Analysts briskly predicted a 25% jump in sales of Avandia, which is widely marketed to consumers. Today the drug's very survival is in doubt.

The cancer drug Iressa (gefitinib; AstraZeneca) is another miracle medicine that has fallen on hard times. Pivotal studies failed to show a statistical survival benefit, prompting FDA to limit Iressa's availability to "cancer patients who have already taken the medicine and whose doctor believes it its helping them." Robert Nagourney, MD, CEO of Rational Therapeutics (Long Beach, CA) calls Iressa's fate "a debacle of historic proportions" because the drug actually did work miracles, in some patients. Early in Iressa's clinical development, Nagourney discovered a cellular signal for response to the drug which identified responders but would have limited Iressa's market significantly. AstraZeneca ignored this bit of information, he says. Today, instead of being hailed as a personalized medicine success story, Iressa's main claim to fame is the frequency with which Wall St. Journal editorials call for the drug's unrestricted use.

As this issue was going to press, the latest dust-up over uncertain trial results and novel personalized medicine broke: Dendreon's Provenge (sipuleucel-T) treatment for prostate cancer. Dendreon (Seattle, WA) has been developing a therapy called "active cellular immunotherapy" (ACI) by which a cancer patient's own "antigen presenting cells" (see photo) are extracted, activated with a bioengineered cell that mimics a cancer cell, then returned to the patient. The goal is that the treated antigen cells will sensitize the patient's own T cells to attack the cancer.



THE 'ANTIGEN PRESENTING CELL' THAT IS PART OF DENDREON'S IMMUNOTHERAPY TECHNOLOGY. credit: Dendreon

Dendreon had applied for fast-track approval from FDA, but in early May, the agency review panel issued an "approvable letter" which didn't stop commercial activity but required Dendreon to perform larger clinical trials. The decision led to an overnight drop of more than 60% in the company's stock, and to a grass-roots protest movement among prostate cancer patients and loved ones, reminiscent of AIDS activism of the 1980s. For its part, Dendreon says that the review panel's request for additional information could be met with interim results from an ongoing clinical trial and that it anticipates "interim survival rates in 2008." Essentially, the sooner the company reports results, the sooner investors (some of whom have already filed lawsuits against the company) will be mollified—especially if the results are both positive and conclusive.

The ongoing Provenge episode highlights both the opportunity—a treatment for often-fatal prostate cancer—and the challenge of personalized medicine. Dendreon had installed the Process Manufacturing, Supply Chain Planning, and other modules from Oracle Corp. to handle the complexities of routing individual patients' cells through an [elaborate manufacturing process](#) and then back to the patient.

In a [study](#) by Deloitte Consulting, the company categorized personalized medicine treatments on a scale from "one drug for one phenotype (essentially, current treatment of patients that exhibit disease symptoms) to "one pill for one patient" (a treatment

personalized to the individual patient). Dendreon's pathway is definitely in the latter side of the scale; and about such treatments, Deloitte said that the success of this model may be well in the future (see sidebar, [Here's looking at you: 'individualized' medicine](#)).

Cell-based testing

Nagourney founded his first personalized medicine venture in 1986, and Rational Therapeutics eleven years ago. The company claims its cell culture methodology maintains cancer cells in their native state, making its cell-based assays of chemo compounds more reliable. Rational relies on cells, rather than genetic tests, because "the complexities and redundancies of human biology are beyond the ken of genomics," according to Nogourney. In vitro chemotherapy assays have demonstrated benefit, but Rational Therapeutics has not been uniformly successful in obtaining reimbursement for its assay. The "full boat," for sixteen drugs plus synergy analysis, costs about \$3,500 but only about half of patients using the test are reimbursed. Payors will "get into the game," Nogourney notes, "when they realize the odds of a patient getting better are much higher than without the test."



RICH KOLLENDER, QUAKER BIOVENTURES

Like Rational Therapeutics, Precision Therapeutics (Pittsburgh, PA) tests cells from excised tumors against a panel of chemotherapy agents, singly and in combination, through the company's ChemoFx assay and analysis algorithm. Rich Kollender of Quaker Bioventures (Philadelphia), which owns an unspecified chunk of Precision Therapeutics, tells Pharmaceutical Commerce, "This is where medicine is moving, but it won't happen overnight."

Precision published data in early 2006 demonstrating ChemoFx's ability to predict drug responses in ovarian cancer. Patients whose cells were classified as "resistant" to chemotherapy averaged nine months before their cancer progressed. Those in the "intermediate response" group averaged 14 months to progression, while those found to be "sensitive" to chemotherapy remained stable up to publication of the study.

Quaker Bioventures is excited at these results. "Other companies have tried to do this and

failed,” Kollender comments. ChemoFx enjoys patent protection, not to mention coverage by Medicare and more than 400 insurance companies. With a course of chemotherapy costing tens of thousands of dollars (and no money-back guarantee), insurers evidently view the bill for testing a panel of medicines (at \$450 per drug) against specific tumors as a bargain. Precision participates in a number of clinical trials, including one large cooperative group trial examining the predictive accuracy of ChemoFx. Despite its stellar reputation among insurers and study directors, the company has no relationship yet with drug developers. “We’ve been in touch though,” says CEO Sean McDonald.

BOX: The View From a Reference Laboratory

Personalized medicine may play out as a struggle among providers of proprietary diagnostics, specialty diagnostics firms that target specific diseases, and reference laboratories. The latter typically provide a broad range of plain vanilla tests (cholesterol, electrolytes, etc.) for physicians and hospitals.

Unlike most reference labs, PersonaDX (Newton, MA) runs only proprietary, targeted diagnostics. Its test, based on a genetic factor, predicts which solid tumors will metastasize. The idea is that patients with very low probability of tumor spread may opt for less-aggressive therapy. PersonaDX focuses on cancers that carry a reasonable chance of survival, particularly tumors of the breast and prostate. Cancers in these non-vital organs must spread before they turn deadly. PersonaDX estimates the cost of 19 months of breast cancer chemotherapy at \$80,000. “So the test can save insurance companies a lot of money,” comments CEO John Garrett, Ph.D. The company partners with Buffalo, N.Y.-based Roswell Cancer Center, where the diagnostic technology originated.

Standard breast cancer care calls for surgery, chemotherapy, and radiation, but some patients with very small tumors are already passing on aggressive chemotherapy. Armed with the PersonaDX Coignet-Factor blood test, physicians can guide patients by a molecular marker rather than tumor size, which is at best an imprecise predictor of a cancer’s virulence.

PersonaDX hopes to bring the test to market in early 2008. The remainder of this year will be spent opening a new facility, expanding clinical studies, and obtaining more data. “This is how to get our product in front of physicians,” Garrett says. The company also expects to clarify their test’s regulatory status with FDA (the agency does not regulate it), and to meet with insurers to apprise them of the test’s benefits.

Garrett could not provide a cost per test, but was sure it would not be astoundingly expensive. “There’s a history, given the value the test provides, of insurers approving tests to reduce costs.”

Finding their way

It is fair to ask, given the facts, if the very ideal of personalized medicine does not scare the hell out of top drug companies (several ignored an offer to comment in this article). No company relishes turning over sizeable pieces of a profitable business through an act of

altruism, not to mention because a test from a tiny diagnostics company suggests it should.



DREW FROMKIN, CLINICAL DATA

Still, Drew Fromkin, CEO of Clinical Data (Newton, MA) warns against painting big pharma with an equally-sized brush on this issue. “Drug makers must drive growth, revenue, and profitability, and personalized medicine runs against their prevailing business model. Some firms will try to buck the trend as long as they can.” But many realize that personalized treatments are inevitable and are trying to find their way within that paradigm. “Besides, it’s becoming more common for FDA to step in and limit the market for a drug anyway, post-approval.” Companies can save themselves quite a bit of grief, Fromkin says, by addressing safety questions normally reserved for Phase IV before submitting their New Drug Application.

Fromkin believes that the impetus for personalized medicine will come from payors, not drug firms. “Insurers are paying for drugs that do not provide value, and have been desperate to eliminate the shotgun approach from prescribing.” He brings a unique perspective, having cut his management teeth as VP for business development at pharmacy benefits giant Medco, and from his current company’s business.

Clinical Data develops pharmacogenomic tests that associate genes with positive or negative treatment outcomes. The company also has a drug, vilazodone, in Phase III testing for both depression and anxiety. Response rates for antidepressants range from 30% to 50%. By applying Clinical Data’s genetic test before prescribing vilazodone, Fromkin expects the response rate for those eventually receiving the drug to hit 75%.

The company has a pipeline of tests for other drugs. It is working on an assay for clozapine, the antipsychotic that has fallen from favor due to serious side effects, among them a 1% incidence of agranulocytosis, a deadly depletion of white blood cells. The company has identified a genetic marker for this complication which, when applied, reduces risk to a level approximating that of other antipsychotic medications.

One of personalized medicine’s greatest opportunities lies in the potential for pure-play,

technology-heavy diagnostics firms to provide effective, profitable tests for responses to common drugs. Nanosphere (Northbrook, IL) designs gold nanoparticle-based molecular probes for genetic and protein tests. The company's first product, currently under FDA review, tests for the likelihood of adverse blood coagulation events such as clotting, deep vein thrombosis, and stroke. Nanosphere's is also working on a test for metabolism of the anti-clotting drug warfarin. Such tests are not amenable to "companion" or combination products.



BILL MOFFITT, NANOSPHERE

"Think of them as a companion test after the fact that fill a niche need," says CEO Bill Moffitt. "Coumadin [branded warfarin] has been on the market for twenty years, but tests are only now emerging. The diagnostics industry is playing catch-up with genomics." Nanosphere is planning an additional pharmacogenomic test for the cytochrome p450 family of genes, which drive liver metabolism for 65% of psychiatric and other drugs.

BOX: What About Pharmacogenomics?

Even Robert Nagourney of Rational Therapeutics and cell-based assay fame, realizes that personalized medicine will eventually rely mostly on genetic, not cell-based assays. "I'm a conduit to next-generation tests," he says.

The future of personalized medicine lies not with cell-based assays but in pharmacogenomics – the marriage of pharmacology and genetic testing. Where cell-based assays find the optimal treatment or combination from an array of possibilities, pharmacogenomics normally focuses on one or more genes targeted by a single drug. Gene-based tests therefore lend themselves to the drug/diagnostic "combination product" brand of personalized medicine. Gene testing is already used to achieve optimal dosing for the anti-cancer drug 6-mercaptopurine in pediatric leukemia: Patients unable to metabolize the drug, as measured by an active gene for the drug-metabolizing enzyme, are given a smaller dose.

The poster child for genomic personalized medicine is Herceptin (trastuzumab; Genentech).

As a pre-condition for receiving Herceptin, patients undergo a test to measure a gene that confers a tumor's susceptibility to the drug. Similarly, Gleevec (imatinib; Novartis) is administered to chronic myeloid leukemia patients who are "Philadelphia chromosome positive" by one of three generic tests for the gene. Erbitux (cetuximab; Imclone) for colorectal, head, and neck cancers, and Tarceva (erlotinib; OSI/Genentech), for lung cancer, also employ standard laboratory tests for the mutant genes these drugs target.

Although any number of labs and techniques can detect mutant genes, this area of pharmacogenomics is ripe for proprietary tests, invented alongside the drug and owned by the drug developer and/or a partner in the diagnostics field. This business opportunity will evolve as more drugs are approved with companion diagnostics.

RxDx connection

Combining diagnostics capabilities with pharmaceutical production is very obviously the goal of Roche, the Swiss pharma giant that already owns a majority of Genentech. Roche announced in June that it has been in discussions for several months with Ventana Medical Systems (Tucson, AZ) as a possible acquisition. In mid-June, Roche said that it could make a hostile offer—unusual in this market—and in late June went ahead with an approximately \$3-billion offer, about 45% over Ventana's then-current stock price. Ventana projects annual sales for its current year at around \$285 million.



ROCHE DIAGNOSTICS' AMPLICHIP. credit: Roche

Ventana has had considerable success with diagnostic and clinical tests for cancer, particularly the Herceptin product sold by Genentech. Roche, in turn, has a substantial Roche Diagnostics Div., one of whose products, the AmpliChip, has been an early commercial offering in patient-specific diagnostics. Roche believes that the tissue-based diagnostics market (as exemplified by Ventana) is worth around \$1 billion in current sales, and is growing at double-digit rates.

Such a combination is coming to be called the “RxDx” business; it is rare that one company would be the source both of the drug product and the diagnostic test. But as the genetic testing technology progresses, such combinations could become the norm.

The road from hype to hope

The hype surrounding personalized medicine is faintly reminiscent of other “big drug” initiatives: risk-based drug development, process analytics, and FDA’s Critical Path initiative come to mind. The principles behind these catchphrases are doing fine, but none have delivered revolutionary benefits that have justified their hype.

Personalized medicine is different on several levels. Its major impetus arises not from the industry or regulators (although both have played roles), but from outside dissatisfaction with business as usual. And for a change, smaller companies like those mentioned in this article are, in their own ways, dictating terms to drug-makers in ways that would be unimaginable for a specialty pharmaceutical company. Perhaps the most significant difference is that personalized medicine really matters, and the word is getting out. Eventually, patients will demand tests before undergoing costly, painful treatments, and physicians will be accountable for knowing about these tests.

But for hype to morph into hope, the drug industry must transform itself at every level, end to end. Business as usual will no longer be good enough.

“Clearly, the process of drug development must change dramatically,” says Terry Hisey, managing principal at Deloitte (Philadelphia), “because the blockbuster model is incompatible with personalized medicine.”

Regardless, believing in personalized medicine poses some fairly deep questions. How will drug companies respond when tests show their drug to be highly effective, but only in 11% of the potential patient population? What can medicine offer patients whose test results suggest no medicine will help? “Personalized medicine has the look and feel of orphan drugs, without the speedier review process or economic assurances,” Hisey notes.

A \$1.5-billion-a-year drug is a blockbuster; five \$300-million drugs, taken together, do not add up. Unless the costs for developing a \$300-million New Chemical Entity can be harmonized with the expected financial return, no one will develop such drugs. Charging significantly more for targeted therapies will work only to a point.

And when five times as many drugs are approved, as some predict, where will the industry find five times the number of clinical investigators and study patients? How will FDA come

up with five times the current number of (overworked) regulatory reviewers and statisticians? Where will industry find the manufacturing capacity to produce five times as many products? Conducting preclinical and human trials overseas can lower clinical testing costs, but regulators have traditionally been wary of approving drugs tested in gene pools that differ significantly from the one where the drug will be used. Besides, the idea goes against the very idea of personalized medicine.

Clearly, regulators need to re-invent the approval process, streamlining it while discarding hallowed legacy practices that are more fetish than science. Every aspect of drug discovery, development, and manufacture must change as well. Gone, one hopes, will be regulators' infatuation with micro-managing non-critical or non-value-producing activities, and the gleeful acquiescence of regulatory officers at drug firms.

Eventually, big pharma may simply morph into "big marketing." But if the economic and regulatory environments change sufficiently to make a \$300-million-a-year drug attractive for Pfizer, will such a product not become as attractive to a much smaller innovator company?

Another scenario sees top pharmaceutical firms specializing along disease management lines: in-licensing or co-marketing portfolios of personalized, smaller-market drugs as a package deal to physician specialties, along with a test or two. Companies could, for example, cover the entire hypertension market with multiple drugs, some developed in-house and some not, and augment those offerings with broad-spectrum drugs for related conditions.

Drug and diagnostic companies working together, with drug targets perhaps based on a diagnostic marker – not the other way around – could grease the wheels for personalized medicine.

There is also a dark side to the personalized medicine revolution. Terry Hisey of Deloitte believes that private insurers will demand "increasing levels of behavioral and financial responsibility."

Mandatory preventive interventions in asymptomatic individuals are becoming increasingly feasible as data on patients, populations, and diseases accumulate and acquire a critical mass of predictive capability. Heading off cardiovascular disease, diabetes, and the sequelae of obesity gets insurers excited but will almost certainly raise concerns with civil libertarians. Some employers already enforce "healthy" lifestyle habits, for example non-use of tobacco, as a condition of employment. The American single-payor healthcare system, if it ever arrives, will almost certainly demand lifestyle concessions as a condition for receiving "free" health services.

Personalized medicine might also take some of the wind out of the sails of pharma reps. Inscribed musical notepads notwithstanding, promoting a drug as the "best" in its category will be impossible when the label limits it to a fraction of affected patients. In such a world, diagnostics will almost certainly trump pharmaceuticals. Test firms will emerge supreme, selling directly to physicians, competing among themselves as drug firms do today, and

offering notepads that sing a new tune. PC