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THE BIOTECH INDUSTRY'S DAILY MONITOR

Personalized Medicine: From Concept to Reality

by John Carroll

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Last summer, Medco Health Solutions unveiled an unusual collaboration with the Food and Drug Administration.

The giant pharmacy benefits manager said it would harvest the results of genetic tests done for its base of members and explore how their genetic profiles influenced physicians' use of medicine. For Medco, it's a chance to find out whether new insights into genetics are leading to more intelligent decisions on the right dosages of the right medicines. For its part, the FDA will gain a better understanding of managing the risks associated with drugs. And it will identify the barriers to persuading U.S. doctors to rely on genetic testing to hone each individual's treatment.

When Medco and FDA made their announcement, only about two dozen pharmacogenomic tests were available to determine a patient's likely response to a drug. But that is changing fast. Companies such as Clinical Data and Genomic Health, along with a slew of competitors, have been gearing up new tests.

For payers, the Promised Land can't be reached too quickly.

"We're all about making this field happen as fast as it appropriately should happen," Medco's chief medical officer, Robert Epstein, told the *Wall Street Journal*.

"To be sure, biology is complex," noted Edward Abrahams, the executive director of the Personalized Medicines Coalition. "But the promise of personalized medicine--greater efficacy, safer drugs, preventive treatments and potentially lower costs to the healthcare system--should encourage us to be hopeful about the future."

For the biopharma industry, that future is already here. As major pharma companies position themselves to market drugs in years to come, they're seeing fewer blockbuster therapies on the horizon. The future lies in following the development model used by biotech companies to advance new medicines designed to target smaller populations with much more effective therapies.

"The era of dependence on a single or a couple of large blockbuster drugs certainly should be over," Pfizer CEO Jeff Kindler told the *Financial Times*. "Lipitor sells \$12 billion a year. You can't build a company predicated on the belief that you're going to find such a drug."

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The post-blockbuster era

"Even after typical 'blockbuster' drugs are marketed, only 30 percent of them achieve sales that match or surpass their multibillion-dollar R&D costs," said Lesa Mitchell, vice president of Advancing Innovation at the Kauffman Foundation. "Based on the high-profile successes of some stratified medicines, however, the biopharmaceutical industry is beginning to realize the deficiencies in the economics of the blockbuster business model. This is one driver of increased interest and investment in developing personalized medicines, a task often best pursued by small biotech companies."

To quicken the advance of these new therapies, she says, nonprofit disease advocacy groups are likely to fund developers who have the technology to advance new, targeted front-line therapies. Meanwhile, new work in genetics is providing a daily parade of mutations and genetic variables that deepen our understanding of how diseases are triggered and how they can be fought.

Reviewing the research work being done in just one field--Parkinson's disease--the noted geneticist Dr. Jeffery Vance can already point to a much better understanding of the complex ailment.

"Genetic research has shown that PD does not have a single cause and that different individuals will have PD for different reasons," observed Vance, who was recruited from Duke University in 2006 along with his wife, Dr. Margaret Pericak-Vance, to start the Miami Institute of Human Genomics at the University of Miami.

"In fact," said Vance, "we now know PD is really a group of similar but different diseases that all affect the brain in the same way and thus clinically look the same. Now that we begin to see some of the genetic factors that underlie PD, we can begin to understand the environmental factors that affect PD. One of the most interesting environmental influences on PD is cigarette smoking. Multiple studies have now shown that people who smoke cigarettes have less risk for developing PD than non-smokers."

Not that people should take up smoking, he adds. Developers need to understand how that mechanism of protection works, and design a therapeutic that can do what smoking can do for people at high risk of developing Parkinson's--without exposing them to an increased threat of cancer.

States roll out the welcome mats

Seeing the potential of genomic research to revolutionize medicine and the healthcare system, states have rushed to build the perfect environment for it. Florida, for example, has helped attract hundreds of new researchers and world-class institutes such as the Max Planck Florida Institute, under construction next to Scripps Florida's new research center.

But that's just one of a broad array of efforts to make the state a leader in personalized medicine. Other initiatives include the creation of two Research Centers of Excellence--one for biomolecular identification & targeted therapeutics and another for nano-bio sensors--as well as the Florida Institute for the Commercialization of Public Research, to help uncover promising new technologies, and the Florida Opportunity Fund, to increase the availability of seed and early stage venture capital.

The H. Lee Moffitt Cancer Center & Research Institute formed a for-profit venture with Merck--M2GEN--that will examine tumor samples for unique molecular biomarkers

Personalized Medicine
– From Concept to
Reality

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that can help developers design a new generation of individually tailored cancer therapies. And the state of Florida, Hillsborough County and the City of Tampa provided funds to help establish a new research center for M2GEN.

“Moffitt will be a valuable partner as we move forward in our efforts to develop and deliver personalized cancer care,” said Dr. Stephen Friend, executive vice president and franchise head, oncology and neuroscience, at Merck.

The trend toward individualized treatments has inspired a host of public-private collaborations. Late last year philanthropists put up \$45 million to recruit Nobel laureate Lee Hartwell, a director of the Fred Hutchinson Cancer Research Center, to head up the Partnership for Personalized Medicine. The group is tapping the expertise of Arizona State University’s Biodesign Institute and the Translational Genomics Research Institute to make the promise of this new science a reality for patients.

“With the team of scientific and clinical research excellence we are assembling, our goal is to transform medicine from the current ‘one-size-fits-all’ approach to one that is targeted around a patient’s unique genetic and molecular profile,” says George Poste, director of the Biodesign Institute.

And as sequencing technology becomes less expensive, it will grow more important for drug developers.

An economy of scale

The first time the human genome was sequenced, the price rang up at \$3 billion. A year ago, sequencing cost a million dollars. Just a few months ago, that price had plunged to \$60,000. And if the scientific team at Complete Genomics is right, you can look for a discount price of \$5,000 by next spring.

But the price cuts won’t stop there. As scientists access new technology, they’re advancing in a race to the world of \$1,000 sequencing, making it possible for people to obtain a blueprint of their bodies’ genetic code. For developers, though, a relatively small investment in sequencing can pay off with drugs that can command a hefty price.

“Where we see this headed from our perspective is scale,” says Cliff Reid, the CEO of Complete Genomics. “Sequencing a complete genome is more a curiosity than a discovery tool. The only way to do discovery is with scale. We need to sequence thousands of people with a disease.” And that means reducing costs to the point where mass sequencing is affordable for researchers. By setting the fee at \$5,000 in 2009, he adds, the tipping point has arrived.

“That is the first half of scale,” he adds. “The second half of scale is computing the amount of data you get with hundreds of thousands of genomes. It’s breathtaking. The existing biotech community is not ready for that amount of data. So we’ve come at this from the perspective that if people are to get value from huge data loads, we have to solve the computing problem as well. So there’s a service aspect to this as well.”

For developers, he says, there’s real value in identifying a patient population that’s far more likely to respond positively to a new therapy. Reid isn’t predicting a radical, overnight change in the process. But if new technology can slice five percent off the cost of a clinical trial, he adds, that’s a net savings of \$4.8 billion for the industry.

Personalized Medicine – From Concept to Reality

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The new technology behind personalized medicine is already making a significant difference in the way that drugs are advanced in the clinic. In September, the Burnham Institute was awarded a six-year, \$97.9 million Molecular Libraries Probe Production Centers Network grant from the NIH, which will help in the screening and discovery of chemical compounds that could become the next generation of medicines. A major part of the work will be done at Burnham's new facility at Lake Nona (Orlando), which will have a pharmacology core facility and an ultra-high throughput screening system capable of screening more than 2 million chemical compounds per day.

Another sophisticated method for drug discovery is used by AstraZeneca, which announced in late October that it is extending a research pact with the University of Texas M.D. Anderson Cancer Center.

"Earlier access to drugs destined for the clinic has permitted the identification of biomarkers and combinations with existing agents that will permit individualization of cancer treatment," said Robert C. Bast Jr., M.D., vice president for translational research at M. D. Anderson. "In an atmosphere of trust and collaboration, it has been possible to eliminate unnecessary delays in moving drugs into the clinic. In one case, we reduced the time to initiate a Phase I clinical trial by 3 months, while fully meeting regulatory requirements."

"Over the last three years we've identified several biomarkers that might be of value in identifying response," Bast tells *FierceBiotech*. "We're also working on imaging probes that can be used early on, sometimes in a matter of days, to identify people who are actually responding to new therapies. And we're also looking at combinations of AstraZeneca drugs and more conventional agents. You're going to need more than one drug to inhibit a cancer growth."

AstraZeneca's work with M.D. Anderson is helping to streamline the clinical trial process, says Brent Vose, the pharma company's vice president of oncology therapy. Non-small cell lung cancer is a prime example, he points out. "They've been taking patients with non-small cell lung cancer and depending on their clinical or genetic profile looking at the best option for those patients in a trial setting."

A cancer trial with Zactima has been using the new technology to address which population is likely to benefit most. And similar work is underway with Iressa in Asia.

"By selecting the population you can have patients get a better outcome," says Vose. M.D. Anderson is also working on similar programs with two other major drug developers-- GlaxoSmithKline and Exelixis--and has a third partnership that will be announced soon.

Marketing drugs

Drug makers can reduce the considerable risks--and costs--involved in gaining approvals and entering new markets by developing companion diagnostic tests. These tests define groups of patients most likely to benefit from various therapies--and least likely to experience adverse reactions.

"The biotech industry is transitioning from one focused principally on treating sickness to one that is promoting 'wellness,'" said Stephen Burrill recently. "The era of personalized medicine is upon us...one that emphasizes predictive and preventive medicine. Not surprisingly, diagnostics and nutraceuticals companies have been very successful riding this new paradigm."



Roche has been among the most aggressive companies to marry diagnostic tests with new drugs. The pharma giant is betting billions of dollars that new cancer drugs developed at Genentech can be matched to patients with new tests. That's a big reason why it bid \$43.7 billion for the Genentech shares it doesn't already own. And why it also mounted a \$3 billion offer for Ventana Medical Systems, which develops those tests.

After Roche completed its acquisition of Ventana, the pharma giant announced plans to invest an additional \$100 million next year to accelerate Ventana's work. Ventana is expanding its campus and beefing up its staff from 750 to 1,000 people. And Roche CEO Severin Schwab has turned up at the company repeatedly to tout technology that can use information on cell structure to determine whether patients will respond to drugs for cancer or infectious diseases.

Just before the Roche takeover, Ventana Medical Systems and the Critical Path Institute had won a \$2.1 million grant to establish standards for the performance of companion diagnostic tests for cancer. By creating a model for companion diagnostics, they say, they can offer the FDA a faster route to approval. That in turn will speed up the use of targeted cancer drugs.

Once the tests become available, payers will make them a requisite for any patient who needs the therapy.

"From a managed care, payer, consumer, and provider perspective, this industry is really in dire need of some new tools," says Drew Fromkin, CEO of the pharmacogenetics company Clinical Data. "There is a dearth of technology out there that is making a difference in improving medical and therapeutic economics while improving clinical outcomes."

Payers have already been questioning why they should reimburse doctors for drugs that only work 10 or 20 percent of the time. And drugs that can't demonstrate a relatively high response rate are running up against deep skepticism at the FDA.

According to a recent issue of Zitter Group's Managed Care Oncology Index, health plan executives feel they're paying for too much care that doesn't benefit patients. That belief is particularly prevalent in cancer care; they see those costs as inflated by 20 percent. And that 20 percent, they believe, simply should not be reimbursed.

Even as the personalized-therapy field undergoes an explosion of growth and new investment, though, plenty of challenges lie ahead.

Educating everyone

For starters, says Dr. Susan Blanton, an expert at the Miami Institute of Human Genomics, the public is burdened with common misconceptions about genomic medicine. And given the broad misunderstandings about health in general, considerable work will be needed to fill in the gaps.

"While this can be addressed through education, 30 percent of the American public has only poor to fair literacy and approximately 50 percent have low 'health literacy,'" notes Blanton. "Much of the currently available information is written at a level well above what it should be."

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“There is also a general lack of knowledge about the practical, ethical, legal, and social implications of emerging genetic information and technology. Lastly, there is a certain level of mistrust of the government, researchers and physicians that interferes with the public’s willingness to accept personalized medicine.

Providers need to be educated, too, Blanton said. “Among healthcare providers in the community setting, there is a lack of knowledge about genetics, genetic testing and/or genetic counseling. This is particularly true for diseases with a more complex etiology.

“Many providers report a lack of confidence in handling patient concerns about disease risk, family history, and genetic testing. They are also concerned about issues of confidentiality and legal liability. Lastly, most providers simply are unable to devote the time required to take and assess a detailed family history.”

Barriers at the medical system level are, as a group, the most difficult to address, she adds. In general, the medical system is designed to be reactive, not proactive. Personalized medicine will only truly have an impact when utilized proactively. This will require a restructuring of reimbursement by the government and private insurance companies to better cover such things as collecting and reviewing family history. And payers will have to cover a wider scope of genetic testing.

For example, although the FDA has recommended genetic testing prior to initiating Coumadin therapy, many private insurance companies--and Medicare and Medicaid--do not cover this cost, she observes. This may partly stem from conflicting studies on the cost-benefits of testing.

Assessing the clinical validity and utility of genetic discoveries takes significant time and resources, often with little financial incentive from industry. There is a dearth of genetic professionals to provide the necessary support to primary care providers and to patients at an elevated risk for a particular disease. Health care disparities continue to be a barrier. Many individuals lack insurance and/or the necessary funds to seek health care other than on an emergency basis.

“There is no system for the management and processing of genetic information,” says Blanton. “How will an individual’s genetic information be tracked and stored so that it is easily available for integration into their care? Lastly, there is currently no successful model for applying genomic medicine in primary care. While the state of Wisconsin is beginning an initiative to revamp its healthcare system and integrate genomic medicine, it has just started.”

And there’s no turning back.