Denise Myshko

Creating a Personalized Medicine Strategy

Pharmaceutical development processes are changing to address the unique challenges and opportunities presented by personalized medicine.

Considered broadly, healthcare is personal. The goal of medical practitioners has always been to get the right drug to the right person at the right time at the right dose. But now industry experts say personalized medicine is at a tipping point as a multitude of factors converge, including advances in technology, dropping price points, increased knowledge of biology and the molecular basis of disease, healthcare reform, and a shift from a volume-based business model to a value-based business model, as well as the upswing in adoption of molecular diagnostics by physicians and their acceptance by payers.

Personalized medicine is at the core of a larger trend within healthcare, which is becoming more individualized, predictive, and preventive in nature and encompasses personal health record management, disease management, and wellness and nutrition, according to experts at PwC.

Gerry McDougall, partner of health sciences and personalized medicine practice at PwC, says a strategy focused on personalized medicine is more attractive now than it has been in the past.

"Science and technology continue to advance rapidly," he says. "A move toward a value-based health system opens up business opportunities around prevention and prediction of disease and wellness."

PwC estimates that the core personalized medicine market alone — comprised primarily of diagnostic tests and targeted therapies — accounts for $24 billion in sales and will grow 10% annually to $42 billion by 2015.

Mr. McDougall says there has been an evolutionary shift in medicine.

"Ten years from now, looking at disease at the molecular level will be the way medicine is practiced," he says. "This is how oncology is viewed now. Oncologists currently look to segment different types of cancer. For example, breast cancer isn't one disease; it's a multitude of diseases."

According to Joel Ackerman, CEO of Champions Oncology, scientists are only starting to fully understand the complexity of cancer in a way that will give clinicians the tools they need to start personalizing care.

"There are so many possible mutations and so many other factors — epigenetics, metabolics, or methylation — that distinguish one cancer patient from another and the analytic tools, and data needed to personalize the care are just not available yet."

Additionally, he says, costly tests would need to be performed to assess each type of tumor.

"A full sequencing of the tumor could cost tens of thousands of dollars," he says. "These tests also generate a tremendous amount of data, and we don't know yet how to interpret or analyze the data yet to come up with a personalized plan of care."

A report from RNCOS states that the market is presently dominated by oncology applications, but therapeutic applications of personalized medicines will extend to new therapy areas in the coming years. According to its new research report Personalized Medicine Market Analysis, the U.S. market for personalized medicine is anticipated to grow at a CAGR of around 12% during 2009-2015. Growth will be driven by factors such as treatment cost savings, early detection of diseases, patient compliance, drug safety, and optimization of therapies.

While still in the early stages, personalized medicine, RNCOS analysts say, is steadily emerging as the new healthcare paradigm, a paradigm that not only promises the improvement of an individual's treatment outcome and

Major Trends in Personalized Medicine

- Growing number of companies entering the space, but not without difficulty
- Entry of companies from outside the health industry
- Collaboration required in order to succeed

Source: PwC.
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reduces healthcare expenditure, but is set to transform the biopharmaceutical and molecular diagnostics markets in the coming years.

Jim Prutow, partner at PRTM, agrees that personalized medicine is at a tipping point and will impact the delivery of treatments in the next five to 10 years.

"The reason, technology," he says. "Polymerase chain reaction (PCR) has been around for a number of years and is now being adopted in the clinical space. The cost of next-gen sequencing is coming down, and the reliability and ease of use are going up, which will make next-gen sequencing ready for the prime-time clinical market in the next five years. Economically, it is now feasible to develop personalized medicines."

As researchers from the Tufts Center for the Study of Drug Development point out, personalized medicine is a disruptive technology that does not come cheaply or easily. Personalized medicine requires a significant investment in ancillary technologies, including those related to target validation, early toxicology markers, and micro-sequencing.

Wide implementation of personalized medicine that involves tailoring an individual patient's treatment based on that patient's specific genetic makeup is still in the future, but there is and will continue to be a shift among pharmaceutical companies toward developing high-value, smaller-market share drugs that will allow companies to get better pricing. Experts say many of these markets are also prime areas for developing diagnostics in conjunction with therapies. (Editor's Note: Please see the Partnering for Diagnostics article in this issue for more on companion diagnostics.)

According to David Manyak, Ph.D., executive VP of drug discovery services at Caliper Life Sciences, if the broader view of personalized medicines is defined as tailoring a treatment to groups of individual patients who exhibit common molecular characteristics, or biomarkers, to optimize therapeutic benefit or minimize the potential for adverse events, then personalized treatments have already reached the market.

"The FDA currently requires a companion biomarker test for 13 approved drugs and recommends, or provides for information purposes only, a companion biomarker test for another 56 currently marketed drugs," he says.

Experts point to Herceptin and Gleevec as the first groundbreaking personalized medicine therapies. Herceptin is a targeted monoclonal antibody that addresses HER2 positive breast cancer, 20% of all invasive breast cancers. Gleevec, for the treatment of chronic myeloid leukemia (CML), targets the abnormal BCR-ABL protein in CML cells that causes the build up of white blood cells.

Today, almost all life-sciences companies are using information related to genetic variation and its effects to define disease more precisely and to enhance the safety and efficacy of new treatments.

> "The goal of personalized medicine must be to improve outcomes for patients."
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> **DR. DAVID MANYAK** / Caliper

> "Right now the space between diagnostics and therapeutics is still quite large."
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> **DR. DAVID DE GRAAF** / Selventa

According to Tufts CSDD, between 12% and 50% of current clinical pipelines involve personalized medicines, and developing personalized medicines has led companies to change their R&D paradigms.

Dr. Manyak says most of these personalized medicines for which there is a required companion diagnostic are oncology drugs that target the mutation or other patient-specific marker that is identified by the paired diagnostic test.

He predicts that the number of personalized medicines with corresponding companion diagnostics will increase dramatically in the next five years.

"Although relatively few late-stage clinical candidates incorporate companion diagnostic trials at present, almost every new drug development program now includes parallel biomarker discovery and development programs, the first step toward a companion diagnostic," Dr. Manyak says.

He adds that there is an opportunity to rescue drugs as a means to recover past investments. Adding a companion diagnostic could potentially convert initially broad-based medicines that failed in development into personalized medicines that succeed. This can be accomplished through positive patient selection to identify individuals for whom the drug is more likely to work and by negative selection to exclude patients who may have personalized markers for potential adverse reactions to the drug, he says.

Lilly's Erbitux for the treatment of a certain type of cancer of the head and neck and Amgen's Vectibix for the treatment of colon cancer are often cited as examples of products that have associated tests to determine which patients will respond. Patients enrolled in the clinical studies were required to have evidence of positive EGFR expression. EGFR positive individuals are more likely to respond to the drug than those with reduced EGFR expression. In addition, certain KRAS mutations lead to unresponsiveness to these drugs, and patients are tested for these mutations as well.

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> **GERRY MCDOUGALL** / PwC

Additionally, personalized medicine can be used to address the risk of side effects after product approval. One of the most common examples cited is the case of the blood thinner warfarin. Patients taking this product have frequent tests for several markers, including CYP2C9, which presents an increased bleeding risk; VKORC1, which can cause resistance

The Personalized Medicine Landscape

Industry/Sector	Key Challenges	Key Opportunities	Key Barriers
Pharmaceutical, biotech, and medical device companies	» Moving from general to specific treatments, and from disease treatment to prevention	» Reducing time, cost, size and failure rate of clinical trials » Capitalizing on preferential use of and premium pricing for drugs of proven effectiveness » Reducing the number of drugs recalled due to safety concerns	» Changing research funding models and drug approval regulations » Addressing pricing and reimbursement » Identifying appropriate incentives for innovation » Addressing changing revenue streams (i.e., shift from blockbuster model to smaller, targeted markets) » Navigating the cultural shift required to work with diagnostics companies to match drugs with companion diagnostics » Developing the ability to share R&D information internally and with external collaborators » Recognizing the need to share "precompetitive data" to avoid redundant research
Diagnostic companies	» Developing and validating new diagnostics to enable personalized medicine	» Capitalizing on a growing market driven partly by new, value-based reimbursement policies » Creating new partnerships with pharmaceutical companies » Capitalizing on new distribution models to create new businesses	» Addressing joint Dx/Rx approval processes / regulations, including the daunting cost of traditional randomized controlled trials » Addressing pricing and reimbursement practices » Determining if, when, and how to partner with drug companies » Identifying and mobilizing resources needed to educate physicians about diagnostic tests » Developing improved decision support tools to assist physicians in taking actions based on test results
Health systems, AMCs, and other providers	» Providing cutting-edge care while controlling health care delivery costs » Getting reimbursed for providing wellness and prevention services » Operationalizing a consumer-oriented business model	» Developing new models of care » Increasing revenue » Improving quality/outcomes	» Adapting to the "unbundling" of the hospital and to non-traditional competitors » Making operational changes » Correcting misalignment of incentives » Managing consumer/patient expectations for costly and potentially unnecessary diagnostic tests
Government and private payers	» Embracing innovation » Controlling health care reimbursement costs while improving health care outcomes to increase value per dollar spent	» Influencing new reimbursement models » Identifying risk more precisely while delivering improved quality	» Realigning provider incentives » Collecting and disseminating outcomes data

Source: PwC. For more information, visit pwc.com.

to warfarin; and protein C deficiencies, which have been associated with tissue necrosis following warfarin administration.

Novartis' Prexige is an example of a product with serious side effects that could experience new life with a companion diagnostic. The COX2 pain reliever was associated with serious liver side effects. The product did not receive approval in the United States and was removed from the market in Europe and other markets.

Company officials say researchers have discovered a marker that identifies patients who would be at risk. The company has refiled the product in the EU as Joicela as a drug-device combination.

Challenges of Developing Personalized Medicines

Experts say while there are many opportunities associated with personalized medicine, there are just as many challenges. The industry needs to work through issues such as identifying the right biomarkers, conducting clinical trials with smaller patient populations, managing co-approval pathways of companion diagnostic/therapeutic offerings, and optimizing value propositions in the face of more sophisticated payers and benefit managers.

Another significant challenge is understanding the basic biology of the disease and drug target at the preclinical stage, Dr. Manyak says.

"This requires a breadth of technology platforms that can build an experimentation bridge from in vitro to in vivo to human, as well as a breadth of therapeutic area and safety/predictive toxicology applications to define the complete disease biology," he says.

Dr. Manyak says converting knowledge related to the disease biology into a robust test or assay system for identifying the relevant marker in patients and enabling the potential implementation of a personalized medicine presents another challenge.

"The companion diagnostic needs to be prospectively validated in human clinical trials that parallel the clinical trials of the personalized medicine," he says. "Both compo-

nents need to demonstrate efficacy, which may be the greatest challenge of all, to gain utility for patient stratification and personalized therapy."

David de Graaf, Ph.D., president and CEO of Selventa, says companion diagnostics are often developed too late in the process.

"It's crucial to know which patients will respond and which won't to a medication," he says. "Right now the space between diagnostics and therapeutics is still too large to achieve this goal. Diagnostics tend to be developed very late in the process, which adds costs and increases cycle times. The key is having broadly available molecular data. This will make a huge difference in being able to drive personalized medicine forward."

Dr. de Graaf says pharmaceutical companies often wait until Phase II trials — when they are not seeing the response they want — before they investigate a diagnostic approach.

"This is the point during which companies come to us to develop a classifier to identify potential responders from nonresponders," he says. "There needs to be a new business model that allows companies to engage in this particular piece of research much earlier and share the risks as they take particular tools forward."

Mr. Ackerman agrees that personalized medicine requires the R&D model to change.

"Drug companies need to invest more money in preclinical and Phase I research to understand which patient populations are ultimately going to respond to the drugs and which ones won't," he says. "This will allow them to develop their drugs faster and cheaper, and they can power trials with smaller patient populations."

Mr. Prutow says another hurdle is going to be the mainstream adoption of personalized medicine.

"Physicians have to be able to understand the science, and few doctors have had genetics training," he says. "One of the barriers to overcome is educating the broader general physician community around the value of patient data."

Alexis Kertsburg, Ph.D., president of BioPath Consulting, says there needs to be a joint effort by pharmaceutical and diagnostics companies to educate physicians.

"The sales reps who are detailing diagnostics need to be very familiar with the pharmaceutical side and the reps on the pharmaceutical side need to be familiar with the science behind the diagnostics," he says. "It is also crucial that both understand how diagnostics and therapeutics are used together to offer personalized medicine to patients."

Pharmaceutical companies, Dr. Kertsburg says, need to form specific committees that combine all of the departments — marketing, sales, medical affairs, regulatory, etc. — that focus strictly on promoting the widespread use of personalized medicine to healthcare professionals.

Strategies for Personalized Medicine

Companies are employing different approaches to developing personalized medicines. Some companies have established internal groups that work across therapeutic areas to focus on biomarkers, while others integrate these activities within therapeutic groups. Other companies are teaming up with external partners, including academic medical centers and diagnostic developers, to advance personalized medicine.

This year, AstraZeneca launched a new function within the company specifically geared toward personalized healthcare and biomarkers. Within this function, the company is bringing in external experts around the diagnostic space.

AstraZeneca executives say they are looking to provide targeted therapies across all therapeutic areas. Each of the drug projects that has a personalized healthcare strategy also has a multidisciplinary diagnostics subteam that works with internal diagnostic partners.

Two years ago, Novartis launched an internal molecular diagnostic division within Novartis Pharma to realize the personalized medicine vision for the company. The company is focused on the molecular pathways that may be shared by various diseases and has captured a wealth of new targets through the systematic mining of molecular pathways. Novartis is building capabilities internally while looking at partnering on content, technology, and distribution channels.

The company works with external partners to leverage technologies and, as needed, will acquire or in-license specific intellectual property and capabilities. Company executives, however, stress they continue to work with partners for development of the diagnostic tests themselves.

Industry experts say a different development expertise and cycle are needed for generating personalized medicines and companion diagnostics.

"The pharmaceutical industry needs a much more collaborative development model at a macro level," Mr. Prutow says. "Specifically, companies need to focus on how the diagnostic or biomarker is going to impact the development of the therapeutic. For some pharmaceutical companies, this might mean completely outsourcing the diagnostic portion. As a result, more diagnostic companies will become more effective in partnering with pharma companies."

Mr. McDougall says collaborations with diagnostic companies, providers, and patient advocacy groups will help pharmaceutical companies address the business challenges, as well as the regulatory and reimbursement challenges.

"A more open innovation model will be key," he says. "Company size has not necessarily proven to be a competitive advantage. Nimbleness and creativity are needed, and these traits are often found in smaller to mid-size companies." PV

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