BY DENISE MYSHKO

MOLECULAR DIAGNOSTICS: Creating More Focused Treatments

Molecular diagnostics have already begun to revolutionize healthcare. They are being used in clinical practice and in the development of prescription drugs. Experts say molecular testing will be even more widely used in the future.

Experts have been saying for years that molecular diagnostics will transform not only the way prescription drugs are developed and dispensed, but also the entire healthcare delivery system. Their predictions are coming true: the molecular diagnostic market is exploding, with reported value estimated to reach $7 billion by 2011. New biomarkers are continually being discovered, and platforms and testing technologies are advancing.

The number of companies involved in molecular diagnostics has increased exponentially during the past few years, with more than 500 companies having been identified.

QUICK FACT

THE GLOBAL MOLECULAR DIAGNOSTICS MARKET IS EXPECTED TO REACH $7 BILLION BY 2011.

Source: Piribo

Molecular diagnostics has emerged as the fastest-growing segment of the in vitro diagnostics industry, with a compound annual growth rate of 19%, according to a report last year from Piribo. Infectious disease has the biggest market share of 70% but future growth is expected to come from oncology testing, genetic testing, and pharmacogenomics testing.

"We believe molecular diagnostics are going to be at the center of where healthcare needs to go over the next decade," says Michael Nohaile, Ph.D., global head of Novartis Molecular Diagnostics. "Molecular diagnostics allow physicians to detect disease early on and to have better treatment choices and better patient monitoring."

Tadd Lazarus, M.D., medical director at Roche Diagnostics, says molecular methods have been used for many years in the research environment.

"Now molecular diagnostics are being widely used in clinical care because they can more accurately and reliably diagnose various medical conditions," he says. "These technologies are being used effectively in moving the industry toward personalized medicine."

For the pharmaceutical industry, Dr. Nohaile says, the use of molecular testing is critical because therapies have become more complex.

"These advancements allow us to focus the therapies on the patients who need them," he says. "This means the outcomes are much better over a patient population, which therefore enhances what we're trying to do with pharmaceuticals."

At AstraZeneca, 10% of the company's current clinical pipeline has a pharmacogenomic strategy, says Cecilia Schott, Pharm.D., business development director for personalized healthcare, at the company.

"We believe those compounds will be driving success in Phase III trials, and we are looking for a true partnership with diagnostic companies and with regulatory authorities," she says. "For those products still in development, we start by looking at how robust the diagnostic is and whether it is going to help the end user make a choice about the best medication for patients."

Molecular Diagnostics Throughout Development

Dr. Lazarus says almost all pharmaceutical companies are using a number of molecular tools across the spectrum of pharmaceutical development, beginning with the initial discovery of active molecules with molecular-based systems.

"The criteria for getting a diagnostic test to the market are very different in Europe than in the United States."

ANDY FELTON
Life Technologies

"There are also molecular techniques that are being used to manufacture drugs, especially biopharmaceuticals that involve culturing organisms as part of a quality control test," he says. "This is a more recent development, but it represents an advancement in pharmaceutical manufacturing. Molecular methods are replacing some of the historically slow quality control assays."

Oncology seems to be on the leading edge of where molecular diagnostics are going and being applied.

"There are many reasons for this focus," Dr. Nohaile says. "There has been a lot of work conducted to understand the science and the molecular pathways involved in oncology. That said, we believe molecular diagnostics apply everywhere. We're doing work in oncology and in other areas, such as cardiovascular, immunology, and pain."

Market penetration of molecular assays will increase in the next few years in part because of the maturation of the technology itself, according to a report from Kalorama Information. Most of the research activity in molecular testing is focused on diagnosing, treating, and monitoring cancer. And as more is known about disease processes, these tests will also impact patient care for other chronic diseases, such as neurological conditions, autoimmune diseases, diabetes, and cardiovascular diseases.

Molecular assays and lab tests in general hold the key to outcomes research for the new generation of biotherapeutics, researchers from Kalorama Information say. That's because biotherapeutic products face the threat of poor market penetration unless they can prove to payer groups that they will improve patient outcomes and be cost-efficient compared with incumbent techniques.

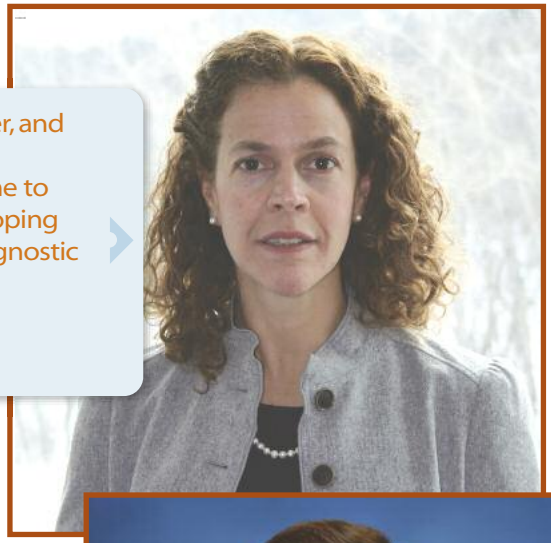
Pharmacodiagnostics, the melding of molecular tests with therapeutic decision making, is the hallmark of personalized medicine and is anticipated to be a high growth market segment.

Kalorama researchers say this is because regulatory agencies, such as the FDA, are encouraging protein and gene biomarker discovery to avoid new drug failures in late-stage trials and to make drug therapies more effective.

On average, drugs for diseases such as Alzheimer's, asthma, diabetes, hepatitis, and cancer have response rates of 25% to 80%, according to Kalorama Information; the U.S. Centers for Disease Control estimates that in the United States alone, serious adverse drug reactions cause an estimated 100,000 deaths a year.

"Aligning the technology, the biomarker, and the drug is a challenge; we still need to determine when exactly is the right time to start investing resources against developing the combined pharmaceutical and diagnostic product."

DR. CECILIA SCHOTT
AstraZeneca



Regulatory Issues

Dr. Lazarus says regulators, especially those at the FDA, are increasingly looking at the approval of molecular diagnostics from the perspective of having pharmaceutical-type requirements.

"Previously, a diagnostic test had to have excellent specificity, sensitivity, and reproducibility," Dr. Lazarus says. "Now, in addition to all of these criteria, we're also required to provide clinical outcomes related to the diagnostic, which has changed the game in terms of submissions. Submissions have become more 'pharma like' in terms of the number of clinical specimens tested, the number of patients involved, and data needed related to clinical outcomes."

"Molecular testing is already revolutionizing healthcare. In the future, molecular technologies will continue to be used, but they will be applied more widely."

DR. TADD LAZARUS
Roche Diagnostics

Dr. Nohaile says another issue is whether the FDA will allow for retrospective data to be included in submissions.

"Diagnostics often have retrospective data sets," he says. "Regulators are still struggling with the extent to which they will accept retrospective data versus demanding prospective data."

Despite lingering issues, the FDA approved a label change for Amgen's Vectibix to reflect data related to patients whose tumors harbored the mutant KRAS gene.

Scott Patterson, Ph.D., executive director, medical sciences, at Amgen, says the approval was based on a prospective statistical analysis of results generated from samples collected from an already completed trial.

"All of the endpoints had been met and we had the opportunity to interrogate banked samples," Dr. Patterson explains. "We spent 18 months collecting samples through the efforts of those in the development organization, and we ended up with a sample result ascertainment of 92%. We found that all of the benefit of Vectibix resided in those patients who had wild KRAS tumors." (Editor's Note: For more on the KRAS story, see the digital edition.)

Dr. Patterson says one of the major con-

Issues Impacting the Molecular Diagnostic Market

- This new era requires sophisticated, sensitive assays for infectious disease management, disease detection, and drug treatment decisions. On the other hand, these tests should be user friendly and cost-effective.
- There is a demand for faster test turnaround time from sample collection to results availability.
- There is a demand for a large menu of tests available on a single platform since molecular tests must account for variability in targets.
- There is a demand for test systems that are easy to use by nonlaboratory personnel.
- Molecular assays and lab tests in general hold the key to outcomes research. These products face the threat of poor market penetration unless they can prove to payers they will improve patient outcome and be cost efficient.

Source: Kalorama Information.
For information, visit kaloramainformation.com.

Sound Bites From The Field

PHARMAVOICE ASKED EXPERTS IN THE FIELD WHAT ARE SOME BEST PRACTICES FOR DEVELOPING COMPANION DIAGNOSTICS IN TODAY'S ENVIRONMENT. THEIR RESPONSES SHED LIGHT ON THE EVOLVING LANDSCAPE OF MOLECULAR DIAGNOSTICS.

Gerald McDougall is Partner in Charge of PricewaterhouseCoopers' Personalized Medicine and Health Sciences Practices. For more information, visit pwc.com/us/en/health-industries, or e-mail gerald.j.mcdougall@us.pwc.com.

"The advance of personalized medicine and the growing use of companion diagnostics fits perfectly with macro trends in health policy, business, and science moving the health system toward an era of more individualized, preventive care. Through the integration of diagnostics and therapeutics, companion diagnostics permit detection of diseases at early stages of development, thus allowing for a wider range of treatment options.

While the benefits of early disease detection are indisputable, the challenge when it comes to personalized medicine is drawing a direct connection between a diagnostic and the treatment decision.

The health system is moving toward value-based purchasing and outcomes-based reimbursement; companion diagnostics could be crucial to pharma's ability to prove that its products add value and are more effective, comparatively, than other interventions.

As a best practice, pharmaceutical companies and diagnostics companies are beginning to collaborate much more closely not only with each other but with others across the healthcare continuum to seek greater cooperation on pricing and appropriate reimbursement coverage.

While collaboration is imperative, formal partnerships between pharmaceutical and diagnostics will depend on the emergence of a clearer regulatory pathway for stand-alone diagnostics and for companion diagnostics in tandem with therapies and greater evidence around the predictive power of companion diagnostics."

Austin Tanney, Ph.D., is Scientific Liaison Manager, Almac Diagnostics, which is a personalized medicine company whose core expertise is in the provision of genomic-based solutions. For more information, visit almacgroup.com.

"There are a number of key considerations in developing companion diagnostics. From the perspective of biomarker discovery, it is important to bear in mind from the outset that it is a process of product development as well as a scientific exercise. The aim is not just to find an interesting biomarker, but ultimately to develop a clinically applicable test. It is, therefore, important that the biomarker be transitioned easily into the clinic.

When working in oncology, we believe this is a key reason to focus on the use of formalin fixed paraffin embedded samples, which is the current standard for tissue storage in clinical practice, and it would be ill-advised to try to make major changes to standard clinical practice. It is also important that the test is robust, reliable, reproducible, and applicable on a well-established and trusted platform.

We recognize that most molecular tests are best suited to immuno-histochemistry or quantitative PCR, but it is important to be aware that the discovery and delivery platforms may not be the same, and this must be considered and planned for from the outset. Obviously it is also critical to bear in mind that technical and analytical validation can be as important as clinical validation and the study design must reflect this.

The key message in companion diagnostic development is that it is a process that begins with biomarker discovery and ends with a clinical test. The best practice is to approach the entire process from this perspective and plan, design, and implement the development accordingly."

cerns the agency has with retrospective data is that there needs to be high ascertainment sample results to reduce the chance of potential differences between tested and nontested patients that could skew the results. Another concern is whether the analyte to be measured is stable during storage.

"Thankfully in this case, we were looking at DNA for a somatic mutation," he says. "DNA is extremely stable, and one advantage we had was that what we were measuring wasn't going to degrade."

Stephen Little, Ph.D., VP of personalized healthcare at Qiagen, says U.S. regulators are enthusiastic about molecular testing.

"Strategically, we are all aligned to molecular testing being a good thing," he says. "Regulators and companies want it to happen. But there are issues still to be dealt with, such as what study designs should look like and the use of retrospective data."

FDA officials say the agency is currently working on a guidance for a regulatory path for companion diagnostics, and they hope to issue that guidance by the end of this year.

Andy Felton, director of the CE instruments product line at Life Technologies, says in Europe there are a number of diagnostics on the market because of differing registration requirements.

"The criteria for getting a diagnostic test to market are very different in Europe than in the United States," he says. "In the United States, the test requires a systems approach; the FDA requires that the assay and the instrument are registered together. In Europe, companies can register an assay separately."

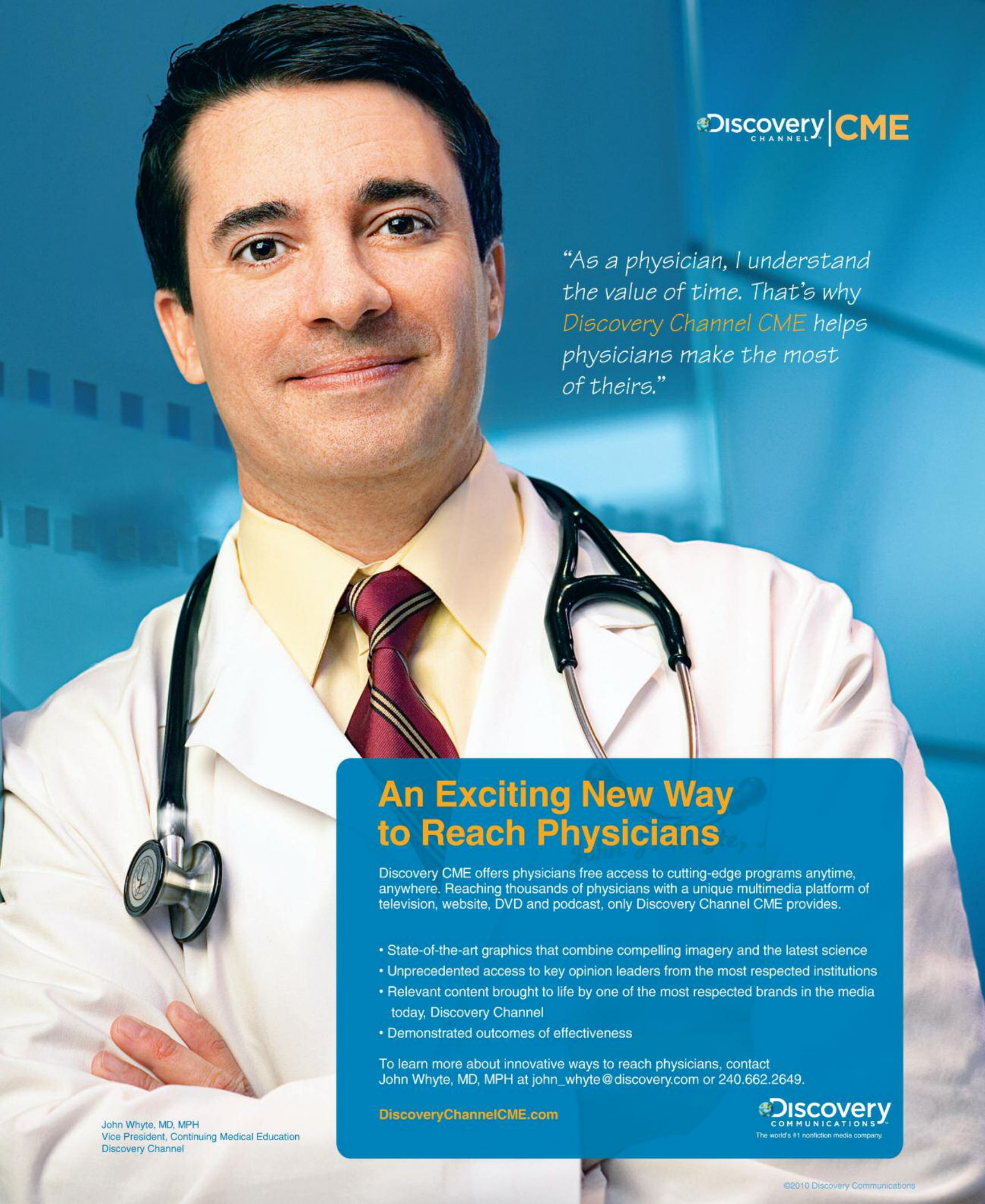
According to a report from Kalorama Information, at least 80% of the molecular assay tests performed are concentrated in the developed world — North America and Western Europe.

But Europe is a stronger market in terms of growth — in sales, not the number of tests — and the European process of product regulation allows for easier entry of new technologies.

Working in Partnership

Dr. Nohaile says another big challenge, especially in the area of companion diagnostics, is aligning diagnostic and pharmaceutical companies to work together.

"There needs to be a way to fuse the best of what pharmaceutical companies bring to the table and the best of what diagnostic companies do," he says. "The technical work and the diagnostics have to be combined with the pharma clinical trial infrastructure to generate a compelling data package on how a product is



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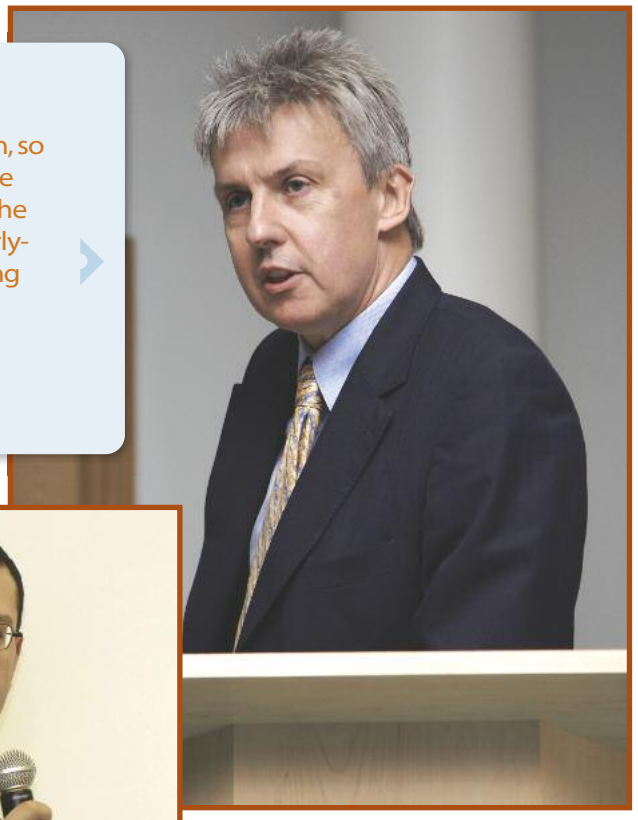

"Pharmaceutical and diagnostic companies should partner early on, so they can coordinate the biomarker assay with the development of an early-stage diagnostic leading into a full diagnostic product."

DR. STEPHEN LITTLE
Qiagen

"We believe molecular diagnostics are going to be at the center of where healthcare needs to go over the next decade."

DR. MICHAEL NOHAILE
Novartis Molecular Diagnostics

going to help people. Putting these components together is one of the keys to success, and many people are working on doing this."

Novartis created its Molecular Diagnostic unit as a way to try to address this challenge.

"We started within our pharma division so that we could be tightly tied to our pharmaceutical development counterparts," Dr. Nohaile says. "We know their processes intimately. We are on site with the core development team right from the beginning. This is an advantage in developing these types of diagnostics." (Editor's Note: See the digital edition for more on Novartis Molecular Diagnostic unit and what other companies are doing in this area.)

Dr. Little agrees that there often is an issue about the timing of developing companion diagnostics.

"Pharma companies need to start thinking about companion diagnostics during Phase I or even preclinical development, which ensures no opportunities are missed," he says. "By doing a few things correctly early on, a lot can be saved later."

Dr. Patterson says as much as researchers want to include patient selection as well as pharmacodynamic biomarkers from the first-in-human studies, often they learn about the biology that informs patient selection through the development process.

"Unfortunately, we often don't know enough about human biology to be able to reveal what the patient selection biomarkers are necessarily going to be before we go into a Phase III pivotal trial," he says. "This is a real timeline issue for everybody. If we all knew more about human biology, the selection of the pharmacodynamic biomarkers would be easy, and the selection of the patients who would respond would be easy."

AstraZeneca's Dr. Schott says designing clinical trials is another challenge for developing molecular diagnostics with new drugs.

"The challenges are to prove the clinical utility of a diagnostic tool and the efficacy of the drug during the trial," she says. "We need to address the clinical trial design to assure that the right patients are really benefiting from the right drugs. We ask the appropriate questions for traditional clinical trials for drugs and now we need to do the same thing for combination diagnostic trials." ✦

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BY DENISE MYSHKO

MOLECULAR DIAGNOSTICS: A Core Capability for Pharma

Several companies have taken the lead in pushing molecular diagnostics forward.

One of the first companies to address molecular diagnostics was Roche. At Roche, the molecular diagnostics division focuses on developing predictive tools that can assist in patient prognosis and treatment. The company's portfolio is based on polymerase chain reaction (PCR) technology and applies clinical diagnostics in six key areas: virology, women's health, microbiology, blood screening, genomics, and oncology.

PCR is a technology used to amplify, or copy on a large scale, specific sequences of DNA. The technology was developed by scientists at Cetus in 1983. Roche acquired worldwide rights and patents to PCR in 1991. The first diagnostic tests using PCR were introduced in 1992; Roche introduced Amplicor Chlamydia trachomatis Test and Amplicor HIV-1 MONITOR Test, which outside of the United States.

Since then, the company has evolved the technology from a manual process to an automated one.

"The use of specific biomarkers paired with a pharmaceutical agent, so-called companion diagnostics, is at the heart of the diagnostics industry's contribution to personalized medicine," says Tadd Lazarus, M.D., medical director at Roche Diagnostics.

"It is widely recognized that drugs should be developed with specific target populations in mind to both maximize efficacy and minimize side effects. Finding those populations is the detective role of the diagnostic. The use of the Roche molecular test using the PCR method to minutely determine the quantity of circulating HIV in patients prior to and during combination anti-retroviral therapy has been the foundation for the revolution that has changed the face of HIV/AIDS from a terminal diagnosis to living with a chronic infection."

Another example is in the pairing of the Roche hepatitis C PCR test with the Roche pegylated interferon, Pegasys, in combination with Copegus (ribavirin).

"This pairing has allowed physicians to accurately predict which patients' genotype I chronic hepatitis C infection would benefit from a full treatment course with these two drugs in as little as 12 weeks, thereby sparing patients potential side effects and society the cost," Dr. Lazarus says.

A recent example of the application of this technology is the February 2010 Roche and Merck agreement to collaborate on a developmental test for cancer-related gene mutation. By identifying cancers that harbor a dysfunctional p53 gene, the companies can determine which patients are most likely to respond to investigational therapeutic candidates.

Roche AmpliChip technology combines two DNA amplification and detection technologies to screen for genetic mutations in cells. The Roche PCR is used to amplify or make copies of genetic material, and Affymetrix high-density microarray technology is used to capture and scan the amplified DNA.

For Novartis, molecular diagnostics is key to the core business model, says Michael Nohaile, Ph.D., global head of Novartis Molecular Diagnostics.

"Our belief is that molecular diagnostics is going to be a critical capability if pharma companies are going to be successful," he says. "We will continue to build up the capabilities of this business. A large number of programs are already under way, and we anticipate a significant portion of our portfolio will have a companion diagnostic. We also expect to have a nice portfolio of stand-alone diagnostics that aren't directly tied to our pharmaceuticals but are in related areas."

Novartis has been increasing its efforts in this area significantly over the years, to the point where almost every program now has a biomarker component involved.

"What's new is our move to commercialize molecular diagnostics so that physicians and patients have access to innovative test to improve patient outcomes," Dr. Nohaile says. "We're building the core capabilities to evaluate the biomarkers identified by our colleagues in NIBR and to develop them for commercialization in various platforms, often in partnership with others."

To pursue this business strategy, Novartis Molecular Diagnostics will stand on its own alongside the company's other individual business units.

"We've had a strong translational medicine group for many years, which has been used on the research side to help identify and validate biomarkers and show the efficacy of various early-stage compounds in animal models and in the clinic to help select patients, monitor outcomes, and provide a higher chance to succeed," Dr. Nohaile says.

One example of how Novartis has applied this technology is with lumiracoxib. In December 2009, the company submitted lumiracoxib 100 mg once-daily in combina-

Application of DNA Assays

By 2015, DNA assays will be used routinely in the clinical setting for:

- Alzheimer's disease
- Asthma
- Autoimmune disorders, such as osteoporosis and arthritis
- Cancers (all)
- Cardiovascular disease
- Deafness
- Depression
- Diabetes
- Hemophilia and other clotting disorders
- Inherited diseases, such as multiple sclerosis and cystic fibrosis
- Multiple sclerosis
- Parkinson's disease
- Prenatal genetic screening
- Tissue typing

Source: Kalorama Information.
For information, visit kaloramainformation.com.

tion with a genetic biomarker discovered by the company's pharma research group under the brand name Joicela for marketing authorization in the European Union for the treatment of signs and symptoms of osteoarthritis (OA). The genetic biomarker can identify patients at risk for certain liver-related side effects from lumiracoxib and make them ineligible for therapy.

"This drug provides effective pain relief, and the supporting safety evidence around lumiracoxib in OA is one of the best in its class, but it caused very rare liver side effects," Dr. Nohaile says. "In collaboration with our teams in NIBR and pharma, we identified a marker that can screen out the people who would be at risk of certain liver related side effects, and make them ineligible for therapy."

This would be one of the first examples of a molecular diagnostic-based drug rescue in the industry. Lumiracoxib was marketed under the brand name Prexige, which was approved in the EU in 2006, but was withdrawn from the market in several countries the following year because of serious liver adverse events.

AstraZeneca's Iressa is another example of how a diagnostic can provide benefit to a product. Iressa was approved in July 2009 in the European Union for the treatment of adults with locally advanced or metastatic non-small cell lung cancer with activating mutations of EGFR-TK (epidermal growth factor receptor-tyrosine kinase).

The application in Europe for Iressa had been submitted several years earlier, but in 2005 AstraZeneca withdrew its application following data from a Phase III international study in pretreated patients not eligible for further chemotherapy.

This study did not meet its primary objective of a statistically significant improvement, but did confirm a number of important clinical benefits for Iressa, including tumor shrinkage and a significant improvement in time to treatment failure.

Iressa acts by inhibiting the tyrosine kinase enzyme in the EGFR pathway, blocking the transmission of signals involved in the growth and spread of tumors. A mutation in the EGFR is a characteristic occurring in 10% to 15% of lung cancer patients, and studies have shown that these types of tumors are particularly sensitive to Iressa.

As an example, Qiagen developed one of the diagnostic tests for the detection of EGFR mutation.

Additionally, AstraZeneca's Boston R&D site was recently made the company's global headquarters for infection research.

"Infection is one area where diagnostic tools are key to patient treatment and for personalizing care," says Cecilia Schott, Pharm.D., business development director of personalized healthcare at AstraZeneca. "This therapeutic area is a fantastic opportunity for us. We want to get the technology closer to the patient at the time of a hospital admission or at the time the physician sees the patient, so he or she is selected for the right drug the first time." ✦

The KRAS Story

The market approval of Amgen's Vectibix for colorectal cancer is an example of how biomarkers and molecular testing can be used to advance a product.

"This is a primary example of how personalized medicine can be enabled," says Scott Patterson, Ph.D., executive director, medical sciences, at Amgen. "It also defined a population that didn't respond to a biomarker, which is something that people had not always been considering."

Vectibix is a fully human monoclonal antibody against the EGF receptor and its first indication was in metastatic colorectal cancer patients whose previous therapies had failed them. The drug was first approved in the United States in 2006; it had a significant benefit a small percentage of patients.

"We knew that upon approval of our therapy in the United States we wanted to do something to improve the response rate, which was around 10%," Dr. Patterson says.

Not long after the product's initial U.S approval, European authorities issued a negative opinion. In the meantime, Amgen researchers continued to study Vectibix in relation to the KRAS mutation.

The frequency of KRAS mutation in colorectal cancer is around 40% to 50%. For many years, the EGFR pathway was known to include a number of oncogenes, genes that when activated could lead a cell to become a cancer cell.

One of those genes was KRAS. There has been 30 years of work on KRAS, and it was known to be downstream of the EGFR receptor.

"One could conclude that this is a straightforward biomarker," Dr. Patterson says. "But there was some information that clouded what seemed obvious. First, there were papers published that reported that the mutation was prognostic and others that reported it wasn't.

"Second, some xenograft studies showed that some human cell lines that had a KRAS mutation were sensitive to the anti-EGFR antibody," Dr. Patterson continues. "We thought we understood human biology but we didn't. The cells should have been resistant to therapy but there were some literature reports stating that a small number of patients with tumors with mutated KRAS gene had responded to anti-EGFR therapy."

"We investigated samples that had been banked from some of our Phase II single-arm studies for mutational status and objective response, progression free survival, and overall survival," he says. "Even though it was a limited set, we were able to identify patients with KRAS mutations who responded to therapy."

Anti-EGFR antibody therapies work by blocking the activation of EGFR, thereby inhibiting downstream events that lead to malignant signaling. But it is hypothesized that in patients whose tumors harbor a mutated KRAS gene, the KRAS protein is always turned on, regardless of whether the EGFR has been activated or therapeutically inhibited.

The company was able to prespecify the statistical analysis plan, select the vendor of the assay for a kit that researchers believed had the potential for a companion diagnostic, analyze all of the samples in a laboratory that had validated the assays according to appropriate guidelines and was blinded to patient outcomes, obtain the results, analyze the results according to pre-specified statistical analysis, and resubmit the product to the European regulatory authorities.

"They accepted the data and changed their negative opinion to a positive opinion because the results were startling," Dr. Patterson says. "There were no responders and no benefit to patients who had KRAS mutations following receipt of anti-EGFR therapy."

The company provided the same data set to the FDA in September 2007, which triggered an oncologic drugs advisory committee meeting in 2008. The company received a label change to include the KRAS information in July 2009.