Denise Myshko

Companion DIAGNOSTICS: Partnering for Success

Pharmaceutical and diagnostic companies are teaming up to co-develop drug-companion diagnostic combinations.

As the development of personalized medicine gains momentum, device and pharmaceutical companies are collaborating in their development efforts. They are creating partnerships for the development of diagnostics to accompany clinical trials.

In fact, there has been an acceleration of companion diagnostics partnerships, according to a report published last December by PwC. This will continue as long as innovation and growth continues in key areas, such as molecular and tissue diagnostics.

The drivers for this, say PwC executives, are the demand from payers and regulators for biomarkers and diagnostics to improve drug performance and provide more cost-effective products. By 2020, if drug-diagnostic co-development becomes routine, most leading pharma companies are expected to change their business model to incorporate significant in-house diagnostics capabilities, PwC executives predict.

"There is likely to be an increase in the number of partnerships formed in the industry between pharmaceutical companies and diagnostic companies to take companion diagnostics to the market," says Trevor Hawkins, senior VP, strategy and innovation, at Siemens Healthcare Diagnostics. "We are in very active discussions with large pharmaceutical companies as well as up-and-coming companies and others to help them bring these novel therapeutics to the marketplace."

Siemens has entered into several partnerships, one with Viiv, an alliance between GSK and Pfizer with products on the market and in development to treat HIV/AIDS; and one with Tocagen, a clinical stage, biopharmaceutical company developing products for the treatment of cancer.

Partnering is a way to mitigate the risk of developing a companion diagnostic, says Robert Copeland, Ph.D., chief scientific officer, at Epizyme.

"We are not going into the diagnostic business," he says. "Part of a risk-mitigation strategy is to work with partners that have established platforms in which there is a large footprint in the clinical diagnostic world so that we are not absorbing the risk of developing a novel platform technology at the same time we are developing a novel therapeutic. We are looking for partners that have experience in the type of platforms that are amenable to the targets we're going after and have experience working with the regulatory agencies to reach approval with other programs."

Diagnostic Personalization

Dr. Copeland says right from the beginning of development, the Epizyme considers a companion diagnostic strategy.

"Since we are identifying enzymes that are genetically altered, those genetic alterations then frame how we're going to select patients who are most likely to benefit from treatment," he says

The decision to pursue a companion diagnostic is often made on a case-by-case basis, says Eric Hedrick, M.D., chief medical officer, at Epizyme.

"In certain cancers, there are diagnostics in current use in the clinic in small populations, albeit not FDA-approved tests," he says. "This might be a situation where we'd use the clinically available test from the outset of development. Other situations might require that we pursue development of the companion diagnostic for approval at the same time that we initiate clinical trials of the drug."

Dr. Copeland says the avalanche of genetic data that has accrued over the last decade has defined a new paradigm for oncology.

"We believe the future of clinical oncology is going to be personalized therapeutics, defining the driver genetic alterations in specific therapeutic modalities that address those alterations and then, through companion diagnostics, identify those most likely to benefit from a specific therapeutic modality," he says. "This is a sea change in how cancer is going to be treated in the future."

The molecular diagnostics field plays a vital part in personalized medicine and has greatly expanded over the past 20 years, growing by more than 20% annually compared with most other laboratory procedures, according to a report earlier this year by Tri-Mark Publications. Companion diagnostics, although smaller at present, is one of the fastest-growing segments in the in vitro diagnostic (IVD) market.

And, according to a recent Kalorama Information report, diagnostic tests that can direct a therapy to a specific patient to boost outcomes are experiencing faster sales growth than that of the overall IVD market. This particular category of personalized medical tests has recorded growth anywhere between 7% and 38% per year, compared with the more modest 2% to 6% growth recorded by IVDs in general.

Personalized medicine tests such as fluorescent in situ hybridization (FISH) for cancer screening, CYP450 tests for psychiatric therapy, individual microbiologic assessments to treat infectious disease, and tissue transplant

> **“Regulatory guidelines have driven us to work with pharma companies early on to make sure the test of record is used in the pivotal trial, enabling the device then to gain approval with data that include analytical performance and establish clinical utility within that trial.”**
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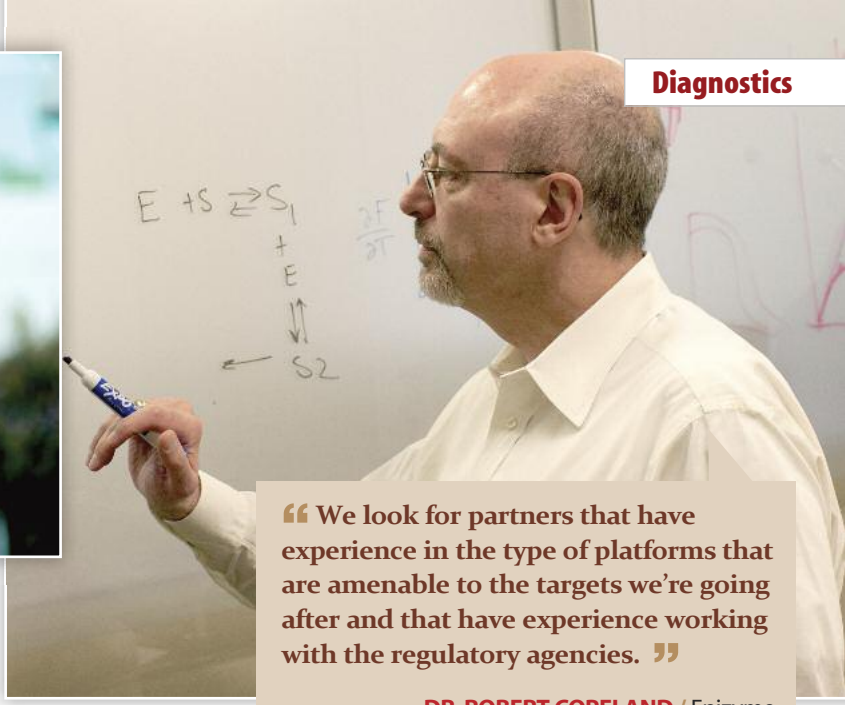
> **DR. WALTER KOCH** / Roche Molecular Diagnostics



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> **DR. ROBERT COPELAND** / Epizyme

typing, rose to $28.1 billion in 2011, Kalorama researchers say.

Diagnostic Impact on Trials

Walter Koch, Ph.D., VP and head, global research, at Roche Molecular Diagnostics, says the addition of a companion diagnostic can change a trial for the better.

“This is especially true when it’s a targeted therapy that biology suggests is going to only be effective and safe in a given subpopulation,” he says. “If we know, for example, that half of the patients have a mutated gene and, therefore, are the only patients likely to respond, then by selecting that portion of the patient population that is now enriched for response, the trial can be smaller, faster, and more successful.”

> “One of the challenges is designing the companion diagnostic in the right way on the right platform to meet the needs of how a drug will be used once it’s out in the field and commercialized.”
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> **TREVOR HAWKINS** / Siemens Healthcare Diagnostics

> “Identifying subsets of patients can become a logistical challenge, and well-coordinated screening efforts are often required to identify patients who might be eligible for the trials.”
>
> **DR. ERIC HEDRICK** / Epizyme

The In Vitro Diagnostics Market

- New entrants are continuing to add to vitro diagnostics (IVD) businesses. For some newer IVD entrants, recent deal activity may represent only a beginning. Look for these companies to pursue additional acquisitions to maintain the momentum required to achieve critical mass quickly.
- Major companies are responding in kind. If current industry leaders do not respond with significant acquisitions, they may lose market share in key segments. Deals might be challenging because of increasing competition for the most compelling new technologies.
- Private equity houses are searching for opportunities. An increase in bigger private equity-backed deals are likely to crystallize, provided capital markets do not slump.
- Major pharmaceutical companies are buying molecular or tissue diagnostics businesses. Though this kind of deal activity has been slow in recent years, some major pharma companies will be increasingly motivated by the confirmation of the drug-diagnostic co-development model. Those not part of a company with a significant IVD division have started building business development teams with diagnostics expertise to support better licensing decisions, and some of these companies will consider buying a diagnostics business to deepen their expertise, increase technology options, and provide direct commercial access.
- Several companies are driving the development of a wave of new tests for early detection of major cancers. Only time will tell whether the market adopts the concept of using noninvasive in vitro diagnostics for early detection. If it does, a major diagnostics or pharmaceutical company could move to acquire one or several of the promising new ventures in this field.

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

Dr. Koch says this was true in the development of Zelboraf, Roche/Plexxikon’s small-molecule treatment for BRAF mutation-positive metastatic melanoma. Zelboraf received FDA approval in August 2011. It is also approved in the European Union, Switzerland, Brazil, Israel, Canada, and New Zealand.

The companion diagnostic, cobas 4800 BRAF V600 Mutation Test, is manufactured by Roche Molecular Systems. FDA approval of the test was received simultaneously and was based on data from the clinical study that also evaluated the safety and effectiveness of Zelboraf.

Dr. Koch stresses the importance of working with diagnostic partners early in the development process.

He says in the case of the work the company has done with Zelboraf, Roche Molecular Diagnostics had very early notice about the need for a companion diagnostic.

“If we are approached early, even before entry into humans, we can work on a prototype that could be filed as an investigational device exemption,” Dr. Koch says. “Then when the Phase I extension trials are done, the test is in place to start to examine whether patients with the mutation are going to respond. The diagnostic can be used in Phase I to start to see signals in some patients.”

Theresa LaVallee, Ph.D., senior director of translational sciences oncology, at MedImmune, says companion diagnostics can be used to specifically select patients based on certain characteristics.

“It’s critical to go into clinical studies with a hypothesis, therefore there is a need for pharmacology data from animal models,” she says. “The companion diagnostic essentially selects a biomarker, a protein, a gene, or a cell and, based on this characteristic, it can be determined which patients will benefit from the therapy.”

Dr. LaVallee says not every therapy needs a companion diagnostic.

“If a particular biomarker is in 90% of the patient population, there is no reason to screen because 90% of the people are going to respond,” she says.

As an example, Dr. LaVallee says MedImmune has a product in development, Medi-551, which is a CD19 directed antibody in B cell malignancies.

“About 90% of people with B cell malignancies have CD19, and while we are taking a personalized healthcare approach by treating people with B cell malignancies, we don’t have a companion diagnostic,” she explains. “We selected the patient population based on the disease. But if in that patient population only 30% of the patients had CD19 then we would have to test for the expression of that biomarker before we enrolled patients into treatment.”

The need to test for a biomarker, she says, changes how trials are conducted.

“We have to account for the screening time and we have to demonstrate early on that there is a lack of benefit in the biomarker-negative patients,” Dr. LaVallee says. “While there are data that would suggest that a patient will benefit, we also have to demonstrate that the hypothesis is correct by showing the patients who don’t have the biomarker don’t benefit.”

Dr. Hedrick says adding a diagnostic to a trial is both a positive and a negative.

“On the plus side, if the diagnostic truly does predict who is going to benefit from the drug, there is a much higher probability of successfully developing a drug that will benefit patients,” he says. “But that presents some challenges. With many of these molec-

ularly defined populations, we are talking about subsets of patients within a particular disease. So identifying these patients can become a logistical challenge, and well-coordinated screening efforts are often required to identify the patients who might be eligible for clinical trials."

The Regulatory Environment

Experts stress the regulatory environment for companion diagnostics is evolving. In an FDA guidance issued last year, regulators indicated they intend to review each IVD companion diagnostic device submission within the context of, or in conjunction with, its corresponding therapeutic product, and FDA review of the test/therapeutic product pair will be carried out collaboratively among relevant FDA offices.

For a novel therapeutic, the FDA will consider whether a companion diagnostic is essential for the safe and effective use of the product, and if so, its use will be in the labeling of the therapeutic.

Dr. Hedrick points out that biopharma companies now have to consider a parallel process of getting the diagnostic test through regulatory review.

"The development programs should be perfectly aligned," Dr. Hedrick says. "We plan for both in parallel. For a drug in a defined population, the burden of proof for getting the drug approved is establishing that the drug is safe and effective in the population identified. The diagnostic provides the opportunity to identify patients with the relevant genetic alternations." PV

EXPERTS

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