

## Making Molecular Diagnostics Ready for Prime Time

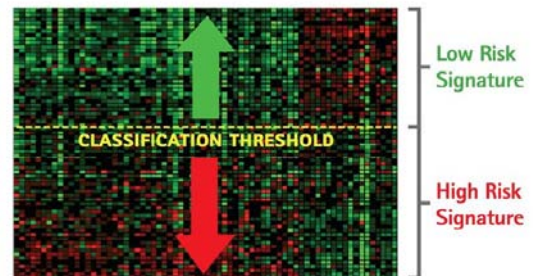
*Practical considerations slow the adoption of tests for personalized cancer care*

Since the Food and Drug Administration's (FDA) 1998 approval of trastuzumab (Herceptin; Genentech), oncology has been at the vanguard of personalized medicine: the vision of obtaining a diagnosis—and possibly a prognosis—from a patient's genetic material and tailoring treatment accordingly. But without the accompanying diagnostic test, developed by Dako, to determine breast cancer patients' *HER2* status, the drug's success wouldn't have been possible. What began as a research one-off—a clinical molecular diagnostic test—has grown into an industry that increasingly influences medical practice.

Today, hundreds of gene mutations and changes in gene expression are known to affect the development of different cancers, and many have been proven clinically relevant to the course and treatment of the diseases.

“This is an exciting time to be in the molecular diagnostics area,” says Rajyalakshmi Luthra, PhD, professor and scientific director of the Molecular Diagnostic Laboratory at M.D. Anderson Cancer Center. “The technology and science are merging together very well, complementing each other and the targeted therapies.”

Luthra's lab offers more than 40 in-house molecular tests covering almost all types of cancers. As at many other academic hospitals, the lab also serves as a reference laboratory for community hospitals and independent oncologists. Additionally, the pathology department sends out samples for tests that they can't perform due to intellectual property or other commercial restrictions (e.g., testing for *BRCA1* and *BRCA2*



The first *in-vitro* diagnostic multiple index assay approved by the FDA, MammaPrint analyzes 70 critical genes in the breast cancer metastatic cascade and stratifies patients into two distinct groups, for low risk or high risk of distant recurrence.

*Agendia*

mutations in breast and ovarian cancers). “With all the targeted therapies, more and more cancers are being analyzed for mutations in kinases and other actionable targets,” she says, noting that M.D. Anderson's doctors not only utilize the lab but routinely ask her team to develop new tests.

At the Oncology Cancer Center at the University of California, San Francisco, Laura van 't Veer, PhD, professor of laboratory medicine and director of applied genomics, is establishing a lab focused specifically on translating research findings into clinically validated molecular tests. In the 1990s, van 't Veer led development of a 70-gene prognosis signature for breast cancer at the Netherlands Cancer Institute and cofounded the diagnostic firm Agendia to commercialize the test as MammaPrint. It was the first *in-vitro* diagnostic multiple index assay approved by the FDA.

Van 't Veer, who serves as Agendia's chief research officer, estimates that use of molecular diagnostics in oncology has more than doubled in the last 5 years. “We are now in a transition period,” she says. “In a few years, we'll do it for everybody.”

## MULTIPLE REGULATORY REQUIREMENTS

A complex web of regulations for clinical testing complicates the development and introduction of new molecular tests, however. In the United States, the FDA oversees the evaluation and approval of diagnostic tests that are manufactured and sold as kits to clinical labs around the country. At the same time, to ensure basic quality control, all clinical-testing labs in the United States are accredited under the Clinical Laboratory Improvement Amendments program, which is run by the Centers for Medicare and Medicaid Services. Each state also has its own certification agency and rules, and many labs are independently certified by the College of American Pathologists.

Currently only the FDA approval process is designed to ensure the utility, reliability, reproducibility, and safety of medical tests. But in advanced molecular diagnostics, many labs, such as Luthra's, use assays they've devised themselves—so-called laboratory-developed or “homebrew” tests. Some diagnostic companies also offer tests, performed in their own labs, that have not gone through the FDA approval process. Such tests can still be useful and reliable, Luthra says, but oncologists must make their own evaluations about individual assays and labs, which is time-consuming and onerous.

The FDA process itself is lengthy and demanding. Even among those who support FDA regulation of molecular diagnostics, many believe the current framework is unsustainable.

For companion diagnostics, designed to guide use or nonuse of a targeted therapy, the FDA requires prospective data from trials in which the same patient is tested for the biomarker and the long-term outcome of the therapy. “Now that we are in the era where we can have multiple tests and multiple drugs for a whole patient population, it's impossible to do this phase I, II, and III path for

all of them,” says van 't Veer. “It will cost too much, it will cost too many patients, and it will take us 10 or 15 years for every such combination. We need to start to do this in a different way.”

She suggests the FDA consider allowing more neoadjuvant studies, in which potential new drugs are given to patients before surgery, to speed up the process.

Another possibility would be adopting a system more like that used in Europe, where the process of bringing molecular tests to market is more straightforward, says Stephen Little, PhD, vice president of personalized healthcare at Qiagen. “You can justify the use of a test with retrospective data,” he says, even in the case of companion diagnostics. “The science can move very quickly. The regulators cannot move as quickly.”

## LIMITS ON FDA APPROVALS

That's one reason an FDA-approved test isn't always the best option for oncologists and patients, says Luthra.

She cites vemurafenib (Zelboraf; Roche), a *BRAF* inhibitor approved in August for late-stage melanoma. The label states that an FDA-approved test must be used in conjunction with the drug, but the approved companion diagnostic, also made by Roche, is designed to detect a common mutation, V600E (GTG>GAG) in the *BRAF* gene. Luthra says that melanoma patients with less common dinucleotide mutations affecting codon 600, such as V600K (GTG>AAG), that may be missed by companion diagnostics, might still benefit from vemurafenib. But under FDA guidelines, doctors cannot give them the drug, as confirmation of *BRAF* V600E mutation-positive melanoma using an FDA-approved test is required before treatment with vemurafenib.

She says that although such mutations might be identified and tests easily developed, obtaining

FDA approval for the diagnostic would require extensive clinical trials that might be so large and expensive as to prohibit their conduct.

Creating even more regulatory uncertainty, the FDA is working to bring all laboratory-developed tests under its authority.

Some labs have done *BRAF* mutation analysis using lab-developed tests for several years in a variety of diseases, including colon cancer, thyroid cancer, melanoma, and certain gliomas. Although the labs cannot market homebrew *BRAF* tests as companion diagnostics for vemurafenib, they're not necessarily violating regulatory policy by using them. The clinical lab community worries that may change as the FDA adopts new rules about laboratory tests that could disrupt patient access to molecular tests. Labs might have to make new capital investments to support the various technical platforms used in different FDA-approved companion diagnostics—and may not be able to afford to do so, Luthra says.

## THE PRICE OF ADOPTION

Cost already plays a role in the speed at which doctors have adopted molecular testing, Luthra says. She estimates the average range for the cost of molecular diagnostic assays is \$400 to \$1,000, with detection of each individual gene mutation comprising a separate test. “That is a bit expensive, and the costs need to come down,” she says. “You want technologies that can look at multiple markers simultaneously for a decent price.”

In the long term, she hopes next-generation sequencing technologies will help; many diagnostics companies are investigating such methods.

Health care payers have also been reluctant to reimburse for molecular diagnostics. In a survey done earlier this year, Joshua P. Cohen, PhD, a research assistant professor at the Tufts Center for

the Study of Drug Development, found that even when a diagnostic is included on a drug's FDA label, payers do not necessarily require it and often do not pay for it. He says that in a few cases molecular diagnostics and targeted drugs have been clearly linked to health outcomes, but most still lack conclusive evidence. “Because they're not quite there, payers are reluctant to reimburse, at least comprehensively,” he says.

However, this seems to be slowly changing. In the past year, Medicare has begun reimbursing more molecular diagnostics, which is often the first step to wider payer acceptance.

Steven Shak, MD, chief medical officer of Genomic Health Inc., says that some payer groups have established standard questions they require to be answered before authorizing reimbursement, for instance, peer-reviewed studies of a test's clinical value, its impact in changing the course of treatment, and its health-economic impact. A test's inclusion in treatment guidelines developed by physician groups such as the American Society of Clinical Oncology and the National Comprehensive Cancer Network can also increase payer acceptance.

“The bottom line is, it's not easy and it's not inexpensive to bring scientific rigor to the clinical setting and to meet the needs of patients, physicians, regulators, and payers,” he says. “One of the biggest issues is there needs to be adequate reimbursement for diagnostic tests in order for us as a community to continue to enable the investment in clinical studies and in standardization that it takes to do it right.”

— Erika Jonietz

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