

# A Bump in the Road:

## Laboratory Developed Tests Defend Their Regulatory Position

By John Watson

Optimistically poised at the beginning of the long road towards personalized medicine, the irascible diagnostic testing industry encounters an unlikely speed bump in the form of Genentech.

Citing a potential risk to patient safety, Genentech, the massively successful drug company that has developed several blockbuster agents based on cutting-edge genetic information, filed a Citizen Petition last December requesting that the US Food and Drug Administration (FDA) increase its regulation over the diagnostic testing industry. In the wake of that filing, the diagnostics industry has launched a comprehensive defense of their products, and is making their own case for what level of regulation they would like to see be set in place. In addition, they are warning of significant investor drop off if the government acts on Genentech's request.

### Opening Arguments

In their petition, Genentech is seeking for the FDA to apply the same scientific and regulatory standards for all "in vitro diagnostic tests intended for use in drug or biological therapeutic decision making." Currently, the FDA directly regulates diagnostic tests in kit form as medical devices. However, those laboratory-developed tests (LDTs) developed by clinical laboratory companies for in-house testing are monitored by the Centers for Medicare and Medicaid Services, under the Clinical Laboratory Improvement Amendment (CLIA), which provides a lower regulatory hurdle for companies to get over before sending their products onto the market. Genentech's petition requests that the FDA initiate rule-making with concurrent enforcement action against companies not backing up marketing claims with data.

According to Genentech spokesperson Edward J. Lang Jr., "CLIA doesn't

really address claims about clinical validity and utility." He further explained that given the FDA reviews medicines and medical devices for clinical claims, "that if there's going to be a test that will make a claim that will influence treatment decisions, then that claim should be reviewed by the one body in the United States whose job it really is to look out for patients."

Individual LDT companies and the umbrella organizations representing them (chiefly, the Coalition for 21st Century Medicine and the American Clinical Laboratory Association) have launched several counterarguments in the months following Genentech's initial petition. These arguments have followed a few key lines of reasoning that include:

- Laboratories providing diagnostic testing must already meet rigorous guidelines set forth by CLIA, state accrediting agencies, and various professional societies.

- For LDTs to be optimally effective, they must quickly incorporate recent clinical breakthroughs regarding new biomarkers and genomic information—something that would be all but impossible if an extra regulatory hoop was added.
- Increased costs and delays stemming from new regulation would deter investors from placing money in fledgling companies, thereby reducing the number of available diagnostic tests (especially for rare and low-volume diseases), with a corresponding negative impact on patient care.

### Impact on Investors

This turn of events is particularly notable for occurring at a time when LDT companies are uniquely primed to benefit from the push towards personalized medicine, as many tests are designed to select patients for individual therapies. Additionally, all signs from the new administration in Washington, D.C. indicate that diagnostics could be a significant facet of the push towards healthcare reform. As a senator, President Obama authored the Genomics and Personalized Medicine Act, and has since discussed how early screening for cancer and other forms of pre-

ventative medicine (the very hallmarks of the diagnostic testing industry) can drastically reduce payer burdens. Therefore, it is no surprise that those involved in the LDT industry are worried that increased regulation could take the wind out of the growing field's sails, and in turn, dry up investor interest.

Amit Kumar, PhD, President and Chief Executive Officer of CombiMatrix, a molecular diagnostics company that produces the LDT HerScan™ and other cancer and congenital abnormality tests said, “Additional regulation will make it difficult for investors to continue putting capital into this industry, and that will stifle innovation and progress, especially in this market environment where it’s very difficult for companies to secure capital. This should be balanced with the benefits of innovation for patients and shareholders.”

Echoing Kumar, Jeffrey N. Gibbs, JD, a lawyer with Hyman, Phelps & McNamara (Washington, D.C.), who works with many diagnostic companies, said, “If [the FDA] adds a regulatory hoop that’s inappropriate, unduly burdensome, inflexible, and ill designed, [I think it will have an adverse effect on investments].” He also thought [cont. on pg 16 >>](#)



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that the current traditional FDA medical device regulatory system with its 510(k)s, premarket approval applications, quality system regulation, medical device reports, and labeling “just does not fit the lab model.”

According to Gibbs, the recommendations laid out in Genentech’s petition don’t seem to be entirely actionable from the FDA’s stated viewpoint which makes “it pretty clear that through a citizen petition you can ask for matters of general policy, but you can’t ask for enforcement proceedings.” Gibbs believes that it would be wholly inappropriate for the FDA to respond to Genentech by saying they will take enforcement activity against Lab X because of their offering an LDT. “It’s also inappropriate to take enforcement action, and then have rulemaking. It’s really reversing the correct sequence,” he said.

### Diagnostics Industry’s Proposal

In a detailed response to Genentech’s petition, the Coalition recently laid out its own proposal for increased oversight. Its main feature was the creation of an online registry in which thorough information regarding various LDTs is provided, so that physicians, patients, and payers alike could judge for themselves whether a company’s data backs up marketing claims.

“You would not have the negative impact of notice-and-comment rulemaking or trying to shoehorn LDTs into the device regulatory regime under the FDA laws, but it would give people data, knowledge, and visibility, and allow for much better decision making,” said Gibbs.

This is closer in line to the system currently in use for off-label drugs, which the Coalition sees as a comparable facet of literature-based treatment. Gibbs said he has a hard time seeing the difference in principle between using literature to support treating a new kind of cancer for an approved oncology agent versus using literature of comparable size and quality to decide that a test is predictive of response, nonresponse, or adverse events for an LDT.

Genentech, however, does see a difference. “If a medicine is being used off-label, that means it has already (at least once) been reviewed and approved by the FDA and that the maker is required to report safety events after it hits the market,” said Lang. According to Lang, Genentech’s approach has always been that even though something is being used off-label, “we still like to generate the data to take to the FDA to get their review and garner approval.” He asserted that the company understands evidence-based medicine, “but at the same time if you’re making a test and you’re going to claim to predict who is going to respond, and there’s a risk of potentially crossing someone out who may have responded because of a test error, we’d like to see that reviewed.”

Some LDT companies say they’re not paying much attention to Genentech’s petition, and are instead quietly waiting for the FDA to finalize and release its “In Vitro Diagnostic Multivariate Index Assay” (IVDMIA) regulations, which will set new standards for the industry. No date has been set for its release, and Gibbs reports that

some companies are waiting to see if it will ever be finalized. If and when it is released, however, the guidelines will bring some much needed certainty, according to Ronen Tamir, Chief Commercialization Officer of Rosetta Genomics, which has several LDTs that utilize patients’ microRNA data. “Once they’re published, they’ll lift the unknown factor that’s sort of hovering above the industry regarding what the FDA will do,” he said.

### Partners or Adversaries?

Although none of those interviewed for this article cited it as a possible reason, there has been speculation in the press that Genentech’s other motive behind the petition was to reduce the number of tests that, in turn, could limit the number of patients receiving its targeted therapies.

“A company claiming that we’re focused on patient numbers and the size of markets is someone who doesn’t really know who Genentech is,” said Lang. “This is a company that focuses more on how great of a need there is for the patient, rather than looking at the size of the population who will be taking the drug.”

Genentech’s petition made a point of only singling out diagnostic companies (e.g., Rosetta Genomics and CombiMatrix) that produce tests possibly used in selecting patients for the company’s drugs. This has perhaps left Genentech open to criticism that they’re protecting their bottom line. For example, a recent editorial in *Nature Biotechnology* (2009;27:209) noted that the com-



pany had signed deals with certain diagnostic companies (i.e., Dako) to produce sanctioned tests. “Among the tests that Genentech would like to see examined closely by the FDA are home brews used for assessing patient suitability for Herceptin treatment, uses that erode Genentech’s royalties from sales of ‘official’ companion diagnostic kits,” the editorial stated. Lang responded by saying that such royalties are only a small fraction of the company’s earnings.

Whatever its outcome, Genentech’s petition has placed a spotlight on the sometimes adversarial relationship between pharmaceutical and diagnostic companies. Gibbs thinks that’s because big pharma and diagnostic companies often don’t understand each other; that they speak a different language. “I think for big pharma there’s a concern that personalized medicine is going to reduce sales of drugs,” he said. “But more companies,” he added, “also realize the value of diagnostics, and Genentech is actually a leader here. If you can improve safety and efficacy through diagnostic tests then you have a better chance of FDA approval, reimbursement, and outcomes.” He expects pharma companies to embrace diagnostic tests over time.

An early case study in how this might work was seen after biomarker data revealed that the 40 percent of colon cancer patients with K-ras mutations were unlikely to benefit from treatment with Erbitux® [cetuximab; Bristol-Myers Squibb] or Vectibix® [panitumumab; Amgen]. The finding had an immediate economic impact

on Erbitux sales, which likely as direct result fell 2 percent in Q4 ’08. But rather than downplay the data, both companies are actively petitioning the FDA to exclude patients with K-ras mutations from receiving their treatments.

Responding to the companies’ request, the FDA may have even given a glimpse of the level of LDT regulation they’ll be supporting in their upcoming guidelines, when they wrote the following in an official briefing document from December of last year: “The informed use of in vitro diagnostic devices (IVDs) is at the heart of increasingly personalized medicine. When the indications for use of an FDA-approved or licensed therapeutic agent are tied to results from an IVD, FDA clearance or approval of the IVD is also needed. A prominent example is the link between results from HER2 testing and the indications for use of the drug Herceptin for the treatment of breast cancer. FDA’s regulation of the marketed IVD (a ‘companion diagnostic’) aims to ensure that the claims and performance characteristics of the test support the informed use of the therapeutic agent throughout the commercial life cycles of both products.”

Regardless of what this portends for the FDA’s final verdict, the theory that the pharma industry will eventually move to embrace personalized medicine is one shared by LDT manufacturers such as Kumar, who said, “Big companies are slow to change and have to hit their targets. It’s not easy for them to innovate, but I think they’ll be dragged into it.” Kumar also

thinks that simple economics will have the greatest impact—not only in driving the big companies in the direction of personalized medicine, but also because economically, the current costs are way too high. “Business models will adjust to benefit from the personalized medicine paradigm in such a way that it will be very important for them to head in that direction from the standpoint of future profits,” he said.

Tamir from Rosetta iterated that almost every major pharmaceutical company has established a diagnostic division, “and usually this division is not intended to bring diagnostic products to the market, but rather to find the right companion diagnostic for drug development.” He feels that most of the time, companies are looking to diagnostic companies to help identify the correct segment of the patient population to enter in clinical trials.

Added Rosetta’s Chief Scientific Officer, Dalia Cohen, PhD, “Dr. Steven Gutman, the head of the Office of In Vitro Diagnostic Device Evaluation and Safety who just retired, gave several talks saying that diagnostics will lead drug development in the future, and not vice versa. Basically, that means finding the diagnostic to identify the patient that has a high unmet medical need and then developing the treatment component.”

Perhaps then in the future, it’s the companies making these diagnostic tests that will be filing the Citizen Petitions, rather than defending themselves against them. **JW**