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A balancing act

Contrary to Genentech's claims, turning over all *in vitro* diagnostics to the US Food and Drug Administration (FDA) is the wrong approach to achieve better clinical validation of tests.

It's not often that a drug maker approaches the FDA requesting more stringent oversight. So when Genentech filed a citizen's petition late last year asking the US regulator to expand its jurisdiction to encompass all *in vitro* diagnostic tests, the diagnostics industry took notice. In recent weeks, the company has argued that across-the-board FDA oversight of diagnostics used to guide therapeutic decisions is needed because many so-called home-brew tests currently marketed under the Centers for Medicare and Medicaid Services' Clinical Laboratory Improvement Amendments (CLIA) lack both "analytical and clinical validity." What's more, Genentech wants The FDA to immediately pull many of these tests from the market until adequate "scientific evidence of their validity" can be provided.

Several motivations lie behind Genentech's move. The first, mentioned frequently in the petition, is "the potential risks to patient safety" associated with the current regulatory situation. In basing its position on patient safety, the company is unsubtly poking an FDA hot button. However, as the American Clinical Laboratory Association (ACLA)—an umbrella group representing many home-brew providers—argued last month in its response to Genentech, no substantive evidence of harm resulting from the use of any of the thousands of home-brew tests approved under CLIA has yet come to light.

A second motivation—and one only obliquely mentioned in the petition—is the potential threat to Genentech's business. The company's strongest objection is to the proliferation of what it sees as diagnostic tests that make unsubstantiated claims intended to guide specific drug or biologic therapeutic decision making. 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 company also cites a range of home brews that physicians can use to exclude certain patient groups from using Genentech drugs, such as Rituxan, Avastin and Tarceva. These tests clearly have an impact on the company's revenue from drug sales and bottom line, although this is not mentioned in the petition.

The fact that more stringent regulations are aligned with Genentech's business interests does not invalidate its concerns for patient safety or its desire to ensure that diagnostic methods conform to an appropriate standard of scientific validity and clinical utility. The company's petition argues that, as more diagnostics are designed for high-volume, complex diseases, clinical utility is more difficult to ascertain and validate. In this respect, it has a point. At present, and probably for many years to come, the association of human molecular variation with disease and drug response will be exploratory and rudimentary. Far from being able to say what genetic variation means, researchers are still merely cataloging somatic and germline variation in the genome. In parallel, next-generation sequencing and whole genome association studies are broadening the seam of information from which diagnosticians can draw. So, yes, clinical utility is, and will be, difficult to pin down. But Genentech's call for FDA intervention is almost certainly not an appropriate response, and for several reasons.

First, the FDA currently has insufficient staffing and financial resources to carry out its existing responsibilities. Without a significant investment in staff and training, it certainly could not review the thousand or so diverse home-brew approaches currently on the market, let alone the burgeoning number of new tests stemming from ramped-up sequencing projects. One need only look at the rapid evolution of knowledge relating to *KRAS* mutations in predicting patient responses to epidermal growth factor receptor inhibitors to appreciate how fast the diagnostic field is moving.

Second, the FDA's approach is too stultifying to be appropriate for regulating a field that is so unstandardized and in which the technology and knowledge is evolving so rapidly. The FDA does regulate diagnostics kits through its 510K or premarketing approval pathways. But there are significant costs tied to that regulation, the two most important of which are the delay in reaching the market and the chilling impact on innovation in a sector that already has low margins and poor investment.

Third, the FDA would be regulating in direct opposition to market forces. One of the principal drivers for home-brew diagnostics is their ability to deliver cost savings to the US healthcare system. If a diagnostic system can help avoid expensive-to-treat adverse drug effects or can help avoid wasteful use of noneffective drugs, then there will be a strong incentive for payors to seek out those tests. Indeed, the size of the incentive for the payors to undertake the test is exactly the same as that for Genentech to get the tests removed from the market. Genentech might need to look as closely at its revenue model as payors are looking at theirs.

The final reason that FDA regulation is a bad idea, at least for now, relates to raising the level of awareness about the significance of molecular genetic data. Genentech has argued in its petition, and rightly so, that the clinical claims made by some of the home-brew manufacturers have not been independently verified. However, it also seems to believe that independent verification by the FDA is the only way of informing the patient, physician and payor communities. In reality, channeling all tests through the FDA would serve only to make physicians and payors look for a tick in the 'FDA-approved' box. It would divert them from acknowledging the uncertainties attached to these tests and from regarding the underlying techniques or conclusions in the right context.

If there is a key message from Genentech's intervention, it is that skepticism and a spirit of enquiry with respect to these tests should be maintained by the research community, physicians and payors: leaving verification to the FDA would stop that intellectual pursuit dead. And it may even set the field of personalized medicine back by years.