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## Genetic Testing

# FDA Verdict Could Determine Future Of Personalized Medicine

Robert Langreth, 12.15.08, 3:30 PM ET

The future of personalized cancer drugs could be determined in a crucial debate Tuesday at the Food and Drug Administration.

An FDA advisory panel is set to debate what standards need to be applied before gene tests are recommended with cancer drugs to select which subset of patients are likely to benefit. At issue is what should be done when a drug is first approved for everyone, and only later researchers figure out that it only works in patients with certain gene variants.

This is exactly what has happened with Erbitux from Bristol-Myers Squibb and Eli Lilly as well as **Amgen's** Vectibix. They are currently approved broadly for advanced colon cancer patients who have failed other treatments. But only this year did gene researchers figure out drugs are utterly ineffective in about 40% of colon patients with a certain gene mutation called *kras*.

Amgen is pushing for a label change that would require a genetic test before the drugs are used in colon patients, and Eli Lilly's Imclone Systems also wants the drug label to be updated with gene test information. Strangely, it is the FDA that apparently has held back so far. "I don't believe that any patient with mutant *kras* should be receiving Vectibix," Amgen R&D head Roger Perlmutter told Forbes recently. But "it has not been easy to convince the FDA."

Analyst Les Funtleyder of Miller Tabak & Co. predicted in a note today that there is a "good chance" that the panel will vote to require a genetic test with the drugs. "We see an almost inevitability to the continued growth of personalized [medicine] as more biomarkers/genetic tests are created to determine a priori chances for therapeutic successes," he wrote.

In an ideal world, gene alterations predictive of drug response would be identified in advance and then used to select patients during clinical trials leading to approval.

That is what happened with Herceptin for breast cancer from Genentech. But more often, researchers are first testing their cancer drugs on everyone with a given tumor and only later figuring out what patient subsets the drugs are effective in. This creates the potential for all sorts of murky after-the-fact analyses that can sometimes yield red herrings.

The Food and Drug Administration generally frowns on such "retrospective" studies. That's because if you do enough data analyses on a drug, even one that doesn't work at all, you can eventually find a group in which the drug appears to be effective--entirely by chance. Meanwhile, scientists are continuously coming up with possible biomarker tests that may predict whether a given drug is likely to be effective, or is likely to just cause side effects. But most of these tests haven't been confirmed in large trials.

The Erbitux-*kras* finding appears to be rock solid, despite its retrospective nature. Top cancer centers are already using the gene test to select patients. But future gene tests to match cancer drugs to patients likely to benefit could get very complicated very fast. There are hundreds of targeted cancer drugs in testing, and dozens upon dozens of possible gene mutations could have an impact on whether a drug works. Few gene-testing studies yield the sort of clear-cut results seen in the case of *kras*, Erbitux and Vectibix.

Numerous new studies are coming out all the time. When should they be included in a drug label? Just this week, Italian researchers pinpointed another gene mutation present in about 10% of colon cancer patients that appears to render Erbitux and Vectibix ineffective. They did gene testing on tumors from 113 colon patients who had previously taken either Erbitux or Vectibix. None of 11 patients with the so-called BRAF V600E mutation responded to the drugs; conversely, none of the patients who responded to the drugs had the BRAF mutation, according to results in the *Journal of Clinical Oncology*.

How many genes should oncologists test patient tumors for before using a drug? And how conclusive does gene test data have to be before allowing it to go on a drug's label? If the FDA is too permissive, it could end up allowing useless cancer drugs to be approved. But if the FDA takes too hard a line on allowing in diagnostic test information, it could hamper the development of cancer drugs for years to come. Merck, Pfizer, GlaxoSmithkline and numerous other companies could be affected by the agency's decision.