FDA To Regulate Direct-to-Consumer Genetic Tests

By Vicki Brower

On July 22, the U.S. Food and Drug Administration told Congress that the agency was planning to regulate genetic tests sold directly to consumers. Jeff Shuren, M.D., J.D., director of the FDA’s center for devices and radiological health, testified at a House subcommittee hearing that problems with direct-to-consumer (DTC) genetic tests included faulty data analysis, exaggerated clinical claims, fraudulent data, lack of traceability, poor clinical study design, and poor clinical performance.

On the same day, the Government Accountability Office issued a highly critical report of the tests, citing, among other problems, misleading test results, deceptive marketing, and other questionable practices.

Controversy has long simmered about whether, or how, to regulate genetic tests, in particular DTC tests (see sidebar). But the events on July 22 brought the issue to a head. In the months that followed, articles in Nature, the New England Journal of Medicine, The Economist, and other publications debated DTC genetic testing. Critics pointed to all the issues raised in the hearing and report, and more broadly, the government’s responsibility to protect consumers; supporters stressed an individual’s right to unfettered access to genetic information. And with FDA regulation of some sort a virtual certainty, both sides began to focus on what aspects of the industry should be regulated and just how far the regulations should go.

Rapid Increase
It took nearly two decades for the debate, and the FDA, to reach this point. Back in 1990, when the Human Genome Project began, genetic tests were available for about 100 diseases—most of them caused by just one faulty gene, such as the mutations that cause Tay-Sachs and cystic fibrosis. As genomic technologies matured and sequencing became less costly, companies began developing tests for a wider range of complex, multigenic, common diseases. These were initially offered by laboratories used by physicians, but more recently dozens of companies have begun marketing such tests on a DTC basis.

The first advertising campaign for a genetic test, Myriad Genetics’ BRACAnalysis, took place in the early 2000s. It included television ads for the test, which detects mutations in the BRCA1 and BRCA2 genes that raise the risk of breast and ovarian cancers. Myriad also advertised in the playbook of the Broadway play, Wit, which was about a professor dying of ovarian cancer. Audrey Chapman, Ph.D., professor of medical ethics and humanities at the University of Connecticut School of Medicine in Farmington, analyzed that campaign and concluded that it essentially marketed the BRCA1 and BRCA2 test to the general public, even though it is not an appropriate test for most of the population (American Journal of Bioethics, June 2008). She said that many women who requested the test received results without any counseling or were given incorrect results by physicians without genetic expertise.

By 2007, the number of genetic tests had increased to well over 1,000; hundreds of these were DTC tests for medical and health-related conditions (see Statbite). In cancer, some tests are for high-penetration genes, such as BRCA1 and 2 (which are not sold DTC but through physicians). Testing for such high-risk genes has clinical utility; for instance, women with the BRCA mutations may use the information to decide on frequent screening or other preventive measures.

But more recently, tests for low-penetration, single-nucleotide polymorphisms (SNPs) have proliferated despite the low degree of risk associated with SNPs and the test results’ lack of clinical utility. A position paper that the American Society of Clinical Oncology issued in February called attention to problems with testing for these low-penetration variants and recommended that oncologists support testing for them only if clinical utility has been established and the results can be adequately interpreted.

The tipping point seems to have come last May, when Pathway Genomics announced that it would begin selling its home-use genetic test, intended to detect risks of breast cancer, among other diseases, at thousands of Walgreen stores nationwide. That’s when the FDA notified the company that it could not market the test, which the agency considered a medical device, without regulatory review and clearance. Over the next 2 months, the agency contacted 19 other companies, including 23andMe, Navigenics, deCode Genetics, and Illumina, and asked for data to back up claims that their DTC tests could detect risks for cancer and other diseases.

“We are now creating protections that are clearly missing,” said Alberto Gutierrez, Ph.D., director of the FDA’s office of in vivo diagnostic device evaluation and safety. Although the agency has had the authority to regulate
laboratory-developed tests, it has not done so because earlier tests were low-risk, well-characterized tools, he said.

But now regulation is on the way. Just before the hearing on Capitol Hill, the FDA held a 2-day meeting for stakeholders, followed by a 60-day period for public comment to gather opinions on developing the best regulatory framework.

Dueling Opinions
Many of the opinions focus on what happens after the test is performed. In one of the Nature editorials, Arthur Beaudet, M.D., chair of the department of molecular and human genetics at Baylor College of Medicine in Houston, argues that the interpretation of tests should be left to board-certified specialists. “My focus is that the FDA should not try to regulate assessment of clinical sensitivity, clinical specificity, and clinical utility to any specific extent in their process,” he said. He proposes that genetic testing be regulated in two parts, similar to imaging, where the FDA regulates the machines that do the imaging but board-certified radiologists interpret the results. Board-certified molecular geneticists, molecular pathologists, and “in the future, perhaps, board-certified genomics” should interpret genetic test results, he said.

Ellen Matloff, director of genetic counseling at the Yale Cancer Center in New Haven, Conn., agrees that interpreting test results takes a specialist. In a recent study, she showed that even genetic tests ordered and interpreted by physicians often result in incorrect diagnoses, recommendations, and unnecessary procedures. Matloff argues that only certified cancer geneticists should advise patients (Connecticut Medicine, August 2010). “All genetic tests, whether sold over the Internet or ordered by a doctor, should receive the same FDA oversight as pharmaceuticals, with risks and benefits clearly stated outright, the way that commercials for Viagra do,” she said.

Building Up to Regulation
Concerns about genetic tests, especially those marketed directly to consumers, grew through the past decade and crescendoed this year.

- 2001 Secretary’s Advisory Committee on Genetics, Health, and Society (SACGHS) recommends that the U.S. Food and Drug Administration (FDA) review all new genetic tests
- 2006 U.S. Government Accountability Office (GAO) issues report on direct-to-consumer (DTC) nutrigenetic tests, advertised as a source of gene-based guidance on diet
- 2007 FDA begins meeting with DTC genomics companies
- 2008 SACGHS identifies multiple regulatory gaps in oversight of genetic testing
- 2009 U.S. Federal Trade Commission investigates claims of two nutrigenetics companies, leading to discontinuation of sale of testing kits
- 2010 American Society of Clinical Oncology issues statement on DTC genetic tests
- SACGHS urges the U.S. Health and Human Services Secretary to consider additional oversight
- FDA stops sale of Pathway Genomics’ home-use tests at the Walgreens pharmacy chain
- FDA writes to 19 more companies selling DTC tests, asking for the data behind their marketing claims
- FDA holds public meeting to begin dialogue with stakeholders concerning regulation of tests
- GAO report cites “misleading test results” and “deceptive marketing practices”
- House Subcommittee on Oversight and Investigations holds public hearings on DTC tests

In a second editorial in Nature, Gail Javitt, J.D., research scholar at Johns Hopkins’ Berman Institute of Bioethics, argues that focusing on how the genetic tests are marketed is a mistake. Nor should the FDA create a separate regulatory scheme solely for DTC tests, said Javitt, who also serves as counsel at the law firm Sidley Austin in Washington, D.C. Her position is that regulatory agencies need to create a broad framework to ensure the quality of all health-related tests.

“Just because a test is sold DTC doesn’t mean it’s a bad test, although the fact that it is being sold DTC is certainly a factor that should be considered in addressing its risk,” she said. “A DTC test may test for a high-risk condition, such as BRCA1/2 status, or a low-risk condition, such as type of earwax, and should be regulated according to risk, not solely on how it is marketed. We need to think more broadly about where greater scrutiny is needed for higher-risk tests, not just about how they are sold.”

But cancer geneticist Kenneth Offit, M.D., at Memorial Sloan-Kettering Cancer Center in New York, does see particular danger in DTC marketing of genetic tests because of the uncertain quality of the tests and the absence of counseling. While often sold, until recently, as entertainment or for educational purposes to elude regulation, he said, “these genetic tests are, in fact, medical tests, and as such should be put in a medical context, which would require government regulation and genetic counseling for patients.”

Offit also strongly criticized the quality of the tests. “DTC tests and many other [laboratory tests] are based on genomewide association research studies [identifying SNPs] and offer incomplete, ambiguous, or clinically meaningless information,” he said. “Many of these tests are for very common, low-penetrance genetic variations, which are associated with low or very modest increase in risks.”
The FDA is now considering requiring counseling for DTC tests for high-risk mutations, “which have the potential to cause distress,” Gutierrez said. Such distress, well known to clinical geneticists, results from ambiguous test results.

“We see the same negative effects in women tested for the BRCA genes who were given ambiguous results as those seen in patients in the early 1990s who received ambiguous test results for Huntington disease,” Offit said. “Women with such results, such as missense mutations or ‘variants of unknown significance,’ often experienced more upset than those testing either positive or negative for a known mutation.”

**Access to Genetic Information**

Not surprisingly, companies like Pathway Genomics support patients’ unfettered access to genetic information. Even those who want regulation acknowledge that access to health information is not an issue to be dismissed lightly. The law favors allowing consumers access to information relevant to their health, and the trend is toward not suppressing their access to such information, said Javitt, the lawyer from Johns Hopkins. A complete ban of the tests would be difficult for the FDA to justify, she wrote.

The industry argues that the tests offer educational value for patients even when the results may not be clinically useful. “We do not believe that every report need have a direct clinical action associated with it—there can be a substantial personal...”
benefit, too,” said Brian Naughton, Ph.D., founding scientist of 23andMe. “Educating someone that they have average risk for a disease may also be important and useful information . . . education is a critical first step toward our goal of meaningful integration of genetic information into clinical care.”

James Evans, M.D., Ph.D., associate professor of genetics at the University of North Carolina School of Medicine in Chapel Hill, countered this view in his August editorial in the New England Journal of Medicine. “While direct consumer involvement in the genetic revolution is to be welcomed, consumers must be protected from unrealistic claims and misinterpretations of complex, dynamic genomic information,” he wrote.

Some think that this protection can come in the form of education about the tests. “The need to protect patients doesn’t mean restricting information, but rather ensuring that they receive balanced information about DTC tests, both risks and benefits,” said Matloff.

With the FDA now requiring DTC companies to supply data to support their claims, or risk having their tests taken off the market, the agency appears to be moving toward greater review, if not restriction, of the DTC tests.

And the industry, for its part, seems to accept that times are changing. Daryl Pritchard, Ph.D., director of research programs advocacy at the Biotechnology Industry Organization, said that it welcomes establishing uniform regulations for genetic tests, with mandatory registration for certain tests for moderate- to high-risk genetic mutations. (A public, voluntary registry for genetic tests was established in March at the National Institutes of Health; it is expected to be online next year.)

Although it is not yet clear what the final regulations will look like, Gutierrez said that the agency plans to convene a permanent panel of experts to review companies’ claims as the tests are produced.