GENEWATCH

DIRECT-TO-CONSUMER GENETIC TESTING: WHAT'S THE PROGNOSIS?

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Genetics has been making news lately, in large part because of the growing pains of a new and controversial industry: direct-to-consumer (DTC) genetic testing. DTC genetic testing raises questions involving privacy, how medical tests should be ordered and understood, who should regulate access to genomic information, and how individual consumers will understand and act upon such information.

DTC genetic testing has been around on a small scale for some years, but began in a new form in November 2007 when three companies (23andMe, Navigenics and DeCodeMe) launched their genome-wide scan services within days of each other. Suddenly, individuals could send in a sample of their DNA and receive ancestry information or a wide variety of medical risk information based on the latest discoveries in genetics. In October 2008, TIME magazine recognized the 23andMe personal genome service as "Invention of the Year." Celebrities turned over samples of their DNA at trendy and well publicized "spit parties."

Non-medical services, like ancestry testing, provoked few criticisms. The same was not true of medical risk reporting, which was immediately criticized on two counts. Firstly, the companies were reporting in most cases on DNA variants of common diseases, discovered through statistical comparisons in genome-wide association studies. While these associations were well-established for large populations, they typically accounted for only a tiny fraction of total disease risk. Genetic testing of this kind was hard to justify for an individual, since it provided no clearly useful information to either the patient or the health care provider.

Secondly, it seemed possible that other risks, like family history and lifestyle-currently much better predictors of common disease-might be de-emphasized to the detriment of the DTC genetic testing consumers. Thus, a customer who was obese and had a strong family history of type 2 diabetes might well receive a low genetic risk score for the disease. To be fair, the leading companies have taken care to be accurate on their websites as to the modest effects of genetic risk information, and the importance of other risks.

By 2009, the DTC controversy revolved around conflicting visions of the future of personalized health care. To its supporters, DTC genetic testing offered private, scientifically supported and personalized information about the state of one's health-away from the intrusive gaze of insurance companies, freed from the paternalistic intermediation of harried and often uninformed clinicians seeking to preserve their economic advantage in an already dysfunctional health care system.

To its detractors, DTC genetic testing was exploiting widespread misunderstanding of genetic

determinism to market common DNA risk variants that were poorly understood by the scientific community, and provided little useful information to consumers. DTC genetic testing was simply the latest in an unending series of health-related pseudo-interventions, ranging from colonics to nutraceuticals, for the privileged who could afford the extra cost. And the major challenge was to keep conventional medical practitioners from taking it seriously, lest the cost of medical testing be driven up in response to dubious genetic "risks."

Fast forward to 2010 and the controversies have evolved, but by no means disappeared. For one thing, DTC companies have expanded their offerings to include the identification of variants associated with rarer, more highly penetrant diseases, as well as carrier states. Examples include BRCA1, cystic fibrosis, PKU and Tay-Sachs. These disorders are more "fully penetrant" because if an individual carries mutations, he or she will either have the disease or be at high risk to develop the disease. Thus, the nature of the information being offered in the DTC genetic testing space is changing. Such changes have the potential to make the test results medically relevant for a small number of people. But this may also increase the potential for public misunderstanding, since companies will now be offering clinically meaningful rare DNA variant information alongside clinically less relevant, common DNA variant information.

Another disruptive development this year concerns the Food and Drug Administration's (FDA) regulatory actions. In May 2010, DTC genetic testing almost went retail when the Walgreens drugstore chain announced it would stock $30 DNA collection kits for the DTC company, Pathway Genomics. The attempt to go to market was blocked at the last moment, and the controversy triggered new scrutiny and new revelations.

This summer the FDA decided to investigate the use of what it calls laboratory developed tests (LDTs), which had previously been unregulated.1 The agency's main concern was focused upon genetic tests intended for use without medical supervision. FDA scrutiny has grown for several reasons, among them greater complexity of genetic testing, the role of labs located far from the primary care setting, the involvement of profit-making firms and the focus on poorly understood genetic risks for common diseases. The FDA notes that patient risks include "missed diagnosis, wrong diagnosis, and failure to receive appropriate treatment."

The agency later announced it was holding public meetings to gather stakeholder views on LDTs. As shown through the diverse testimony presented at its July public meetings,2 clinicians, researchers, advocates and business executives are far from united on the issue of whether or how to regulate genetic tests. During the July hearings, the General Accounting Office (GAO) made a surprise announcement that it had surreptitiously taped telephone conversations between investigators and representatives of the DTC testing companies. The GAO played the tapes on the record, and exposed a number of inaccurate statements made by company representatives.

It is worth noting that the proposed oversight of marketplace behavior will not necessarily ensure that the services in question will improve in accuracy or prognostic value. These goals are not often achieved through regulation, and physicians are not necessarily the best gatekeepers to determine the pros and cons of ordering genetic tests. Moreover, although commercialization has brought these regulatory concerns to the forefront, the development of innovations in genetics is

clearly benefiting from the energy and imagination of the biotechnology and DTC testing industries. It may be that the interplay of commercialization and scientific innovation that is represented in the DTC genetic testing industry will prove to have long term value to society. The FDA is thus keeping a close eye on how innovation will be affected by its actions.

The Human Genome Project, completed in 2003, is rightly regarded as one of the great scientific achievements of our generation, well worth its $2.8 billion cost. But what scientists have achieved in the intervening years is every bit as significant: new technologies that have reduced the cost of DNA sequencing to one one-hundred-thousandth of what it was originally. It is considered inevitable that within the next 5 years, whole genome sequencing will be available to any individual for under $1,000! As it turns out, the big challenge for the future will not be the sequencing technologies, but the cost and difficulty of interpreting the huge amounts of data they generate.

Therein lies the dilemma for scientists and regulators. On one hand, the DTC testing companies may continue to be innovators in the interpretation of personal genetic data. On the other hand, the companies concerned will have to make a concerted effort to develop and refine precautionary measures covering a wide range of medical and ethical issues. Many unsettling results can turn up as part of an otherwise routine screening. A child might, for example, be found to have a variant associated with one disorder, say autism spectrum disorder-and the very same variant might later be determined to cause a separate neurodegenerative disorder. How will this development be reported and explained to the consumer? What procedures if any should be in place for tracking individual customers long after they've ceased doing business with the testing company? Examples abound of the challenges created by incidental and unexpected findings, and there may be no ready answers. While informed consent is the universal goal, making it work universally is not a simple matter.

Some experts suggest the crucial problem with DTC testing is lack of supervision by qualified medical personnel. Medical supervision may often be desirable, even essential. But there is another perspective here. Even the experts, including medical geneticists, continue to struggle with incomplete and incompatible genetic databases, poor risk models and disagreements over interpretation. Moreover, many primary care physicians are not well versed in genetics and may not know what kinds of tests their patients need. In other words, it is unrealistic to expect that medical supervision in and of itself will turn DTC tests—or any genetic tests—into accurate and reliable tools.

In summary, difficult questions face medical professionals and members of the public in their attempts to evaluate genetic tests. What does a set of genetic results actually reveal? How will they help promote medical care? And what difference will testing make to the individual's quality of life? These are not theoretical questions. Right now many in the testing business are raising the public's expectations by making suggestive statements like this one from a company Web site: "Let your DNA help you plan for the important things in life."[3]

Given its mandate, the FDA will have to devote its attention to high-profile issues, especially patient safety, while encouraging innovation as best it can. Even then, the regulator can only do

so much to manage public expectations, and rising consumer demand for inexpensive tests is certain to be a strong market mover as this debate unfolds. Over-regulation of a service that consumers want could simply drive such services off-shore where they could operate over the internet with impunity. In any case, no amount of market regulation can take the place of well designed and well-funded research that will help geneticists and other scientists understand the complexities of the human genome in the service of better medical care.

Do customers of DTC genetic testing services really understand what they are purchasing? Do they understand the results? Do they consult their physicians about the information? Are unnecessary medical tests ordered or are valuable health lessons learned from the overall experience? At the present time, we simply do not have all the answers. The National Human Genome Research Institute (NHGRI) has recently funded a proposal to implement the first "before and after" survey of DTC genetic testing in order to better understand these questions.

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ENDNOTES

1.http://www.nytimes.com/2010/06/12/health/12genome.html?scp=1&sq=fda%20genetic%20test&st=cse

2.http://www.fda.gov/MedicalDevices/NewsEvents/WorkshopsConferences/ucm212830.htm

3. https://www.23andme.com/health/