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Are Genetic Tests Adequately Regulated?

Neil A. Holtzman

The Human Genome Project has engendered genohype, from early pronouncements that our destiny is in our genes to recent declarations that new discoveries will minimize or prevent the appearance of disease phenotypes altogether. With claims like these, it is no wonder that companies have sprung up to identify the presence of susceptibility-conferring genotypes (SCGs). As early as 1995, over 50 biotechnology companies were developing or providing tests to diagnose genetic disorders or predict the risk of their future occurrence. Common complex disorders, usually of adult onset, such as Alzheimer's disease and breast and colon cancer, make up the single largest category for which tests are under commercial development.

The "educational" materials prepared by companies for physicians and patients considering genetic tests can be another form of genohype. Their claims for predictive tests for common complex disorders have frequently exaggerated clinical validity (the probability of a detectable SCG occurring in those who would get the disease and that those with a detectable SCG would get the disease) and utility (how a positive predictive test result could help people cope with future disease).

"The Human Genome Project has engendered genohype..."

For example, no systematic effort was made to ascertain the proportion of women with breast cancer who had known SCGs before tests were marketed for them. Educational brochures gave varying estimates of risk, some based on data gathered from high-risk families rather than providing more appropriate, population-based probabilities. Unless they are informed about the small proportion of diseases for which SCGs account, asymptomatic people who are tested and found to have a negative test result might falsely believe that they are no longer vulnerable. A test for the apolipoprotein E-e4 allele (apoE4) was marketed to predict the risk of Alzheimer's disease (AD), for which this allele represents only a 20 to 29% risk, despite the absence of any means of preventing or ameliorating the disease. The company withdrew it as a predictive test after professional and consumer groups objected but introduced it a few years later as a diagnostic test in people with symptoms of AD.

This situation has arisen because of the double standard the U.S. Food and Drug Administration (FDA) uses to regulate in vitro clinical diagnostic devices. If a genetic test is to be marketed as a kit, the manufacturer must first demonstrate its clinical validity to FDA's satisfaction. FDA's scrutiny of the labeling of a test kit, which can include information for patients about potential benefits, can also ensure that the test's utility is not exaggerated. If, on the other hand, a test is marketed as a clinical laboratory service, the laboratory providing the service does not even have to notify FDA. FDA admits that it has the authority to regulate clinical laboratory tests marketed as services but says that it does not have the necessary resources to do so.

Most companies that have developed genetic tests to predict or diagnose common complex disorders market tests as services. The quality of laboratories providing genetic tests as services is regulated under the Clinical Laboratory Improvement Amendments (CLIA) of 1988. CLIA requires that a laboratory demonstrate that it can accurately and reliably measure the analytes that its tests are designed to assay, but CLIA does not require a lab to provide evidence of any test's clinical validity or utility.

When women at risk of breast cancer learned about the predictive uncertainties of testing from sources independent of the companies offering them, they were much less eager to have tests. Thus, all stakeholders, including test developers, will be better served if data on tests' clinical validity and utility begin to be collected before they are marketed. This was the unanimous recommendation of the Task Force on Genetic Testing, which included representatives of commercial test developers. This recommendation could easily be implemented if FDA regulated genetic tests marketed as services as stringently as it regulates tests marketed as kits.

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