



Risks and Benefits of Direct-to-Consumer Genetic Testing Remain Unclear

Bridget M. Kuehn

FOR AS LITTLE AS ABOUT \$400, A consumer can hire 1 of several companies to scan his or her entire genome for about a million genetic variations in hopes of identifying the presence of variants associated with an elevated risk of developing a disease. But lingering uncertainties about the validity and clinical implications of such results raise the question of whether marketing these tests to consumers is premature.

The unprecedented speed with which high-throughput techniques for extracting genetic information are being translated into commercial products—bypassing traditional professional and regulatory gatekeepers—has left scientists and clinicians playing catch-up. But professional organizations and regulators are beginning to weigh in on how these products should be used, and scientists are launching efforts to systematically answer the questions raised by these tests.

SMALL RISKS

One of the biggest unanswered questions is whether scanning an individual's genome has any clinical value. The companies offering the procedure market it as a tool individuals can use to assess their future health risks and take any indicated preventive measures.

But some scientists say it is not clear whether consumers will derive any such health benefit from the testing. The tests do not identify genetic variants that are diagnostic, but rather use microarray technology to screen for surrogate genetic markers, called single-nucleotide polymorphisms (SNPs), that have

been associated with an increased risk of developing a disease.

Kenneth Offit, MD, MPH, chief of the clinical genetics service at the Memorial Sloan-Kettering Cancer Center in

is so small, there is no clear course of action for physicians or patients to take.

UNANSWERED QUESTIONS

There are also many basic scientific questions that remain to be answered about the genetic markers the tests identify and their connection with the development of disease. Lawrence C. Brody, PhD, head of the molecular pathogenesis section at the National Human Genome Research Institute in Bethesda, Md, explained that the companies are using data from case-control genome-wide association studies. Such studies attempt to identify some of the genetic factors that are more common among individuals with a disorder than among controls. These studies cannot demonstrate causation, and many of the markers being used by the testing companies have not been validated by other groups or by studies that explain the molecular mechanism by which these genes might lead to disease.

Although such studies are not intended to be used as a basis for genetic testing, their results are very rapidly being translated into such tests, Brody noted. "As soon as someone publishes a paper with an association, someone can start testing the next day," he said.

Additionally, because these genetic factors are only weakly associated with disease, it is likely that to cause illness, they must interact with other genetic or environmental factors that have not yet been recognized, said Kathy Hudson, PhD, director of Johns Hopkins University's Genetics and Public Policy Center in Washington, DC.

"We don't know the whole picture," Hudson said.



Direct-to-consumer microarray genome scans are touted as providing consumers a glimpse into their future health, but some critics question the clinical relevance of their findings.

New York City, said that many, though not all, of the genetic markers the tests scan for have been associated with a very small increased risk of disease. For example, he explained in a *JAMA* commentary, the tests can be used to identify SNPs in the *FGFR2* gene that have been associated with a 1.2-fold increased risk of developing breast cancer (Offit K. *JAMA*. 2008;299[11]:1353-1355). This small increased risk is comparable to that faced by women whose first pregnancy occurs after age 35 years. In either case, because the risk

**PATIENT REACTION**

The companies offering personal genome profiles typically provide customers with a report that outlines their risk factors for certain diseases, including some explanation of what the results mean. Most also offer some genetic counseling, usually by telephone. But there are a lot of unanswered questions about how much individuals will understand the information they are provided and what they will do with it.

Brody noted that there are some data indicating that genetic test results may not have the intended effect of reducing risky behaviors. For example, a study in which individuals who were identified as having a high risk for colon cancer found that few knew 1 year later that they were at elevated risk. Brody said these data suggest that the individuals did not understand the test results.

Studies on the reaction of patients who receive results from tests for *BRCA* mutations that confer an increased risk of breast and/or ovarian cancer also raise some concerns about whether giving individuals ambiguous results may be harmful. Offit explained that when *BRCA* mutations that confer an increased risk of breast and/or ovarian cancer was initially rolled out, there was a lot of concern that women who were notified they were at high risk would experience negative psychiatric outcomes. The literature indicates that women who received such news were upset initially, but that they were able to adjust to the news as they learned about interventions or prevention strategies that might help them, he said. Women who found they were not at elevated risk are often relieved, but some experience survivor guilt. But a subset of women who have an indeterminate missense mutation in the *BRCA* gene and who thus receive unclear results experience the most distress, which persists as long as the uncertainty remains.

Offit noted that genome-wide testing might cause distress for individuals with similarly ambiguous results, especially when no preventive or clinical interventions are available.

Others question how physicians will react when a patient approaches them

Resources on Genetics and Health

National Human Genome Research Institute. Information for clinicians (<http://www.genome.gov/27527599>) and for patients and the public (<http://www.genome.gov/19016903>)

Human Genome Project. Genetic disorder information on the Web (http://www.ornl.gov/sci/techresources/Human_Genome/posters/chromosome/diseaseindex.shtml)

Genetic Alliance. *Understanding Genetics: A Guide for Patients and Professionals* (<http://www.geneticalliance.org/understanding.genetics>)

National Organization for Rare Disorders. Information and resources for clinicians and patients dealing with rare genetic disorders (www.rarediseases.org)

with genomic testing results that indicate a small elevated risk of diabetes or cardiovascular disease. For example, Hudson said, concerns about liability or a patient's anxiety may compel physicians to order tests or provide interventions they ordinarily would not offer.

Brody and colleagues have taken the first steps toward answering some of these questions by launching the Multiplex Initiative, a study that will offer healthy adults aged 25 to 40 years screening for genetic variants associated with 8 common health conditions—type 2 diabetes, heart disease, hypercholesterolemia, high blood pressure, osteoporosis, and lung, colon, and skin cancer (McBride CM et al. *Nat Genet.* 2008;40[8]:939-942). The individuals, all members of a large non-profit health insurer, will be referred to a secure Web portal, where they will have access to in-depth information about the testing. Those who opt for testing will receive a report of their results in the mail and a telephone call from a research-educator who will help explain the results and answer questions. The researchers will collect data about who opts for the testing and what kinds of information individuals access on the Web site and analyze patient medical records to determine whether the results trigger other medical interventions.

Beyond the scientific questions raised, many groups are questioning the propriety of companies marketing health risk information directly to consumers without a physician's in-

volvement and with minimal outside oversight. The US Food and Drug Administration does not regulate so-called homebrew tests that are offered directly by the laboratory that created them. The Centers for Medicare & Medicaid Services has some involvement in overseeing the quality of laboratory testing, such as the qualifications of personnel and the handling of samples. However, while the agency periodically assesses laboratories' proficiency in conducting certain tests, genetic tests are not among those evaluated.

But the Federal Trade Commission and others have tested the companies' results by sending samples to multiple laboratories and comparing the results. The companies' results are usually accurate, said Hudson, who said the platforms the companies use to do the testing are very robust.

"The real issue with genome-wide arrays is what does the information mean," she said.

Another question that has been raised is whether the tests should require a physician's order, as most medical tests do. The companies argue they are not offering medical care, said Hudson, though they advertise the potential health benefits of such testing.

ACTIONS BY STATES

Some states have entered this debate. Both New York and California have issued directives to the companies that a physician's order is required for microarray genome scans. At press time,



2 California-based testing companies had obtained licenses to offer their testing to residents of the state. According to the California Department of Public Health, physicians can submit orders for such tests on behalf of their patient or the companies can offer the tests directly to a consumer who is counseled by a company-employed physician who places the order.

The American Medical Association and the American College of Medical Genetics also have weighed in, stating that genetic tests should be administered under the supervision of a physician. **A statement by the American Society of Human Genetics, which Hud-**

son helped to draft, emphasized the importance of verifying the accuracy of test results and ensuring that individuals do not receive misleading information about their test results (http://www.dnapolicy.org/resources/ASHG_DTC_statement.pdf).

While regulators and professional bodies sort out the appropriate use and oversight of such tests, physicians may face the prospect of counseling patients who present with the results from genomic testing. Brody suggests physicians treat the risk information gleaned from such tests as they would observable disease risk factors. For example, if a patient expresses concern

that their test results indicate they are at elevated risk of developing diabetes, their physician can say, "I'm glad you are thinking about diabetes. Here is what we know about preventing diabetes. . . ."

Brody noted that many of the risk factors identified by the tests are associated with diseases for which preventive measures exist. However, some patients may learn they have a genetic marker indicating an elevated risk for a condition such as Alzheimer disease, for which there is no clear preventive action to take. In such cases, he said, "physicians will be placed in an awkward situation." □

Emergency Departments See High Rates of Adverse Events From Antibiotic Use

Mike Mitka

ANTIBIOTIC-ASSOCIATED ADVERSE events are responsible for an unexpectedly high rate of visits to emergency departments, accounting for nearly 1 in 5 visits for medication-related adverse events, according to new findings by scientists with the US Centers for Disease Control and Prevention (CDC).

The researchers analyzed 6614 cases of drug-related adverse events gleaned from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance project (2004-2006) and outpatient prescriptions from several national sample surveys. Based on these data, the researchers estimated a rate of 10.5 emergency visits per 10 000 US prescriptions written for antibiotics generated by patient visits to private practice offices, hospital clinics, and emergency departments, resulting in about 142 500 visits annually to emergency departments. Antibiotic use accounted for about 19% of all drug-related adverse events seen in emergency de-

partments. The findings were posted online August 11 in *Clinical Infectious Diseases* (Shehab N et al. *Clin Infect Dis*. 2008;47[6]:735-743).



Antibiotic-associated adverse events, such as this hypersensitivity rash due to penicillin, are bringing higher than expected numbers of patients to emergency departments.

"Most shocking is how some of the antibiotic classes were right there [with rates of emergency department visits as high as those seen] with warfarin and

others we perceive as dangerous medications," said Jeffrey A. Linder, MD, MPH, an assistant professor of medicine at Harvard Medical School in Boston. Linder wrote an accompanying editorial (Linder JA. *Clin Infect Dis*. 2008; 47[6]:744-746).

The CDC researchers estimated the rate of emergency department visits for adverse events attributable to amoxicillin or penicillin at 15.5 per 10 000 outpatient prescription visits. They noted that visits to an emergency department attributed to "high-risk" medications such as warfarin, insulin, and digoxin were 20.6 per 10 000 outpatient prescription visits.

ALLERGIC REACTIONS

Of the presentations to emergency departments for antibiotic adverse events, the researchers found that nearly 79% were for allergic reactions (such as rash and anaphylaxis) and 19% were for adverse effects such as diarrhea, dizziness, and headache. Nearly 94% were treated and released or left against medical advice, while about 6% were admitted, observed, or transferred.