The Evolving Field of Genetic Testing

Wendy R. Uhlmann (M.S. 1987) is a board-certified genetic counselor in the Medical Genetics Clinic and clinical assistant professor of internal medicine and human genetics. Past president of the National Society of Genetics Counselors, she currently serves on the Medical Genetics Working Group of the Board of Scientific Counselors of the National Center for Biotechnology Information. She updates us here on genetic testing in the age of the human genome.
**Q:** What is the status of genetic testing today? How comprehensive is it in terms of diseases and disorders?

**A:** With the Human Genome Project, a lot of progress has been made in terms of gene identification, but there’s been a lag in translating these advances to actual genetic tests. According to the GeneTests database, there are now 595 labs testing for 2,247 diseases — 1,981 on a clinical basis and 266 on a research basis. By the time this article comes out, there will be even more. Most of these tests are for genetic disorders that affect a small proportion of the population. Testing is advancing at a clip, but there are also limitations in the tests.

**Q:** What kind of limitations?

**A:** For many genetic conditions, we have limited ability to predict clinical outcomes for identified gene changes and lack effective treatments. With some genetic tests, you find “variants of unknown significance,” which means you’ve identified a gene change that’s different from the normal DNA sequence and the clinical significance is unknown. That’s one of the big challenges: When you see a change in the DNA sequence, is it a disease-causing mutation, a rare sequence variant, or a common polymorphism? Selecting the right genetic test and lab is critical, because different labs testing for the same condition may use different methodologies, different mutation panels, with different test sensitivities. When you identify the same gene change in unrelated and even related individuals, there can be variability in age of onset and disease course. That means there have to be other genes and environmental factors involved. The fact is that genetics isn’t necessarily destiny and for many conditions, you can’t just say that because you have a specific gene change, this is what’s going to happen. That’s why genetics expertise is needed in test selection and interpretation, and why pre- and post-test counseling to make sure patients understand the benefits, risks and limitations of testing is so important.

**Q:** What does a positive test result mean?

**A:** It means you have found a gene change that causes the genetic condition. Clinical significance depends on the genetic condition, test indication, and whether the patient is symptomatic or asymptomatic. Genetic test results can be complex. You can have the gene change and not develop symptoms, and family members and others with the same gene change can have different disease courses.

**Q:** And a negative test result?

**A:** A negative test result in the face of known gene mutations in the family can be very reassuring. It can rule out a condition or bring you back to the general population risk. A negative test result in the absence of testing an affected family member can be very limiting — you don’t know if you’re negative because of limitations in today’s testing technology, or because you didn’t inherit the gene change.

**Q:** What are the pros and cons of undergoing gene testing?

**A:** It can sometimes mean the end of a long diagnostic journey and put a name to patients’ symptoms. It can help with management of care to know that this is the actual condition in the family and we have proven that with the test. Other pros are the ability to test other at-risk family members which could affect their care. For example, recommended screening for a genetic condition can be eliminated for family members who test negative and initiated for those who test positive. Knowing results can also be important for life planning. The cons are the limitations and cost of testing, which may or may not be covered by insurance, and potential implications for insurance coverage like life and disability. Another con is false reassurance; some people may feel that because they’ve tested negative, they’re in the clear when, in fact, the test may not
identify all gene changes. People can over-interpret results and think they’re going to have all these symptoms and problems; they may not understand that other factors can have an impact and there’s still a lot we don’t know.

Many medical tests, like a complete blood count, affect just the patient, but a genetic test result can affect other family members, as well as family dynamics and perceptions of self. There are ethical issues that arise including testing children, familial disclosure of genetic test results and whose rights take precedence when testing could reveal carrier status of a family member who does not want this information known.

Q: Are there specific concerns with the direct-to-consumer (DTC) test kits available on the Internet?
A: A genetic test does not take the place of a genetics evaluation and risk assessment. The distinction to make is that there is genetic testing that’s being offered direct-to-consumer that is not offered in clinics and is not standard of care. In addition to significant concerns about the genetic tests offered, there are others that center on consumers making testing decisions independent of their doctor, without the context of their medical and family history and without the medical background to make an informed testing decision — and interpret the results. Another concern is people thinking they’ve had the genetic test for a specific disease when in fact what they’ve had is testing for single nucleotide polymorphisms associated with disease genes but of limited predictive value. As the Government Accounting Office investigation last summer showed, you can send the same sample to different direct-to-consumer companies and receive contradictory disease risk predictions, which demonstrates the limitations of these tests and why they are not standard of care.

I do think DTC companies are here to stay. The reach of the Internet, and the availability of home tests like those for pregnancy and HIV, set a precedent for consumers testing outside the doctor’s office. The challenges are to determine which genetic tests to offer direct-to-consumer, what information to provide pre- and post-testing and by whom, and the needed oversight so that DTC tests are safely integrated into health care.

Q: Where will further advances in genetic testing take us?
A: We’re going to keep developing new tests, allowing us to help more patients. I think some genetic tests will become part of the battery of tests for an annual physical and others utilized before prescribing medications. Currently, there are genetic tests available before proper vetting, I’d like to see the genetics and medical communities come around more quickly to say whether they think a test is ready for prime time and to establish practice guidelines.

The NIH is developing a national Genetic Testing Registry as a resource for not only clinicians but also potentially for researchers, the general public and third-party payers. This centralized database of available genetic tests will have links to information important for the evaluation and selection of a test, including analytical and clinical validity. In short, genetic testing offers much promise in health care but we have a lot of work ahead of us.