

## Genetic Testing: More Validation Is Needed

Genetic testing has emerged from a relatively esoteric discipline only a few years ago to a multimillion-dollar industry. Today, there are more than 1200 different genetic tests available clinically and nearly 300 more available on a research basis, from over 600 different laboratories worldwide.<sup>1</sup> The volume of genetic testing is estimated to have increased by 25% per year between 1997 and 2006,<sup>2</sup> and there is no reason to believe that this growth is slowing.

There are 2 main types of genetic tests: those used to test for inherited single gene disorders, and the more recently developed genomic assays that analyze the genetic signature associated with a particular disease, usually a specific form of cancer. These genomic assays analyze acquired, rather than inherited, genetic changes seen in tumors, with the goal of selecting groups of patients to receive the most effective treatment based on the genetic signature of the tumor. For example, breast cancer genomic assays, such as Oncotype DX, can identify those women with estrogen receptor positive, lymph node negative breast cancer who are most likely to benefit from chemotherapy. However, despite widespread use for several years, evidence is still lacking on the impact of these assays from both a patient care and an economic perspective.<sup>3,4</sup>

From an ethical perspective, a key concern with respect to genetic testing has been the potential for discrimination: would insurance companies and employers use genetic test results as a basis to exclude persons from receiving health care coverage or from consideration as job candidates? This concern was addressed on May 21, 2008, when President Bush signed into law the Genetic Information Nondiscrimination Act of 2008 (GINA; HR 493), which had received overwhelming bipartisan congressional support. This ended 13 years of lobbying by genetics professionals and family advocacy groups and the introduction of many different versions of legislative proposals.

GINA prohibits group health plans from using genetic predisposition information to deny coverage to a

healthy person or to charge that person a higher premium. GINA also prohibits employers from using genetic predisposition information when making decisions about hiring, firing, job placement, or promotion.<sup>5</sup> The hope is that GINA will give consumers the assurance they need to access potentially beneficial genetic testing, particularly those tests that can predict a predisposition to a particular condition for which there may be an effective medical or lifestyle intervention, without fear of discrimination by health insurers or employers. GINA protects consumers only from discrimination by health insurers and employers and does not apply to life insurance, disability insurance, or long-term-care insurance. Some states have passed legislation that addresses genetic discrimination for life, disability, or long-term-care insurance, but gaps exist and there is inconsistency among state statutes.<sup>6</sup>

The cost of genetic testing is also a concern. Some genetic tests can cost as much as several thousand dollars, depending of the complexity of the test and patent/license status. Given the generally high price tag, clinical utility must be at the forefront of consideration when ordering these tests. There must be a clear benefit in terms of the potential for improved care. Traditionally, medical tests have been assessed strictly on whether they can be expected to improve health outcomes for the person being tested. For genetic tests, clinical utility is defined based on a number of factors including<sup>7</sup>:

- Reduction in morbidity or mortality of the person tested by providing information that leads to improved patient care through modifications in treatment plans.
- Provision of information about the health of the person being tested or of family members, even in the absence of an effective treatment or cure.
- Provision of information about reproductive decision making.

While most genomic assays fall into the first category, genetic tests for inherited disorders typically will be applicable in 2 or 3 of the categories. However, there is often not a great deal of published evidence available to adequately assess the clinical utility of a given test or given use of a test, and this can be frustrating for both health care professionals and patients. There is a need, therefore, for evidence-based evaluation of genetic tests to establish their clinical utility.<sup>8</sup>

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**Table. Hayes Genetic Test Rating Scale**

Hayes Rating	Description
A	Established benefit
B	Some proven benefit
C	Potential but unproven benefit
D1	No proven benefit in health outcomes
D2	No proven benefit, insufficient evidence

Hayes, Inc, is in the process of compiling evidence demonstrating clinical utility and clinical validity of various genetic tests. Each year, Hayes generates more than 150 unbiased, evidence-based reports that are used by 65% of US health care insurers as they develop coverage policies. (Hayes's research is also used by hospitals and employers for health technology decision making.)

Using the Centers for Disease Control and Prevention's ACCE model, the Hayes Genetic Test Evaluation Program has evaluated the clinical evidence for 12 genetic tests to date and will evaluate the clinical evidence for at least another 40 genetic tests in the next 12 months. The ACCE model measures:

- Analytical validity, or the ability of a genetic test to accurately and reliably measure the genotype of interest.
- Clinical validity, or the ability of a genetic test to detect or predict the associated disorder (phenotype).
- Clinical utility, or the ability of a genetic test to improve health outcomes.
- Ethical, legal, and social implications, including safeguards and impediments considered in the context of other components.

Once the evidence is evaluated, the genetic tests are given a Hayes rating (Table) score. The 12 tests evaluated to date represent 33 distinct uses of genetic testing. However, only 24% of these uses have obtained Hayes ratings of B or higher, indicating that only a low percentage of test uses assessed to date is linked to demonstra-

ble improvements in patient care. This is not because the technology is not promising but rather because, in many cases, insufficient clinical studies have been performed to validate that the test leads to better patient management and/or improved clinical outcomes.

More than half (55%) of test uses received a rating of C or D2, indicating that there is insufficient published evidence to evaluate that particular use of the test. These ratings may change as additional clinical studies are performed. The literature is monitored frequently, and reports are updated when significant new information becomes available. However, the result of these evaluations indicates that genetic testing has a long way to go before it can be recommended for widespread adoption in health care. Currently, the evidence of clinical validity and clinical utility is insufficient to justify the high cost of genetic testing, except in limited circumstances.

Genetic testing is a rapidly growing and evolving field with enormous potential to positively inform patient care. The passage of GINA is a major step toward improving access to genetics services while decreasing patient anxiety regarding possible discrimination. The medical and scientific communities must next take the steps necessary to ensure that appropriate studies are done to demonstrate the benefit of each new genetic test for patients, before adoption of the test into clinical use. ■

## References

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