Chapter 10

Ensuring the Quality of Genetic Testing in the United States

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Why is the Quality of Genetic Testing Important to Public Health?

Genetic tests for about 1,000 health conditions have been developed, of which more than 600 are currently available for clinical testing.[1] Many genetic tests identify DNA variants; others measure biochemical markers or analyze chromosomes. Most are used for diagnosis of rare single-gene disorders or chromosome abnormalities, and a few are used for newborn screening.[2]

A growing number of genetic tests may have population-based applications, including determining the risk of developing a disease or condition in the future (e.g., predictive testing for breast cancer or cardiovascular disease), and recognizing genetic variations that can influence response to medicines (**pharmacogenomics**). These genetic tests, therefore, have the potential for broad public health impact.

Pharmacogenomics
Refers to the use of genomic techniques to enhance drug development and define drug responses.

About GeneClinics and GeneTests

The GeneClinics and GeneTests Web site, a publicly funded medical genetics information resource, contains comprehensive reviews of common genetic disorders and information on available genetic tests. Either of these links will take you to the Web site: http://www.geneclinics.org or http://www.genetests.org.

Genetic Testing Issues

Important issues that have been raised regarding genetic testing include the need to:

- facilitate translation of research findings to quality testing in clinical and public health settings,
- prevent premature commercialization of tests before safety, efficacy, and cost-effectiveness can be established,
- provide information on proper use of genetic tests to health care providers, policy makers, and the public,

- maintain adequate oversight of genetic testing,
- monitor the use of genetic tests and ensure appropriate access to testing and related clinical services, and
- address complex social issues posed by genetic testing.

Who Considers These Issues in the United States?

In 1997, the National Institute of Health (NIH)—Department of Energy (DOE) Task Force on Genetic Testing issued a report on genetic testing in the United States that provided recommendations on how to ensure the development of safe and effective genetic tests.[3] In 1998, the Department of Health and Human Services (HHS) established the Secretary's Advisory Committee on Genetic Testing (SACGT) to provide advice on medical, scientific, ethical, legal, and social issues raised by the use of genetic tests. In consultation with the public, SACGT considered potential mechanisms and options for evaluating genetic tests, providing information about genetic testing to stakeholders, and enhancing testing oversight.[4]

In 2003, HHS established the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS), in order to address genetic issues in a broader scope and continue discussion on oversight of genetic testing. Other public and private entities that consider issues related to the safety and effectiveness of genetic tests include:

- federal and state government agencies,
- professional associations,
- laboratory accreditation organizations,
- health plans and healthcare payers,
- policy groups, and
- patient advocacy organizations.

What Oversight Currently Exists for Genetic Testing?

In the United States, laboratory testing devices and kits are subject to FDA oversight. When tests are packaged and sold as kits or testing systems to laboratories, the FDA requires data collection and evaluation as part of pre-market approval or clearance. Currently, however, almost all genetic tests are developed by laboratories in-house and are called **"home brew"** tests, and are not available as FDA-approved kits.

"Home Brew"
Almost all genetic tests are performed by laboratories that have developed these tests in-house.

At present, the Centers for Medicare and Medicaid Services (CMS) provide oversight for "home brew" testing by regulating clinical laboratories under the Clinical Laboratory Improvement Amendments (CLIA); http://www.cms.hhs.gov/clia. CLIA regulations require laboratories to be responsible for all phases of the testing process and focus on laboratory quality systems and in-house analytic validation—analytic validity defines the ability of a test to measure accurately and reliably what it purports to measure. Currently, clinical cytogenetics—the analysis of human chromosomes—is recognized as a specialty area under CLIA, but a broader specialty of genetics does not yet exist. As a result, there are no specific requirements at the federal level for laboratories performing molecular and other types of genetic testing.

Watch for …
The CDC, in partnership with CMS, has been working to introduce a genetic testing specialty under CLIA to establish specific requirements for laboratories performing genetic testing. A Notice of Proposed Rule Making for a genetic testing specialty under CLIA is expected in the near future.
http://www.phppo.cdc.gov/dls/genetics/policy.asp

"Home Brew" Genetic Tests and the FDA

To date, the FDA has not regulated "home brew" genetic tests offered by laboratories as clinical services, but regulation remains an option. The FDA does provide a standard of measurement for regulating certain testing reagents as analyte-specific reagents (ASRs). ASRs are used as components in laboratory-developed ("home brew") genetic tests and can be sold only to laboratories certified under CLIA to perform high-complexity testing.

It should be noted that FDA review is designed to evaluate a test's performance, including analytic validity, clinical validity, and some aspects of clinical utility. Clinical validity defines a test's ability to detect or predict a particular disorder. Clinical utility defines the risks and benefits associated with the introduction of a test into practice, including the impact of positive and negative test results on health outcomes, cost-effectiveness, and ethical, legal and social issues associated with test use. Many points considered in assessing the clinical utility of a test, however, are outside the usual purview of FDA and CLIA review.

FDA News - December 17, 2003…
FDA Approves Lab Tests for Genetic Clotting Risk - The FDA announced approval of the first DNA-based laboratory tests for an inherited disorder.
http://www.fda.gov/bbs/topics/NEWS/2003/NEW00998.html

How Do States Regulate Genetic Testing?

Some state agencies regulate laboratories performing genetic testing through licensure of personnel and/or facilities. For example, New York requires laboratories to submit validation data for approval prior to offering patient testing. South Dakota requires that genetic tests be performed in a laboratory that:

- is accredited by a program approved by HHS, such as the College of American Pathologists, and
- enrolls in a proficiency-testing program.

What Private Sector Organizations Are Concerned with Genetic Testing?

Private-sector organizations develop voluntary laboratory and clinical guidelines and standards that help to ensure appropriate performance and use of genetic tests.

Examples of such organizations include:

- American College of Medical Genetics (http://www.acmg.net),
- College of American Pathologists (CAP) (http://www.cap.org),
- American Academy of Pediatrics (http://www.pediatrics.org),
- American College of Obstetricians and Gynecologists (http://www.acog.org),
- American Society of Human Genetics (http://www.asgt.org),
- National Society of Genetic Counselors (http://www.nsgc.org),
- Association of Molecular Pathologists (http://www.ampweb.org), and
- NCCLS (http://www.nccls.org).

What is Needed to Ensure the Safety of Genetic Testing?

In order to ensure the safety and effectiveness of genetic testing in the United States, the following needs have been identified:

- development of a standardized approach for evidence-based review of new genetic tests to establish safety, efficacy, and cost-effectiveness prior to use in routine clinical care,
- ongoing assessment of laboratory practice in genetic testing and identification of needs for quality improvement, and
- clarification of the roles of regulatory and other government agencies, professional organizations, and advocacy groups in genetic test oversight and policy development.

How is CDC Addressing These Needs?

The CDC has initiated a number of activities to address these needs:

Assessing laboratory practice in genetic testing:

- Funding Mt. Sinai School of Medicine to survey the state of practice in clinical molecular and biochemical genetic laboratories. Results showed that genetic testing was available in a variety of laboratory settings, but indicated that specific improvements in quality assurance practices were needed to ensure high quality service.[5]

- Collaboration with Tulane University to assess the variability of result reporting for cystic fibrosis and factor V Leiden testing and evaluate the usefulness of different report formats to physicians in interpreting genetic test results. The findings demonstrated variability in report content, including a lack of some information deemed critical by professional guidelines and recommendations.[6]

- Contracting with Duke University School of Medicine and the University of California at Los Angeles to pilot-test approaches to developing positive controls for genetic tests and help ensure continuous availability of quality control materials for the development, validation, performance, and quality assurance of genetic tests.

More information can be found at: http://www.phppo.cdc.gov/dls/genetics/default.asp.

Evidence-based review and surveillance of genetic tests:

- Establishing a cooperative agreement with the Foundation for Blood Research to develop and test a model process for assembling, analyzing, and disseminating data on the safety and effectiveness of DNA-based genetic tests and testing algorithms. This model process is described by the acronym ACCE, which stands for: analytic validity, clinical validity, clinical utility and ethical, legal and social implications—the four components by which a test is evaluated. Over a 3-year period, five tests for different disorders were evaluated, with a goal of facilitating appropriate transition of genetic tests from investigational settings to use in clinical and public health practice. More information can be found at http://www.cdc.gov/genomics/activities/fbr.htm. See more information about an ACCE review in *Chapter 4, Public Health Assessment of BRCA1 and BRCA2 Testing for Breast and Ovarian Cancer*.

- Conducting a study on the impact of direct-to-consumer marketing. From September 2002 to February 2003, the major U.S. provider of genetic testing for breast and ovarian cancer susceptibility (*BRCA1/2* testing) conducted a direct-to-consumer advertising campaign that targeted women aged 25-54 and their health care providers in two pilot cities, Atlanta, GA and Denver, CO. The CDC study was intended to assess the impact of the advertising campaign on knowledge, attitudes and actions of health care providers and consumers related to breast and ovarian cancer risk and *BRCA* testing.

Suggested Reading On Genetic Test Evaluation:

Haddow JE and Palomaki GE. ACCE: A model process for evaluating data on emerging genetic tests. *Human Genome Epidemiology*. Khoury MJ, Little J, and Burke W, eds. Oxford University Press, Inc. New York, 2003;217-33.

Burke W, Atkins D, Gwinn M, Guttmacher A, Haddow J, Lau J, et al. Genetic test evaluation information needs of clinicians, policy makers and the public. *Am J Epidemiol* 2002;156:311-8.

More information on genetic testing can be found on the OGDP Web site: http://www.cdc.gov/genomics/gTesting.htm

References

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