Testimony of Kathy Hudson, Ph.D.
Director, Genetics and Public Policy Center
& Associate Professor, Berman Bioethics Institute,
Institute of Genetic Medicine & Department of Pediatrics
Johns Hopkins University

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"At Home DNA Tests: Marketing Scam or Medical Breakthrough?"

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Genetics and Public Policy Center
Berman Bioethics Institute ◦ Johns Hopkins University
1717 Massachusetts Ave. N.W., Suite 530
Washington, D.C. 20036
202.663.5971
Fax: 202.663.5992
www.DNApolicy.org

Mr. Chairman and Members of the Committee:

Thank you for inviting me to be here today to discuss the ethical, legal, and social concerns relating to direct-to-consumer clinical genetic testing. I appreciate the opportunity to share with you the results of the Center's work and our policy recommendations in this arena.

My name is Kathy Hudson and I am Director of the Genetics and Public Policy Center and Associate Professor in the Berman Bioethics Institute, the Institute of Genetic Medicine, and the Department of Pediatrics, at Johns Hopkins University. Established with a grant from The Pew Charitable Trusts, the mission of the Genetics and Public Policy Center is to provide independent and objective information and analysis on genetic technologies and genetic policies. We hope our work provides useful tools for decision makers as they respond to the challenges and opportunities arising from advances in human genetics.

I commend the Committee for focusing on this important topic and the GAO for undertaking an investigation of troubling commercial practices with respect to certain genetic tests being offered directly to consumers.

Today I would like to make four points. First, genetic testing is growing rapidly and holds great promise to improve health and health care. Second, the current system for oversight of genetic testing is inadequate. Third, gaps in oversight pose real threats to the public's health. And last, I would like to share some policy recommendations to fill those gaps and help ensure that the promise of genetics is realized.

Current Uses of Genetic Testing

There are many contexts in which genetic tests are used, including forensic testing, ancestry testing, and paternity testing. Consistent with the focus of the GAO investigation, my testimony today will focus only on health-related uses of genetic testing.

Genetic testing is becoming an increasingly important part of medical care. Once the province of esoteric testing laboratories and limited to rare diseases or conditions, genetic tests now are being offered by a growing number of clinical laboratories for an increasing number and variety of conditions or health risks. The number of tests has increased 10-fold over the last decade and continues to grow. Today, there are genetic tests clinically available for nearly 1000 diseases, with hundreds more in development.[1] Genetic tests can be performed at any stage of the lifecycle: on fetuses during pregnancy, newborn babies, children, and adults of all ages.

Genetic tests provide information -- information that can be used to diagnose disease, to predict risk of future disease, and to guide decisions about whether to undergo a medical procedure or take a particular drug or dosage of a drug. Increasingly, genetic testing will

[1] GeneTests, www.genetests.org.

be used routinely in medical care to alert us to future health risks and guide early prevention and intervention. Genetic testing also will be used to help doctors prescribe the right medicine at the right dose for individual patients, thus avoiding costly and sometime tragic adverse drug reactions. The information provided by genetic tests is used to make profound, sometimes life-and-death, decisions. It is therefore imperative that this information be accurate and reliable and relevant to a patient's health.

Gaps in the Regulatory Landscape

Inadequacies in the current oversight of genetic testing identified by the Center[2] and in the GAO report threaten more than the public's pocketbook -- they threaten the public's health. The current regulatory environment fails to ensure the quality either of the laboratories performing genetic testing or of the tests they are offering. While these gaps affect all genetic tests, the ramifications of the current gaps in oversight are particularly evident with respect to some of the tests being offered directly to consumers.

For a genetic test to be of high quality, it must be both analytically and clinically valid. Analytic validity refers to a laboratory's ability to get the correct answer reliably over time, for example, to detect a genetic variation when it is present and *not* detect it when it is absent. Clinical validity refers to whether a particular genetic variation is associated with an individual's current or future heath status. Patients and providers need to know what it means to detect a specific genetic variant and equally importantly what it means if a variant is not detected.

All of us carry many variations in our DNA sequences; many of these are of no known clinical significance. Establishing clinical significance requires scientific evidence that correlates a particular genetic change with a specific health outcome. Gaps in current oversight mean that neither the analytic nor the clinical validity of genetic tests is adequately ensured.

Analytic Validity: What's the Problem with CLIA

Responsibility for ensuring the analytic validity of genetic tests lies with the Centers for Medicare and Medicaid Services (CMS), which implements the Clinical Laboratory Improvement Amendments of 1988 (CLIA). Congress enacted CLIA to "strengthen federal oversight of clinical laboratories to assure that the tests results are accurate and reliable"[3] after Congressional investigations found significant problems in the quality of testing services being provided to the public. The major problems identified by Congress were "lax federal oversight and direction, lack of proficiency testing for many analytes, inconsistent criteria for acceptable laboratory performance, and improprieties by

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[2] Javitt G, Hudson K. Federal Neglect: Regulation of Genetic Testing. Issues Sci. Technol. 2006 Spring; 22(3):59-66; Javitt G, Stanley E, and Hudson K. Direct-to-Consumer Genetic Tests, Government Oversight, and the First Amendment: What the Government Can (and Can't) Do to Protect the Public's Health. Oklahoma Law Review (2004) 57: 251-302; Baruch S, Javitt G, Scott J, and Hudson K. Reproductive Genetic Testing: Issues and Options for Policymakers. Washington, DC: Genetics and Public Policy Center, 2004.

[3] H.R. Rep. No. 100-899, at 8 (1988).

laboratories in handling specimen samples."[4] Deficiencies were particularly apparent in cytological screening of pap smears for cervical cancer. Congress found that many laboratories were reporting false negative results. In other words, women with abnormal, and possibly cancerous, cells were being incorrectly informed that their pap smears were normal.[5]

Congress, in enacting the amendments to CLIA, directed the Secretary of HHS to issue standards for the certification of laboratories, in order "to assure that such laboratories will consistently perform tests in a valid and reliable manner."[6] Proficiency testing, i.e., "a method of externally validating the level of a laboratory's performance,"[7] was a key element of the Amendments. According to the legislative history, Congress believed that proficiency testing should be the central element in determining a laboratory's competence, since it purports to measure actual test outcomes rather than merely gauging the potential for accurate outcomes.[8] Congress found "a number of serious defects in the current system" for proficiency testing.[9]

Unfortunately, 18 years later, these problems persist, and the implementation of CLIA with respect to genetic tests in particular has lagged behind advances in technology.

CLIA prohibits a clinical laboratory[10] from accepting human specimens for analysis unless the laboratory has been issued a certificate. Obtaining a certificate, in turn, requires that CMS or a CMS-approved body accredit the laboratory.

CLIA regulations provide different levels of oversight depending on the "complexity" of a test. Test complexity is determined through an algorithm that takes into account a number of factors including the training and skill required to perform the test and to interpret the results correctly. Tests that are considered "high complexity" are subject to additional test-specific requirements that address issues such as the qualifications of laboratory personnel and that mandate the enrollment in CLIA-approved proficiency testing programs. These test-specific requirements are implemented through the creation of a "specialty area." CMS has created specialty areas for many types of tests, including Microbiology, Diagnostic Immunology, and Chemistry.

Genetic tests are considered high complexity. Unlike other high-complexity tests, however, CLIA has not created a specialty area for most genetic tests. This means that there are no specified quality control, personnel, or proficiency testing requirements

[4] Id. at 16.
[5] Id. at 16-17.
[6] Id. at 27.
[7] Id. at 15.
[8] Id. at 28.
[9] Id. at 15.
[10] CLIA defines a clinical laboratory as a "facility for the biological, microbiological, serological, chemical, immuno-hematological, hematological, biophysical, cytological, pathological, or other examination of materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings." 42 U.S.C. § 263a(a).

mandated under the CLIA regulations for most genetic tests. While some laboratories maintain the accuracy of their testing procedures by voluntarily enrolling in programs for proficiency testing, others do not. In the absence of a genetic testing specialty, it is difficult for health care providers or patients to distinguish between those laboratories that are qualified to perform genetic testing and those that are not.

Several government bodies have identified the creation of a specialty area as integral to adequate government oversight of genetic testing. As early as 1995, the National Institutes of Health and Department of Energy together convened a government task force to review genetic testing in the United States and make recommendations to ensure the development of safe and effective genetic tests. The task force recommended, among other things, that genetic tests not become clinically available unless they had been demonstrated, through independent external review, to be clinically valid. In 2000, the Secretary's Advisory Committee on Genetic Testing (SACGT) issued a report in which it concluded that the current oversight of genetic tests was insufficient to ensure their safety, accuracy, and clinical validity.[11] Among its recommendations, the SACGT proposed that CMS develop a specialty area for genetic testing under CLIA, and that FDA should review all new genetic tests. Neither of these recommendations has been implemented. In 2000, the government announced its intent to develop a specialty area under CLIA.[12] Six years later, no proposal has been forthcoming.

The Genetics and Public Policy Center believes that immediate action by CMS is urgently needed to create proficiency testing standards for genetic testing under CLIA. In November 2005, the Genetics and Public Policy Center called on CMS Administrator Mark McClellan to issue a proposed rule for a genetic testing specialty. Subsequently, nearly 100 groups, comprising patients, industry, health care providers, and women's health advocates, have added their voices and called on the Administrator to issue the proposed regulation.[13]

The GAO report documents real errors occurring in genetic testing laboratories. The GAO submitted a single DNA sample for testing under different assumed identities and received disparate results. While the DNA was identical, the genetic test results were not, with one result indicating that a genetic variant was present and another indicating it was not. Such laboratory errors are simply not acceptable and, for many tests, downright dangerous. Other studies have similarly documented genetic testing laboratory errors.[14]

We believe that laboratory errors such as these could be mitigated by enhanced oversight. A recent study by the Genetics and Public Policy Center provides evidence that the creation of a genetic testing specialty will be an effective approach to reduce analytic errors. Our survey of U.S. genetic testing laboratories revealed a wide range of

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[11] Enhancing the Oversight of Genetic Tests: Recommendations of the SACGT (2000), available at http://www4.od.nih.gov/oba/sacgt/reports/oversight_report.pdf

[12] 65 Fed. Reg. 25928 (May 4, 2000).

[13] See http://www.rhtp.org/documents/CLIAlettertoCMSSecMcClellan.pdf; http://www.geneticalliance.org/ws_display.asp?filter=testing_ltr

[14] Libby E et al. False-negative Factor V Leiden genetic testing in a patient with recurrent deep venous thrombosis. Am. J. Hematol. 2006 Apr;81(4):284-9

laboratory practices with respect to proficiency testing. Moreover, the survey found that laboratories with higher levels of participation in proficiency testing also reported fewer laboratory errors, demonstrating that proficiency testing is integral to quality laboratory testing. These results suggest that creation of a genetic testing specialty and the associated proficiency testing standards will enhance laboratory accuracy. In addition, the survey found a high level of support among laboratory directors for the creation of a genetic testing specialty.

In April 2006, CMS placed the issuance of a proposed rule on its regulatory agenda,[15] and we are cautiously optimistic that a proposed regulation will soon be forthcoming.

In addition to the absence of a genetic testing specialty, there are two other significant problems with CLIA that I would like to bring to your attention. First, the Center has determined that at least some laboratories offering genetic testing do not have CLIA certificates. This finding is quite disturbing and means that these laboratories are not being held responsible for meeting even the basic standards for laboratory quality applicable to all clinical laboratories. The second problem is that information about which laboratories are CLIA certified is not readily accessible to the average consumer or health care provider making if difficult, if not impossible, for doctors and patients to choose quality laboratories. The Center believes that it is in the interest of both providers and patients for CMS to enforce its current regulations more aggressively and to make publicly available the CLIA certification status of all laboratories, including those offering genetic testing.

Clinical Validity

The CLIA statute is focused on laboratory quality, not clinical validity of tests. Currently, there is no government agency with clear responsibility to ensure the clinical validity of most genetic tests. Therefore, each laboratory director makes an independent decision regarding whether a genetic test has sufficient clinical validity for it to be offered to the public. Many laboratories are of extraordinarily high quality and offer only those tests for which there is broad scientific agreement regarding clinical validity. However, several reports, notably the new GAO report, indicate that some laboratories are offering genetic tests to the public in the absence of sufficient evidence of their clinical validity. Moreover, because there is no requirement that laboratories disclose publicly the scientific basis for their tests, it is not possible for consumers to determine whether a test is bogus or is based on real science.

Some have recommended that the Food and Drug Administration (FDA) take responsibility for ensuring the clinical validity of all or some genetic tests. Currently, FDA regulates only those genetic tests that are sold to laboratories as "test kits" under the Medical Device Amendments of 1976.[16] Tests sold as kits are regulated as "in vitro diagnostic devices," and manufacturers of these kits must submit information to the agency demonstrating that the test is, in FDA parlance, "safe and effective." FDA

[15] 71 Fed. Reg. 22537, 22595 (Apr. 24, 2006).
[16] Pub. L. No. 94-295, 90 Stat. 539 (1976).

reviews the information provided and makes a determination regarding the analytic and clinical validity of the test.

To date, test kits are available for only a handful of genetic tests and the vast majority of genetic tests performed by clinical laboratories do not use test kits. Instead, laboratories for the most part use in-house developed methods (so called "home brew" tests). Even if a kit is available, a laboratory does not have to use it but can decide to offer its own home brew version of the test without the need to undergo FDA review.

FDA has provided mixed signals over time regarding its jurisdiction and willingness to regulate home brew tests. In 1997, the agency asserted that "clinical laboratories that develop such tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction."[17] However, the agency also acknowledged that home brew tests were valuable in "providing novel, highly specialized tests in a relatively short time, sometimes for diseases that affect a relatively small proportion of the population."[18] Thus FDA declined to exercise its jurisdiction because of concerns that unduly stringent regulation of home brew tests could be detrimental to public health. However, in the course of the rulemaking process the agency also stated "at a future date, the agency may reevaluate whether additional controls over the in-house tests developed by such laboratories may be needed to provide an appropriate level of consumer protection. Such controls may be especially relevant as testing for the presence of genes associated with cancer or dementing diseases becomes more widely available."[19]

After a number of years of silence from FDA on the issue of home brew genetic tests, recently the agency has sent a few letters to a small number of companies providing genetic testing services advising them that they might be selling unapproved tests in violation of the law. However, FDA's jurisdiction, or perception of its jurisdiction, remains unclear and the agency has not adopted any systematic regulatory approach with respect to home brew tests.

FDA's lack of clarity with respect to its authority over home brew tests is troubling, and has resulted in a "two path system" for the regulation of genetic tests. Those few companies that have invested the time, money, and effort to develop "test kits" face competition from clinical laboratories using home brews. This uneven regulatory playing field provides a disincentive to the development of test kits with clear evidence of clinical validity before entering the market. While FDA has sent a few warning or "untitled" letters to companies offering particular genetic tests that the agency believes may violate the law, its quixotic enforcement efforts in the absence of a coherent regulatory framework may hinder the availability of valuable genetic tests to the public while failing to address the tests of dubious validity.

Any regulatory system for genetic tests must balance the need for evidence of clinical validity with the desire to foster innovation of new tests. Additionally, such a system

[17] 62 FR 62243, 62249 (Nov. 21, 1997)
[18] Id.
[19] 61 Fed. Reg. 10484 (Mar. 14, 1996).

must recognize that not all genetic tests raise the same level of concern and therefore must be sufficiently nuanced to take into account the risks, benefits, and foreseeable uses of each particular test. This is no easy task, but is essential if genetic testing is to fulfill its promise of enhancing public health. Unfortunately, at the present time no government entity has been given a clear mandate to oversee genetic tests, thus these fundamental issues are not being addressed. Not for the first time, science has surged forward and public policy simply has not kept pace.

Concerns about Direct-to-Consumer Genetic Testing

Some have argued that direct access to genetic testing is never appropriate, and that a health care provider's intervention is always required. These arguments are premised on the assumption that genetic information is complex, that consumers lack the requisite understanding of genetics to comprehend test results or place them in proper context, and that consumers therefore run the risk of misinterpreting test results and may make bad health care decisions as a result.

While the concerns expressed about this method of delivery for all or some genetic tests could prove to be correct, data are lacking that would provide support either to DTC critics or its supporters regarding whether, in the absence of the intervention of a health care provider, consumers are capable of understanding genetic information and making medically sound decisions.

However, in the context of the current regulatory environment, direct-to-consumer testing may pose real risks to consumers. Absent safeguards to ensure that the laboratories performing tests are competent to do so, that the tests provide clinically relevant information, and that the claims made about tests are accurate and balanced, consumers have no reliable basis to make informed decisions about the benefits and risks of testing. While some DTC companies may be using only high caliber laboratories and offering only tests generally recognized as clinically valid, there is no way for a consumer to distinguish between the decent and the dubious. At best consumers may be wasting their money; at worst they may be foregoing medically appropriate treatment or undertaking medically dubious treatment as a result of testing and the recommendations made by DTC companies based on test results.

The Tip of the Iceberg

While the GAO's investigation of DTC tests focused on a subset of tests known as "nutrigenomic tests," the field of DTC testing is much broader, with test menus that range from the reputable to the reprehensible. Some of the current DTC offerings include tests that purport to predict vulnerability to depression or risk of Alzheimer disease, to detect fetal gender, to determine athletic potential and risk of sports injury, or to identify the cause of infertility or obesity. Like the nutrigenomic tests investigated by GAO, some of these DTC tests are coupled with the sale of products claiming to treat the ailments identified by the tests or to "match" one's genetic profile, such as "customized" supplements to aid in weight loss.

Given the current low regulatory barrier to market entry, the number and types of genetic tests offered directly to consumers can be expected to expand. While some states prohibit laboratories from offering tests or providing test results directly to consumers, many do not. Moreover, given the Internet-based nature of DTC commerce, enforcing state laws against DTC testing is a challenge.

Conclusion

Quality genetic testing requires good tests and competent laboratories. Tests must be offered only when there is sufficient scientific evidence linking a particular genetic variation with a specific health condition or risk. Laboratories reliably must be able to ascertain the presence or absence of a genetic variation and to appropriately communicate results to providers and consumers. Particularly in the case of DTC testing, laboratories must ensure that claims about the meaning of test results are truthful, balanced, and provide appropriate context so that the results are meaningful and useful to consumers.

Without external scrutiny of genetic tests and testing laboratories, physicians and the public have little assurance that the tests they use to make profound medical decisions are reliable and relevant predictors of their disease risk or treatment outcome.

Genetic testing has tremendous potential to improve the health of Americans. If genetic testing is to gain the public's trust and deliver on its promise of improving health, we must have confidence that the laboratories offering these tests are performing them correctly and that the tests themselves yield information that is relevant to health care decision making. That confidence today is unwarranted.

In conclusion, policy action is needed to enhance the analytical and clinical validity of genetic tests. The Genetics and Public Policy Center offers the following recommendations.

1. CMS must issue a proposed regulation to create a genetic testing specialty under CLIA and Congress should hold the agency accountable for timely action.
2. CMS must enforce its existing regulations and ensure that laboratories offering genetic testing are certified and Congress must provide adequate resources to CMS to enable the agency to carry out this vital function.
3. CMS must make a listing of CLIA-certified laboratories and the tests for which they are certified easily accessible to patients, providers, and policy makers.
4. Laboratories should make data on the analytic and clinical validity of the tests they offer publicly available.
5. A fair and balanced system of oversight needs to be created to harmonize inconsistent and incoherent CMS and FDA rules.

Congress took a bold leap in funding the Human Genome Project with the expectation that it would pay off in benefits to human health. That promise can only be realized if we can have confidence in the quality of genetic tests. Congress enacted CLIA and its

amendments with the expectation that it would ensure the accuracy and reliability of clinical laboratory testing, but those expectations have not been met with respect to genetic tests.

The Center applauds the Committee and the GAO for taking this first step in the investigation of questionable practices with respect to genetic tests sold directly to consumers, and urges the Committee to continue to provide leadership in this area so that we can have confidence that genetic tests can be used to improve and not endanger the public's health. Thank you.