



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

March 5, 2007

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852.

Re: Comments to Docket No. 2006D-0347

Dear Sir/Madam:

The Genetics and Public Policy Center appreciates the opportunity to submit comments regarding FDA's Draft Guidance for Industry, Clinical Laboratories, and FDA Staff - In Vitro Diagnostic Multivariate Index Assays. The Center believes FDA has taken a bold first step in regulating this category of laboratory-developed assays, but that this step raises several questions and concerns whose timely and thoughtful resolution is crucial for public health and the success of genetic medicine.

The Genetics and Public Policy Center was founded in 2002 with a mission to help policy leaders, decision makers, and the public better understand and respond to the challenges and opportunities arising from advances in human genetics. In 2005, with funding from The Pew Charitable Trusts, the Center launched a Genetic Testing Quality Initiative with the goal of improving overall effectiveness, safety, and reliability of genetic testing.¹

Today, there are more than 1000 genetic tests available clinically, and several hundred more available in research settings.² These tests are used to diagnose disease, to predict risk of future disease, and -- more recently -- to guide decisions about whether to undergo a medical procedure or take a particular drug or dosage of a drug.

Yet the regulatory framework for ensuring the safety and effectiveness of these tests is both incoherent and inadequate.³ Most genetic tests are not reviewed by any entity within the federal government before they are offered clinically. To date, FDA has cleared or

¹ Genetics and Public Policy Center, Genetic Testing Quality Initiative, <http://www.dnapolicy.org/policy.gt.php>.

² GeneTests, www.genetests.org.

³ Javitt, G. and K. Hudson. 2006. *Public Health at Risk: Failures in Oversight of Genetic Testing Laboratories*. Washington, D.C.: Genetics and Public Policy Center; Javitt, G. and K. Hudson. 2006. Federal Neglect: Regulation of Genetic Testing. *Issues in Science and Technology*, March 22.

approved only a handful of genetic test kits. Most genetic tests are sold as in-house developed tests (or “home brews”) and each laboratory director makes an independent decision regarding whether and when to make a test available.

In the absence of FDA review, there is no independent review of either a test’s analytic validity, meaning the ability to get the correct answer reliably over time, or clinical validity, meaning the relationship between a particular genetic variation and an individual’s current or future health status. While the Clinical Laboratory Improvement Amendments of 1988 (CLIA)⁴ clearly require laboratories to independently establish the analytic validity of their tests, there is insufficient oversight to ensure that they do so. In particular, no genetic testing specialty area has been established by the Centers for Medicare and Medicaid Services.⁵ Moreover, CLIA regulations do not address clinical validity. Yet clinical validity is profoundly important when considering whether and under what circumstances a genetic test should be available commercially.

Offering tests without adequate evidence of clinical validity endangers more than the public’s pocketbook, it endangers the public’s health. Genetic tests can lead to significant life-altering decisions, such as the decision to undergo surgery, take a drug with significant side effects or refrain from taking a potentially therapeutic drug, bear a child, or terminate a pregnancy. Based on a survey of laboratory directors conducted by the Center in 2006,⁶ a significant number of clinical laboratories lack a clear understanding of what clinical validity even means: 36 percent of those surveyed did not select the correct definition of the term.⁷ Additionally, directors face considerable challenges in establishing clinical validity. While 84 percent of those surveyed agreed that standards should be developed regarding the amount of data required to establish clinical validity of new tests, 76 percent cited lack of clinical data as a significant challenge in establishing clinical validity.

In addition, because FDA traditionally has regulated “test kits” and not “home brews,” there exists an uneven playing field that creates a disincentive to perform research to establish clinical validity and deters innovation of new tests with demonstrated validity. A company that invests the time and effort necessary to develop a test kit for cystic fibrosis, for example, will encounter competition in the marketplace from laboratories offering laboratory-developed cystic fibrosis tests that have not undergone FDA review.⁸

This current “two-path” system has resulted in very few FDA-approved test kits being available. According to our survey, almost 40 percent of laboratories do not use FDA-approved test kits at all, and another 26 percent use them for less than a quarter of the tests they offer.⁹ The main reason for not using FDA approved kits cited by laboratory directors in our survey is that no FDA-approved test kit is available for the disorders tested for by the laboratory.

⁴ 42 U.S.C. § 263a.

⁵ Hudson, K., S. Terry, and P. Lurie, Petition for Rulemaking to M. McClellan, September 26, 2006.

⁶ Hudson, K., J. Murphy, D. Kaufman, G. Javitt, S. Katsanis, and J. Scott. 2006. Oversight of US Genetic Testing Laboratories. *Nature Biotechnology* 24 (9): 1083-1090.

⁷ Unpublished data on file with the Genetics and Public Policy Center.

⁸ Genetics and Public Policy Center, National Genetic Policy Summit, September 20, 2006 (presentation of Greg Hines), http://www.dnapolicy.org/news.past.php?action=detail&past_event_id=38

⁹ Unpublished data on file with the Genetics and Public Policy Center.

The status quo leaves the public health insufficiently protected and fails to reward genetic test manufacturers who perform the research necessary to demonstrate a test's analytic and clinical validity. FDA has a critical role to play in ensuring the safety, effectiveness, and availability of genetic tests. Effective stewardship by FDA is needed to develop and implement a coherent and equitable system of oversight for genetic tests.

FDA's Draft Guidance on IVDMIAs is an important first step in articulating the agency's role in ensuring the safety and effectiveness of genetic tests. However, based on our review of the draft guidance and our consultation with stakeholders, we have identified the following key concerns. First, FDA needs to consider genetic tests holistically, rather than engaging in a piecemeal regulatory strategy. Second, FDA needs to engage all stakeholders -- including device manufacturers, clinical laboratories, patients, and providers -- in discussion before making binding regulatory changes, and to clarify at the outset the overarching goals the agency seeks to achieve in developing a new regulatory process. We note that FDA has used this approach successfully in the past, for example in its regulation of human cell- and tissue-based products.¹⁰ Third, FDA needs to provide sufficient clarity so that the regulated industry knows what it needs to do to comply at the outset, and not through receipt of a warning or untitled letter from the agency.

Turning first to the need for a holistic approach, we note that FDA has yet to convincingly lay out its rationale for singling out IVDMIAs as the starting place in regulating laboratory-based assays. FDA's articulated rationale is that IVDMIAs (1) use clinical data to identify variables, (2) employ a proprietary algorithm to integrate these variables to calculate a patient-specific result; and (3) report the result, which cannot be interpreted by a health care provider without information from the test developer regarding clinical performance and effectiveness.

FDA thus appears to have adopted a purely technology-based approach to the regulation of laboratory-developed tests. While FDA states that, within the category of IVDMIAs, its approach will be risk-based, its initial distinction between IVDMIAs and non-IVDMIAAs does not appear to be risk-based. By separating IVDMIAs from all other laboratory tests, FDA seems to be operating under the assumption that IVDMIAs are, as a class, inherently higher in risk than other laboratory tests. While certain intended uses of IVDMIAs will no doubt put them in an elevated risk category, we are concerned that FDA's piecemeal approach overlooks other high risk tests that do not fall within the IVDMIA framework, while at the same time inappropriately categorizing all IVDMIAs as inherently more risky than other diagnostic tests based on the technology used.

Additionally, FDA's rationale for focusing on IVDMIAs is based on the clinician's inability to independently interpret the results. However, numerous studies have documented the inadequacy of health care providers in interpreting genetic tests outside the IVDMIA definition, thus clinician competence would appear to be an insufficient basis for distinguishing between IVDMIAs and other genetic tests.

¹⁰ U.S. Department of Health and Human Services, Food and Drug Administration. 1997. *Reinventing the Regulation of Human Tissue* (February 28) <http://www.dhhs.gov/news/press/1997pres/970228c.html>.

Second, regarding clarity, there is scant detail provided in the draft guidance, making compliance with its requirements difficult. Uncertainty in the regulatory arena is a significant potential deterrent to innovation, and FDA should provide clear, transparent, directions regarding its expectations. The definition of IVDMIAs is itself quite fuzzy, leaving some to wonder whether their tests are or are not IVDMIAs. While FDA invites questions, we believe a clearer articulation of what tests do and do not fall within the IVDMIA scope would alleviate current confusion. Additionally, FDA has provided little concrete direction regarding how its QSR regulations will interact with CLIA requirements. FDA should quickly issue clarifying guidance to avoid subjecting laboratories to duplicative and potentially conflicting requirements.

Finally, turning to process, while FDA presents this IVDMIA document as “draft guidance,” it represents a major shift in FDA thinking about laboratory-developed diagnostics. While FDA has in the past asserted its authority, as a theoretical matter, to regulate all diagnostic laboratory services as in vitro diagnostic devices, in practice it has left the laboratory sector almost entirely untouched. Yet in this guidance document, FDA for the first time defines a new subset of laboratory tests as regulable. Not surprisingly, the IVDMIA draft guidance created significant anxiety and confusion in the laboratory community. Moreover, as a draft guidance, it ostensibly does not establish “legally enforceable responsibilities,” and an FDA official publicly asserted that the draft guidance was not being enforced.¹¹ Yet, FDA’s response to a Freedom of Information Act request from the Genetics and Public Policy Center revealed that FDA has sent several letters to purveyors of laboratory assays, calling into question the assertion that the FDA is not establishing legally enforceable requirements for at least a subset of these tests. At the very least, FDA is sending confusing signals at a time when clarity is critical. These signals create significant uncertainty in the marketplace, and are counterproductive to the goal of ensuring availability of safe and effective tests. We hope that today’s meeting and FDA’s subsequent interactions with the regulated industry will be characterized by greater notice and explanation regarding FDA’s regulatory intentions.

In summary, we believe that a regulatory system for genetic tests should:

- Ensure that all genetic tests provide accurate information for diagnosis, treatment, or prevention of disease.
- Ensure that the laboratories performing genetic tests are using validated technologies to perform testing.
- Ensure that both providers and patients have adequate information about a test’s benefits and limitations to make informed decisions about whether and when to test.
- Establish a level playing field for all companies seeking to market genetic tests by establishing rational requirements that apply to all players.

¹¹ Woodcock, J. 2006. Comments at the National Genetics Policy Summit. September 20. Audio transcript. Genetics and Public Policy Center, Washington, D.C.

- Employ a risk-based approach that tailors requirements to the degree of risk posed by a test. This approach should take into account the current or foreseeable number of tests performed, the disease or condition (current or future) being tested for, the intended use of the test, the range of likely treatment decisions that will be made based on test results, and the available means of diagnosis or treatment in the absence of the test.
- Require postmarket reporting of problems with testing that led, or could potentially lead, to an adverse clinical event.
- Promote the development of new genetic tests, particularly those for rare diseases and those that can improve current treatment decision-making for life-threatening diseases.

We look forward to working with FDA as it continues to refine its regulatory approach for genetic tests.

Sincerely,

A handwritten signature in cursive script, appearing to read "Kathy Hudson".

Kathy Hudson
Director

A handwritten signature in cursive script, appearing to read "Gail Javitt".

Gail Javitt
Law and Policy Director