In Vitro Diagnostic Multivariate Index Assays; Public Meeting
Docket No. 2006D-0347
Comments of Gail Javitt, JD, MPH on behalf of the
Genetics and Public Policy Center
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My name is Gail Javitt and I appreciate the opportunity to speak today on behalf of the Genetics and Public Policy Center at Johns Hopkins University. We would like to commend FDA for holding this public meeting.

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 availability of genetic testing.

Today, there are more than 1000 genetic tests available clinically, and several hundred more available in research settings. 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 to ensure the safety and effectiveness of these tests is both incoherent and inadequate. Most genetic tests are not reviewed by any entity within the federal government before they are offered clinically. To date, FDA has cleared or 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 its clinical validity, meaning the relationship between a particular genetic variation and an individual's current or future heath status. While the Clinical Laboratory Improvement Amendments of 1988 (CLIA) clearly require laboratories to independently establish analytic validity, there is insufficient oversight to ensure that laboratories do so. Moreover, CLIA has not been interpreted to require that laboratories demonstrate 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 the public's pocketbook, and moreover 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, a significant number of directors lack a clear understanding of what clinical validity even means: 36 percent of those surveyed did not select the correct definition of the term. 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.

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. 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.

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.

FDA's Draft Guidance on IVDMIAs is an important first step in articulating the agency's role. We appreciate FDA initiating this public conversation today.

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. 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. FDA appears to have adopted a purely technology-based approach to the regulation of laboratory-developed tests, and 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.

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 that fall outside the IVDMIA definition, thus clinician competence would appear to be an insufficient basis for distinguishing between IVDMIAs and other genetic tests.

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 lacks sufficient clarity, leaving some to wonder whether their tests are or are not IVDMIAs. 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," the content represents a major shift in FDA thinking about laboratory-developed diagnostics, and, for the first time defines a new subset of laboratory tests as subject to regulation. While an FDA official has stated publicly that the draft guidance is not being enforced, FDA's warning and untitled letters suggest otherwise. 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 conclusion, we believe that an adequate 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.

- Employ a risk-based approach that tailors requirements to the degree of risk posed by a 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.