Research Policy ALERT
THE BIOMEDICAL RESEARCH COMMUNITY'S PREMIER DAILY POLICY RESOURCE
Formerly "The Blue Sheet" & Washington Fax

February 20, 2006

Personalized Medicine: The "Perfect Storm" for Improving Genetic Test Quality - By Kathy Hudson* and Gail Javitt**

Personalized medicine tantalizes the public with its promise of providing the right medicine for the right patient at the right dose, saving lives and preventing dangerous side effects. Delivering this promise, in turn, is predicated on the development and availability of genetic tests that accurately and reliably predict a patient's response to a drug.

Yet the foundation of regulation upon which these tests are poised is shaky, and does not appear sturdy enough to support the promise of personalized medicine. Although the public widely believes that government oversight ensures the quality of genetic tests, this assumption is largely unfounded.

Today, genetic tests are available clinically for more than 900 diseases. Genetic testing has evolved from a pursuit primarily of academic laboratories studying rare diseases to part of mainstream medicine. Genetic testing encompasses a wide net that includes carrier screening to predict one's risk of having a child with a genetic disease, prenatal diagnosis to assess fetal risk of genetic disease, preimplantation genetic diagnosis to select embryos with which to start a pregnancy, and pre-dispositional testing to assess an individual's risk for developing disease in the future. Personalized medicine -- the newest application of testing technology that permits an assessment of whether and how a patient will respond to a particular drug or dose of a drug based on genetic variations in his or her DNA - has captured the public's imagination and has raised expectations for therapies that are safer, more effective, and targeted to individual health needs.

Genetic tests, like many other medical tests, are performed by clinical laboratories. Laboratories can perform tests using so-called "test kits" - free-standing products containing the necessary ingredients and instructions to perform the test - or they can make the test in-house using their own proprietary methods. The vast majority of the tests are developed in-house.

Currently, laboratories that perform genetic testing, whether using a test kit or a

laboratory-developed method, must meet minimum generic standards set by the Center for Medicare and Medicaid Services (CMS) under the Clinical Laboratory Improvement Amendments (CLIA). But these standards are not adequately tailored to the particular complexities that arise from genetic testing. Some laboratories go beyond the minimum through private-sector accreditation, but such accreditation is both voluntary and limited in scope. Unless the laboratory uses a test kit, the Food and Drug Administration (FDA) performs no review regarding a genetic test's analytic or clinical validity, meaning whether the test gets the right answer and provides information that is relevant to a patient's current or future health. To date, FDA has approved only about a dozen genetic test kits, and only three with explicit pharmacogenetic indications.

For more than a decade, federal government officials have been discussing the need for improved oversight of genetic testing. Ten years and two Secretary-level advisory committees later, precious little regulation has been promulgated.

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.

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. Five years later, no proposal has been forthcoming.

Meanwhile, FDA has sent mixed signals about its willingness and ability to assure the safety and accuracy of genetic tests. In 1997 FDA stated that it had jurisdiction over all genetic tests, including those developed in-house by clinical laboratories. More recently, the agency appears to have backed away from this position, with agency representatives stating publicly that the agency lacks jurisdiction over the tests developed by clinical laboratories. At the same time, the agency has recently issued a few letters to companies providing genetic testing services warning them that they might be selling unapproved tests in violation of the law. These letters hint at an attempt by the agency to widen somewhat its regulatory scope, albeit within the confines of its essential "test-kit" only stance.

FDA has taken a somewhat more active interest in genetic tests related to drug prescribing (so-called pharmacogenetic or pharmacogenomic tests), noting their promise of maximizing the therapeutic potential of drugs while minimizing their risks. FDA has issued "guidance documents" to assist drug manufacturers in incorporating

pharmacogenomic data in drug development and labeling. These guidances make clear that, although the precise regulatory framework for pharmacogenetic tests is nascent and evolving, the agency anticipates regulating pharmacogenetic tests.

The guidance is silent, however, regarding in-house developed tests, and does not acknowledge the inherent limitations - not to mention inequity - of a regulatory approach that imposes burdens on the manufacturers of drugs and genetic test kits but not on laboratories that develop in-house pharmacogenetic tests. As a case in point, FDA has approved one test kit to detect a genetic variant that affects the metabolism of many commonly prescribed drugs. However, at least one genetic testing laboratory does not use this kit, and instead offers drug reaction genetic testing using an in-house developed method, leaving the FDA-regulated manufacturer at a competitive disadvantage. Unless FDA's requirements apply to both types of tests, the agency will be ineffective in achieving the goals of its pharmacogenomics guidances.

Quality genetic testing requires good tests and competent laboratories. Tests must reliably be able to detect a particular genetic variation that in turn is correlated with health status or disease risk, and laboratories must reliably be able to ascertain its presence or absence and to communicate results appropriately to health care providers.

Without external scrutiny by adequately trained reviewers, physicians and the public are hard-pressed to distinguish the good performers from the bad, and have little assurance that the tests they use to make profound decisions - to undergo prophylactic mastectomy, or begin a course of therapy - are reliable and relevant predictors of their disease risk or treatment outcome.

The current regulatory environment imposes regulatory hurdles for those who seek to market "test kits," but virtually no hurdles for laboratory-developed tests. This encourages doing less, rather than more, research to find out if a genetic test actually provides information of use to a doctor and patient in making health care decisions. Additionally, the absence of a specialty area under CLIA for most genetic tests impedes CMS's efforts to ensure the quality of genetic testing laboratories.

If personalized medicine is to gain the public's trust - and, equally important, the trust of health care payers - and deliver on its promise of improving health, there must be a sufficient level of 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.

Getting to a system worthy of public trust will require the Department of Health and Human Services to give the necessary direction and resources to the agencies charged with overseeing laboratory and test quality - CMS and FDA - to ensure that they implement needed changes to guarantee quality. Furthermore, it requires that the pharmaceutical industry, which stands to reap the benefits of the success of personalized medicine, exercise its considerable muscle to move the process back on

track, and to support meaningful regulations with measurable results. And, perhaps most important, it requires the public, as the ultimate beneficiary of personalized medicine, to be informed about precisely how little is currently known about the quality of the genetic tests on which personalized medicine is premised.

Now, when personalized medicine is in its infancy, is the time to make sure that it will be raised in a system that ensures that the tests used to guide therapeutic decisions are reliable and relevant and are performed by laboratories whose proficiency has been rigorously and meaningfully assessed.

* *Kathy Hudson, PhD, is director of the Genetics and Public Policy Center and associate professor at the Berman Bioethics Institute, Institute of Genetic Medicine, Department of Pediatrics, Johns Hopkins University*

** *Gail Javitt, JD, MPH, is a policy analyst at the Genetics and Public Policy Center and a research scientist at Berman Bioethics Institute, Johns Hopkins University.*

The Genetics and Public Policy Center acknowledges and thanks The Pew Charitable Trusts for their generous support. The opinions expressed in this article are those of the authors and do not necessarily reflect the view of The Pew Charitable Trusts.