The right prescription for personalized genetic medicine

Gail H Javitt[1] & Kathy Hudson[2†]
[1]Law and Policy Director, Genetics and Public Policy Center, & Research Scientist, Berman Institute of Bioethics, Johns Hopkins University, Baltimore, MD, USA
[2]Director, Genetics and Public Policy Center, & Associate Professor, Berman Institute of Bioethics, Institute of Genetic Medicine & Department of Pediatrics, Johns Hopkins University, Baltimore, MD, USA
Tel.: +1 202 663 5971;
Fax: +1 202 663 5992;
E-mail: khudson5@jhu.edu

"The proliferation of 'direct-to-consumer' testing in the absence of adequate oversight of genetic tests runs the risk of misleading consumers and undermining their confidence in genetic testing."

Pharmacogenetics – the study of how genetic differences influence drug response – tantalizes the public with its promise of providing the right medicine for the right patient at the right dose, saving lives, preventing dangerous side effects and reducing healthcare costs. A key goal of pharmacogenetics is to integrate genetic information into drug development and drug prescribing in order to better match therapies to patients based on specific genetic characteristics.

However, delivering on this promise requires that the right constellation of policies is in place. Such policies must ensure the accuracy and reliability of the genetic tests used to make treatment decisions, while at the same time promoting the development of new tests. Such policies must also create a mechanism for the development of data linking genetic variants to drug response. In particular, data are needed to support concrete dosing recommendations that in turn can be incorporated into drug labels and be used by healthcare providers. Finally, patients must have adequate assurance that the information obtained through genetic testing will be used for their benefit and not to discriminate against them in employment or insurance. Current policies are not up to the task and several key reforms are needed.

Regulatory issues in pharmacogenetics

The idealized scenario for the implementation of pharmacogenetics is that a patient will obtain a genetic test prior to treatment, that the healthcare provider will take the test result into account when prescribing a drug or recommending a treatment, and that this approach will lead to a better patient outcome. However, the regulatory environment is not optimized to facilitate this scenario for two reasons. Firstly, unlike drugs, most genetic tests do not undergo a US FDA review. Secondly, there is not currently an effective mechanism to generate data linking genetic information with drug response or for communicating actionable information to physicians.

Regulation of genetic tests

Today more than 1000 genetic tests are available clinically, with several hundred more available in a research setting. Genetic testing encompasses carrier screening, prenatal diagnosis, preimplantation genetic diagnosis of embryos and predispositional testing to assess an individual's risk for developing disease in the future.

Pharmacogenetic testing is a relative newcomer to the field; only a handful of genetic tests are offered for the purpose of guiding selection and dosing of therapies, such as human epidermal growth factor receptor 2 (*Her2*/*neu*) testing prior to prescribing Herceptin® (trastuzumab) for *Her2*/*neu*-positive breast cancer.

Unlike the Her2/neu test, which was reviewed by the FDA, most genetic tests do not undergo an outside review prior to being offered clinically. Genetic tests, like other laboratory tests, are performed by clinical laboratories. Most genetic tests are developed in-house by the laboratories and made available based on the laboratory director's determination that the tests have adequate analytic and clinical validity. The FDA has historically adopted a 'hands off' regulatory stance with respect to laboratory developed tests. A few laboratories do use 'test kits' – free-standing products containing the necessary ingredients and instructions to perform a test – and the FDA does review the analytic and clinical validity and labeling claims for these tests before they can be marketed. However, only a handful of companies have chosen this route to marketing genetic tests, which is not surprising given that laboratory developed tests do not require any external review before they are marketed. A few of the approved kits, such as the Roche Amplichip® for cytochrome P450 (*CYP*) mutations and the uridine diphosphate glucuronosyltransferase 1 test for irinotecan sensitivity, as well as the *Her2*/*neu* test, are intended for pharmacogenetic use. However, the current 'two path' regulatory system has

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resulted in very few FDA-approved test kits, and there may be few rewards for a manufacturer that has secured approval for a test kit, as other laboratories can develop and market their own non-FDA-approved version of the assay. This inequality of oversight is a deterrent to the development of new, validated kits.

The FDA has recently indicated that it will regulate one small subset of laboratory developed tests it terms *in vitro* diagnostic multivariate index assays (IVDMIAs) [1]. Some IVDMIAs may be used for pharmacogenetic purposes, such as a test that analyzes tumor gene expression to predict risk of cancer recurrence. However, there are few IVDMIAs on the market, so the guidance does not affect most genetic tests that are currently in clinical practice.

Genetic testing laboratories are also subject to oversight under the Clinical Laboratory Improvement Amendments (CLIA), but this oversight is limited [2]. All clinical laboratories must be certified and must comply with regulations aimed at ensuring laboratory quality (e.g., recordkeeping, personnel qualification and duties). Laboratories performing 'high-complexity testing' are subject to additional requirements specific to the testing specialty being conducted by the laboratory. Among other requirements for tests covered by a specialty area is the obligation to enroll in a proficiency-testing program to assess whether a laboratory can perform a test on a patient sample reliably and report the answer correctly.

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However, the CLIA regulations do not contain any specialty area for molecular or biochemical genetic tests. While a federal advisory committee recommended in 2000 that a specialty area be developed, and the Centers for Medicare and Medicaid Services (CMS) claimed for several years to be developing a specialty area for genetic tests, the agency suddenly reversed course in September 2006, announcing that it would not create a specialty area [3]. According to a 2006 survey of genetic testing laboratory directors conducted by the Genetics and Public Policy Center, in the absence of a specialty area requiring proficiency testing, at least a third of genetic testing laboratories do not perform proficiency testing for all or some of their tests [4]. The survey also found that laboratories which reported performing more proficiency testing also reported fewer deficiencies, which in turn was correlated with fewer reported analytical errors [4].

In addition, CLIA regulations do not provide for any external review of the clinical validity of a laboratory's test, and CMS officials have repeatedly stated that clinical validity is 'beyond the scope' of CLIA [5].

The advent of 'direct-to-consumer' (DTC) tests making unproven claims of benefit is one manifestation of the current lack of oversight. Websites marketing testing have proliferated in recent years, offering consumers the opportunity to bypass their healthcare provider and get genetic test results delivered straight to their doorstep (or laptop). While some of these companies offer tests comparable with those routinely used by physicians, others market tests whose validity has not been established. In July 2006, the US Government Accountability Office issued findings of an investigation of four DTC companies marketing 'nutrigenetic' tests, concluding that test results misled consumers by making medically unproven predictions [6].

Some DTC companies offer tests that are explicitly pharmacogenetic in nature. For example, one company offers pharmacogenetic testing of variants in the genes for the CYP enzyme system to guide the treatment and dose selection of selective serotonin reuptake-inhibitors (SSRIs), a class of antidepressants. However, a recent study by the Agency for Healthcare Research and Quality concluded that there is a "paucity of good-quality data addressing the questions of whether testing for *CYP450* polymorphisms in adults entering SSRI treatment for nonpsychotic depression leads to improvement in outcomes, or whether testing results are useful in medical, personal or public health decision-making" [7]. In addition, even if a pharmacogenetic test were adequately validated, it is unclear whether offering it DTC – and thereby bypassing the prescribing physician – would actually improve patient care.

The proliferation of DTC testing in the absence of adequate oversight of genetic tests also runs the risk of misleading consumers and undermining their confidence in genetic testing generally, which in turn may undermine the goals of pharmacogenetics to improve drug selection and treatment.

Recognizing the inadequacies in the oversight of genetic and other laboratory developed tests, Senators Edward Kennedy of MA, USA and Gordon Smith of OR, USA have recently introduced legislation that would classify all laboratory developed tests as medical devices and require laboratories to register with the FDA, list the tests they are performing and submit evidence of the analytical and clinical validity of the tests [8]. The bill would also require CMS to issue a genetic testing specialty. Senator Barack Obama of IL, USA has also introduced a bill that would increase oversight of genetic testing [9]. These bills have garnered the attention of all the key stakeholders in genetic testing and sparked discussions and deliberations that may foster the development of a coherent regulatory framework.

Linking the test & the drug

Her2/neu testing prior to treatment with Herceptin is the 'poster child' for pharmacogenetics, but remains the only example of test and drug codevelopment. In the absence of information in the drug label that links patient genotype with clear prescribing and dosing guidance, healthcare providers are unlikely to incorporate pharmacogenetic information into making treatment decisions, even if they could be confident of the quality of the genetic tests available.

However, developing this body of evidence requires time and money, and it is unclear who has the responsibility or the incentive to develop these data. The current efforts to relabel the anticlotting drug warfarin demonstrate this point. Warfarin is the most commonly prescribed oral anticoagulant for the treatment and prevention of blood clots and is prescribed to more than 1 million patients annually in the USA [10]. However, the correct maintenance dose of warfarin varies from patient to patient. Too high a dose carries a high risk of life-threatening hemorrhage, whereas too low a dose may not prevent blood clots. Adverse events associated with warfarin are costly and affect a largely Medicare-eligible population.

Up to 40% of dose variability is attributable to genetic factors, and variations in two genes in particular – *CYP2C9* and vitamin K epoxide reductase complex subunit 1 (*VKORC1*) – have been linked to warfarin sensitivity and resistance [10]. Based on this, in November 2005, an FDA advisory committee concluded that existing evidence of the influence of *CYP2C9* and *VKORC1* genotypes warranted relabeling of warfarin to include genomic and test information [11]. However, the FDA has yet to require a change in the label. In the meantime, the FDA has itself funded a study – an unusual move by the agency – for the purpose of determining whether genotyping patients achieves the correct dose faster and with fewer initial side effects [12].

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The amount of time it is taking to relabel warfarin – a drug taken by millions of people where the number of variants involved is small, the data reasonably strong and the health and economic benefit potentially dramatic – is a sobering reminder of the challenge of relabeling old drugs to include pharmacogenetic data. More than 50% of prescriptions in 2006 were for generic drugs, that is, those whose patent life has expired. In addition, of 27 currently marketed drugs frequently cited in adverse drug reaction studies, 59% are metabolized by at least one enzyme known to have a variant allele that causes poor metabolism [13]. Thus, there is a pressing need for a sustainable model of data development to support pharmacogenetic relabeling retrospectively, to address currently marketed drugs, as well as prospectively, to inform the development and labeling of new drugs. To influence physician practices and improve clinical care, such data must lead to concrete recommendations in the drug label regarding the treatment decisions that the healthcare provider should make based on the genetic test results.

Securing privacy/ preventing discrimination

Even before sequencing of the human genome began, concerns were raised regarding the possible misuse of genetic test results, in particular by employers and insurers. While the concern regarding genetic discrimination has been framed in terms of genetic testing to predict future disease, the fear of genetic discrimination could also have a negative impact on pharmacogenetic testing. Public mistrust of

genetic testing could slow pharmacogenetic research by making potential participants in clinical trials too fearful to volunteer, and could interfere with patient acceptance of the use of pharmacogenetic testing in clinical care. In addition, genetic markers thought to be of pharmacogenetic relevance only may also prove to relate to future disease risk [14].

Although most of the public believe that employers and health insurers should not have access to their genetic test results [101], individual genetic information is currently protected only by a largely untested patchwork of state and federal laws, which exclude many from protection against discriminatory use. However, after years of languishing, a bill to prohibit genetic discrimination is under active consideration by the 110th Congress and could provide the protection necessary to ease the public's fears [15]. The bill has strong bipartisan support in both the House and Senate, and President Bush has said repeatedly that he will sign the bill if passed.

Conclusion

For more than a decade, federal government officials have been discussing the need for improved oversight of genetic testing and protection from genetic discrimination. A total of 10 years and two Secretary-level advisory committee recommendations later, precious little has been done. Now, when personalized medicine is in its infancy, is the time to make sure that it will be raised in a system that ensures the tests used to guide therapeutic decisions are reliable, relevant and performed by laboratories whose proficiency has been rigorously and meaningfully assessed; that the tests have been validated; that there are data to link test results with concrete treatment actions and that the information will not be misused.

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