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PUBLIC HEALTH

A Case Study of Personalized Medicine

Marketing of unproven tests shows the need for regulatory action to protect public health.

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Personalized medicine through pharmacogenetics promises to revolutionize health care by harnessing individual genetic information to improve drug safety and efficacy. Under a personalized medicine scheme, drug prescribing and dosing no longer would be "one size fits all" but would be carefully tailored to a patient's individual genetic variants. To date, there have been only a few genetic biomarkers whose clinical validity in predicting drug response has been clearly established: HER2-positive breast cancer as a predictor of response to the drug Herceptin being perhaps the best known. However, some foresee the emergence of many more such tests (*1*).

Pharmacogenetic testing presupposes the availability of validated genetic tests, i.e., tests for which there are data linking the presence or absence of specific variants with a specific outcome, such as improved therapeutic response or reduction in adverse events (see figure). Furthermore, it requires that information about the connection between genetic variation and drug response is accurately and truthfully communicated to both health-care providers and patients. As the case study below describes, several barriers currently impede the success of personalized medicine. Today, there is no mechanism to ensure that genetic tests are supported by adequate evidence before they are marketed or that marketing claims for such tests are truthful and not misleading. Misleading claims about tests may lead health-care providers and patients to make inappropriate decisions about whether to test or how to interpret test results (*2*). Misleading marketing claims are particularly troubling when tests are sold directly to consumers (DTC), because there is no health-care provider to serve as a "gatekeeper" to prevent inappropriate test ordering or misinterpretation of test results (*2*). For example, a patient informed of his or her cytochrome P-450 (CYP450) profile might independently change the dose of antidepressant medication with adverse health outcomes. The current situation also could lead both providers and patients to lose trust in the value of genetic testing to improve drug-prescribing decisions (*3*, *4*).

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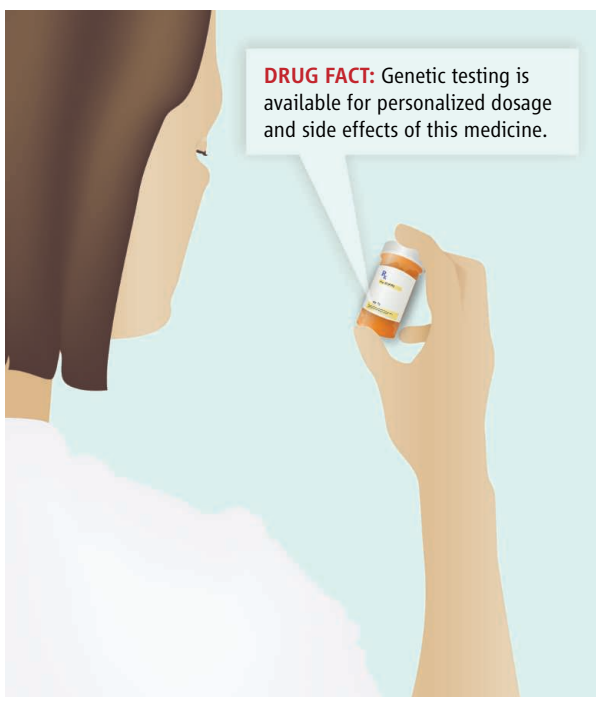
CYP450 Genetic Testing for SSRIs

Many drugs, including the commonly prescribed class of antidepressants, selective serotonin reuptake inhibitors (SSRIs), are either metabolized by CYP450 enzymes or inhibit the activity of these enzymes (*5*, *6*).



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Genotyping of variants in the CYP450 genes can be used to predict the metabolizing strength of the cytochrome enzymes, defined as ultrarapid, extensive, intermediate, or poor. In theory, the profile of genotypic variants can be used to determine a dosage specific to a patient more efficiently than the traditional trial-and-error approach (*7*, *8*). An individual's genotypic profile also may predict whether a particular medication interferes with the activity of another prescribed medication. Hence, there has been interest in genotyping CYP450 genes as a means to better guide SSRI prescribing and dosing. A CYP450 genotyping test cleared by the U.S. Food and Drug Administration (FDA) is available for two genes.

In Fall 2004, the Centers for Disease Control and Prevention (CDC) commissioned an independent, nonfederal expert panel, the EGAPP (Evaluation of Genomic Applications in Practice and Prevention) working group, to examine the validity and utility of genotyping for SSRI prescription. The review of the evidence found convincing data that SSRIs are metabolized by and inhibit the function of CYP450 enzymes and that polymorphisms in CYP450 enzymes are associated with the function and strength of SSRI metabolism (*7*, *9*). However, EGAPP found "no evidence was available showing that the results of CYP450 testing influenced SSRI choice or dose and improved patient outcomes…" (*9*). EGAPP's conclusion "discourages use of CYP450 testing for patients beginning SSRI treatment until further clinical trials are completed" (*9*).

Despite the EGAPP conclusions, at least 15 businesses currently offer CYP450 genotyping services, with four companies making specific claims about the benefit of such testing for SSRI prescribing or dosing. Seryx and DNA Direct outsource the test to LabCorp and provide only interpretation of the genotypes, whereas Genelex provides both the test and interpretation. Both DNA Direct and Genelex offer this test DTC, rather than through a medical provider. All four businesses offer CYP450 genotyping services for a range of pharmaceuticals, not only antidepressants. Some Web sites make explicit claims about the utility of CYP450 testing for particular drugs, such as the claim by Genelex that pharmacogenetic testing is "required to effectively prescribe Paxil" (*10*). Other Web sites are less direct, including information about SSRIs within tables that describe the relations between CYP450 genes and a number of different medications (*11*–*13*). Among the four Web sites surveyed, there were inconsistencies regarding which genes are genotyped for each

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of five SSRIs, a finding that shows the lack of consensus within the community as to what genes are relevant to test for each SSRI. This lack of consensus is likely confusing to both patients and doctors.

Current Regulatory Environment

In most states, laboratories are not required to demonstrate clinical validity before offering new genetic tests to health-care providers and the public. Although clinical laboratories must be certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (*14*), laboratories do not have to demonstrate the clinical validity of the tests they provide to obtain certification. In addition, although FDA regulates manufactured test kits as medical devices, FDA does not regulate most laboratory-developed tests (LDTs). In the case of CYP450 testing, a laboratory may purchase the Roche Amplichip, which is regulated by FDA as a medical device, or it may create an LDT for CYP450 that receives no FDA scrutiny.

Perhaps an even more relevant limitation is that FDA's oversight is limited to the specific uses for which the manufacturer intends the device. Thus, if the manufacturer does not claim that the test is beneficial in selection and dosing of SSRIs, FDA does not require clinical evidence of such benefit from the manufacturer. In the case of the Roche Amplichip test, for example, the intended use cleared by FDA does not refer to any specific drug, but rather states that information about the *CYP2D6* and *CYP2C19* genotypes "may be used as an aid to clinicians in determining therapeutic strategy and treatment dose for therapeutics that are metabolized" by products of these genes (*15*).

Although FDA could, in theory, require manufacturers to demonstrate a test's efficacy for a specific intended use (e.g., CYP450 testing for fluvoxamine) as a condition of test approval, the agency instead has cleared CYP450 tests without clinical studies demonstrating that using these tests is beneficial in the selection or dosing of any particular SSRI. This is consistent with FDA's approach to some other diagnostic devices (such as magnetic resonance imaging machines), where it has left determinations of clinical validity and utility to clinicians and payers.

Finally, although the Federal Trade Commission Act prohibits businesses from making false or misleading claims about their products, the Federal Trade Commission (FTC) has not undertaken enforcement activities against false and misleading claims made by genetic test providers. In July 2006, in response to a U.S. Government Accountability Office investigation and subsequent Senate hearing on the value of genetic tests sold directly to consumers, FTC issued a consumer alert publicizing the questionable claims made for some DTC genetic tests (*16*). As described in this case study, this indirect approach has had no apparent effect on the availability of tests with questionable clinical validity.

Policy Options and Prospects

Federal advisory committees, lawmakers, and stakeholder groups have made recommendations about enhancements in the oversight of genetic testing (*17*–*23*) and the Department of Health and Human Services has made "ensuring that genetic tests are accurate, valid and useful" a critical element of its personalized health-care initiative (*24*). However, to date, the government has not taken meaningful steps to enhance the oversight of genetic testing. Three key policy changes are needed.

Enhanced enforcement by FTC in oversight of misleading claims. FTC has the authority to prohibit misleading advertising claims, but enforcement of this authority with respect to genetic tests has not been a priority for the agency. FTC should use the data analysis generated by EGAPP and others to take decisive action against companies making false or misleading claims about the benefit of genetic testing.

Development of a mandatory registry. Those offering genetic tests, whether DTC or through health-care providers, should first be required to submit information about the test and data supporting the intended use of the tests to a registry that would be accessible to the public. The availability of this information would aid doctors and patients in test selection and interpretation and afford a degree of transparency that currently is absent from the genetic-testing marketplace. Stakeholders representing industry, patients, and consumers support the development of a genetic test registry (*17*–*19*).

FDA oversight of LDTs. When the results of a genetic test will be used to take specific action regarding drug selection or dosing, FDA should first ensure that the test accurately and reliably detects a variant that correlates with drug response and that the claims made by those selling the test are supported by the evidence. Such review is essential for public health protection whether the test in question is based on a "test kit" or an LDT; FDA's review thus should not depend on the testing platform used by the laboratory. Expanding FDA to include those tests that will form the bedrock of personalized medicine will better protect the public against tests that lack adequate evidence of clinical benefit and whose use could lead to selection of ineffective medications, adverse drug reactions, or failure to take a drug that would be effective.

At this early stage of personalized genomic medicine, it is essential to be certain that the regulatory infrastructure is tailored in a manner beneficial to public health.

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ERRATUM

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Policy Forum: "A case study of personalized medicine" by S. H. Katsanis *et al*. (4 April, p. 53). Owing to editorial error, some corrections sent by the author were not made for publication. The author's affiliation omitted the name of the institute and should read as follows: Genetics and Public Policy Center, Berman Institute of Bioethics, The Johns Hopkins University, Washington, DC 20036, USA. In the first paragraph, the reference to "biomarkers" should read "tests" as follows: "To date, there have been only a few genetic tests whose clinical validity in predicting drug response has been clearly established…." In refs. 10 to 13, the date of access to material published online should have been updated to show that, as of 12 March 2008, these companies had not reflected the recommendations of a December report from the expert panel for Evaluation of Genomic Applications in Practice and Prevention.