SYMPOSIUM

Regulatory Agency Consideration of Pharmacogenomics

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This article discusses the current ambiguous state of federal regulatory agency control over pharmacogenomic testing, a subset of genetic testing that combines information about genetic variability with pharmacology in order to improve drug recommendations. An analysis of the common three terms used to evaluate regulation of pharmacogenomic testing: research validity, clinical validity, and clinical utility, followed by a case study involving U. S. Food and Drug Administration (FDA) regulation of laboratory developed tests, illustrates the present gap in pharmacogenomic oversight. The existing agency overlap in regulating pharmacogenomic testing leads to unclear or even contradictory authoritative advice. Exp Biol Med 233:1498–1503, 2008

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The regulatory requirements for pharmacogenomic research, parallel drug development, and use in the clinic are not entirely clear. Since 1993 there have been a series of meetings, task forces, working groups, and cabinet level advisory committees to determine which federal agency should regulate which aspects of pharmacogenomic research and use. The most recent Advisory Committee to the Secretary of Health and Human Services (Secretary), called the Secretarial Advisory Committee on Genetics, Health, and Society (SACGHS), has been working on this issue for several years. Last November the SACGHS published its draft report, and its final report to the Secretary is due at the end of April 2008. In their February 12, 2008 open public meeting, a consultant to the SACGHS presented the current regulatory scheme (Fig. 1). This chart, while amusing and confusing, is not entirely accurate and I expect the SACGHS will refine it. Yet it provides some idea of the crazy quilt of supervision—and lack of supervision—of genetic testing, including pharmacogenomic testing, a subset of genetic testing.

Federal Oversight of Pharmacogenomic Research

In this paper "genetic testing" refers to the analysis of chromosomes, genes, single nucleotide polymorphisms (SNPs), and gene products (e.g., proteins or enzymes) to determine whether a genetic alteration related to a specific disease or condition is present in an individual. "Pharmacogenomics" refers to the "the science of determining how genetic variability influences physiological responses to drugs, from absorption and metabolism to pharmacologic action and therapeutic effect" (1). Pharmacogenomic information can help determine which patients should avoid a drug because they are likely to experience an adverse event from the drug or because the drug is unlikely to offer them benefit. It can also be used to determine which patients should take a particular drug because the drug is likely to produce benefit, or to determine what the dose of a drug should be, depending on a patient's metabolism.

During the pure research phase, there is little federal oversight of genetics research, other than obligations that accompany the collection of samples and informed consent. However, once the research is used in combination with drug development, or is used to provide information and advice back to a patient or physician, the regulatory schemes become more complex.

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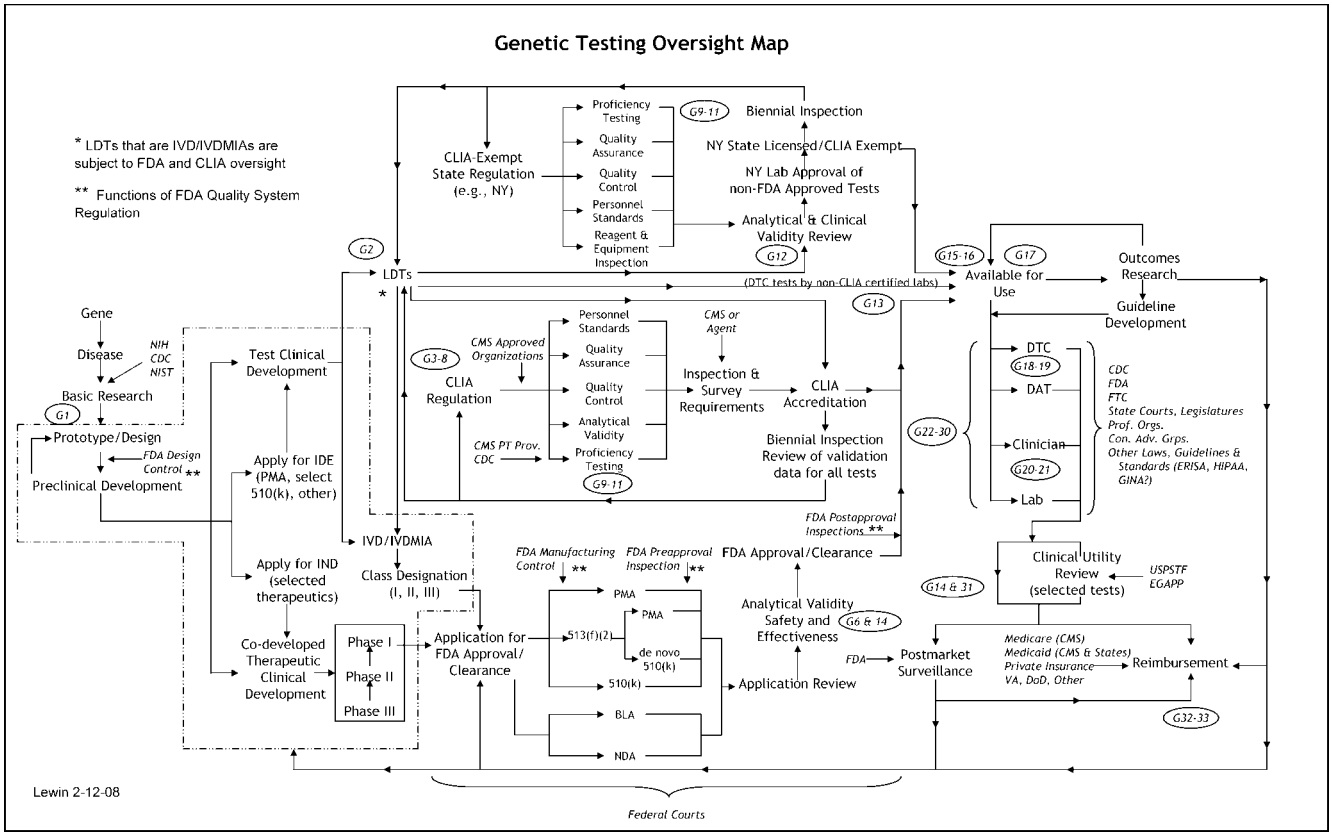

Figure 1. Genetic testing oversight map.

There are three terms that are widely used regarding the regulation of any genetic test, including any pharmacogenomic test.

1) Does it have "analytical validity"? This is the measure of the test's ability to accurately and reliably detect the genotype of interest. The pertinent questions relate to sensitivity, specificity, and quality control. Analytical validity does not answer the question of whether there is any point to detecting the genotype of interest.

2) Does it have "clinical validity"? Clinical validity relates to whether there is a connection between the measured genotype and a disorder or phenotype of interest. Here we again ask about sensitivity and specificity, but also about the prevalence and penetrance of the mutations in the population studied, whether the test has been validated in other populations, and the positive and negative predictive values of the test. Clinical validity requires a demonstration that the test is able to detect or predict the associated disorder or phenotype in patients. There is controversy about the type of data needed for clinical validity, and it will depend on the particular use of the test. Pharmacogenomic tests are used to select patients to receive or avoid a particular drug therapy, or to stratify patients in some other way. The data must, therefore, demonstrate that the test is able to select (or deselect) patients with a biomarker (analyte) of interest.

3) Does it have "clinical utility"? Clinical utility answers the question of whether, by using the test, it is likely that the patient care will change. Is there a suitable intervention? Will the patient be better off? Some add a broader public health or health care system calculus to the question of clinical utility: What are the financial costs and benefits to using the test? Will it make a positive contribution to the public health? These are the toughest and most controversial questions, and the clinical utility of only a few genetic tests have been established. Clinical utility is generally demonstrated through prospective controlled clinical trials, but even those might not answer all of the broader public health-related clinical utility questions (see, for example, Ref. 2).

There is an additional question sometimes asked, which is: 4) Is it ethical to conduct the test? This arises from early views that genetic information is special, more powerful information that should be handled in ways different from other medical information. This concept of "genetic exceptionalism" has influenced the debates on the proper regulation of genetic testing, though it is less pertinent to pharmacogenomic testing. But even if one does not accept "genetic exceptionalism," it is still important to consider the privacy and discrimination aspects of pharmacogenomic testing.

Analytical Validity

Two federal agencies may be involved in reviewing a test's analytical validity. Analytical validity includes not just

test measurements and cut-off values, but also the regulation of the actual testing by laboratory personnel. The regulatory scheme differs if the test is run using a "kit" sold by a medical device company to a clinical laboratory, or if the test is run at the clinical laboratory without the use of a kit. A diagnostic test kit is packaged with all the necessary components and is marketed for use in many laboratories. Kits must be reviewed by the Food and Drug Administration (FDA) before they can be sold (3). The latter non-kit tests are called "laboratory developed tests" (LDTs) or "home-brew" tests. With respect to the physical act of testing a sample by laboratory personnel, there are two principal players—the FDA's Center for Devices and Radiological Health (CDRH), and the Centers for Medicare and Medicaid Services (CMS).

If a non-federal laboratory is not doing pure research, but is giving information back to individual patients or physicians, then that laboratory must comply with the Clinical Laboratory Improvements Act of 1988—called "CLIA." CLIA is administered principally through CMS. The CLIA program is designed to assess laboratory competence and quality, and as part of its requirements, it mandates that tests be analytically valid. The CLIA program does not require clinical validity or utility. Under CLIA, all genetic tests—including pharmacogenomic tests—must be conducted in a laboratory certified to handle "high complexity" testing. This is true even of academic laboratories, though many do not comply with CLIA requirements. CMS recently rejected calls for more extensive regulation of genetic testing, essentially rejecting "genetic exceptionalism" as a reason for increasing requirements for genetic tests (4). I anticipate that the SACGHS will recommend to the Secretary that CLIA-certified laboratories be required to conduct more proficiency testing for genetic tests.

In addition to CMS and its oversight of clinical laboratories through CLIA, the FDA's CDRH has authority over products used in clinical laboratories and clinical laboratory testing systems, procedures, and reporting, although it has used that authority infrequently. The FDA already regulates the general purpose and analyte specific reagents used in laboratories, laboratory systems that use sophisticated computer programs, and other laboratory activities. It is almost inevitable that the FDA will regulate most of the laboratory-based activities used in pharmacogenomic testing, whether the pharmacogenomic testing is done through kits or through LDTs. Increased FDA oversight would provide consistency in regulatory requirements for the LDTs and kits. It would also provide greater assurance of test quality by evaluating tests regardless of how the test is packaged or where it is performed.

Clinical Validity and Utility

When the FDA exercises oversight of tests, it reviews clinical validity and utility, and CDC has also played a role in assessing the clinical utility of some types of genetic testing. The stringency of the FDA's review of any diagnostic test depends on the "intended use" of the test. That is why the FDA is less interested in ancestry tests than tests to determine whether a patient should take a particular drug. One of the challenges the FDA has faced since the beginning of genetic testing is how to triage its oversight. The agency does not have the resources to review all of the genetic tests coming out of the academic community and industry, so it must focus on the tests that will have the greatest impact on the most patients. Pharmacogenomic tests are among the tests that meet these criteria.

The clinical validity and utility of pharmacogenomics lie at the intersection of testing and drug use. The interplay between a pharmacogenomic test and a drug prescribing decision is principally regulated by the FDA's Center for Drug Evaluation and Research (CDER). However CDER, CDRH, and the FDA's Office of Combination Products all have a role to play in pharmacogenomic drug development. This is because CDER approves the drug, CDRH approves the test, and the Office of Combination Products is involved whenever a drug or biologic and a device are being developed together. Primary decision-making authority lies with CDER and CDRH, however. Both of those FDA centers evaluate clinical utility, but only on a patient-specific level, not on the broad public health level that is favored by some, including the Centers for Disease Control and Prevention (CDC).

The FDA recognized in 2002 that it needed to better understand what was going on within the industry with respect to pharmacogenomics before it could adequately regulate in the field (see, for example, Ref. 5). In May 2002 the FDA proposed that companies voluntarily submit exploratory pharmacogenomic information to the agency during drug development with the understanding that the data would not undergo formal regulatory review (6). Several companies were willing to assist the FDA, and their Voluntary Genomic Data Submissions (VGDS) improved the FDA's understanding of the field. In November 2003, the FDA took pharmacogenomic drug development a step further and published a draft guidance on pharmacogenomic data submissions (7). It also held a workshop to discuss not only voluntary submissions, but also areas where pharmacogenomic data would be required under FDA regulations (8). The FDA's guidance on pharmacogenomic data submissions was finalized in March 2005, and a companion guidance reflecting the FDA's greater understanding of the field was published in August 2007 (9).

The FDA has also tried to provide additional guidance to industry with its "one stop shopping" web page devoted to pharmacogenomics (10). This site contains other guidance documents that are relevant for pharmacogenomic submissions, such as standardization of data submissions, statistical analyses, and qualification of a biomarker. It also includes a "decision-tree" to help a company or laboratory think through the requirements of a regulatory submission to

the FDA. And the FDA has promised additional guidance documents on clinical trial design for phase III trials, adaptive trial design, and designs to increase heterogeneity in patients by enriching the study population based on gene variants (11).

There are several types of pharmacogenomic tests and the various different intended uses of the tests drive the data submission requirements. In one type, there is relevant genetic data on factors such as metabolism and clearance, where the relevant genes may impact prescribing decisions for numerous drugs. For example cytochrome P450 (CYP450) influences the metabolism of numerous drugs, including warfarin and codeine, and the human leukocyte antigen allele HLA-B*1502 is associated with dangerous, sometimes fatal skin reactions and toxic epidermal necrolysis following treatment with carbamazepine. Another type of pharmacogenomic test is when a therapy is targeting only tumors with particular genetic profiles that differ from normal cells. Obviously it is important to know if the tumor matches the targeted approach. Examples of these targeted therapies are Glevec, Erbitux, and Herceptin. There is a draft drug-device co-development guidance document to help explain the FDA's current thinking about development approaches and regulatory requirements for this type of test (12).

There are many other challenges in the drug-pharmacogenetic test co-development space, including when genetic testing should start, how and when samples should be tested, whether retrospective analysis are sufficient and whether confirmatory randomized trials are always going to be required. These issues will play out over the next couple of years.

IVDMIAs—A Recent Example of FDA Regulation of LDTs Involving Analytical and Clinical Utility

The FDA does not currently regulate all LDTs. For example, the FDA has decided to exercise its enforcement discretion and not regulate rare disease tests. It has also not focused its attention on genotype determinations or chromosomal copy number determinations. However, in 2006, the FDA proposed to expand its regulatory reach over a subset of LDTs. The FDA proposed that it regulate those lab-based in vitro diagnostic tests that combine the values of multiple variables and use an interpretive function to yield a single, patient-specific result—which might be a classification, score, or index—that is intended for use in diagnosis or treatment of a disease, where the result's derivation is non-transparent and cannot be independently derived or verified by the treating physician (13). These are called "in vitro diagnostic multivariate index assays", or "IVDMIAs" for short, and many of them are intended for pharmacogenomic uses. Because of confusion over the scope of the FDA's plan, and concern that it might lead to expanded FDA regulation over more types of LDTs and to overall increased regulation of clinical laboratories by the FDA as well as CMS, the clinical laboratory community has resisted the FDA's efforts.

The basic premise of the FDA's draft IVDMIA guidance is that the agency should exercise oversight over tests that do not permit a physician to deconstruct the test and determine the true meaning of the test for a particular patient. Thus an IVDMIA is defined as a test that analyzes multiple variables to arrive at a single number that correlates with how the patient should be treated. For example, after examining several SNPs and applying the test algorithm, an IVDMIA might say "your patient scores a 5." You would then look up the meaning of number 5, and find out that patients with scores from 1–10 are likely to have recurrent colon cancer while patients with scores from 20 and up do not. Or that patients with scores from 1–10 should get chemotherapy but patients with higher scores should not. So from the FDA's perspective, since the physician cannot reverse engineer the test, he or she must accept the test score, and the meaning of the test score, on blind faith. The FDA proposed that, rather than let physicians fly blind, the agency would analyze and determine the analytical and clinical validity of the test system.

The FDA has already approved at least one IVDMIA, Agendia BV's MammaPrint, a LDT that determines the likelihood of breast cancer returning within five to ten years after initial onset of a woman's breast cancer. Agendia compared the genetic profiles of a large number of women who had breast cancer and identified a set of 70 genes whose activity confers information about recurrence. The MammaPrint test measures the level of activity of these genes in the woman's surgically removed breast cancer tissue, and then uses a specific algorithm to produce a score that determines whether the woman is at low risk or high risk for metastasis (14). The FDA then created a new category of immunology and microbiology devices, called a "gene expression profiling test system for breast cancer prognosis," (15) and created a guidance document on the types of controls that must be in place for such a test (16). Other tests of the same type will have to follow the same criteria.

If the FDA goes forward with its guidance on IVDMIAs, many clinical laboratories will have to determine whether they are using an IVDMIA and therefore need to submit pre-marketing applications to the FDA. The FDA permits laboratories and other companies to come into the agency for a discussion on the regulatory standards for medical devices and required data to support submissions (17).

A Challenge with Respect to Clinical Validity and Utility

While the regulation of pharmacogenomic testing is in its earliest stages, there are challenges with regard to who is giving authoritative advice on the use of pharmacogenomic tests. The first pharmacogenomic test kit approved by the

FDA was Roche's Amplichip Cytochrome P450 Genotyping test kit, which allows physicians to use a patient's genetic information to pinpoint the right dose of certain medicines for cancer, cardiac disease, and psychiatric illnesses. The FDA decided that this information had clinical validity and it was worthwhile for physicians to know a patient's CYP450 status before making certain prescribing decisions, in particular because of potential drug-drug interactions. The FDA has included CYP450 information on the labels of several drugs, including selective serotonin reuptake inhibitors (SSRIs) (18).

The CYP450 test was in the news in early April 2008, when a *Science* Policy Forum article complained that some clinical laboratories were making claims that CYP450 tests could be used to determine what SSRI a consumer might take (19). In a companion news release, the authors claimed the "marketing of unproven tests a threat to public health" (20). The *Science* article relied on a study commissioned by CDC that looked at the studies on CYP450 tests and their use in prescribing SSRIs. This CDC funded group called EGAAP—which did not include anyone from the FDA and which did not have access to the proprietary data used by the FDA to approve the CYP450 test kit or the drug labels—decided that the CYP450 test should not be used in SSRI prescribing decisions because it had no clinical utility (21).

This situation presents a conundrum for everyone relating to pharmacogenomic testing—who's in charge of giving authoritative advice to clinicians about the use of these tests? The FDA approved a CYP450 test kit and found that that CYP450 variants have usefulness for clinician decision-making for several drugs, including SSRIs. The use of the test is described on several drug labels approved by the FDA. Yet EGAPP says this is not useful information. So are the companies making false or misleading claims? Not if you agree with the FDA. Should a doctor bother testing a patient? Not if you agree with EGAPP. Clearly there is more work to be done.

Conclusion

It would be difficult to overestimate the importance of having solid data supporting the use of pharmacogenomic tests. Responsible companies and clinical laboratories offering these tests will have such data regardless of federal oversight. However, expanded FDA oversight will ensure standardization of the types and extent of data supporting the tests, and will meet public expectations that the government has reviewed important medical technologies. Not all genetic tests require federal oversight but pharmacogenomic tests are a subset of genetic tests that should be subject to FDA oversight because of their medical importance.

The challenge for the federal government and involved private parties is to get from here to there in a reasonably well-coordinated manner, ensuring as little interagency duplication as possible, and always remembering that undue delay in bringing tests to market can also cause adverse health consequences. The FDA is plainly moving in this direction; accomplishing the goal, however, will not be easy.

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3. The CDRH's Office of In Vitro Diagnostics has extensive regulatory information on its website. U.S. Food and Drug Administration. Office of In Vitro Diagnostics. 2008. http://www.fda.gov/cdrh/oivd/officeinfo.html. All medical devices are classified into one of three classes: I, II, and III. Class I devices have only general controls such as proper labeling and good manufacturing practices. Class II devices receive pre-market clearance based on scientific studies, and they are sometimes required to meet pre-specified regulatory requirements. Class III devices receive pre-market approval based on the most extensive scientific data and studies.
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12. U.S. Food and Drug Administration. Draft drug-diagnostic co-development concept paper. April 8, 2005. Available at: http://www.fda.gov/cder/genomics/pharmacoconceptfn.pdf. FDA opened Docket No. 2004N-0279 to receive comments on this topic.
13. The FDA's first effort to regulate IVDMIAs was in a "Draft guidance for industry, clinical laboratories, and FDA staff: in vitro diagnostic multivariate index assays" released on September 7, 2008. FDA opened a public docket to receive comments on the draft guidance. Docket No. 2006D-0347. After reviewing comments and holding a public meeting, FDA published a second draft guidance with the same name on July 26, 2007. The second draft can be accessed at http://www.fda.gov/cdrh/oivd/guidance/1610.pdf. FDA has not finalized the guidance.
14. U.S. Food and Drug Administration. FDA news: FDA clears breast cancer specific molecular prognostic test. February 6, 2007. Available at: http://www.fda.gov/bbs/topics/NEWS/2007/NEW01555.html. Agendia submitted data to FDA to validate this intended use. The studies determined that the test was "useful in predicting time to distant metastasis in women who are under age 61 and in the two earliest stages of the disease (Stage I and Stage II) and who have tumor size equal to or less than five centimeters and no evidence that the cancer has spread to nearby lymph nodes (lymph node negative)."
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