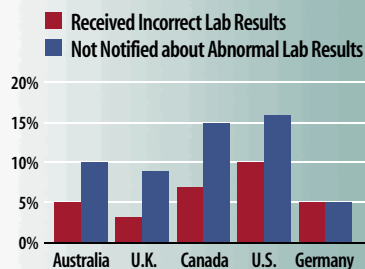


SURVEY GIVES U.S. HEALTH CARE SYSTEM POOR GRADE

One-third of U.S. patients with health problems report experiencing medical mistakes, medication errors, or inaccurate or delayed lab results, according to a new international health policy survey supported by the Commonwealth Fund. The 2005 survey of six nations—Australia, Canada, Germany, New Zealand, the United Kingdom, and the U.S.—is the eighth in a series of cross-national surveys of medical care systems in advanced industrialized countries. The 2005 survey interviewed adults from each of the six countries who had recently been hospitalized, had surgery, or had health problems, and assessed their views on the health care systems in their respective nations.

Patients in all countries reported safety risks, poor care coordination, and inadequate chronic care treatment, but the U.S. stood out for high error rates, inefficient coordination of care, and high out-of-pocket costs that led people to go without care. Thirty-four percent of U.S. patients said that they had experienced at least one of four types of errors: mistakes in medical treatment, incorrect medication or improper dosage, and inaccurate or delayed lab results. Thirty percent of Canadians reported experiencing one of these errors, as did

Patients Reporting Lab Errors in Past 2 Years



Source: 2005 Commonwealth Fund International Health Policy Survey of Sicker Adults

roughly one-fifth of patients in the other nations surveyed. Most patients in each country—61% to 83%—said the health care providers involved did not tell them about the mistakes.

At least one-fifth of patients (19% to 26%) in the six countries reported communication gaps between themselves and hospital staff, and one-sixth said they would have liked greater involvement in decisions made about their care. One-third of U.S. respondents said that either test results or records were not available at the time of appointments or that doctors duplicated tests. This was the highest rate among the six nations.

As discovered in past surveys, the U.S. health care system continues to place undue financial burdens on patients, particularly when compared to other industrialized nations. Fifty-one percent of U.S. adults with health problems said they did not visit a doctor when sick or fill a prescription due to cost concerns. Additionally, one-third of U.S. patients spent more than \$1,000 out-of-pocket for medical bills in the past year. In contrast, 65% of U.K. adults reported zero out-of-pocket medical costs.

The full results of the survey and concurrent analysis can be found online at <http://content.healthaffairs.org/cgi/content/full/hlthaff.w5.509/DC1>

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The Challenges of Pharmacogenomic Tests

Has Personalized Medicine Arrived?

BY RICHARD PIZZI

When the Food and Drug Administration (FDA) cleared Roche Molecular Systems' (Pleasanton, Calif.) AmpliChip CYP450 genotyping test in January 2005, many experts hailed the event as the birth of a new era in personalized medicine.

The first pharmacogenomic microarray designed for clinical applications, the AmpliChip detects specific genetic variations in the cytochrome P450 gene that can provide information on how well an individual will metabolize certain classes of drugs, thereby allowing clinicians to tailor drug therapies to the individual's genetic makeup. Since Roche released the chip for sale in the U.S. in June 2005, labs now have ready access to pharmacogenomic technology. But before this new era of personalized medicine can become firmly established, some major alterations in the drug-prescribing process need to occur. Like other revolutionary changes in medicine, adoption of the new test will take time as physicians gain an understanding of how to order and use the results of the test, and as labs incorporate the AmpliChip and other pharmacogenomic testing options into their menus.

Most physicians already recognize that not all patients respond similarly to certain drug therapies, but the label "pharmacogenomic test" may scare not only clinicians, but also patients who might be worried about a test that examines their genetic makeup. Pharmacogenomics is not new, however, says Michael Murphy,

See **Pharmacogenomics**, continued on page 3



FDA Proposes New CLIA Waiver Guidelines

Boost or Blow for POCT?

BY JULIE MCDOWELL

Despite their pledge to ease regulatory burdens on diagnostic manufacturers pursuing waived status for their test kits, the Food and Drug Administration's (FDA) recent draft guidance is demanding more evidence to demonstrate an insignificant risk of harm or an erroneous result when the test is performed by an operator with little or no laboratory testing training. The agency says that initiatives such as validation studies linked to hazard analysis, detailed in this September 2005 document, "Draft Guidance for Industry and FDA Staff: Recommendations for Clinical Laboratory Improvement Amendments of 1988 (CLIA) Waiver Applications," deal with quality and accuracy concerns raised by the laboratory community when tests are performed outside traditional lab settings. But some in the lab community are voicing concerns that the revised criteria will do little to stem quality problems and noncompliance currently plaguing many waived labs and will also make it more difficult—and less attractive—for IVD companies to dedicate resources to pursue the development of waived devices, such as point-of-care (POC) tests.

One of the primary motives behind the new waived criteria is to keep pace with burgeoning POC technology, explained Steven Gutman, MD, Director of FDA's Office of In Vitro Diagnostic Device Evaluation and Safety, Center for Devices and Radiological Health. "The point of the waived test category is to allow for simple and error proof tests to be available for use in settings that are not subject to the traditional regulation," he said. The Centers for Disease Control and Prevention (CDC) first drafted the waiver criteria rule in 1995, and over the past decade, federal officials have learned better ways to evaluate new tech-

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A New Era in Personalized Medicine

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president and CEO of Gentriss Corporation (Morrisville, N.C.). He calls it a “new term for an old science” and points out that researchers have worked for years on uncovering genetic mutations that are useful in predicting, among other things, drug metabolism. “But pharmacogenomics gets more attention now because it has matured to the point where it can be used in a very practical sense to help ensure that safe and effective drugs are taken to market,” Murphy said. As the clinical utility of the first wave of pharmacogenomic tests is proven, more will likely follow and may provide the tipping point that makes personalized medicine an essential part of modern medical practice.

The AmpliChip and Personalized Medicine

“Personalized medicine” is a catchphrase for the practice of clinical medicine that relies upon the ever-advancing science of pharmacogenomics and pharmacogenetics. Pharmacogenetics is the study of the role of inheritance in inter-individual variation in drug response, and a primary inspiration for this type of research has been the promise of individualized drug therapy. Rapid developments in human genomics have resulted in the evolution of pharmacogenetics into pharmacogenomics. Scientists hope that this research will ultimately allow clinicians to order genotyping tests that can predict how patients metabolize different drugs, thereby increasing drug efficacy and reducing the number of adverse drug reactions (ADRs) that may account for as many as 2.2 million hospital events and up to 100,000 deaths per year in the U.S (see box).

The labs that are bringing the Roche AmpliChip in-house believe that its potential to bolster patient safety will ultimately make it a very marketable test. The AmpliChip uses Affymetrix (Santa Clara, Calif.) microarray technology and polymerase chain reaction (PCR) technology to detect variations in the cytochrome P450 2D6 and 2C19 genes. It reports 29 known polymorphisms in the CYP2D6 gene and two major polymorphisms in the CYP2C19 gene. Detection of the CYP2D6 polymorphisms allows for the identification of 33 unique alleles.

The enzyme encoded by the 2D6 gene plays a primary role in the metabolism of drugs used to treat depression, schizophrenia, bi-polar disorder, cardiovascular disease treated with beta-blockers, attention deficit/hyperactivity disorder, among others, while the enzyme produced from the CYP2C19 gene metabolizes many anti-convulsants, proton pump inhibitors, benzodiazepines, and anti-malarials. The AmpliChip CYP450 test ultimately provides a predictive phenotype for patients—poor, intermediate, extensive, or ultra-rapid metabolizer. It is these designations that are intended to help clinicians tailor prescriptions to an individual patient’s needs.

Spectrum Laboratory Network (Greensboro, N. C.) has been offering the AmpliChip test to clients since late September, although the lab has worked with Roche to acquire the test since it received FDA clearance in January. Taylor McKeeman, Chief Operating Officer at Spectrum, explained that his company received the instrument that reads the chip’s results in June and spent most of August and September performing validation studies. Spectrum decided to offer the Am-

pliChip test because the company believed that the initial costs of investment would be more than eclipsed by demand over the long run, once clinicians realized the incredible utility of a test that could prevent ADRs. “If you consider that five percent of all hospital admissions are due to negative dose effects—basically therapeutic overdoses—this test will be useful because it helps eliminate the ‘hit-or-miss’ methods by which clinicians currently determine whether a patient is a fast, moderate, or non-metabolizer of a certain drug,” McKeeman said. “This type of test gives physicians some real foresight—the ability to determine scientifically that one drug will work and another might not.”

A.K.A.: Predictive Testing Technologies

The hope of developing an effective means of therapeutic drug monitoring drives most current pharmacogenomic research. McKeeman calls these tests “predictive testing technologies” because they are not simply diagnostic but may provide prognostic information that can help direct therapies for multiple disorders in a patient over time. Being first, as well as using DNA microarray technology, earned the Roche AmpliChip a lot of press, but other technologies exist and are in use in U.S. labs.

Some labs have developed their own “homebrew” assays, while others have adopted commercial platforms. For instance, ARUP Laboratories (Salt Lake City, Utah) first began investigating pharmacogenomics four years ago and began offering tests to its clients for CYP2D6 in 2002, CYP2C9 and 2C19 in 2004, and more comprehensive tests for all three CYP450 genes in July 2005.

“Every clinical group that I have spoken with is interested in these tests,” said Gwen McMillin, PhD, Assistant Professor of Pathology at the University of Utah and Medical Director of ARUP’s Toxicology Laboratory. She explained that most of the studies that have been done so far are with relatively controlled populations, and researchers do not really know how the tests are going to be used in “real world” situations. Still, researchers and clinicians remain hopeful because “we don’t want to put patients in a situation where they are paying for drugs that don’t work and going through lengthy titration periods, trial-and-error essentially, to find the best drug,” McMillin said.

McMillin illustrates the potential of personalized medicine with results from a recent ARUP study on the antidepressant venlafaxine. Depressed patients were titrated with the drug until they achieved full response. ARUP laboratorians then compared blood concentrations of venlafaxine and its active metabolite with patient genotypes to determine any relationship. “We discovered that there was a clustering of drug concentrations with genotypes and effective doses,” McMillin said. “This suggests that one might use pharmacogenomic testing to obtain the patient’s genotype before selecting the drug to find out whether the drug would be useful and what might be the ideal starting dose.” ARUP also plans pharmacogenetic studies with antipsychotic medications and anticoagulation therapies, an area of research that McMillin thinks may be particularly promising.

The ARUP pharmacogenomics program currently uses the Tag-It reagent system from Tm Bioscience (Toronto, Canada) and performs analyses on the Luminex (Austin, Tex.) bead array platform. McMillin cautions labs

PGx: A Routine Part of Testing in the Hospital?

Sometime in early 2006, Dartmouth-Hitchcock Medical Center hopes to initiate a pharmacogenomic study that could help change the way clinicians prescribe medication at the Lebanon, N.H., institution. The hospital’s pharmacogenomics group—consisting of clinical laboratorians, pharmacologists, and physicians—is proposing to genotype all admitted patients in an attempt to determine whether routine pharmacogenomic testing is cost-effective in a clinical setting. The team will not test for clinical phenotype nor will they test for the propensity to develop a particular disease, but only to determine the therapeutic efficacy of different classes of drugs.

Gregory J. Tsongalis, PhD, Dartmouth-Hitchcock’s Director of Molecular Pathology, says that this project has been in the works for almost 2 years. The concept grew out of the pharmacogenomics group’s review of relevant studies in an attempt to determine how to use the information to improve patient care.

“We believe that the impact will be incredible throughout the hospital,” Tsongalis said. “Everyone from the pain clinic to the neuropsychiatric clinic will be affected. And the oncology department is especially excited about targeting therapies using pharmacogenomics.” He added that hospital administrators and physicians believe that the program, although initially expensive, will have such a positive effect on patient management that there will be major cost-savings in the future, especially because the population served by the hospital is rooted in the New Hampshire area. “The savings in the pharmacy alone could justify such a program,” Tsongalis said. “Not to mention the institutional costs of adverse drug reactions that might be eliminated if this works in the way we think it will.”

Tsongalis and his colleagues are currently examining a variety of pharmacogenomic technologies, and have yet to decide on the various platforms that will be used in the study.

“In some sense, I think this technology could bring laboratory medicine back to the lab,” Tsongalis said. “In past days of lab medicine, the lab directors served more routinely as clinical consultants than we do now. I think pharmacogenomics may give us the opportunity to be clinical consultants once again.”

interested in setting up the tests that understanding the differences among gene test panels remains a major challenge in the evolving field. “You really have to know what you’re getting when you order one of these tests,” she said. “Some panels are more comprehensive than others, and alleles may be detected with different sets of mutations. This has tremendous potential, but people need to be patient because no one fully understands how to use the technology in the clinic right now.”

Psychiatry and Beyond

As in the ARUP program, the laboratorians who perform pharmacogenomic testing at

the Mayo Clinic (Rochester, Minn.) have worked closely with clinicians in psychiatric medicine. Clinician demand drives the Mayo pharmacogenomic program, explains Dennis J. O’Kane, PhD, Associate Professor of Laboratory Medicine at the Mayo Clinic College of Medicine, and he thinks that psychiatry seems to be ahead of the pack. “There has to be an unmet clinical need for us to initiate a new program,” he said. “We’ve got about six tests that can be ordered, most of which are useful predominantly for psychiatry. Although we’ve had testing since 2003, we’re still developing the program.” Mayo offers the CYP2D6, 2C9, and 2C19

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tests, but can also provide clients with results for catechol-O-methyltransferase (COMT) and serotonin receptors 2A and 2B, which are helpful to psychiatrists treating patients for bipolar disorder and schizophrenia.

But O'Kane and his Mayo colleague, Loralie J. Langman, PhD, anticipate that pharmacogenomic testing will expand in the coming years to encompass other medical subfields. "The CYP2D6, 2C9, and 2C19 tests will probably be the first to show up in smaller labs, perhaps in three to five years," Langman said. "But as we sort through the science and improve clinician education, there will be great interest in the realm of cancer pharmacogenetics, for example." O'Kane added that there are increasing opportunities for research and development in the realm of cardiogenomics as well. "The CYP genes are involved in disposition of many of the cardiac medicines and in drug/drug interactions," he said. "There also may be real benefits in testing for LDL receptor polymorphisms and in trying to determine which statins will not cause side effects." O'Kane and Langman agree, however, that the cardiac and cancer tests may not be available for several years.

Gentris CEO Murphy agrees that cardio- and cancer pharmacogenomics will likely be in great demand in the future, especially as patient advocacy groups encourage clinicians, laboratorians, and the pharmaceutical and diagnostics industries to make more of these tests available to the general public. "The majority of the interest that we see is coming directly from patients," Murphy said. "The Herceptin story is one that many in the general public can relate to, and they will want these technologies as they learn more about them. But we have to do a better job of educating physicians and the public."

Making PGx Routine: Regulation and Costs

Those knowledgeable about pharmacogenomic testing are well aware of its potential benefits, but the challenge of increasing public and physician awareness, not to mention the goal of making such testing routine in smaller labs, will take time. At the October 2005 meeting of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS), Steven Gutman, MD, Director of the FDA Office for In Vitro Diagnostic Device Evaluation and Safety, part of the Center for Devices and Radiological Health (CDRH), emphasized the importance of regulatory oversight as pharmacogenomic technologies become more widespread and are marketed to physicians and patients. "Twenty percent of medications in the U.S. would have dosing requirements affected by the AmpliChip," Gutman said when providing an example of the potential impact of pharmacogenomics. He stressed the need for industry and the FDA to work closely together, because although these technologies have "analytical strengths" they also suffer from some "clinical weaknesses." To address this emerging area, FDA established the Interdisciplinary Pharmacogenomics Review Group (IPRG), whose mission is to establish a scientific and regulatory framework for reviewing genomic data. The IPRG is an agency-wide review group, whose members include individuals from various FDA centers including the CDRH and the Center for Drug Evaluation and Research (see box).

Murphy agrees that the pharmacogenomics industry needs FDA guidance in order for the field to advance. He wants the FDA to clearly label which tests are critical

or highly-recommended for a particular drug—both previously approved drugs and drugs that the FDA plans to approve. "They have started to do this—a re-labeling initiative—and one recent example is the cancer drug irinotecan" he said. "But I believe that the FDA must be very clear about this, because the health care industry isn't going to be willing to spend the money on pharmacogenomics and physicians aren't going to bother doing these tests unless there's some direction."

Another aspect of pharmacogenomic testing that must be addressed before it gains widespread acceptance is the issue of cost. "These tests are not inexpensive," McKeeman said. He explained that Spectrum invested approximately \$150,000 for their instrumentation, and the cost per test can approach \$400. "It's not at the point where you would call it a 'high profit margin' test," he added. "I don't expect a hospital lab or small reference lab would be willing to put that kind of money into it, unless they believed that they have a niche business that they could corner, and I really don't think this will be a niche business."

Weighing cost versus benefit becomes crucial when labs consider implementing tests like these. "They are expensive now, but the cost of these tests will go down over time," McMillin said. "Although if one considers the cost of trying multiple drugs—like anti-depressants—over the course of a few months, with no guarantee that they will work, a test like this begins to look very cost-effective." Due to the expense involved in establishing a pharmacogenomic testing program and the current uncertainty about the market for such tests, larger reference labs and major academic medical centers do most of the testing. But the numbers of labs offering the tests increase every year. "A year ago there were a very small number of labs performing this testing," McMillin said. "That's probably doubled or tripled since then. The number of requests that we get has

gone up a lot in the last few months. Still, this testing is nowhere near routine, and it won't be routine until we have more data."

Laboratory Rocket Science

A few other hurdles will challenge the rapid spread of pharmacogenomic testing, but may only delay the inevitable movement of genetic testing into a majority of labs. Not unexpectedly, reimbursement issues are a significant problem. Murphy points out that reimbursement for the currently available genetic tests often does not match the costs of providing the tests, and suggests that physicians and smaller labs will be less reluctant to move into pharmacogenomics if reimbursement more closely harmonizes with laboratory costs.

As with many new laboratory procedures, educating clinicians about the tests presents a challenge. Many clinicians may never have heard of pharmacogenomic tests, and they will probably have little idea what to do with the results of the tests when they receive them. Langman thinks that this may be the greatest barrier to testing, because physicians will have to understand and appreciate the importance of these tests if they are going to order them routinely. "It's reasonably easy to hold workshops and seminars in order to reach clinicians," she said. "But it's almost essential—especially in larger institutions—to have one person who is really excited about a test like this in order to spark interest among their colleagues."

There is no lack of excitement among laboratorians who design and perform these tests, however. As the testing expands and focuses on more application-specific panels that include genes beyond metabolism—like genes associated with drug transport and reception—enthusiasm will likely rise outside of the larger labs that do most of the current testing. "We're really excited about the potential of pharmacogenomics," said McKeeman. "It's what we in the laboratory business call 'rocket science.'" CLN

FDA Working with Industry to Expedite Review of PGx Data

The FDA's Center for Drug Evaluation and Research (CDER) has created a system to facilitate the review of pharmacogenomic data that will optimally lead to a more streamlined and effective evaluation and approval process for pharmacogenomic technologies. The Interdisciplinary Pharmacogenomics Review Group (IPRG) is the body responsible for reviewing Voluntary Genomics Data Submissions (VGDS)—a mechanism that the FDA calls a "novel way of sharing information" that will benefit both industry sponsors and regulatory scientists.

Since most current pharmacogenomic data are of an exploratory or research nature, FDA regulations do not require that these data be submitted as part of an Investigational New Drug (IND) application or that complete reports be submitted with a New Drug Application (NDA) or a Biologics License Application (BLA). In such cases, the VGDS system allows sponsors to provide data voluntarily, in order to prevent delays in reviews of submissions where pharmacogenomic data are an integral part of a drug development program.

Speaking at the October 2005 SACGHS meeting, Allen Rudman, PhD, Associate Director of CDER's Office of Clinical Pharmacology and Biopharmaceutics, said that IPRG had received 23 VGDS requests to date and has already scheduled or held 12 review sessions. These include multiple VGDSs on different drugs and follow-up on VGDS submissions of initial studies. "VGDS submissions have provided FDA with significant pharmacogenomic data and information in numerous therapeutic, scientific, and technical areas which would otherwise be unavailable," Rudman said.

Rudman also explained that although the FDA does not develop pharmacogenomic tests, it can encourage them to be developed. He said that information gleaned from the VGDS program will be critical to guiding the drug development process, and he added a few words of advice for the pharmacogenomics industry. "Pharmacogenomic research needs to be seen in the context of biomarker development and validation as well as disease management to expedite the approval of new drugs and indications."