

## MANY AMERICANS HAVE "LOW" HEALTH LITERACY, SAYS IOM

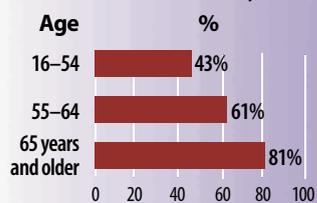
According to a study released last month by the Institute of Medicine (IOM), nearly 90 million Americans have trouble obtaining, processing, and understanding the basic information and services they need to make appropriate decisions regarding their health. The IOM is calling this phenomenon "low health literacy," and describes how the nation can address the problem in *Health Literacy: A Prescription to End Confusion*.

"If health professionals were able to take the time to ask their patients to explain exactly what they understand about their diagnoses, instructions, and bottle labels, the caregivers would find many gaps in knowledge, difficulties in understanding, and misinterpretations," wrote Harvey V. Fineberg, MD, PhD, President of the IOM.

There are steps that can be taken to improve the situation, however. In its report, the IOM identifies a long list of efforts that can be undertaken by HHS and other public and private sector organizations to stimulate the development of health literacy knowledge, measures, and approaches.

Health care systems and providers are being asked to develop and support programs to reduce the negative effects

### Percentage of U.S. Population with Limited Health Literacy Skills\*



\*Numbers represent those with literacy skills below high school level, and are taken from the National Adult Literacy Survey. The IOM committee asserts that this group has limited health literacy as well. Source: *Health Literacy: A Prescription to End Confusion*, IOM, April 2004.

of limited health literacy. To accomplish this, the IOM suggests that providers engage consumers in the development of health communications and infuse insights gained from these activities into the health messages they create every day. The IOM also recommends that health care providers explore creative approaches to communicate health information using print and other communication outlets, and urges groups like the National Committee for Quality Assurance and JCAHO to begin collecting data on providers' efforts in health literacy assessment. Further, said IOM, these groups and others should clearly incorporate health literacy into their accreditation standards.

"Comparatively little attention has been devoted to enabling patients to comprehend their condition and treatment, to make the best decisions for their care, and to take the right medications at the right time in the intended dose," concluded Fineberg. "As this report makes clear, *Health Literacy*—enabling patients to understand and to act in their own interest—remains a neglected, final pathway to high-quality health care." To read more about the report, go to the IOM Web site at: [www.iom.edu/report.asp?id=19723](http://www.iom.edu/report.asp?id=19723).

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## Bringing Pharmacogenomic Assays to Market

### How Will the FDA Regulate These New Tests?

BY SUE AUXTER-PARHAM

For years, the laboratory community has been waiting with anticipation for the wave of pharmacogenomic assays in development at drug and diagnostic companies to come to market. Although no DNA-based tests with specific pharmacogenomic indications for use have yet been approved by the Food and Drug Administration (FDA), some assays are beginning to trickle into the agency for review. At the AACC TDM Renaissance and Pharmacogenomics Forum III: Managing the Future meeting, held in Baltimore, Md., February 12–13, Gentris Corporation (Morrisville, N.C.) announced that it has submitted its first pharmacogenomic assay to the agency, and other companies are likely following suit.

As more of these assays make their way to the FDA, the agency is developing guidance documents that could more clearly delineate how manufacturers can navigate the regulatory process. "We're now seeing a convergence of efforts from all sides—from the scientific community, from the regulatory agencies, and from the manufacturers—to create the pathways that will bring pharmacogenomic tests to market," observed Steven Wong, PhD, Professor of Pathology and Director of Clinical Chemistry/Toxicology, TDM, Pharmacogenomics, and Proteomics at the Medical College of Wisconsin in Milwaukee,

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## New CVD Guidelines for Women Grounded in Women's Research

### AACC Takes Important Step with Endorsement

BY PENNY ALLEN

Evidence-based medicine, the integration of the best research evidence with clinical expertise, is increasingly becoming an integral part of the medical decision making process. However, when it comes to women's health issues, the database of clinical studies is limited. In the past, clinical studies included far more men than women, thereby skewing the findings, as well as any guidelines that were developed from them. But with the increasing recognition that women's health issues in the areas of coronary and cardiovascular disease are different than men's, researchers are now taking steps to study target populations of women. For the first time, new guidelines for the prevention and treatment of cardiovascular disease in women, which were published by the American Heart Association (AHA) in February (*Circulation* 2004;198:672–693), have as their foundation research on women—and extrapolation from research on men that has been carefully evaluated in terms of its appropriateness for women. AACC, along with 21 other medical organizations, has endorsed these new guidelines.

In the past decade, the Food and Drug Administration (FDA) and government research offices have mandated assessment of gender effects and inclusion of women in clinical trials, ushering in the beginning of data specific to women. According to Nanette Wenger, MD, one of the authors of the guidelines and Professor of Medicine in the Division of Cardiology at Emory University School of Medicine, Atlanta, Ga., the new AHA guidelines are a reflection of this initiative. "This

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# Regulating Pharmacogenomic Tests

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and Chair of both AACC's Pharmacogenomics Advisory Committee and Molecular Pathology Division. "We've already created a top ten list of pharmacogenomic tests that we hope diagnostic companies will develop," said Wong (see box, p. 6), adding that the FDA may use the list as well to prioritize its efforts in creating guidance documents for manufacturers of pharmacogenomic assays.

## The Pharmacogenomics Data Submissions Draft Guidance

Currently, the FDA has regulatory pathways for submitting DNA-based technologies for review, and IVD manufacturers can use these for some pharmacogenomic assay submissions. The regulatory framework becomes more complicated, however, when a pharmacogenomic assay is tied to a drug via the drug's labeling. "If a company's aim is to develop tests for drug metabolism, they can do that now since the tests will apply to many drugs. However, if a test is included on the label of a specific drug, that would require regulatory co-devel-

opment of the test and the drug," explained Gualberto Ruaño, MD, PhD, President of Genomas (New Haven, Conn.), a "physiogenomics" company that looks for relationships between genomic markers and enhanced human health and disease prevention.

Ruaño, who also serves on the board of the Personalized Medicine Coalition (see box, at right) as one of its founding directors, added that the FDA is working on a different regulatory mechanism for these types of drug/assay pairs. This summer, the agency is expected to release the final version of its draft guidance for industry, which will be called "Guidance for Industry: Pharmacogenomic Data Submissions." According to the FDA, the document was developed to encourage pharmaceutical and biotech companies to conduct pharmacogenomic testing during drug development, and clarifies how the FDA will evaluate the resulting data. The FDA's goal is to "smoothly integrate" pharmacogenomic testing into the drug development process, and as this is accomplished, more drugs will be paired with pharmacogenomic tests when they are

# Personalized Medicine Coalition Forming

Pharmaceutical companies, in vitro diagnostics manufacturers, universities, academicians, and others are joining together to form a non-profit organization called the Personalized Medicine Coalition (PMC) that will be devoted to furthering the burgeoning field of pharmacogenomics. Gualberto Ruaño, MD, PhD, President of Genomas (New Haven, Conn.), and one of the founding directors of the PMC, says that it will be an advocacy and education foundation to promote personalized medicine. "The Personalized Medicine Coalition will disseminate information about pharmacogenomics, acting as a public forum for discussion of issues. It will also create a means of having different stakeholders come together and work toward a common goal," he said. "Ultimately, we want the coalition to be the information source for talking about the implementation of personalized medicine."

approved by the FDA.

The draft of this guidance document, which is currently available on the agency's Web site (see box, p. 7), provides specific criteria and recommendations on submission of pharmacogenomic data for investigational new drug applications (INDs), new drug applications (NDAs), and biological license applications (BLAs). This includes information on what data is needed, and how the FDA will or will not use such data in making regulatory decisions. The FDA is currently working on further guidance that

will address the co-development of pharmacogenomic tests and pharmaceuticals.

With the release of a final Pharmacogenomic Data Submissions guidance document, the labeling of certain drugs will likely change significantly—perhaps in a way that will encourage more pharmacogenomic testing, noted Ruaño. "There's already a precedent for recommending pharmacogenomic testing on a drug label. The label of the drug Strattera [atomoxetine HCl, Eli Lilly and Company, Indianapolis, Ind.], for

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## Standardizing the Language of Pharmacogenomics

With the advent of pharmacogenomics regulation, the FDA has adopted standard definitions for a number of terms related to this new field of medicine. For the most part, the following terms, which are defined in the Draft Guidance on Pharmacogenomic Data Submissions, are the same as those created by the Biomarkers Definitions Working Group and published in *Clinical Pharmacology & Therapeutics* (2001;69:89–95):

**Biological marker (biomarker):** A characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.

**Pharmacogenetic test:** An assay intended to study interindividual variations in DNA sequence related to drug absorption and disposition (pharmacokinetics) or drug action (pharmacodynamics) including polymorphic variation in the genes that encode the functions of transporters, metabolizing enzymes, receptors, and other proteins.

**Pharmacogenomic test:** An assay intended to study interindividual variations in whole-genome or candidate gene single-nucleotide polymorphism (SNP) maps, haplotype markers, and alterations in gene expression or inactivation that may be correlated with pharmacological function and therapeutic response.

**Valid biomarker:** A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is an established scientific framework or body of evidence that elucidates the physiologic, toxicologic, pharmacologic, or clinical significance of the test results.

**Known valid biomarker:** A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is widespread agreement in the medical or scientific community about the physiologic, toxicologic, pharmacologic, or clinical significance of the results.

**Probable valid biomarker:** A biomarker that is measured in an analytical test system with well-established performance characteristics and for which there is a scientific framework or body of evidence that appears to elucidate the physiologic, toxicologic, pharmacologic, or clinical significance of the test results. A probable valid biomarker may not have reached the status of a known valid marker because, for example, the data elucidating its significance may have been generated within a single company and may not be available for public scientific scrutiny. In addition, the data elucidating its significance, although highly suggestive, may not be conclusive; and independent replication of the results may not have occurred.

**Voluntary genomic data submission (VGDS):** The designation for pharmacogenomic data submitted voluntarily to the FDA.

# More Guidance Documents Planned

**Pharmacogenomic Tests**, from page 3

example, which is used for attention-deficit hyperactivity disorder, states that tests are available to detect poor metabolizers. With the adoption of this guidance document, however, the labels will likely become much more specific," he said. For example, Ruaño explained, a label for a new drug could potentially state that tests for metabolism based on DNA markers are available for CYP2D6, CYP3A1, and that these tests should be performed to determine the right dosage of the drug. Such specificity in the labeling will likely lead to more physicians using the pharmacogenomic assays prior to prescribing the drugs, Ruaño opined. "If you have a label on a drug that states the drug has particular tests related to its metabolism and the DNA constituency of the patient, and these tests are required to determine dosage, that's more powerful than the informational statement that's on Strattera's label today," he said.

While the guidance document on pharmacogenomic data submissions appears to be moving forward smoothly at the agency,

there have been differences of opinion about some of the content. The main areas of controversy appear to be in the labeling section, and in the area of the document that defines the terms used in pharmacogenomic data submissions (see box, p. 3). "The definition of a biomarker has become one of the focal points of the whole process," said Wong, because the data that are being encouraged by the FDA for submission by pharmaceutical companies are mostly genomic in nature, and opinions differ on whether the term "biomarker" should be more narrowly defined.

## Should the Multiplex Testing Guidance Be Modified?

These differences of opinion are expected to be resolved by the FDA's Center for Drug Evaluation Research (CDER) and the

Center for Devices and Radiological Health (CDRH), which are working together to finalize the pharmacogenomic data submissions guidance. The two centers have also just begun working on the document that will address the co-development of pharmacogenomic tests and pharmaceuticals, and CDRH is working on other initiatives that will also help facilitate the review of pharmacogenomic assays.

One of the documents CDRH has developed is a draft guidance called "Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns." The Office of In Vitro Diagnostics Device Evaluation and Safety (OIVD) released the document about a year ago, and some believe that there could be an opportunity to amend it so that it more specifically addresses pharmacogenomic testing. "The multiplex document was initially formulated as a guidance document for molecular testing, but it could

be restructured so that it would have much more focus for pharmacogenomics," noted Wong, who is working with other AACC members on a continuing basis to identify where AACC could be most helpful in developing further guidance related to pharmacogenomic testing.

## SACGHS and Pharmacogenomics Regulation

Pharmacogenomics is not only a major priority for the FDA, but also made a list of priorities developed by the Secretary's Advisory Committee on Genetics, Health and Society (SACGHS) in March. "In terms of pharmacogenomics, we, as a society, are attempting to discover to what extent we should individualize the practice of medicine and use genetic determinants to target pharmaceutical intervention, and to what extent we should use genomics to identify new drug targets," said Emily Winn-Deen, PhD, of Roche Molecular Systems in Pleasanton,

## The Top Ten Pharmacogenetic Tests

According to Steven Wong, PhD, Professor of Pathology and Director of Clinical Chemistry/Toxicology, TDM, Pharmacogenomics, and Proteomics at the Medical College of Wisconsin in Milwaukee, the following list of tests, which were derived from an AACC survey of subscribers to the Pharmacogenomics Working Group listserv and participants in the recent TDM Renaissance III meeting in Baltimore, may be used by the FDA to prioritize the development of guidance documents for pharmacogenomic assays. For the top two tests, CYP2D6 and TPMT, the agency is already in the process of developing guidance documents.

Rank	Analyte
1	CYP2D6
2	TPMT (thiopurine S-methyltransferase)
3	CYP2C9
4	CYP2C19
5	NAT-2 (N-acetyl transferase)
6	CYP3A5
7	UGT1A1(Uridinediphosphoglucuronosyltransferase)
8	MDR1/P-Glycoprotein (medium-chain dehydrogenase/reductase)
9	CYP2B6
10	MTHFR (Methylene tetrahydrofolate reductase)

Calif., speaking at the March 1-2 SACGHS meeting. “How should the clinical validity or utility of pharmacogenomic tests be established? How will the pharmaceuticals that are already on the market be reassessed, and what can the federal government do to improve the chance that this technology will be integrated and used to improve patient care? These are some of the questions that need to be answered,” she said.

In the area of pharmacogenomics, SACGHS plans to organize a fact-finding panel of diverse experts, including FDA staff, industry representatives, clinicians, and others, to explore obstacles to the integration of pharmacogenomics into clinical practice. The committee also plans to address concerns over coverage and reimbursement for genetic technologies, such as those used in pharmacogenomic testing, by gathering data and preparing a report that will describe current issues in coverage and

reimbursement for such technologies. The report will also make recommendations about how coverage and reimbursement can be enhanced in order to improve access to health-related genetic technologies and services in all health care settings.

According to Rúaño, obtaining appropriate coverage and reimbursement is essential to the survival of pharmacogenomics. “The next challenge in pharmacogenomics is reimbursement, but the field may have a champion in the new administrator at the Centers for Medicare and Medicaid Services. When he was the FDA Commissioner, Mark McClellan identified pharmacogenomics as a key action point for the agency, and hopefully, he will bring that mission to CMS as well,” he said. McClellan moved from the FDA to CMS in March.

In the meantime, the FDA, laboratorians, and manufacturers appear to be finding some common ground regarding what con-

stitutes appropriate regulation of pharmacogenomic assays. “What everybody agrees on is that metabolism profiling of patients using DNA markers for drug metabolism has reached maturity, and therefore, there is the expectation that the metabolism of drugs in development will be profiled genetically,” said Rúaño. The next leap is the use of these DNA markers in the practice of medicine prior to the administration of therapeutic interventions.

The submission of the first DNA-based pharmacogenomic tests to the FDA signals the beginning of pharmacogenomic testing’s movement into clinical practice, observed Wong. “My gut feeling is that we’re almost there,” he said, adding that the recent submissions of pharmacogenomic tests to the FDA are “sending a clear signal to manufacturers not to wait too long in developing and preparing their pharmacogenomic assays for FDA review.” 

## Where to Find Pharmacogenomic Test-Related Guidance

Currently, the FDA has two draft guidance documents on its Web site that address pharmacogenomic testing. The first is called “Draft Guidance for Industry: Pharmacogenomic Data Submissions,” and can be found at: [www.fda.gov/cder/guidance/5900dft.pdf](http://www.fda.gov/cder/guidance/5900dft.pdf).

The second, called “Multiplex Tests for Heritable DNA Markers, Mutations and Expression Patterns: Draft Guidance for Industry and FDA Reviewers,” is available at: [www.fda.gov/cdrh/oivd/guidance/1210.pdf](http://www.fda.gov/cdrh/oivd/guidance/1210.pdf).

Also, to follow the activities of the Secretary’s Advisory Committee on Genetics, Health, and Society, which will be examining issues related to pharmacogenomic testing over the next year, go to: <http://www4.od.nih.gov/oba/sacghs.htm>.

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