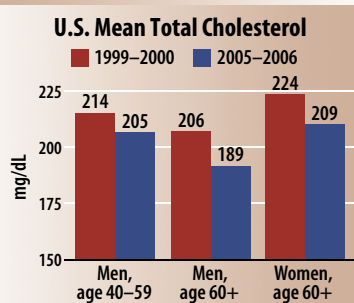


MEAN TOTAL CHOLESTEROL LEVELS FALL

Mean serum total cholesterol levels in adults age 20 and older have fallen below 200 mg/dL, according to a report from the CDC's National Center for Health Statistics. The report, based on data from CDC's National Health and Nutrition Examination Surveys, notes that the figure for 2005–2006 was 199 mg/dL, a drop of five points from the mean of 204 mg/dL in 1999–2000.

CDC authors note that the 2005–2006 figure meets a Healthy People 2010 target calling for mean serum cholesterol levels among adults below 200 mg/dL.

Reduction in mean serum total cholesterol for men over 40 and women over 60—the groups most likely to take statins—appears to have driven the decline in total cholesterol levels. Between 1999–2000 and 2005–2006, mean levels among men ages 40–59 dropped 9 points, from 214 mg/dL to 205 mg/dL, and dipped 17 points, from 206 mg/dL to 189 mg/dL, for men age 60 and older. Meanwhile, women age 60 and older had a decline of 15 points, from a mean of 224 mg/dL to 209 mg/dL. While the report did not specifically mention statin use, it did note little change in total cholesterol levels during



Source: CDC National Center for Health Statistics

this same period of time for people in other sex and age groups.

While the decline in total cholesterol levels is good news, the report doesn't give a complete picture of the state of cardiovascular risk due to blood lipids, the report notes. "Other fractions of total cholesterol, specifically LDL and HDL, are needed to assess the clinical risk of high total serum cholesterol in individuals. These components of cholesterol were not addressed in this analysis."

Overall, 15.7% of adults age 20 and older had high serum total cholesterol—defined as 240 mg/dL—during 2005–2006. More women had high total cholesterol than men, especially after age 60. Overall, 17.3% of women had high total cholesterol, versus 13.8% of men. Among those age 60 and older, 23% of women had high total cholesterol, versus 10% of men.

One piece of good news is rates of cholesterol screening that increase with age. During 2005–2006, 70% of women reported being screened in the previous five years, versus 65% of men. Both men and women age 60 or older had higher screening rates, 91% and 88% respectively.

View the report at: www.cdc.gov/nchs/data/databriefs/db02.pdf.

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Targeted Therapeutics in Non-Small Cell Lung Cancer

How Molecular Assays Guide Their Use

BY DEBORAH LEVENSON

Advanced non-small cell lung cancer (NSCLC), the leading cause of cancer-related deaths worldwide, is usually diagnosed at a metastatic or advanced stage, when median survival is just eight to 10 months. Therapeutic agents called tyrosine kinase inhibitors (TKIs), small molecules that target the epidermal growth factor receptor (EGFR) gene, can extend survival for certain NSCLC patients. These drugs may be most useful for those NSCLC patients with mutations in particular areas of the gene that encodes EGFR. Present in about 10% of NSCLC cases in North American and Western European patients, these mutations occur at a much higher rates—up to 50%—in Asian countries and in patients of Asian ancestry. The mutations are also more common in women and nonsmokers who have adenocarcinomas with bronchioalveolar features.

Now, updated guidelines from the National Comprehensive Care Network (NCCN), an alliance of 21 leading cancer institutions, are the first to specifically recommend that oncologists consider lab tests to see if one TKI, erlotinib, will be effective in patients with no history of smoking and either a known active *EGFR* mutation or extra copies of the gene. Erlotinib is marketed as Tarceva in the U.S. by OSI Pharmaceuticals (Melville, N.Y.) through a partnership with

See **Lung Cancer**, continued on page 3



CMS Rolls Out New CLIA Policy Changes

What Labs Can Expect

BY PHIL KIBAK

Five years after releasing the final quality control rules under CLIA, CMS last month instituted new policy changes that on the surface seem small, but which many laboratorians regard as significant. The agency announced in August 2007 that it now will cite labs that don't comply with certain new 2003 requirements under CLIA, which previously prompted only an "educational" letter of notification about the problems identified. These include test method verification, maintenance and function checks, calibration, and calibration verification. Laboratories have had since 2003 to become familiar with these requirements, but starting January 1 they will no longer receive a letter giving them an opportunity to correct the deficiency before action is taken. However, just as with all other deficiency citations, laboratories have a chance to submit a "plan of correction" describing how the deficiency will be rectified, and if done in time, no action will be imposed.

The threat of a citation for these deficiencies does not appear to upset too many laboratorians. "In my opinion these changes will have very little impact since most labs are inspected by CAP, COLA, or the Joint Commission," said Sharon Ehrmeyer, PhD, Professor of Pathology and Laboratory Medicine at the University of Wisconsin Medical School (Madison). "Most labs are already doing these things and device manufacturers have protocols to ensure that their customers can fully comply with the regulations."

But what has again stirred controversy in the laboratory community is CMS's endorsement of equivalent quality control (EQC). Laboratorians also learned in the latest round of CLIA updates that CMS plans to keep EQC in force for the immediate future, until the QC policy under development at CLSI is complete.

See **CLIA Changes**, continued on page 5

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Clinical Laboratory News

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EGFR Test Steers Treatment

Lung Cancer, continued from page 1

Genentech (San Francisco, Calif.). Tests for mutations of the *K-ras* oncogene, which are more common in patients with a history of smoking, may be useful in determining which patients are unlikely to respond to TKIs.

The tests determine appropriateness of a treatment that offers varying survival benefit, from just a few months to a year or more. And the assays are costly. The *EGFR* mutation and *K-ras* assays generally cost between \$700 and \$1,000 each, while another assay that detects extra copies of the *EGFR* gene is a bit less, at \$400 to \$700. But they are worth considering, maintained David S. Ettinger, Chairman of the NCCN committee that wrote the guidelines, and the Alex Grass Professor of Oncology at the Sidney Kimmel Comprehensive Care Center at Johns Hopkins Medical Center in Baltimore, Md. "If you look at the big picture, incremental gains in survival add up. We're talking about advanced disease here." He's hopeful that current trials of approved and newly developed TKIs may yield therapies for early stage NSCLC. "We first learn about new agents in advanced disease. As research progresses and we refine the guidelines, we will become more specific in our recommendations," Ettinger noted. He receives grants support from Genentech and is a member of both its speaker's bureau and advisory board.

Guidelines Suggest Molecular Tests

Issued in September 2007 to update a version released in January of that year, the NCCN guidelines explain that *EGFR* is found on the surface of epithelial cells in various cancers and mutations in certain areas of the *EGFR* gene that govern the protein's activity. Certain *EGFR* mutations are significantly associated with positive response to TKIs, according to the guidelines.

Currently oncologists can order an immunohistochemistry test—which is not mentioned in the guidelines—and the two molecular *EGFR* tests. Mutation assays sequence the whole gene or certain parts using the polymerase chain reaction (PCR), while the second molecular assay determines how many copies of the gene are present in a tumor using fluorescence in situ hybridization (FISH). Either is acceptable, according to NCCN, but the choice continues to be a matter of debate among oncologists and pathologists. Currently, Genzyme (Cambridge, Mass.) offers both molecular *EGFR* assays and *K-ras* tests, as do some academic cancer centers and reference labs.

K-Ras Mutation: Will TKIs Work?

The *K-ras* gene modulates cellular proliferation and differentiation. Found in 15–30% of lung adenocarcinomas, mutations are strongly associated with tobacco smoke exposure. "*K-ras* mutations are associated with intrinsic TKI resistance, and *K-ras* gene sequencing could be useful for the selection of patients as candidate for TKI therapy," the guidelines maintain. For the patient, having a *K-ras* mutation is bad news because it's unlikely he or she will respond favorably. Genzyme's *K-ras* test uses a modified mini-sequencing platform to fluorescently detect genomic alterations at

codons 12 and 13 in tumor specimens.

Ettinger usually orders *K-ras* and *EGFR* tests together, reasoning that "with a *K-ras* mutation, odds are the patient won't respond to TKIs." However, he's not completely opposed to skipping both tests for patients with particular clinical characteristics. "If you're limited in what's available for second line therapy, if the patient has a limited smoking history and is female, you may just want to put them on TKIs. There's a judgment call here," he said. Others advise more stringent criteria for prescribing the drugs. "I wouldn't deny TKIs if tests didn't demonstrate an *EGFR* mutation, but I would deny them if a patient had a *K-ras* mutation," explained Maureen Zakowski, MD, Attending Pathologist at Memorial Sloan Kettering Cancer Center (MSK) in New York, N.Y. and Professor of Pathology at Cornell University's Weill Medical College. Mark Ladanyi, MD, Chief of the Molecular Diagnostic Service and Attending Pathologist at MSK, pointed out that *K-ras* and *EGFR* mutations never happen in the same tumor. MSK receives research funding from Genentech and AstraZeneca (Wilmington, Del.), which also markets a TKI inhibitor.

While the guidelines and MSK's treatment strategy both emphasize that a *K-ras* mutation probably means TKIs won't benefit a patient, it's not entirely clear that having the *K-ras* mutation automatically means TKIs won't work, according to one researcher who has studied an *EGFR* assay that determines gene copy number and has received research funding from AstraZeneca, Genentech, and OSI Pharmaceuticals. According to Fred R. Hirsch, MD, PhD, Professor of Medicine and Pathology, University of Colorado Cancer Center in Denver, "The *K-ras* mutation occurs in twenty percent of unselected NSCLC patients. So you would think that eighty percent of patients would benefit from TKIs. But only about fifty percent of the patients do. That's a gap of thirty percent, so I don't think the *K-ras* story is completely understood. We're working on identifying that thirty percent through prospective studies."

The updated guidelines are already drawing increased attention to the *EGFR* and *K-ras* tests. Until now, Genzyme has seen slow but steady growth in demand for these assays, according to Bruce Horten, MD, Genzyme's National Medical Director. "We've seen quite a bump up in demand since the NCCN guidelines were released," he commented.

TKIs: Just One Now

Thus far, the FDA has approved two small-molecule drugs that target the tyrosine kinase activity of *EGFR* for patients with advanced NSCLC who haven't responded to chemotherapy. Both erlotinib and gefitinib, marketed as Iressa (AstraZeneca, Wilmington, Del.), act as competitive inhibitors of ATP-binding at the active site of the *EGFR* kinase. However, following release of data from two failed clinical trials required by FDA as a condition of gefitinib's 2003 approval, the drug was effectively removed from the market in 2005 via label language that stated the drug should be used only in patients who had experienced prior benefits. Erlotinib remains the only approved

Another Test Expected For Targeted NSCLC Therapy

In January, Genzyme announced an agreement with Moffitt Cancer Center in Tampa, Fla. that gives the company exclusive worldwide diagnostic testing rights to the discovery of two proteins that may help predict how patients respond to platinum drugs and gemcitabine, both of which are used to treat patients with NSCLC.

In its announcement, Genzyme said it would develop and market an assay that can be used to measure the expression levels of two proteins, ribonucleotide reductase and excision repair cross-complementation group 1, which are expressed by the genes *RRM1* and *ERCC1*, respectively. Both proteins are involved in DNA synthesis and repair. The test would be used to guide first-line treatment for NSCLC patients and could help them avoid unnecessary side effects from ineffective treatment, the company added.

A Moffitt research team lead by Gerold Bepler, MD, PhD has shown that expression level of the two proteins correlates with patient response to platinum drugs and gemcitabine, Genzyme noted. At least one published paper from Bepler and his team strongly suggests that tumoral *RRM1* expression is a major predictor of response to gemcitabine and platinum therapy, as is *ERCC1* to a lesser extent (*Journal of Clinical Oncology* 2006; 24: 4731–4743).

In addition, a 2007 paper by Bepler and colleagues concludes that high expression of both *RRM1* and *ERCC1* is a determinant of survival after NSCLC surgery. (*NEJM* 2007; 356: 800–808). An accompanying editorial by Adi Gazdar, MD, deputy chief of the Hamon Center for Therapeutic Oncology and Professor of Pathology at the University of Texas Southwestern Medical Center in Dallas, notes that the two gene markers could affect selection of both those NSCLC patients with resected early-stage tumors who do not require adjuvant therapy and those patients who are not likely to benefit from conventional chemotherapy for advanced disease.

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TKI inhibitor of *EGFR*, although several others are in development.

TKIs' effectiveness is limited, however, because patients generally become resistant to them in less than a year, although some centers report that a few patients will take them for three years or more. Several studies are attempting to learn how resistance develops, with at least one gene fingered as the culprit (See Box, page 3).

A Choice of *EGFR* Assays

There are two different methodologies to determine *EGFR* abnormalities in NSCLC. Mutation assays sequence the gene to allow examination of specific regions, namely exons 18–21. Exon 19 deletions are particularly good indicators of possible TKI response, the NCCN guidelines indicate.

Genzyme's mutation test microdissects cells from specific tumor-rich areas, from which DNA is extracted and then amplified by PCR. Next comes bidirectional sequencing of exons 18 through 21 in the tyrosine kinase domain of the *EGFR* gene. Other labs offer partial analysis of the entire *EGFR* gene, as well as this examination.

While the NCCN guidelines recommend both the FISH and mutation assays, lab directors and recent review articles by researchers at Massachusetts General Hospital (MGH) and Harvard Medical School in Boston, Mass. note a debate as to which test is superior. The frequency of *EGFR* mutations in TKI-responsive cases is now well-established, according to authors of both articles, who noted that studies show that most patients who respond to TKIs have the mutations. But the articles also point out that certain research has also concluded that *EGFR* gene amplification, while not as predictive of response, may be equally as predictive of improved survival.

Ladanyi is a strong proponent of the mutation assay. He noted about 25 studies that confirm the link between mutations in *EGFR* and response to TKIs, pointing out that fewer have identified a link between copy number and such response. "Mutant *EGFR* can be amplified, but not always," he explained. "The correlation between copy number and response is really due to *EGFR* amplified cases also being mutated. The key process is mutation. If they were separate processes, we would see cases with mutations where the other non-mutated copy of *EGFR* was also amplified."

Ladanyi noted that recent research from MSK and other institutions, currently in press at *Journal of Clinical Oncology*, tested NSCLC tumors for both *EGFR* mutation and copy number and found lower response to TKIs among patients who had increased *EGFR* copy number but no mutations.

Noting practical concerns, Zakowski said she finds the mutation assay easier to use. "It's the quickest, cleanest method. It tells you exactly what has mutated," she explained. "FISH requires slides, it's more time-consuming, and is subject to interpretation."

A Case for FISH

Some evidence suggests that giving TKIs to patients with extra copies of *EGFR* can increase survival, even if these patients test negative for *EGFR* mutations and do not have an initial response. One such study by Hirsch and colleagues at University of Colorado Science Center and researchers at Italian centers looked at tumors from

For More Information

The following are useful sources of information on tests to detect *EGFR* and *K-ras* abnormalities:

- ▶ The National Comprehensive Cancer Network's Non-Small Cell Lung Cancer (NSCLC) Guidelines are available at www.nccn.org/professionals/physician_gls/PDF/nscl.pdf.
- ▶ A review article by Daniel Haber, MD, Lecia Sequist, MD and their colleagues at Massachusetts General Hospital summarizes the biology of *EGFR* in NSCLC, the clinical and molecular predictors of whom will benefit from *EGFR* tyrosine kinase inhibitors, use of patient-specific molecular profiling, and future directions of related research (*Journal of Clinical Oncology* 2007; 25: 587–595).
- ▶ Another review article by Haber and colleagues summarizes the results of genetic, biochemical, and clinical studies focused on somatic mutations of *EGFR* that are associated with TKI's effectiveness. The review also explains how understanding the genetic heterogeneity of epithelial tumors and devising strategies to prevent their resistance to TKIs are essential to successful use of the agents (*Nature Reviews Cancer* 2007; 7: 169–181).

102 NSCLC patients on gefitinib and tested them for *EGFR* status by FISH, DNA sequencing, and immunohistochemistry. Multivariate analysis showed that only high *EGFR* copy number, not mutations in the gene, were associated with better survival (HR 0.44; 95% CI 0.23–0.82) (*Journal of the National Cancer Institute* 2005; 97: 643–655).

According to Hirsch, a difference in the incidence of *EGFR* mutation—about 10% of NSCLC patients versus 35% to 40% of patients with extra copies of *EGFR*—means this method could potentially identify more patients who could benefit from TKIs. "Mutation is associated with a dramatic response to drugs, but is less so in Western populations," he maintained. "The correlation of mutations with better survival is more clearly demonstrated in Asian populations. Future prospective studies might demonstrate survival benefit in mutation-positive patients. But which test is more appropriate when? Neither the FISH nor the mutation test is approved for diagnostic testing in clinical practice right now."

Current mutation testing methods aren't perfect, according to a recent editorial by Ladanyi and William Pao, also of MSK (*Clinical Cancer Research* 2007; 13: 4954–4955). Mutation tests must be quicker and more accurate before they become standard of care, they write. One problem is that some clinical samples do not have easily detectable levels of mutant *EGFR*. For a mutation to be detected by conventional direct sequencing, the tumor cells must comprise 25% of the total cells present in a given sample, they note. A lesser proportion could result in false-negative results after direct sequencing. Pao and Ladanyi point to more than a dozen recent papers reporting improved methods of detecting mutations.

Problems with *EGFR* Assay Studies

Retrospective analysis of clinical trials that aim to determine the predictive value of mutation and amplification assays have produced conflicting results in part from the studies' different approaches, clinical designs, and variable interpretation of results, according to the *Journal of Clinical Oncology* review article.

The paper's first author detailed a few of these problems. First, most trials of *EGFR* assays and TKIs are still retrospective, explained Lecia Sequist, MD, MPH, Instructor at Harvard Medical School and Assistant Physician at MGH. "Lots of randomized trials didn't require tissue samples at the time of patient enrollment, and the

molecular studies are based only on patients who happened to have tissue available post hoc," Sequist added. As a result, different research teams have had various results. "There's no clear theme to the publications regarding *EGFR* gene amplification by FISH. Some studies have shown a benefit for TKI therapy in FISH-positive patients and others have not found one. It's very interesting work, but it's still shaking out."

At least four prospective studies have used *EGFR* mutations as a method for selecting patients for TKI therapy, according to Sequist. She is lead author of one such study, currently in press at the *Journal of Oncology*. "We screened patients for *EGFR* mutations and treated only those that were positive with first-line gefitinib. We observed a response rate of fifty-five percent and a progression-free survival of 9.2 months. These results are two to three-fold of what is typically seen with standard chemotherapy in the first-line setting. While a randomized study needs to be performed for confirmation, the initial results with this strategy are promising."

Hirsch hopes that research by the FDA's Critical Path Initiative (CPI), which aims to speed the development and evaluation of cancer therapies, will lead to an FDA-approved *EGFR* test for NSCLC. The CPI's Oncology Biomarker Qualification Initiative, which was launched in February 2006 and includes members from FDA, NCI, and CMS, is planning a clinical trial that will directly compare predictive value of protein expression, mutation, and FISH *EGFR* assays, according to Maryellen de Mars, PhD, Director for Clinical Biomarkers in the Rockville, Md. office of the Critical Path Institute. Her nonprofit organization is coordinating the effort for the federal agencies.

The Test of the Future

Proponents of both the mutation and FISH assays agree that decisions about treating patients with *EGFR* mutations are unlikely to rely upon one particular kind of assay or marker in coming years. "It may be that the diagnostic paradigm should be a combination of tests because nothing by itself is 100% perfect," Hirsch remarked. "My sense is that mutation assays are definitely important and give lots of information. FISH is probably important too, and together they may be more so," added Sequist. "These cancers are complex. No one test gives you the golden answer. There probably will be a panel eventually and lots of centers, including Massachusetts General Hospital, are working on them."

CLN

CLIA Modifications Implemented

CLIA Changes, from page 1

“These changes are another incremental step toward full implementation of EQC, and the concept of EQC was a very significant change for labs,” noted Robert Murray, JD, PhD, Technical Consultant with Midwest Diagnostic Pathology (Park Ridge, Ill.). “Laboratory personnel are well acquainted with the notion that two external samples need to be run daily for QC. But EQC replaced that with the idea that maybe there are other things that can be done to reduce the risk of error as effectively or even more effectively.”

Changes Small, But Surprising

Accreditation standards do not mandate EQC, so laboratories can continue their current practice unchanged. “Most hospital labs are accredited by CAP. Long before CLIA came into existence, CAP had its own set of standards that incorporated concepts like PT, QC practices, and personnel standards,” said Murray. “CAP accreditation standards make implementation of EQC an option, so laboratories that choose to continue the traditional practice of running two levels of control daily may continue without change. Also, labs in doctors’ offices are accredited by COLA, which also has its own standards and also does not, to my knowledge, mandate EQC. So, life will not change much in these labs until the accrediting agencies adopt EQC.”

But Judy Yost, Director of the Division of Laboratory Services for CMS, says several accrediting organization have options for QC similar to EQC. These include COLA and the Joint Commission. She also notes that CAP has a flexible capability for labs to reduce external QC.

Ron Laessig, PhD, Professor of Population Health Sciences and Pathology at the University of Wisconsin (Madison) and Director of the Wisconsin State Laboratory of Hygiene agrees that not much will change for labs now. “These are very minor changes, but they tell you the way surveyors will carry out inspection activities,” he explained.

EQC Revisited

The 1992 CLIA regulations included “phase-in” QC requirements to enable previously unregulated facilities performing unmodified, moderate complexity testing the opportunity to understand and meet the new requirements. During the phase-in, these laboratories were allowed to follow the manufacturer’s instructions to meet the requirement to perform two control procedures per day. Between 1992 and 2003, the manufacturers developed functional or electronic checks or internal controls that in most cases monitored only limited portions of the test system and did not monitor the complete analytic process. The final rule, published in January 2003, combined the moderate and high complexity QC requirements into one set of standards applicable to non-waived testing. These regulations included a provision requiring daily testing of two levels of external control material, unless CMS approves an equivalent procedure in the State Operations Manual (SOM) guidelines. As noted in the 2003 regulation, the control procedures requirements were developed

to monitor the accuracy and precision of the complete analytic process.

James Westgard, PhD, Emeritus Professor of Pathology and Laboratory Medicine at the University of Wisconsin Medical School (Madison), a staunch opponent of EQC, suggests that changes in laboratory operations and personnel may have actually led to the development of EQC as an operational concept. “With the advent of CLIA rules in 1992, personnel standards were reduced, allowing many people to perform laboratory tests with minimal training and understanding of the testing process,” he said. “One area of great difficulty has been QC, as evidenced by CMS’s own data showing that five to ten percent of laboratory deficiencies are in quality control.”

The recent announcement from CMS is significant, he added, because it now declares that EQC will be recognized as “legal.” “That is,” he explained, “that laborato-

ries following the EQC guidelines will be in compliance with the regulations. But that doesn’t mean it’s necessarily good laboratory practice. In fact, the EQC guidelines are not scientifically valid—how does a ten-day validation protocol prove that a method is sufficiently stable so that QC only needs to be run once every thirty days?”

Yost objects to Westgard’s characterization. “EQC was always legal under CLIA, under 493.1256 in the 2003 regulations. Labs have a choice to do two levels of external QC or EQC,” she explained. “In fact, the protocol has been in place since 2004 in the Interpretive Guidelines on our Web site. EQC has been used by labs successfully since that time with no evidence of harm.”

Westgard maintains that labs will tend to adopt EQC because it is the least amount of QC possible under CLIA. “CLIA provides three different QC recommendations—the lab should implement the right QC procedure to ‘detect immediate errors that occur due to test system failure, adverse

environmental conditions, and operator performance; monitor over time the accuracy and precision of test performance that may be influenced by changes in the test system performance and environmental conditions, and variance in operator performance.’ Second, CLIA provides a default of two levels of QC per day, which eliminates any need to think about the right QC procedure. Third, CLIA allows laboratories to implement a procedure—EQC—that allows reduction of QC to two levels once per month. That’s the preferred option that most laboratories will want to implement because that is the least amount of QC possible.”

But Westgard’s criticisms miss the mark, according to Yost. “Labs don’t live by QC alone. They are required to be sure that their overall quality systems—proficiency testing, personnel competency, and quality assessment—are all in good standing in order to continue reduced QC. And, they are still doing internal QC every day,” she explained. “It is only the external QC that has

Top 10 CLIA Deficiencies

Laboratorians may want to be especially aware of these areas, which are the most frequently cited laboratory deficiencies.

Regulatory Cite	Deficiency	Number of Labs	Percentage of Labs
493.1236(c)(1)	At least twice annually, the laboratory must verify the accuracy of any test or procedure it performs that is not included in subpart I or this part.	1,087	5.80%
493.1252(a)	Test systems must be selected by the laboratory. The testing must be performed following the manufacturer’s instructions and in a manner that provides test results within the laboratory’s stated performance specifications for each test system as determined under 493.1253.	1,066	5.69%
493.1289(a)	The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and when indicated, correct problems identified in the analytic systems specified in 493.1251 through 493.1283.	1,018	5.43%
493.1252(b)	The laboratory must define criteria for those conditions that are essential for proper storage of reagents and specimens, accurate and reliable test system operation, and test result reporting. The criteria must be consistent with the manufacturer’s instructions, if provided. These conditions must be monitored and documented.	965	5.15%
493.1251(b)	The procedure manual must include the requirements for specimen acceptability, microscopic examination, step-by-step performance of the procedure, preparation of materials for testing, etc.	925	4.93%
493.1239(a)	The laboratory must establish and follow written policies and procedures for an ongoing mechanism to monitor, assess, and, when indicated, correct problems identified in the general laboratory systems requirements in 493.1231 through 493.1236.	789	4.21%
493.1291(c)	The test report must indicate positive patient identification, name and address of the laboratory where the test was performed, the report date, test performed, specimen source, result, and units of measurement or interpretation.	761	4.06%
493.1407(e)(5)	The laboratory director must ensure that the quality assessment programs are established and maintained to assure the quality of laboratory services provided.	713	3.80%
493.1283(a)	The laboratory must maintain an information or record system that includes positive identification of the specimen, date and time of specimen receipt, condition and disposition of specimens that do not meet the laboratory’s criteria for acceptability, the records and dates of all specimen testing including the identity of the personnel who performed the test.	638	3.40%
493.1252(d)	Reagents, solutions, culture media, control materials, calibration materials, and other supplies must not be used when they have exceeded their expiration date, have deteriorated, or are of substandard quality.	633	3.38%

Total number of laboratories surveyed by CMS = 18,746

Data based on the most current survey conducted on or after January 12, 2004

OSCAR data as of 8/10/2007

Source: CMS

been reduced for EQC. Labs in hospitals and reference labs are not impacted by this policy since they are mostly high complexity and do much more QC than is mandated by CLIA. These policies impact mostly labs performing moderately complex tests utilizing robust technologies.”

EQC the Same For Now

When EQC was first instituted, it was seen as a means of easing the burden on labs that might be financially strapped or have limited personnel resources because labs could reduce the frequency of performing QC. “But CMS came out in 2005 and admitted ‘we blew it’ with the concept of EQC,” noted Ehrmeyer. “They tried to offer a simple

solution to what is a very complex problem, but it lacks scientific validity and is not appropriate in every case. Instead of retracting this concept, they are now trying to rationalize it.” However, implementing EQC remains an option, not a requirement, as long as the laboratory director reviews the manufacturer’s QC approach and says, based on 10 to 30 days of external QC data, that EQC adequately monitors the method.

“The idea to keep EQC is an interim decision that will be revisited when revised QC policies are in place,” said Yost, referring to forthcoming documents from CLSI. “We did admit that we needed policies and procedures for QC that are scientifically valid at a QC CLSI meeting in 2004–2005 and

are continuing to participate and support a process to do so, using experts from industry, labs and government.”

Filing Complaints at Issue

In a highly subscribed December 6 AACC audioconference titled “New Developments in CLIA and QC,” Yost and James H. Nichols, PhD, Associate Professor of Pathology at Tufts University School of Medicine (Boston, Mass.) and Director of Clinical Chemistry at Baystate Health System (Springfield, Mass.), discussed other CLIA issues, including filing complaints.

In 2006, a review by the Government Accounting Office titled “Clinical Labs: CMS and Survey Organization Oversight Is Not Sufficient to Ensure Lab Quality,” government officials expressed concern over the limited options CMS offered for laboratory workers filing complaints related to lab quality. The report specifically cited anonymity concerns and unfamiliarity with filing procedures. In her presentation, Yost rebutted these issues and pointed to guidance in this area provided in revised Interpretive Guidelines, the CMS Web site, a soon-to-be-released brochure, a CMS letter directed to professional organizations, toll-free telephone numbers in State Health Departments, and CMS central and regional offices that can be accessed via e-mail, regular post, voice/telephone, and fax. “CMS uses a sophisticated data system to track complaints and every complaint made is followed up in some manner,” Yost said. Complainants wishing to file anonymously can do so, she added. Nichols added that labs should familiarize staff with the com-

plaint policy and should post the contact telephone numbers to file complaints.

Yost and Nichols also reminded the audioconference audience about proficiency testing (PT) referral, stating that laboratory personnel need to be aware of circumstances that could place the lab in jeopardy. Intentional or unintentional PT referral for either regulated or unregulated analytes can result in the most serious CLIA penalties, including loss of CLIA certificate for one year, cancellation of Medicare/Medicaid payments, inability of the lab director to direct any lab for two years, and placement of the lab on the CLIA Annual Lab Registry on the CMS Web site.

EP Documents on QC in Development

In the near future, laboratorians will have an additional resource to guide their QC protocols. During the audioconference, Yost and Nichols referred to several EP documents being developed by CLSI, including *Quality Management for Unit-Use Testing: Approved Guideline for Quality Control of Unit-Use Devices* (EP18), which is currently undergoing revision. Both speakers indicated that the new guidance documents will provide comprehensive and flexible guidelines for quality management models that will identify potential sources of errors in unit-use test systems, starting from specimen collection through reporting of results. The recommendations will be applicable to various devices and settings and are practical to implement, so that sources of error (potential failure modes) are identified, understood, and managed.

One particularly murky issue that the



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To obtain a CD of the AACC audioconference, "New Developments in CLIA and QC," go to www.aacc.org and click on publications and then audioconference CDs; or call AACC Customer Service at (800) 892-1400 or (202) 857-0717.

new guidelines cover is the relationship between labs and manufacturers. According to Nichols, the new QC document defines user–manufacturer quality partnerships and specifies areas of responsibility via an error matrix by covering potential sources of error in the preanalytic, analytic, and postanalytic process. "For example, a manufacturer may insert a device that can check freezing or overheating during shipment. Then the lab should be responsible for checking that device every time they open up a new shipment," Nichols explained. "If that device is broken or somehow indicates that the shipment has been degraded, they need to return that shipment and request a replacement before they implement testing. This is an example of the user–manufacturer partnership. This gets the lab thinking more about risk, the frequency of errors, what types of errors can occur, what are the consequences of those errors, and how we can decrease laboratory errors."

In discussing the concept of QC and risk management, Nichols cited two examples and how management processes can differ with each. In a system that uses an analyzer and a reagent, the device may have many moving parts and there may be some internal checks to detect mechanical and electronic failures; however, not all parts and

sources of error may be detectable by internal checks. Also, the reagent is intricately linked to the analyzer and may be susceptible to environmental effects or conditions. Two levels of control each day can detect error from many sources—the analyzer's mechanical and electrical systems, storage and drift for the reagent, the operator, and the environment. External QC may adequately detect systematic errors that persist over time, but may fail to detect random errors that occur with single samples.

He also described the example of a device that uses a test cartridge. In such a system, most errors occur with the cartridge, while the device itself only reads the signal and may perform an electronics check, temperature check, and integrity check. In such a system, the lab director must balance the requirements for twice daily external controls against the cost and availability of alternative controls within the test system. If the manufacturer provides cartridge stability data and the lab ensures storage as recommended, what else, Nichols asked, needs to be done? Another issue to be resolved by the lab is how internal controls specific to the test lessen the risk of operator or sample errors.

Two other EP documents—*Presentation of Manufacturer's Risk Mitigation*

Information for Users of In Vitro Diagnostic Devices (EP22) and *Laboratory Quality Control Based on Risk Management (EP23)*—are under development. EP 22 will offer guidance to manufacturers about evidence needed to support QC recommendations. "There is no validated, peer-reviewed model for linking risk assessment data directly to a QC frequency. Dr. Curtis Parvin of Washington University in St. Louis and Dr. Marina Kondratovitch with the FDA are trying to develop a mathematical model to come up with figures for a frequency of external QC," Nichols told listeners. "EP 22 has been approved in a draft format but until it's published in its final form we won't know exactly what it's going to say."

EP 23 is intended to help laboratorians develop laboratory-specific QC protocols based on manufacturer information. It will provide guidance to labs on developing effective, cost-efficient QC plans that combine the unique device, unique laboratory environment—personnel, competency, temperature, and storage—and unique clinical application to come up with a specific QC plan for that lab setting and for that device. The new guideline will also assist laboratorians in merging pertinent local regulations with manufacturer-supplied data and information about the individual laboratory into a specific QC plan. After implementation, lab directors will also want to have the ability to modify the lab's QC protocols based on ongoing trends and events for continuous quality improvement. "Concepts being considered for this document include: How do I, as a lab di-

rector, know that the internal controls on these devices can substitute for two levels of external QC?" Nichols explained. "Will the internal controls detect environmental exposure, deviations in operator technique, and other factors with the same frequency or sensitivity as external QC? What factors did the manufacturer consider when making this recommendation and did the manufacturer place the same emphasis on certain errors that I see most frequently in my hospital and clinic settings?"

According to Yost, EP 22/23 are intended to supplement and/or replace EQC. "That's the whole story here!" she said. "The idea to keep EQC is an interim decision that will be revisited when revised QC policies are in place. We have changed nothing regarding EQC since it was instituted in 2004."

Advice to Lab Directors

Moving forward, Yost suggested that laboratories should follow a current, lab-director signed procedure manual for all tests. Nichols added that it's imperative for lab personnel to keep up to date with changing regulations. "Changes are occurring based on changes in philosophy and a shift toward risk management and systems to manage quality," he said. "It may mean less external QC and more reliance on internal device checks and error codes, but you'll need evidence to back the decisions made in your lab to the inspectors. Remember, too, that the lab director is ultimately responsible for determining method quality and must decide comfort level with extent of validation studies, calibration, and QC procedures." CLN

Warfarin Pharmacogenetics

The Challenges of Laboratory Testing

BY LINNEA M. BAUDHUIN, PHD

Each year, about 2 million people begin warfarin therapy to prevent or treat blood clots (1). However, as many as 43,000 patients experience the drug's life-threatening bleeding complications that require emergency treatment. In recent years, underlying genetic factors have been shown to account for approximately 35–40% of the variation observed in how patients respond to warfarin (2). In light of the potential dire consequences of incorrect warfarin dosing, the FDA recently approved updated labeling for Coumadin (Bristol-Myers Squibb, New York, N.Y.), the brand name version of warfarin, to highlight the importance of warfarin pharmacogenetic (PGx) testing and to suggest that physicians incorporate the information obtained from such testing into warfarin dosing decisions. Manufacturers of generic warfarin are also expected to add similar information to their products' labeling. Shortly after the FDA approved the updated labeling, it cleared the first genetic test for warfarin sensitivity, and other manufacturers have announced plans to submit similar tests to the FDA.

These recent developments place the clinical laboratory in a unique position to help usher in the era of personalized medicine in which a patient's genotype is used to select the appropriate drug and dosage.

and stroke, atrial fibrillation, and orthopedic surgery.

Because warfarin has a narrow therapeutic window, achieving a stable international normalized ratio (INR) through

on other factors, including sex, body size, age, drug-drug interactions, nutritional status, and comorbidities such as liver disease. If the warfarin dose is too high, the patient is at risk for major bleeding complications, such as intracranial hemorrhage, especially during the first weeks of therapy. On the other hand, if the warfarin dose is too low, the patient is at risk for dangerous blood clots that could potentially cause a thromboembolic stroke or other serious complication.

Although warfarin can be a very effective drug, its narrow therapeutic index also leads to a high rate of adverse drug events (ADEs). In fact, it ranks among the top ten drugs associated with serious ADEs—including a major bleeding frequency rate as high as 10–16% (4)—making it one of the drugs most frequently associated with hospital emergency department visits due to ADEs. Overall, anticoagulants were ranked as the primary cause of ADE-related deaths in 2003 and 2004 (3). Consequently, in October 2006, the FDA instituted a black-box labeling change to warfarin emphasizing the serious bleeding risks associated with the drug and the importance of regular INR monitoring.

While physicians have traditionally used nongenetic factors to individualize warfarin therapy, clearly, the ADE data show that nongenetic factors alone are insufficient for predicting warfarin dose variability in many, if not the majority, of cases. In fact, a combined approach incorporating both nongenetic and known genetic factors can account for 50–60% of warfarin dose variability (1, 5).

As mentioned above, the FDA updated the warfarin package label in August 2007 to provide information about genetic testing for warfarin sensitivity and encourage physicians to use the data to reduce ADEs. While the FDA stopped short of requiring genetic testing prior to a patient taking the drug, labs are likely to see more requests for testing as physicians become aware of how to use this information to better define dosing strategies on an individualized basis.

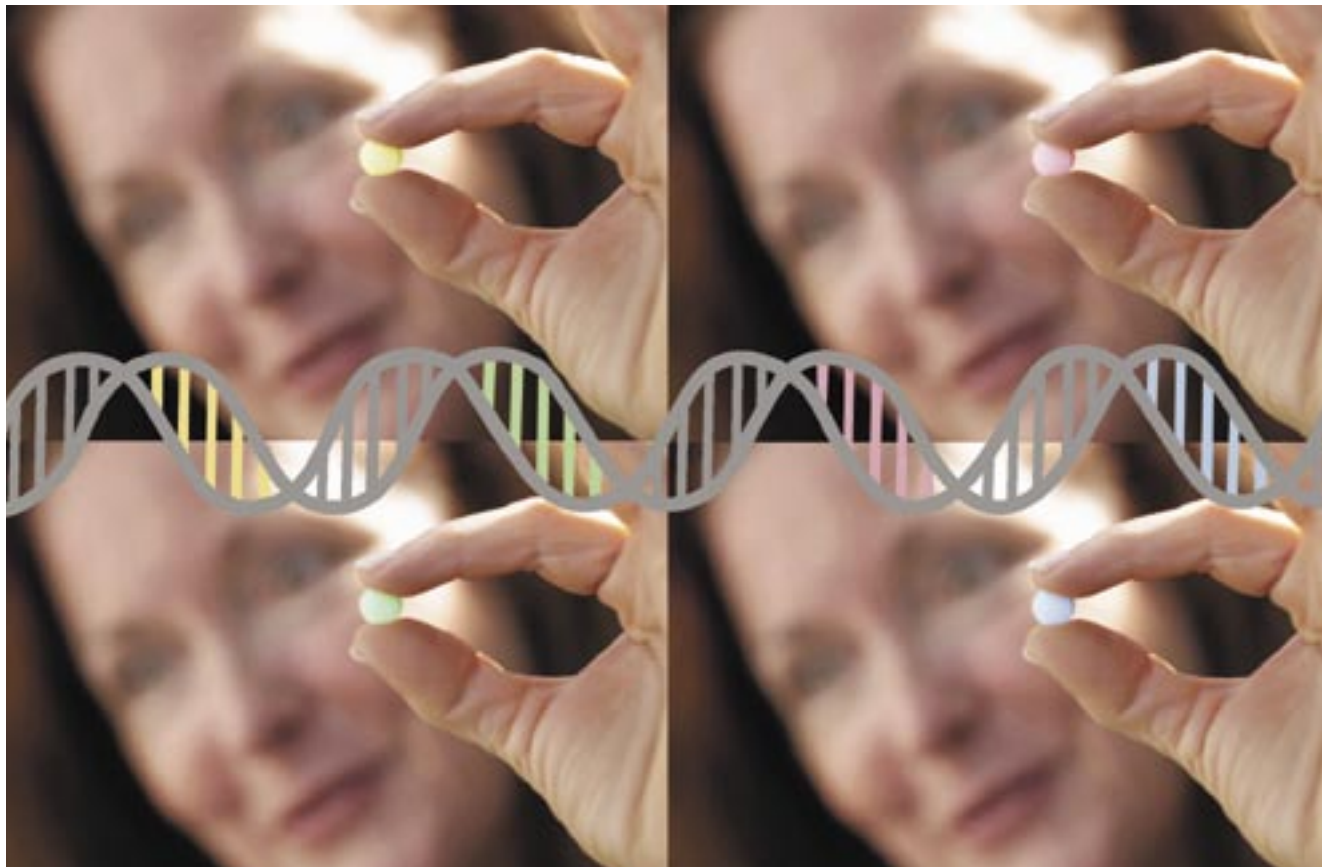
However, this field is not without significant challenges for the laboratory.

A Warfarin Primer

One of the most commonly prescribed drugs, warfarin is a coumarin-based anticoagulant that is often used for the short- and long-term management of thromboembolic and hemostatic disorders, such as deep-vein thrombosis, pulmonary embolism, inherited thrombophilia, and antiphospholipid syndrome. Physicians also prescribe warfarin for a number of other medical conditions and treatments, including the prevention of myocardial infarction

dosing and titration has been a significant challenge for physicians, largely due to multiple factors affecting an individual's warfarin sensitivity and resistance. Dosing is monitored by coagulation testing, generally 4–5 days after initial loading dose and at regular intervals thereafter, to maintain the INR within specific limits. Physicians typically give patients an initial warfarin dose of 2–10 mg, but depending on INR results, the weekly maintenance dose can range from 4–80 mg (3).

In addition to the genetic factors related to warfarin's metabolism and action, an individual's response to the drug also depends



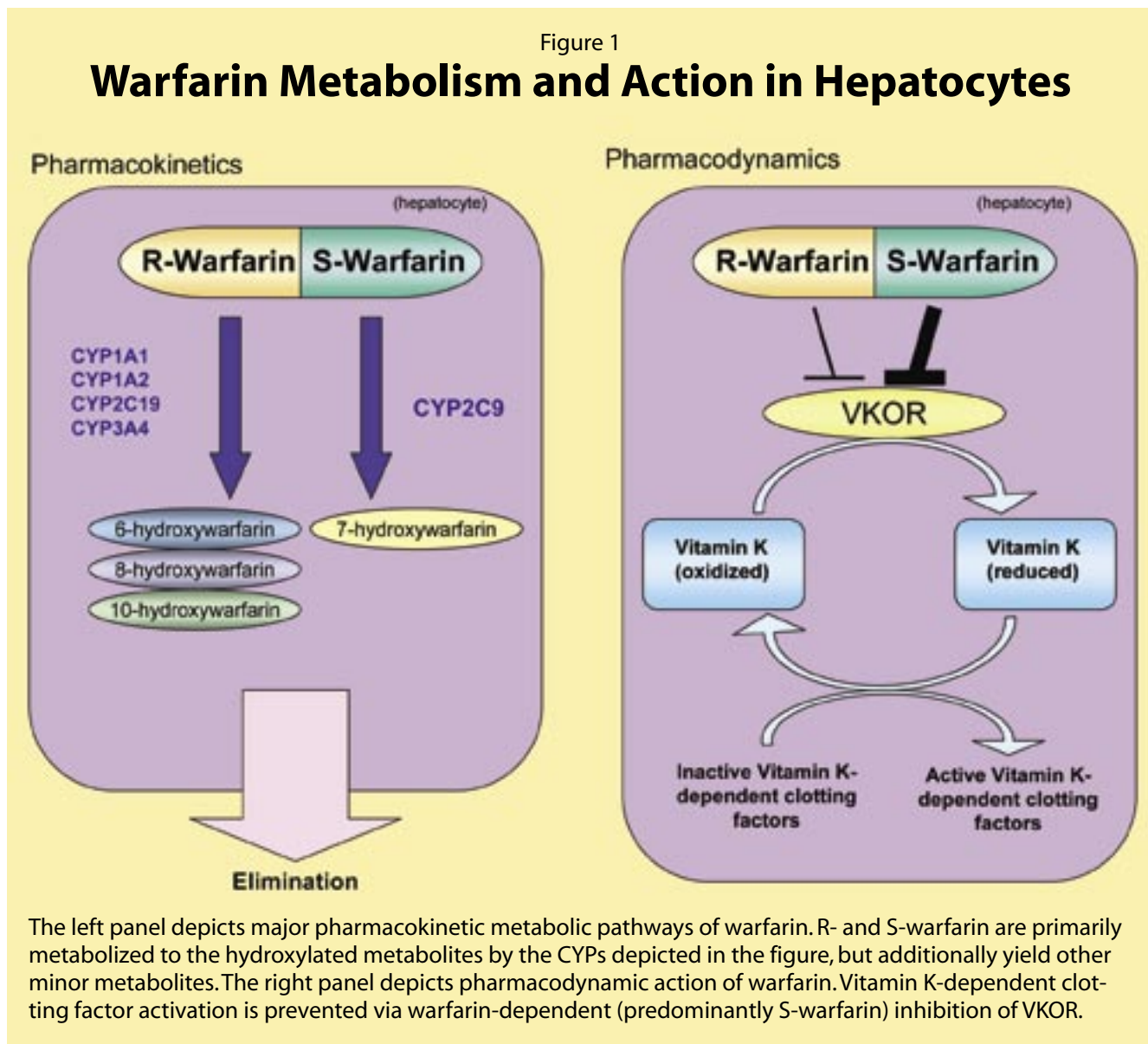
Warfarin Pharmacogenetics

Pharmacogenetic analysis of clinically relevant genetic markers is emerging as a useful tool to predict an individual's response to certain drugs, as well as a means to avoid potential ADEs. The science of warfarin PGx is unique, however, in comparison to other PGx applications, since it is based on both the pharmacokinetics and pharmacodynamics of the drug (Figure 1), rather than solely on one or the other. The major genes implicated in pharmacokinetic metabolism and pharmacodynamic targeting of warfarin are cytochrome P450 2C9 (*CYP2C9*) and vitamin K epoxide reductase complex subunit 1 (*VKORC1*).

To understand the effect of these genes, it is helpful to look at the chemical structure of warfarin, which is comprised of a racemic mixture of stereoisomers, known as R- and S-enantiomers. As the principal active form of warfarin, S-warfarin is approximately three to five times as potent as the R-enantiomer in inhibiting the enzyme vitamin K epoxide reductase (VKOR). The hepatic *CYP2C9* enzyme is primarily responsible for the metabolism of S-warfarin (Figure 1).

Genetic polymorphisms affecting *CYP2C9* activity occur at a fairly high frequency in some populations and may result in decreased clearance of S-warfarin (Table 1). These individuals are more sensitive to the drug, and normal doses tend to result in more frequent overmedication with warfarin, increased INRs above the therapeutic target level, and the potential for serious bleeding events. One study documented that individuals carrying the two most commonly studied *CYP2C9* polymorphisms, *2 (2608C>T) and *3 (42614A>C), have a two- to threefold greater chance of bleeding during initial warfarin dosing (3).

The most common (or wild-type) allele for *CYP2C9* is *CYP2C9**1, which is associated with normal or extensive enzyme activity. The allele frequency of *CYP2C9**1 in Caucasian, African American, and Asian populations is approximately 80–82%, 83–98%, and 97–98%, respectively (1). *CYP2C9* alleles that are known to lead to inactive enzyme or reduced enzymatic activity include *CYP2C9**2, *3, *4, *5, *6, and *11 (Table 1). Of these variants, *CYP2C9**2 and *3 are more frequently present in Caucasians, 8–13% and 6–10%, respectively, but comprise <1–4% of alleles in African Americans and Asians. In the Asian population, *CYP2C9* alleles other than *1 and *3, which occur with 1–2% frequency, are not



observed at an appreciable frequency. In addition to the *CYP2C9**2 allele, *5 and *11 each occur with a frequency of approximately 3% in African Americans. An additional allele, *CYP2C9**8 has been shown to occur in approximately 6% of African Americans, but its effect on enzyme activity in the presence of warfarin has not been determined.

Pharmacodynamically, warfarin acts by inhibiting VKOR, which interferes with recycling of vitamin K and decreases its availability (Figure 1). Since vitamin K is necessary for the activation of key coagulation factors—factors II, VII, IX, and X, and proteins C, S, and Z—a decreased pool of vitamin K leads to thrombin formation. VKOR is encoded by the *VKORC1* gene, which has multiple polymorphisms that affect its expression. In particular, a polymorphism within the promoter of *VKORC1* (-1639G>A) decreases expression of the

gene: a heterozygous or homozygous adenine (A) at position -1639 in the *VKORC1* promoter significantly reduces VKOR expression compared with individuals who are homozygous for a guanine (G) at that position. Studies have demonstrated that the wild type -1639G *VKORC1* promoter has 44% higher activity compared to the variant -1639A promoter (6). As expected, the -1639A genotype corresponds to warfarin sensitivity, so that a patient with this genotype will require a lower dose of warfarin compared to the -1639G genotype. The frequency of the lower dose, warfarin-sensitive homozygous *VKORC1* -1639A genotype is approximately 14–17% in Caucasians, 72–78% in Asians, and 4–5% in African Americans (4, 7). The high frequency of this *VKORC1* promoter polymorphism in Asians is thought to explain the majority, but not all, of the warfarin-sensitive phenotypes in this population.

Laboratory Testing for Warfarin PGx

Incorporating results from genetic testing of both *CYP2C9* (*2 and *3) and *VKORC1* (-1639G>A) into warfarin dosing prediction models is expected to account for approximately 50–60% of the variability in warfarin response (1, 5). With the increased emphasis on patient safety and preventing ADEs, as well as the widespread use of molecular diagnostic technologies in clinical labs of all sizes, many labs have initiated or are considering warfarin PGx testing.

But significant challenges for performing this test exist, including: choosing an appropriate analytical platform; meeting the demand of rapid turnaround time; providing meaningful interpretation of results,

such as dosing guidance based on genotype and potential drug-drug and drug-*CYP2C9* interactions; and keeping abreast of reimbursement and regulatory issues.

Today, labs have a choice of several molecular platforms to devise homebrew *CYP2C9* and *VKORC1* genotyping tests, including bead-based systems, microarrays, fluorescent probe-based assays, allele-specific PCR, and pyrosequencing. Labs may also choose to use a commercial assay recently cleared by the FDA. The Verigene Warfarin Metabolism Nucleic Acid Test (Nanosphere, Northbrook, Ill.) is a pharmacogenetic test to assess for warfarin sensitivity that uses a multiplexed platform for detecting nucleic acid targets for the *CYP2C9**2 and *3 polymorphisms, as well as the *VKORC1* 1173C>T polymorphism, which is in strong linkage disequilibrium with -1639G>A).

Laboratory-developed assays allow labs to define their own set of polymorphisms for warfarin sensitivity based on the ethnic populations served. For example, alleles other than *CYP2C9**2 and *3 that predominate in European Caucasian populations may be required for appropriate testing in other populations, such as *CYP2C9**5 and *11, which occur more frequently in individuals of African descent. Other factors that influence the lab's choice of analytical platforms include cost, ease of use, and turnaround time.

In fact, turnaround time is a major issue in warfarin PGx testing. The importance of obtaining a patient's genotype prior to initiating warfarin therapy has been promoted by many supporters of personalized medicine. While the highest risk for warfarin-

Table 1

CYP2C9 Alleles and Effect on Enzyme Metabolism

<i>CYP2C9</i> Allele	Nucleotide Change	Effect on Enzyme Metabolism
*1	None (wild type)	Normal (extensive) activity
*2	430C>T	Reduced activity
*3	1075A>C	Minimal activity
*4	1076T>C	Reduced activity
*5	1080C>G	Reduced activity
*6	818delA	No activity
*11	1003C>T	Reduced activity

Table 2

Sensitivity to Warfarin Based on Combined CYP2C9 and VKORC1 Genotypes

Warfarin sensitivity	CYP2C9 genotype	VKORC1 promoter genotype
Normal	*1/*1	G/A
Less than normal	*1/*1	G/G
Mild	*1/*2	G/G
	*2/*2	
	*1/*3	
Moderate	*2/*3	G/G
	*1/*2	G/A
	*2/*2	
	*1/*3	
	*1/*1	
High	*3/*3	G/G
	*2/*3	G/A
	*1/*2	A/A
	*3/*3	G/A
Very high	*2/*2	A/A
	*1/*3	
	*2/*3	
	*3/*3	

associated ADEs is during the initial phase of therapy, the necessity of a single day turnaround time for genotyping CYP2C9 and VKORC1 is controversial. This is largely because variants in these genes do not affect warfarin volume of distribution but rather the time for plasma warfarin concentration to achieve therapeutic levels (VKORC1) and steady state (CYP2C9) (2).

Reynolds et al. (2) promote a standard initial dose of warfarin, 5 mg/day, for the first 3–4 days of therapy. In this scenario, if genotyping is initiated on day 1, then with a maximum 4-day turnaround time for genotyping, the results could be incorporated into maintenance dosing strategies. The “standard initial dose/genotype-guided maintenance dose” approach is especially appealing in the acute/emergent setting and when the test must be sent out to a reference lab, which precludes the possibility of a 1-day turnaround time.

On the other hand, the advantages to knowing a patient’s genotyping results prior to initiating therapy cannot be disregarded. If a patient’s genotype-guided maintenance dose is known prior to initiation of therapy, then ideally, the maintenance dose would essentially be the same as the initiation dose. Another advantage to upfront genotyping is related to the timing of the first INR measurement. As mentioned above, patients are usually tested 4–5 days after the initial warfarin dose is given, and this INR is used to titrate the subsequent dose until the patient achieves a target INR. However, in an individual with a warfarin-sensitive CYP2C9 genotype, the time to achieve warfarin steady-state plasma concentrations is delayed. Measuring the patient’s INR at the standard 4–5 days would be premature (2). In such cases, if the genotyping results were available prior to initiating treatment, the first INR measurement could be scheduled more appropriately. Overall, by having the genotyping results upfront, more comprehensive counseling on the recommended

therapeutic management plan could be provided to the patient at an earlier stage. This approach could lessen the number of ADEs and may give both the clinician and patient an increased level of confidence when selecting a warfarin dosing schedule. For these reasons, labs may choose to implement rapid, 1-day genotyping.

Other factors that labs need to consider are the number of staff required to do the testing within the desired turnaround time, the level of training required, and how to review results and release reports. Results of CYP2C9 and VKORC1 genotyping can range from a report with minimal dosing guidance to one with more explicit dosing guidance depending on patient information available to the lab at time of testing. While several warfarin dosing algorithms exist, there is neither enough data nor a consensus that supports highly specific genotype-based warfarin dosing guidance for all patient populations (8). In addition, unless the client provides such information when ordering the test, it is difficult for the lab to obtain patient information such as age, body size, co-drugs, etc., in a timely fashion. Clearly, these factors influence how specific the dosing recommendations can be.

Nonetheless, the lab is in a position to provide some general warfarin dosing guidance based on the genotype analysis. At a minimum, the lab report should indicate which genotypes have a normal, mild, moderate, high, or very high sensitivity to warfarin (Table 2). In addition to sensitivity, the lab should also provide general guidance regarding frequency of INR monitoring and warfarin dosing. For example, an individual who is CYP2C9 *1/*3, or heterozygous for the *3 polymorphism, and VKORC1 -1639 G/A is predicted to have a moderate sensitivity to warfarin, so more frequent INR monitoring and warfarin dose reduction should be considered.

The value of knowing a patient’s geno-


type for CYP2C9 extends beyond warfarin. Because many other drugs are influenced by this gene, it will also be important for labs to consider including other information in the patient genotyping results, such as any patient-specific potential drug-CYP2C9 interactions, a list of more common drug-CYP2C9 and drug-warfarin interactions, and a reference to the warfarin package insert. For example, co-administration of warfarin with drugs known to decrease the activity of CYP2C9, including amiodarone, fluconazole, fluvastatin, fluvoxamine, isoniazid, lovastatin, and ticlopidine (9), will lead to an increased possibility of toxicity, particularly in individuals with CYP2C9 variant alleles.

While drug-CYP2C9 and drug-warfarin interactions are important for the laboratory to recognize and report, oftentimes the list of drugs the patient is taking is not provided to the laboratory. In this case, it can become a major undertaking that requires additional staff time to track down this information in a timely fashion. In these situations, the responsibility should fall on the client to consult with the lab and/or a clinical pharmacologist if needed. In addition, because of the paucity of information regarding specific warfarin dosing guidance for most drugs that interact with CYP2C9 or warfarin, it is very difficult for the laboratory to provide that information when reporting testing results. An exception to this is when the patient is taking amiodarone, atorvastatin, or azole or sulfa antibiotics, in which case, an approximate 15–25% warfarin dose reduction is recommended.

The Wave of the Future

Although the field is just emerging, personalized medicine clearly represents the wave of the future. As experience with warfarin PGx grows, laboratorians will want to closely monitor physicians’ attitudes toward this new practice for patient dosing. In addition, forthcoming resources and guidelines will help laboratorians add warfarin PGx to their labs’ menus. The American College of Medical Genetics (ACMG) is currently drafting a warfarin PGx laboratory testing standards and guidelines document that is expected to contain their recommendations for laboratory reporting of results. A draft of general guidelines regarding PGx genotype reporting is also available from the National Academy of Clinical Biochemistry on its Web site (10).

Overall, while the promise of warfarin PGx is apparent, there are many hurdles to overcome in providing optimal individual patient management. The forthcoming laboratory practice guidelines from ACMG and NACB will likely have a significant impact on improving and standardizing clinical warfarin PGx testing. Furthermore, many centers are currently conducting studies to investigate and better establish warfarin dosing algorithms.

Eventually, clearer and more widely accepted warfarin dosing guidance based on a combination of genetic and nongenetic factors will likely become available. Such guidance will greatly enhance the clinical practice of warfarin PGx as well as promote more widespread adoption of its use. 

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CMS Posts Follow-Up From Bidder's Conference

CMS has updated the portion of its Web site that presents information about the competitive bidding demonstration project by posting questions and answers from the December 5, 2007 conference held in San Diego. The series of 10 questions and responses address a number of issues, such

as: will there be an anti-mark-up rule between laboratories? Can referring and reference labs share bid prices with each other if both are submitting bids? And can a lab participate in the demonstration if it enters the competitive bidding area market after the demonstration has started without having participated in the bidding process?

This document can be viewed at www.cms.hhs.gov/DemoProjectsEvalRpts/

downloads/MMA302b_Follow_Up_Bidder_Conference.pdf.

EGAPP Releases Statement on Genetic Testing Recommendations

The CDC's Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group has declined to recommend for or against cytochrome P450 (CYP450) gene testing to guide treatment for patients beginning depression therapy with SSRI drugs, saying that further clinical trials are needed to determine the test's usefulness.

In the first of a planned series of recommendation statements on the use of genetic

tests in clinical practice, the EGAPP Working Group reported it found no evidence linking testing for CYP450 to clinical outcomes in adults treated with SSRIs.

The National Office of Public Health Genomics at the CDC established the EGAPP Working Group in 2005 to support the development of a systematic process for evaluating genetic tests in clinical practice. This independent, multidisciplinary panel prioritizes and selects tests, reviews CDC-commissioned evidence reports and other contextual factors, highlights critical knowledge gaps, and provides guidance on appropriate use of genetic tests in specific clinical scenarios. For additional information about EGAPP, visit www.egappreviews.org.

AACC Presents



GENOMIC TECHNOLOGIES AT THE INTERFACE OF DIAGNOSTICS AND THERAPEUTICS

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If you are interested in emerging gene-based diagnostics and therapeutics—and the intersection of these medical disciplines—plan to join us for AACC's 21st San Diego Conference. As the conference enters into its third decade, this year will examine how molecular and genetic tools can be the catalyst of synergy in the combined field of diagnostics and therapeutics/drug discovery.

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- Applications
- Multivariate Analysis and Genetic Testing
- Infectious Disease Testing

Each session features presentations covering a number of emerging technologies and diagnostic tools, offered by recognized experts in the field. In addition, the Organizing Committee has built in more time for networking, posters and exhibits.

KEYNOTE PRESENTATION

RNAi, Other Mechanisms by Which Cells and Organisms Respond to Genetic Change, and the Implication of These Mechanisms on Human Disease and Health Care

Andrew Fire, PhD, Stanford University
(Nobel Prize in Physiology or Medicine, 2006)

SPECIAL PRESENTATION

Update on Infectious Disease Testing in Emerging Nations
Deborah Burgess, PhD, The Bill & Melinda Gates Foundation

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Our expert faculty includes a Nobel Prize-winner and leading researchers who will show you:

- Implications of RNAi on human disease and health care
- Advanced tools for characterizing and sequencing DNA
- Novel applications of molecular tools in diagnostics and therapeutics
- The FDA perspective on regulation of multivariate index assays



HIV Testing for Pregnant N.J. Women Mandatory

On Dec. 26, 2007 Acting New Jersey Governor Richard J. Codey signed a new law requiring pregnant women to undergo HIV testing at the beginning of pregnancy and during the third trimester. If the mother objects, the healthcare practitioners will note the objection and the newborn will be tested for the virus. If the mother has a positive test result, newborns will also be tested.

According to an article in the *Washington Post*, New Jersey became the fifth state to require HIV testing for pregnant women, and the fourth to require newborn HIV screening. It appears to be the only state requiring both.

The CDC has recommended that HIV screening become a routine part of prenatal testing. CDC estimates are that 100–200 children are infected by their mothers annually.

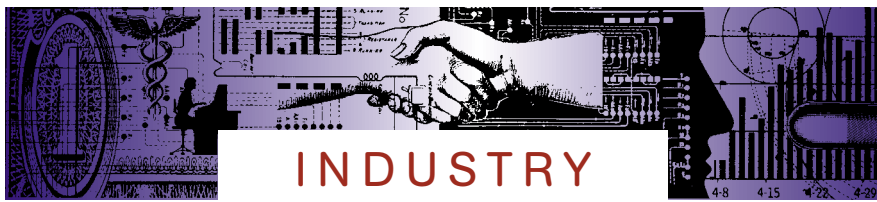
NIH Launches Human Microbiome Project

NIH has officially launched the Human Microbiome Project (HMP), which will use \$115 million over 5 years to support research into microbes that inhabit the human body and their roles in human health and disease.

Advances in DNA sequencing technologies have created a new field of research, called metagenomics, allowing comprehensive examination of microbial communities, even those comprised of uncultivable organisms. Instead of examining the genome of an individual bacterial strain that has been grown in a laboratory, the metagenomic approach allows analysis of genetic material derived from complete microbial communities harvested from natural environments. In the HMP, this method will complement genetic analyses of known isolated strains, providing unprecedented information about the complexity of human microbial communities.

NIH has issued grant announcements for investigators to develop early-stage informatics and hardware tools to advance microbial science. The program initially will sequence the genomes of 600 microbes, creating a total collection of 1,000 microbial genomes and a reference for investigators. For additional information about this project, go to <http://nihroadmap.nih.gov/hmp/>.

For additional information or to register, visit www.aacc.org/AACC/events/meeting/SanDiegoConf2008.htm



Clinical Data Plans PGx Test For New Depression Drug

Clinical Data (Newton, Mass.) announced that it is working on a companion pharmacogenetic test in parallel with a safety study for its depression drug Vilazodone. Researchers will determine the long-term safety and tolerability of Vilazodone while a second trial evaluates genetic biomarkers associated with response to the drug. "With the addition of a genetic test for response to Vilazodone, we can help clinicians more quickly and confidently identify patients who are likely to respond, leading to improvements in patient care and outcomes," said Clinical Data CEO Drew Fromkin. "This is just one example of how pharmacogenetics can lead to more targeted therapeutics and therefore better healthcare." Clinical Data plans to submit a new drug application with the FDA for Vilazodone next year.

Pfizer and Source MDx Collaborate On Companion Diagnostics

Source MDx (Boulder, Colo.) announced a multi-year translational molecular medicine collaboration with Pfizer (New York, N.Y.) to develop RNA-based pharmacodynamic and predictive biomarkers from Pfizer's cancer and inflammation drug programs. Combining Pfizer's experience in genomic profiling with Source MDx's know-how in RNA transcription profiling and circulating rare cells, researchers from the companies will work to establish molecular profiles of response and resistance for important cancer and inflammation drugs. Under the agreement, Source MDx will receive an equity investment and licensing fees, in addition to research and development funding. Source MDx will retain commercial rights to any biomarkers that the venture discovers, but both Pfizer and Source MDx can commercialize any companion diagnostics the collaboration develops.

Siemens Inks Deal with Krelo for TRAb Assay

Siemens Medical Solutions Diagnostics (Tarrytown, N.Y.) announced an agreement with KreLo GmbH Medical Diagnostics (Ulm, Germany) for rights to develop an automated stimulating TSH receptor antibody (TRAb) assay used in the differential diagnosis of Graves' disease. "The new TRAb assay has enormous potential to help diagnose, monitor, and predict the course of Graves' disease," said Joe Bernardo, senior VP, Central Lab Testing, Siemens Medical Solutions Diagnostics. "Siemens continues to focus on new biomarker development opportunities, continually expanding our already comprehensive immunoassay menu and providing the diagnostic tools necessary to diagnose and treat millions of thyroid disease patients."

PerkinElmer To Acquire Pediatrix Metabolic Screening Lab

PerkinElmer (Waltham, Mass.) announced it will acquire the newborn metabolic screening business of Pediatrix Medical Group (Sunrise, Fla.), including Pediatrix's StepOne newborn screening service that targets more than 50 inherited

disorders. "This acquisition would expand PerkinElmer's capabilities to supply STAT laboratories with the most comprehensive newborn screening solutions available," said Robert Friel, COO, PerkinElmer. "Adding laboratory capabilities should strengthen the partnership with our existing customers by enabling us to offer supplemental screening services for disorders beyond those currently mandated by state and federal governments." In addition, Friel said that the acquisition would enable PerkinElmer to provide supplemental support services, such as backup screening in case of emergencies. Details of the cash transaction were not disclosed.

Firms Roll Out Retail Nutrigenomics

Consumer genomics firm GeneLink (Jersey City, N.J.) announced an exclusive, multi-year retail licensing and distribution agreement with Solgar Vitamin and Herb (Leona, N.J.) to market a nutrigenomic line of nutritional supplements. Under the agreement, Solgar will market a brand of nutritional supplements called Nutrigenomx that are tailored to individual consumers' genes based on the results of a GeneLink DNA collection kit and Genetic Compass reporting system. The collection kits and supplements will be available at health food and specialty natural food retailers in North America.



Study Calls for Better Established CK Reference Intervals

Use of appropriately established creatine kinase (CK) reference intervals may improve use of statins and control of dyslipidemia in patients with relatively high baseline CK, new research suggests (*American Heart Journal* 2007; 154: 655–661). In what researchers from two hospitals in Amsterdam, the Netherlands say is the first published study of serum CK activity based on a stratified, random sample of the general population that includes subjects of different ancestry, investigators determined reference intervals for serum CK according to guidelines from the Netherlands' National Committee on Clinical Laboratory Standards and the Nordic Reference Interval. The Surinamese in the Netherlands

Study on Ethnicity and Health (SUNSET) Study included 1,444 individuals age 34–60, of white, South Asian, or African descent who gave samples after 3 days of rest. The calculated upper reference limits equal to the 97.5th percentile for nonblack and black women and men were two to five times higher than that recommended by the assay manufacturer. Thirteen percent of white Europeans, 23% of South Asians, and 49% of black subjects had serum CK activities that exceeded these recommendations. Researchers concluded that variation in CK activity is wider than previously suggested in studies on smaller, nonrandom samples and that relatively high values occur frequently in all subgroups studied after rest. Noting that Adult Treatment Panel III guidelines acknowledge that higher CK activities are found in blacks, the team point-

ed out that the guidelines do not say how high the upper reference limit should be for blacks and suggested upward adjustment of the upper limit of normal for all the subgroups they studied.

Genetic Variants Affect Response to Breast Cancer Therapy

Because genetically determined, impaired tamoxifen metabolism results in worse treatment outcomes, genotyping for certain CYP2D6 alleles can identify breast cancer patients who will have little benefit from adjuvant tamoxifen therapy, according to a recent paper (*Journal of Clinical Oncology* 2007; 25: 5187–5193). German researchers sought to determine the predictive value of 16 variants of the cytochrome 450 enzymes CYP2D6, CYP2C19, CYP2B6, CYP2C9, and CYP3A5 from 206 patients on adjuvant tamoxifen monotherapy and from another 280 patients who didn't get tamoxifen. Median follow-up time was 71 months. Researchers isolated DNA from archival material and genotyped it by matrix-assisted, laser desorption/ionization, time of flight mass spectrometry, and by copy number quantification. Tamoxifen-treated patients with four CYP2D6 alleles, all associated with impaired formation of antiestrogenic metabolites, had significantly more breast cancer recurrences, shorter relapse-free periods (HR 2.24, 95% CI, 1.16–4.33), and worse event-free survival rates (HR 1.89, 95% CI, 1.10–3.25), compared with carriers of functional alleles. Patients with the CYP2C19 high enzyme activity promoter variant *17 had a more favorable clinical outcome (HR 0.45, 95% CI, 0.21–0.92) than carriers of *1, *2, and *3 alleles. "Our findings are particularly important in light of the current debate on the effectiveness of tamoxifen for postmenopausal women with hormone receptor positive breast cancer," the researchers wrote.

Analysis of CD40L May Help Stratify Risk in AF

Enhanced soluble CD40 ligand (sCD40L) predicts vascular events in patients with nonvalvular atrial fibrillation (AF), according to new research suggesting that enhanced platelet activation may play a role in clinical progression of the disease (*Arteriosclerosis, Thrombosis, and Vascular Biology* 2007; 27: 2763–2768). To assess whether sCD40L is a predictor of stroke or myocardial infarction (MI) in patients with nonvalvular AF, researchers from Mount Sinai School of Medicine (New York, N.Y.) and two institutions in Rome, Italy measured plasma levels of sCD40L in 231 patients. Seventy-seven percent had permanent or persistent AF, while 23% had paroxysmal AF. Researchers divided the patients into two groups, one with sCD40L levels above the median of 4.78 ng/mL and the second with levels below that figure, and followed both groups for a mean period of 27.8 months. The two groups had similar distribution of cardiovascular risk factors, age, sex, medication, and serum CRP levels. During follow-up, vascular events occurred in 5.1% of 116 patients with lower levels of

sCD40L and 25.2% of patients with higher levels of the marker. Patients with sCD40L above the median were 4.63 times more likely to experience a vascular event (95% CI, 1.92–11.20). Noting that their data can't be extrapolated to a low-risk population, the researchers called for further study of the marker.

Rapid Chlamydia Test Holds Promise

A rapid chlamydia test using patient-collected vaginal swabs would be an effective, quick diagnostic and screening tool, a recent paper suggests (*British Medical Journal* 2007; 335: 1190–1194). Although nucleic acid amplification tests for chlamydia are generally more sensitive and specific than currently available rapid assays, their turnaround time—one to two weeks—precludes immediate treatment and partner notification. So researchers from five institutions in the U.K. sought to evaluate the performance of a new 30-minute assay, the Chlamydia Rapid Test, devised to aid in diagnosis of chlamydia and serve as a screening tool in settings where staff lack advanced training or laboratory equipment. The investigators studied the test's performance in 1,349 women ages 16 to 54, comparing its sensitivity, specificity, positive predictive value, and negative predictive value to that of a PCR test. Compared with the PCR assay, the resolved sensitivity, specificity, positive predictive value, and negative predictive value of the 30-minute assay were—with 95% CI—83.5% (91–109), 98.9% (1224–1238), 86.7% (91–105), and 98.6% (1224–1242), respectively. Compared with strand displacement amplification assays, sensitivity and specificity of the Chlamydia Rapid Test were 81.6% (40–49) and 98.3% (578–588). The investigators noted that their paper is the first published performance analysis for a CE-marked rapid test for chlamydia with a claim for vaginal swab specimens.

UPDATE

More Guidelines Cite Oncotype

CLN's November 2007 cover story examined gene profiling tests that help determine risk of breast cancer occurrence, including the Mammprint assay marketed by Agendia (Amsterdam, The Netherlands) and the Oncotype DX test developed by the reference lab Genomic Health (Redwood City, Calif.). Now the National Comprehensive Cancer Network's (NCCN) 2008 Breast Cancer Treatment Guidelines, released in January, are the second set of recommendations to give Oncotype a thumbs up. The American Society for Clinical Oncology's updated clinical practice guidelines on breast cancer tumor markers have also recommended Oncotype for patients with newly diagnosed node-negative, ER-positive breast cancer. Meanwhile, in January Agendia announced that it will seek additional FDA clearance for Mammprint to include patients over age 60, using new data from node-negative, invasive breast cancer tumors in older patients. The NCCN guidelines are online at www.nccn.org/professionals/physician_gls/PDF/breast.pdf.

NEWS FROM THE FDA

FDA Clears Two-Hour MRSA Test

Becton Dickinson (Franklin Lakes, N.J.) announced the FDA clearance of its GeneOhm StaphSR assay, making it the first test available to rapidly differentiate two deadly healthcare-associated infections: *Staphylococcus aureus* and MRSA. The assay provides results in 2 hours, directly from positive blood cultures, thereby helping physicians to implement the right antimicrobial therapy. Traditional microbiology algorithms can take up to 2 days to generate results. BD said it has submitted subsequent applications to the FDA to add nasal swab and wound claims to the StaphSR assay.

FDA Clears Multiplex Respiratory Viral Test

Luminex Corporation (Austin, Texas) announced the FDA clearance of its xTAG Respiratory Viral Panel (RVP), the first cleared assay to simultaneously identify 12 viruses and viral subtypes that account for more than 85% of respiratory viral infections. The panel is also the first to detect and differentiate influenza sub-

types H1 and H3, and to identify human metapneumovirus (hMPV). Testing for the viruses separately with traditional methods would take several days for diagnosis, while the xTAG assay provides qualitative results within a few hours. Other viruses identified by the panel include: influenza B; respiratory syncytial virus subtype A and B; parainfluenza 1, 2, and 3; rhinovirus; and adenovirus.

FDA Clears Three-Virus Flu Test

The FDA cleared Prodes's (Waukesha, Wis.) real-time PCR ProFlu+ assay that detects influenza A, B, and RSV from a single specimen. It's the first cleared, real-time molecular test to detect as many as three viruses simultaneously. Results of the test are available in about 3 hours.

Automated Hepatitis B Test Approved

Abbott (Abbott Park, Ill.) announced it received premarket approval from the FDA for its ARCHITECT CORE-M automated hepatitis B assay, a chemiluminescent microparticle immunoassay for

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the qualitative detection of IgM antibodies to hepatitis B core antigen virus. The test is approved to aid in the diagnosis of acute or recent hepatitis B viral infection.

Plague and Tularemia Kits Cleared

Idaho Technology (Salt Lake City, Utah) announced FDA clearance of two new

biothreat detection kits, the JBAIDS Plague and JBAIDS Tularemia detection kits. Both tests use real-time PCR and run on the company's JBAIDS instrument, designed for on-site analysis of dangerous biological pathogens. The kits can be used to test blood, sputum, positive blood cultures, and colonies, yielding results in less than four hours.



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