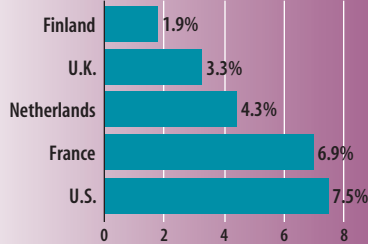


U.S. SPENDS MORE FOR LESS ON HEALTHCARE

Despite spending twice per capita what other major industrialized countries spend on healthcare, and with some pockets of improvement, the U.S. healthcare system is still on average less efficient, less effective, and less accessible than ever, according to a report by the Commonwealth Fund, a nonprofit research group. Compared with benchmarks, the U.S. achieved an overall score of 65 out of a possible 100 across 37 indicators of performance.

Efficiency is a major problem, as well as access to care due to lack of insurance and premiums rising faster than wages. The report notes that in a cross-national survey, 22% of U.S. adults with health problems reported that their test results and medical records were not available at the time of their doctors' appointments. The Netherlands set the benchmark rate of 9%. U.S. patients were also more likely to say their doctors unnecessarily repeated tests—20% vs. a 4% benchmark, again from the Netherlands.

Snapshot: Healthcare Money Spent on Administration



Includes claims administration, underwriting, marketing, profits, and other administrative costs.

Source: Commonwealth Fund National Scorecard on U.S. Health System Performance, 2008.

Overall, wasteful or fragmented care, avoidable hospitalizations, variation in quality and costs, slow adoption of EMRs, and soaring administrative costs were blamed for an average efficiency score of 53 out of 100 for the United States (See Graph).

Access to care is also a problem. As of 2007, 42% of working-age adults were either uninsured or underinsured, up 35% from 2003. More than one-third of adults said they went without care because of the cost in 2007, versus a 5% benchmark. Affordability plays a role, too, according to the report. In 2007, 41% of U.S. adults reported medical debt or problems paying their medical bills.

The report noted that the bright spots are areas for which hospitals must collect and report data on federal websites. For instance, hospital standardized mortality ratios improved 19% from 2000–2002 to 2004–2006. Rates for control of diabetes and high blood pressure also improved. The full report of *The National Scorecard on U.S. Health System Performance, 2008* is available at www.commonwealth-fund.org.

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CLIA Waivers Drive POCT Expansion

How Will Growth Affect Labs?

BY PHIL KIBAK

Once the uncontrollable offspring of the central laboratory, point-of-care testing today plays a vital role in healthcare. The inception of POCT as a replacement for testing in the central lab came from the notion that a test result delivered immediately to the clinician would no doubt translate to improved patient care. While that notion was akin to putting the cart before the horse, the market for POCT devices has contributed significantly to the growth of the overall diagnostics market over the past 10 years. Today, as more diagnostic manufacturers pursue CLIA waiver status for their POC devices, this rapid means of patient testing appears to be headed for an even bigger role in evaluating disease and monitoring patient care.

According to FDA's website, 152 tests and analytes were granted CLIA waivers between January 1 and June 30, 2008. In contrast, a total of 110 tests and analytes received waivers in all of 2000. The list of waived tests and analytes will likely grow as diagnostic manufacturers eye new arenas for POCT products. For example, HemoCue, a subsidiary of Quest Diagnostics, in June announced it had received a CLIA waiver for its HemoCue Albumin 201 system; this was the first such waiver granted to a quantitative POC test for screening, diagnosing, and monitoring microalbuminuria, which can indicate the presence of chronic kidney disease, a growing health problem in the U.S. Companies wishing to tap into another potentially rewarding POCT market prompted the FDA's Hematology and Pathology Devices Panel to meet in July to discuss and make recommendations



See **POCT Expansion**, continued on page 3

Monitoring MPA in Solid-Organ Transplant Recipients

Does TDM Reduce Organ Rejection and Adverse Events?

BY JOHN R. BELL

When a patient receives a solid-organ transplant, the clinician can choose from two immunosuppressive calcineurin inhibitors to prevent organ rejection. Since the 1990s, most have chosen to add mycophenolate mofetil (MMF) or mycophenolate sodium to the therapeutic regimen, both of which are converted to mycophenolic acid (MPA). Although the drug has been associated with lower rejection rates in several trials, it also is associated with an increased incidence of nausea, vomiting, diarrhea, and other symptoms. For patients who experience GI side effects, many clinicians reduce the dosage until the effects subside. But some laboratorians believe adjusting the dosage based on the patient's level of monitored serum MPA is a better way to avoid toxicity while maintaining an immunosuppressive dose.

"There is a growing group of laboratorians, as well as clinicians, who are in favor of monitoring MPA," said Susan Maynard, PhD, director of chemistry and toxicology at Carolinas Medical Center in Charlotte, N.C. "If it requires a certain amount of MPA to provide the immunosuppressant effect, and if different people have different pharmacokinetic parameters, it makes sense to know what their levels are," said Maynard.

Now, a new report, titled *Utility of Monitoring Mycophenolic Acid in Solid Organ Transplant Patients*, conducted by researchers from

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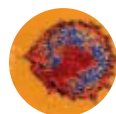
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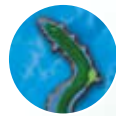
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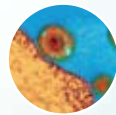
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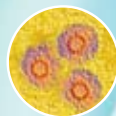
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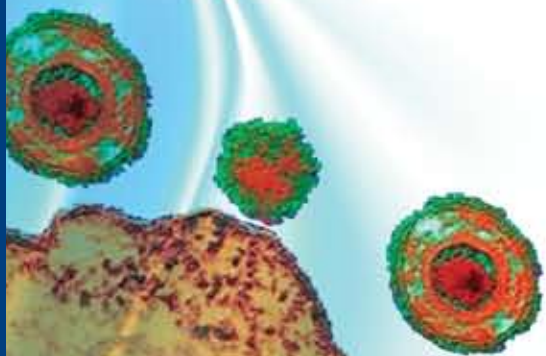
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FDA Considers CLIA Waiver for WBC

POCT Expansion, continued from page 1

on the possibility of granting CLIA waived status to automated differential blood cell counters.

"The driving force behind the growth of the POC market is the physician who wants to see results as quickly as he can get them," said Michael Simonsen, PhD, president of IntelLab, a Mission Viejo, Calif.-based company involved in technology development and market research in the medical device and diagnostics arena. "Physicians don't want to compromise on accuracy but they feel the quicker they can get results, the more efficient they can be."

But Steven Kazmierczak, PhD, professor of pathology at Oregon Health & Science University in Portland, wrote in a recent editorial that some in the medical community question if practitioners might be adopting POC technology too quickly (*Clin Chem Lab Med* 2008;46(1):1-2). "Despite the significant advances in medical technologies, including point-of-care testing, there has not been a corresponding increase in the quality of healthcare delivery," he wrote.

CLIA Waived: Key to Broader Market

Industry interest about CLIA waivers for POCT has recently increased, according to an FDA official. Carol Benson, MA, associate director of the Division of Chemistry and Toxicology in the FDA's Office of In Vitro Diagnostic Device Evaluation and Safety, said, "Many devices obtain waived status because of their over-the-counter availability. But we find we're getting more and more questions from manufacturers who are following guidance recommendations and want to do the proper studies to show their devices are simple, accurate, and have a low risk of erroneous results. About 60% of all CLIA-certified labs are waived labs, so this broadens the market for the manufacturers."

FDA recently revised the guidance under which CLIA waivers are granted, making it more germane for today's POCT, noted Yolanda Cillo, MD, medical director for Abbott Point of Care in East Windsor, N.J. "Manufacturers have to prove under these new guidelines that the test system is safe and effective to use and that the test system has an insignificant risk for producing erroneous results," Abbott, which now has CLIA waived status for its handheld i-STAT CHEM8+ test cartridge, has realized an increase in the number of facilities acquiring i-STAT technology. The company has sub-

mitted additional waiver requests for other i-STAT test cartridges, Cillo noted.

Those devices will have to undergo scrutiny, according to the new guidelines, "Guidance for Industry and FDA Staff: Recommendations for Clinical Laboratory Improvement Amendment of 1988 (CLIA) Waiver Applications for Manufacturers of In Vitro Diagnostic Devices," released in January. Building on a previous draft released in 2005, FDA now has implemented a number of changes, such as recognizing that reference methods may not be available for all device types, placing a greater emphasis on intended users during device testing, stressing the importance of scientific validation associated with a device's risk assessment, and placing extra emphasis on quality control procedures.

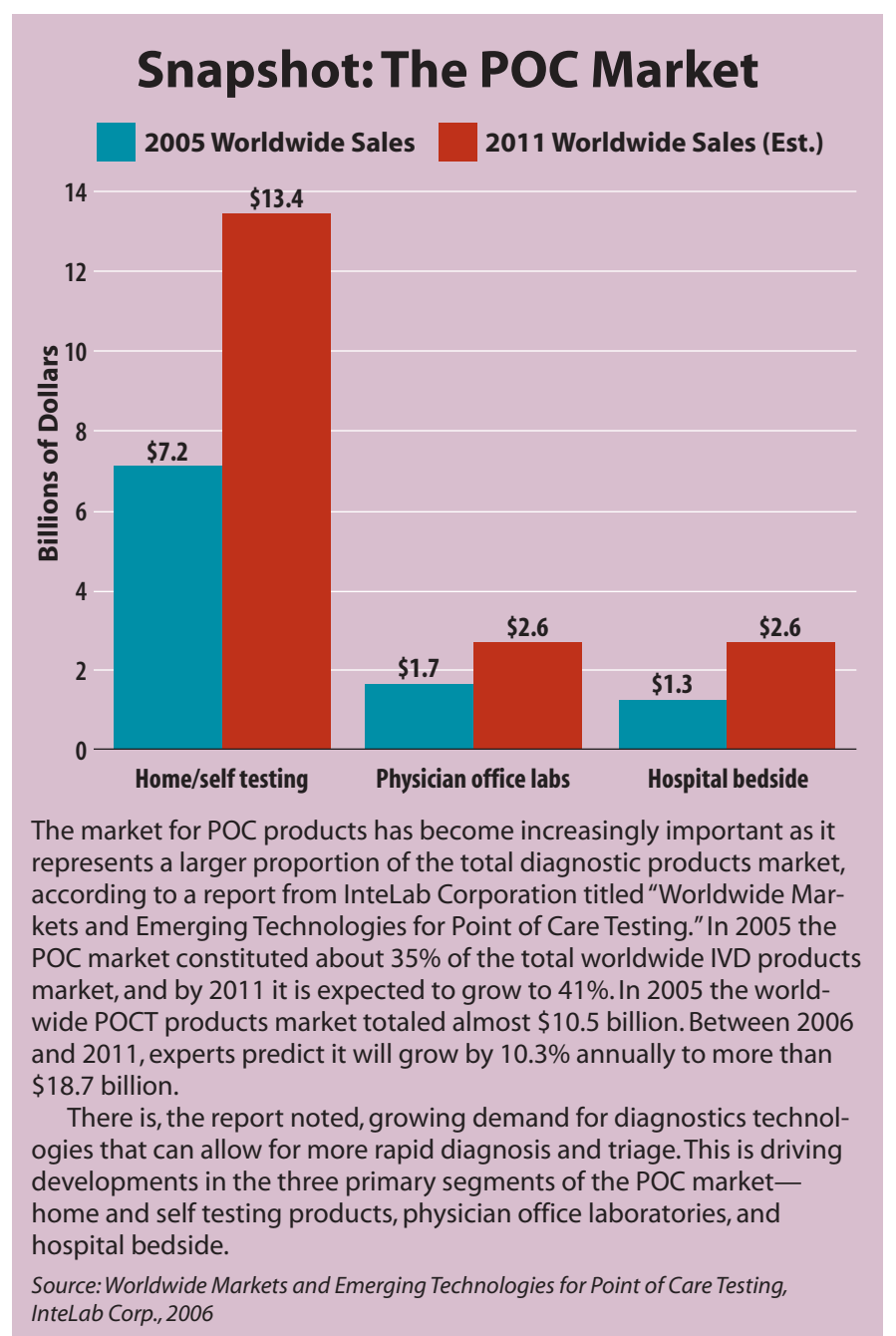
"For a device to be classified as 'simple,' a manufacturer must address certain factors," noted Benson. "Among these are that the instrument must be automated, it must use direct unprocessed samples, the specimen is independent of technique or reagent manipulation, the operator cannot intervene with the device during analysis, its operation requires no technical or specialized training, the results must be easy to read, and all labeling must be clearly understood."

The manufacturer also must perform risk analysis to test fail-safe and failure-alert mechanisms and conduct valid scientific studies to demonstrate accuracy using labeling and educational materials written at no more than a seventh-grade level.

Waivers for Blood Cell Counters?

At the July FDA meeting on automated blood cell counters, agency officials speaking to an expert panel outlined the steps a company needs to take to amass information the agency needs to determine whether to grant a CLIA waiver. "Previously, we have been asked about these instruments, but we've been unable to establish accuracy criteria for them because criteria for acceptable performance are listed in the CLIA regulations for total cell counts only, not for differentials. We did not have the information on how simple they are to operate, how accurate they are, and whether they present a low risk of giving erroneous results," Benson explained.

The 13 members of the expert panel heard some opposition to granting CLIA waivers for these devices. R.J. Ozmon, a laboratorian from Naples, Fla., told the panel



that patient safety would be compromised. "If you approve this request, there will be an unnecessary increase in laboratory errors and mistakes in the physician's office and alternative site testing areas. The physician offices that presently own hematology equipment will discontinue subscribing to proficiency testing programs and will opt not to undergo laboratory inspection by an outside agency for hematology equipment." He cited CMS and CDC studies performed between 1999 and 2003 that pointed to concerns about quality control, which resulted from high staff turnover, inadequate training, not understanding good laboratory practices, and a lack of basic scientific knowledge by operators of waived laboratory equipment.

But Paul Rust, vice president for POC testing at Quest Diagnostics and president of HemoCue, offered a different opinion. He said that automated blood cell counters with waived status offer more choices to physicians. "Physicians can use the device to help them make a diagnosis far more quickly, compared to sending specimens to a reference lab for testing. Providing a near-immediate test result helps patients who could benefit from near-immediate treatment."

In October 2007, HemoCue received FDA 510(k) clearance for its white blood cell analyzer, the HemoCue White Blood Cell (WBC) Analyzer. But with a CLIA waiver for the single-analyte device, Rust said, the analyzer could be used by a much larger number of physician offices in the U.S. than is possible with FDA 510(k) clearance.

Following presentations by FDA officials and a CMS representative the panel, chaired by Dorothy Adcock, MD, medical and laboratory director at Esoterix Laboratories in Englewood, Colo., deliberated over 12 questions. When asked if CBC/differential testing meets the waiver criteria for simplicity and an insignificant risk of

See **POCT Expansion**, continued on page 4

Some Key Factors Driving Adoption of POCT

- ▶ Need for rapid TAT to reduce patient length of stay
- ▶ Demands for easier access to testing, particularly for screening tests such as HIV assays
- ▶ Advances in technology that expand the range of applications while improving quality, usability, and lowering costs
- ▶ Staff shortages
- ▶ Allowing rapid response in emergency situations
- ▶ Growth in the number of CLIA-waived tests

Source: *Worldwide Markets and Emerging Technologies for Point of Care Testing*, IntelLab Corp., 2006

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AACC

POCT Offers Revenue Opportunities

POCT Expansion, continued from page 1

presenting an erroneous result, the panel members believed that “CBC testing as currently performed is not simple and offers the potential for erroneous results.” However, they added that this opinion may change if companies develop instructions that deal with certain variables, as well as ensure adequate training.

Another question they discussed involved explaining the kind of data or information a waiver submission should include to tackle analytical issues, such as biological factors that could produce test variations. The consensus of the panel was that these devices should have mechanisms in place to notify the operator of a potentially confounded result.

Frequency of QC for analytes in the waived setting was also a concern of the panel. “QC is one of the most misunderstood concepts outside the laboratory,” noted Linda Sandhaus, MS, MD, associate professor of pathology at Case Western Reserve University School of Medicine in Cleveland. Another panel member, Anne Rice, MT(ASCP), of the Hemostasis Laboratory at the CDC in Atlanta, said QC should be done daily, but especially when new lots of reagents come into the lab and when new operators arrive.

They also considered the impact of the level of operator training in identifying post-analytical anomalous or incorrect results. They agreed that with current designs, untrained personnel would be unable to recognize problems. However, if the devices are redesigned to take this concept into account, minimal training may be adequate to flag anomalous or incorrect results.

Although the panel did not come to a final conclusion, the matter will be pursued at a September 10–11 meeting of CLIAC in Atlanta.

POC Issues Faced by Labs

While manufacturers and FDA grapple with regulatory issues for POC devices, laboratorians addressed other topics in POCT at a workshop, Hot Topics in Point-of-Care Testing, at the AACC annual meeting in July. Paula Santrach, MD, co-director of POC testing at the Mayo Clinic in Rochester, Minn., uses POC devices to measure activated clotting time to monitor high-dose heparin therapy in cardiopulmonary bypass and in the catheterization lab. “But an issue with these is that there are a lot of manufacturers, and none of the devices is comparable. If you have to change from one device to another, it raises a host of problems,” said Santrach.

“We’ve been using the same methodology here at the Mayo Clinic for 30 years, and I need to change it. And it’s the hardest thing I’ve ever done. It has implications for cutoffs for making decisions, and people are just used to the approach they’ve been using for so long.”

There also are a variety of devices available for POC testing of platelet function, Santrach added. “But in this area the bottom line is that we really don’t know yet how to use the data all these devices provide. No generally accepted standardized definitions of resistance to such drugs as aspirin and Plavix have been established,”

she explained. “And the link between resistance, lab tests, and clinical outcomes also has not been established. So we can certainly measure something, but we may not have a good idea of what it means for a patient from an outcomes perspective, or how we should change their therapy to accommodate the data.”

Infectious Disease Testing: Accuracy Concerns

Sheldon Campbell, MD, PhD, associate professor of laboratory medicine at Yale University School of Medicine, discussed developments in POCT in infectious disease during the same annual meeting session. “The American Society for Microbiology recently issued a report titled ‘Clinical Microbiology in the 21st Century: Keeping the Pace,’ in which the organization suggests that clinical microbiologists embrace POC testing for infectious disease and not resist it,” he said. “But the caveat that goes with that is that a lot of the available POC tests for diagnosing infections don’t meet the accuracy standards of lab-based tests. A physician relying on one of these tests may end up with a diagnosis, but it’s a diagnosis of lesser quality.”

There are viral and bacterial antigen tests—some of them waived—being used in a variety of settings, but their accuracy and limitations are under scrutiny, he added. On the other hand, there are a number of rapid HIV tests available that are actually quite effective. Clinical laboratory professionals need to be engaged in educating the public on the realities these test methods offer. They also need to advocate for additional research on the overall health impact of home HIV tests as well as of other home testing methods.

At present, these rapid methods of detection are insensitive relative to culture and molecular methods that now are available only in the central lab, Campbell explained. “What are really needed in this

area are molecular detection methods at the POC testing level. And it’s coming. There’s continuous evolution in getting those technologies ready for the POC setting.”

The Good News: Increased Revenue Potential

The growth of POCT might seem like a downward turn for test volume in the central lab, but Kazmierczak says it may actually generate more revenue and test volume for the central lab. “People tend to be concerned about test volume and how that impacts the overall work and efficiency of the central lab. The volume in our lab grows consistently by 4%–5% per year, while the volume done by POC testing here grows by about 7%–8% per year. But my gut feeling is that a lot of POC testing is generating more testing for the central lab because some results may be so questionable as to necessitate a second test.”

He added, “A lot of times, you have POC testing being done by people who don’t fully understand what the results mean and may not be trained to interpret the results correctly. When people undergo competency training on these devices it seems to involve more guidance on proper technique than on the ability to interpret a test result. They may just report out whatever the instrument tells them. And even though those results may be totally inaccurate, healthcare practitioners may act on them.”

Doing POCT and Doing It Right

Ten years ago, the central lab may have viewed POC testing suspiciously, thinking that the practice would take business away, said Intelab’s Simonsen. “But that kind of thinking seems to be a thing of the past. Virtually every major hospital today has a POC program that’s run by the central lab. Instead of resistance, what we’re seeing is an attitude that says ‘Let’s do it and do it right.’”

“The increase in the number of CLIA-waived tests available in the U.S. has been one of the factors driving growth in the POCT market, and I expect it to continue,” he concluded. CLN

New AACC POC Certificate Program Focuses on Role of POCT Specialist

In an effort to tackle issues relevant to POCT and POC coordinators, AACC has announced a new program composed of eight online courses—complete with reading assignments and quizzes—leading to a POC Specialist certificate.

POC coordinators may opt to take a single course or the full certificate which requires successful completion of all eight courses and passage of a comprehensive exam. Certificate program students have 12 months to complete all eight courses, which carry 1–2 credits each. The courses cover regulations, policies and procedures, connectivity, quality management, education and training, instrumentation validation and selection, administration, and communication. The goal of the program is to document the knowledge and skills necessary for successful practice as a POC specialist and recognize those individuals who demonstrate mastery of the content.

Marcy Anderson, MS, MT(ASCP), and Barbara Goldsmith, PhD, are chairing the certificate program. Anderson is senior clinical specialist at Medical Automation Systems in Charlottesville, Va. Goldsmith is AACC President Elect and vice president of laboratory services at Caritas Christi Health Care, and director of laboratory services at EXCELL Clinical Laboratories/St. Elizabeth’s Medical Center in Boston.

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*Nathan Hawkins, Co-owner & Co-founder
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Value of Trough Levels Questioned

MPA Monitoring, continued from page 1

McMaster University, Hamilton, Ont., for the Agency for Healthcare Research and Quality (AHRQ), has systematically examined the body of evidence from published studies in hopes of clarifying the benefit to patients. The report called the evidence so far inconclusive and stated that research into monitoring of MPA is still “in its infancy.” But despite the report’s conclusions, some TDM experts say it’s worthwhile.

The Challenge of Trough Levels

One difficulty in monitoring MPA lies in acquiring a value that accurately reflects true serum levels over time, said William M. Bennett, MD, medical director of renal transplantation at Legacy Good Samaritan

Hospital, Portland, Ore. “Technically doing a blood test for MPA is certainly possible,” he said. “The issue is, what does it mean? The drug has very complex pharmacokinetics, and it’s difficult to foresee a practical way to do monitoring if you just do a trough blood level, the way most other immunosuppressants are monitored.”

Alexander Vinks, PharmD, PhD, director of the division of clinical pharmacology Cincinnati Children’s Hospital Medical Center and professor of pediatrics and pharmacology at the University of Cincinnati School of Medicine, believes that monitoring makes sense—but he agrees trough levels are often of little value. “The goal is to optimize exposure response,” he said. “To predict exposure for a drug like MPA,

you cannot rely on trough monitoring only—because the drug has enterohepatic recycling. And that means that the trough cannot predict the hills that were there before. It’s like trying to stand in a valley and predict how high the mountain was before you came to the valley, but there are two mountains, and you may see only one.”

Others, however, say trough levels have proved to be useful for the majority of patients after graft stabilization, when receiving tacrolimus. Leslie M. Shaw, PhD, noted that trough levels of MPA do correspond with AUC levels in patients treated with MMF and tacrolimus, as shown by recent findings from the OptiCept trial, which investigated dosing of MMF in renal patients. The final results of the trial were presented at the International Congress of the Transplant Society in Sydney in August. Two of its major conclusions are that greater MPA

exposure is highly correlated with reduced risk of acute rejection and monitored patients with reduced tacrolimus dosing had reduced treatment failure rates, fewer rejections, and significantly lower withdrawal rates. This is important, because tacrolimus is now used in 80% of transplant patients, noted Shaw, a co-investigator on the OptiCept trial and a professor of pathology and laboratory medicine at the University of Pennsylvania.

The OptiCept trial’s earlier results showed no statistically significant lower rate of rejection for patients whose MPA levels were monitored. This was perhaps one reason for the inconclusive nature of the AHRQ report and Bennett’s reservations about monitoring. “Adjustment based on trough blood level probably leads to over- and underdosing,” Bennett said. “It just hasn’t seemed to correlate with drug exposure or with clinical events. There is tremendous discrepancy in individual absorption.”

Yet the OptiCept trial was designed simply to show that monitoring was not inferior to symptom-based dose adjustment, noted Shaw. “You can safely reduce the calcineurin inhibitor, using MPA monitoring, and you don’t see increases in bad outcomes.” He also pointed to a 1998 prospective double-blind, concentration-control study in renal transplant patients from Michael D. Hale, MD, and colleagues, known as RCCT, which Shaw said “showed unequivocally that maintenance of patients in a target AUC range of 30–60 mg/hr/L achieved a substantial statistically significant reduction in early acute rejection rates,” compared with renal transplants maintained at lower targeted AUC values (*Clin Pharmacol Ther* 1998;64:672-83; *Transplantation* 1999;68:261-66). “Trough concentrations also were significantly correlated with acute rejection but were noisier,” he said.

The European Practice

Maynard, who served as a peer reviewer for the AHRQ report, also believes monitoring makes sense. Yet her institution, like most in the United States, does not monitor MPA—despite having the capability to do so via HPLC/mass spectrometry. One reason MPA monitoring is not widespread, she said, is the difficulty in measuring MPA without such highly specialized lab instruments. “Tacrolimus, sirolimus, and cyclosporine may be measured by HPLC/mass spectrometry, and immunoassay kits are also marketed by various diagnostic manufacturers. So even any small hospital in the U.S. has the capability to monitor these other immunosuppressants via immunoassay,” she explained. “However, mycophenolic acid testing is available only on the Roche chemistry analyzer, and unless the lab has that system, the only other option is HPLC/mass spectrometry, which is not widely used.”

That may be one reason MPA monitoring is more widespread in Europe, Maynard said. “The last time I looked, there were only 37 institutions in the United States reporting mycophenolic acid proficiency testing through the College of American Pathology.” This contrasts with the far greater prevalence in Europe. “That might be due to more centralized TDM analysis in Europe, the fact that MPA has

See **MPA Monitoring**, continued on page 8

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TDM Reimbursement Remains Low

MPA Monitoring, from page 6

been available in Europe longer, or greater availability of pharmacokinetically assisted dosing in Europe.”

Teun van Gelder, MD, PhD, an internist and clinical pharmacologist at Erasmus University, Rotterdam, the Netherlands, has been an author or coauthor of numerous studies of MPA monitoring, including the RCCT study. He also said regulatory differences in Europe versus the US may contribute to the disparity. “It may have to do with the fact that the enzyme multiplied [EMIT] immunoassay has been on the market for many years in Europe, and not in the US,” he said. “Apart from availability of an easy assay, the effort DadeBehring [now Siemens] has done to teach doctors on the added value of TDM for MPA may have contributed to the implementation in Europe.”

Another native of the Netherlands, Vinks, suggested reimbursement and infrastructure as factors in the discrepancy. In the United States, “pathology is doing the tests, but they’re not incentivized to do interpretation, because they’re being reimbursed very little. Plus pathologists are not trained in doing this.” Vinks formerly ran a centralized therapeutic drug monitoring toxicology service for the city of The Hague, comprising five hospitals, 18 nursing homes, one children’s hospital, and two psychiatric clinics. In Europe “the clinical pharmacy people have their own labs, so they run the TDM. And they see it as part of their job not only to provide a number

but also provide a decent interpretation.” That interpretation is important, he emphasized. “A physician cannot do anything with [just] a number. The interpretive step and bringing it back to the physician in a format that he or she can really understand and use is a whole different type of great opportunity—with some challenges.”

Others acknowledged that reimbursement is lacking in the United States but noted that the overall cost for TDM is low for this drug. “Medicare only covers the immunosuppressant drug costs for disabled patients—usually kidney patients, due to disability qualification—or those qualified for Medicare by age. And then, only for the first 3 years post transplant,” Maynard said. However, “the drug is not as expensive [to monitor] as the other drugs.” Shaw shares this sentiment. “The cost to monitor this medicine is relatively small when you compare it to the cost of rehospitalization or extra visits to the hospital,” he said. “It’s dollars of cost; it’s not hundreds or thousands of dollars of cost.”

Concentration Fluctuations

The real question, however, is whether monitoring has an impact on organ rejection rates. This is a difficult question, because the current cocktail of antirejection medications is so effective, noted Shaw, who also served as a technical expert for the AHRQ report. “We now have the lowest rates of acute rejection in the history of the field. The challenge for immunosuppressant drug monitoring is all the greater, since there still is no reliable test of immune sys-

A Web Resource for Monitoring Immunosuppressants

A useful resource for labs considering an MPA monitoring program has been developed by a group at the University Hospital Center Limoges, France.

For MPA, the group uses a three-sample schedule, a graph of which is available on the website, as well as algorithms for all other immunosuppressants.

“The algorithm can come up with a very good estimate of what the profile looks like for a given patient at that point,” said Alexander Vinks, PharmD, PhD. He said that this group has tested the algorithm versus the current standard of care. “They found less rejection in a period of 1 year.”

The information can be found at: www.pharmaco.chu-limoges.fr/abis.htm.

tem suppression, a pharmacodynamic type of test,” he said. “The need for periodically checking MPA concentration exposure, in my view, is to know if your patient is getting an adequate exposure to this immunosuppressive drug,” he explained. “This is relevant because this drug, like the others, has wide pharmacokinetic variability. You don’t know how much it will vary from month to month within a given patient until you track it.”

Clinicians at Shaw’s center order MPA concentration monitoring in renal and heart transplant patients and some other transplant patients, and his laboratory provides the service for several other centers. “Our MPA therapeutic drug monitoring database has accumulated MPA concentration data over time for each of those patients, such that we have a good handle on the within-patient variability, and it ranges

anywhere from a coefficient of variation of about 10% up to 75%. One important goal of TDM is to reduce that variability. In addition to tracking MPA concentrations for each patient, our database has at least 20 demographic and clinical characteristics for each monitored patient. This permits ready review of the individual patient’s history and permits reporting of individualized interpretation of the MPA concentration data.”

He noted that monitoring MPA is different in several ways from the monitoring of the calcineurin inhibitors or rapamycin. “This drug does not exert organ toxicity as [strongly as] the calcineurin inhibitors can. So the urgency for monitoring is less for MPA than for those drugs,” he explained. “I think the issue is that in order for anyone who is not familiar with it to understand and use MPA pharmacokinetic data

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in transplant patients, they're going to have to study it in some detail, because this drug has lots of sources of variability," Shaw added. "And they include individual variability of clearance. That depends on disease state, patient compliance, patient age—pediatric versus adult—and genetic factors. And drug-drug interactions are a very important consideration, too. I think the variability in the mind of the physician is that since the drug has a lower toxicity profile compared with the calcineurin inhibitors, there's less worry about intoxicating the patient. The urgency is not the same." Another source of variability is changing pharmacokinetics relating to time post transplant. "For some individuals, the MPA concentration exposure per unit of MMF dose increases with time—but not for all patients," Shaw said.

A recent review, published after the AHRQ report was released, found that the AUC level of total MPA was associated with the risk of acute rejection but not with toxicity; it concluded that because most studies have been retrospective and/or based on monitoring trough levels in patients on cyclosporine, the evidence in favor of monitoring is "weak." However, the authors did note that monitoring multiple measures immediately post transplant for an AUC may have benefit (*Transplantation* 2008;85:1675-85).

Finding the Right Sampling Model

What options exist beyond trough levels and AUC curves to monitor MPA? The answer may be Bayesian type estimation. Vinks explained: "You have a computer program, and you enter all the patient information. Then you have a pharmacoki-

An Expert Access program on this topic with Susan Maynard, PhD, is available on the AACC website. Search "Events" to locate it.

netic model, which is basically the summary of everything that you have learned from all the patients that you have treated to date." The transplant physician can then enter the current patient's clinical parameters and receive an evidence-based estimate of what the MPA levels will be at different time points, he said. One publicly available example is based in France, at the National Institute of Health and Medical Research (INSERM) (See Sidebar).

"If you do it intelligently, monitoring is always better than not monitoring," said Vinks. However, "most studies haven't done it right, so they could not find any difference between an adequately monitored group and an unmonitored group." With AUC testing, two to four samples are usually collected, at between 0 and 4 or 0 and 6 hours, he said, because most of the action happens early. "Most people don't use any prior information. They just take the numbers as they come and use an algorithm that they developed from their own data or from the data of others."

Shaw noted that the three randomized, controlled trials of TDM for MPA have enrolled approximately 1,800 patients and that the aggregate of all three study populations could yield an analysis that is more conclusive as to the benefit of monitoring. There have been preliminary discussions among the researchers about this possibility, he said.

Eternal Vigilance—the Price of Lower Toxicity?

Despite support for monitoring among laboratorians, the AHRQ report didn't go that far.

"It's very difficult for the scientific community to do these prospective trials, because they're costly, and nobody is investing in this," Vinks explained. "So what you see is a lot of underpowered studies that then report it doesn't work. And so you get this continuous controversy."

Shaw noted that the randomized controlled trials of TDM for MPA—which total four if the 1998 study from Hale, van Gelder, and colleagues is included—make up a larger evidence base for monitoring of MPA than for any other drug. He be-

lieves the preponderance of the evidence is in favor of monitoring. "I think that when you consider whether to monitor, you can simply say, 'Do I want to have an objective assessment of how much drug is in my patient's body, versus not knowing that?' So when you ask it that way, I think it's pretty logical to conclude that it makes perfect sense that you would want to know and make dosing decisions from that information, rather than simply from an empirical dosing schedule." **CLN**

Disclosures: Teun van Gelder, MD, PhD, has received consulting fees and grant support from Hoffman-La Roche, Wyeth, and Siemens. Leslie M. Shaw, PhD, has received funding from Hoffman-La Roche and Novartis.

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Apolipoprotein B

Is it Time to Switch from LDL-C?

BY JOHN H. CONTOIS, PHD, AND JOSEPH P. MCCONNELL, PHD

For nearly two decades, LDL-C has been the cornerstone for assessment of cardiovascular disease risk, as well as the primary guide for preventive therapy. But recently, there has been much debate on the merits of monitoring LDL-C versus apolipoprotein B (apo B). Numerous prospective studies have demonstrated that apo B is more strongly predictive of coronary heart disease (CHD) risk than LDL-C (1). In fact, a recent consensus conference report from the American Diabetes Association and the American College of Cardiology recognizes the importance of apo B measurement (2).

In light of the mounting evidence, laboratorians should become more familiar with the clinical data on apo B as a marker of CHD risk. Here, we review the studies of apo B reported to date and discuss potential advantages of apo B measurement over LDL-C.

Problems with LDL-C

Cholesterol serves as a useful surrogate for estimating LDL particles, but LDL-C concentration can vary widely between individuals with the same LDL particle concentration. In one study, researchers found that the ratio of cholesterol to triglycerides in LDL particles can vary from 1.8 to 11.5 between individuals (3). The majority of subjects, 118 healthy men and women, had large LDL particles with the expected ratio

LDL-C Analytical Issues

Although LDL-C measurement is the gold standard for assessing CHD risk, the calculations and assays are not without flaws. Traditionally, LDL has been defined as the lipoprotein fraction in the density range from 1.019 to 1.063 g/mL determined by sequential density ultracentrifugation. Lipoprotein (a) (Lp(a)), with a density range of 1.045 to 1.080 g/mL, overlaps with LDL. Later, the beta-quantification method

triglyceride/cholesterol ratio, a lack of chylomicrons, and a lack of excessive remnant lipoproteins. Therefore, it cannot be used if patients are nonfasting, when triglycerides are > 400 mg/dL, or if the patient has type III hyperlipoproteinemia. The accuracy of the Friedewald equation begins to fail when triglycerides are >200 mg/dL and the effect is more pronounced at lower LDL-C concentrations. Furthermore, the equation is based on the measurement of total cholesterol, triglycerides, and HDL-C, and therefore is affected by inaccuracies associated with each of the three methods.

There is also a high degree of variation among manufacturers' direct LDL-C assays. Although these assay methods are largely unaffected by fasting status, the existing variability highlights the need for better standardization. Currently, LDL-C assays are not standardized to a common reference material, but instead rely upon comparison to a reference method. The variability with LDL-C assays, however, appear to relate more to inherent assay design than to calibration.

LDL-related CVD Risk

LDL particles, not simply LDL-C, play a central role in atherogenesis. The initiating process is the subendothelial retention of intact apo B-containing particles (4). LDL particles move into the arterial intima through a gradient-driven process, and the rate of passive diffusion is increased when the concentration of circulating LDL particles is elevated. Once inside the intima, the LDL particles bind to proteoglycans and initiate a process whereby the LDL particles are oxidized or otherwise modified and are taken up by monocytes to form macrophages. The cholesterol molecules contained in the LDL particles are passengers, but the intact particles drive the process.

Although apo B is widely considered a distinct risk factor for CHD, it is simply an alternate measure of LDL-related risk because it largely reflects LDL particle concentration. LDL-C, non-HDL-C, and total apo B are, to varying degrees, all measures of LDL-related cardiovascular risk. They are all highly interrelated, and so they have all been implicated as predictors of CHD in

of cholesterol to triglyceride >4. But surprisingly, 21% of subjects had LDL particles that were cholesterol-depleted (cholesterol/triglyceride ratio < 4), indicating that even an accurately measured LDL-C will underestimate LDL particle concentration and, presumably, CHD risk. LDL-C content does not reflect LDL particle concentration because intravascular metabolism can alter both lipoprotein size and lipid composition.

defined LDL-C as the cholesterol in the density fraction >1.006 g/mL minus the cholesterol in the HDL fraction isolated by precipitation. This method, therefore, actually measures intermediate density lipoprotein (IDL) and lipoprotein(a) (Lp(a)) cholesterol along with LDL-C.

The Friedewald equation, which estimates LDL-C, also includes the IDL and Lp(a)-C components and assumes a standard very low density lipoprotein (VLDL)



epidemiological studies. But biologically, they reflect different metabolic processes. Despite a high correlation with CHD risk, these markers are only modestly concordant, indicating that one cannot substitute for another in classifying patients into risk categories. At any given LDL-C level, apo B concentration can vary widely, and vice-versa.

An Overview of ApoB

The apoB gene, located on the short arm of chromosome 2, is 43 kb long with 29 exons. The protein itself is made up of 4,536 amino acids with a molecular weight of about 550 kDa. The two sites of apo B synthesis are the liver, which creates apo B-100, and the intestine, which produces apoB-48. A C-to-T substitution at nucleotide 6666 inserts a stop codon into the apo B mRNA and is responsible for the apoB-48 protein of 265 kDa.

Apo B is a component of all atherogenic or potentially atherogenic particles, including VLDL-, IDL, LDL, and Lp(a). Each of these particles contains one molecule of apo B, making it a direct measure of the number of atherogenic lipoprotein particles in the circulation. However, even in hypertriglyceridemic patients, the vast majority of total plasma apo B is associated with LDL, making apo B an effective surrogate for LDL particle concentration.

The Adult Treatment Panel of the National Cholesterol Education Program (NCEP) suggests an LDL-C goal of <100 mg/dL and a non-HDL-C goal of <130 mg/dL in high-risk patients. An equivalent goal for apo B, <90 mg/dL, has been proposed (5). Stein and colleagues have assessed the comparability of these goals using a database of more than 22,000 individuals from clinical trials. In 14,425 subjects with normal triglycerides (<200 mg/dL), 58% and 66% met the LDL goal and the non-HDL cholesterol goal, respectively. However, only 30% of these same individuals met the apo B goal. In 7,611 subjects with elevated triglycerides, only 17% met the apo B goal,

Table 1

Effect of Statins on LDL-C, Non-HDL-C, and Apo B

	LDL-C		Non-HDL-C		Apo B	
	Baseline (mmol/L)	Reduction at 54 weeks (%)	Baseline (mmol/L)	Reduction at 54 weeks (%)	Baseline (mmol/L)	Reduction at 54 weeks (%)
Atorvastatin	4.60	42.1	5.58	38.4	4.39	31.9
Fluvastatin	4.63	29.0	5.61	25.7	4.34	18.9
Lovastatin	4.60	35.5	5.61	31.8	4.39	25.4
Pravastatin	4.63	28.1	5.61	25.5	4.34	18.7
Simvastatin	4.55	25.6	5.50	32.0	4.29	25.0

From: Walldius and Jungner, J Intern Med 2004; 255:188–205.

while 60% and 51% met the LDL-C and non-HDL-C goals, respectively. Interestingly, the subjects who met the apo B goal were virtually assured of meeting both the LDL and non-HDL goals (6).

In contrast to LDL-C, standardization of apo B assays has made much progress. An IFCC standards committee recognized that bias between manufacturers for apo B was due to a lack of common calibration material. The committee identified a suitable reference material that manufacturers can use to assign values to calibration materials. Subsequent studies have reported a very respectable inter-laboratory CV of 3.1%–6.7% among assays from manufacturers using fresh-frozen patient sera and common calibrators (7).

Furthermore, fasting is not required for apo B measurement. Despite laboratorians' frequent objection that availability of apo B assays is limited, immunoturbidimetric assays have become more widely available for use on a variety of automated platforms.

A Look at Lipoprotein Disorders

Many lipoprotein disorders are characterized by elevated serum apo B concentration. Apo B mediates the uptake of LDL by liver and peripheral tissue via a specific interaction with the LDL receptor. Familial hypercholesterolemia (FH) is due to a de-

fect in the LDL receptor that prevents the clearance of LDL particles from the circulation. An increased number of LDL particles is therefore a hallmark of FH.

Familial defective apo B is a related disorder resulting from a mutation in apo B that prevents binding of the protein to the LDL receptor, resulting in a clinical phenotype similar to FH. Sporadic or polygenic hypercholesterolemia is likely due to overproduction of LDL particles. Hypertriglyceridemia (HTG) with elevated LDL particle concentration, and therefore higher apo B levels, may be the most common dyslipidemia. However, HTG without an elevated LDL particle concentration is probably not atherogenic. Similarly, individuals with Lp(a) excess also appear to have an excess of small, dense LDL particles (8).

The most common and perhaps underdiagnosed lipoprotein disorder, familial combined hyperlipoproteinemia (FCH), was originally defined as a total cholesterol or triglyceride concentration \geq 95th percentile in probands with premature CHD and at least one first-degree relative. Subsequent research has identified an association of FCH with an increase in small, dense LDL particles and demonstrated that FCH is most accurately diagnosed with a panel that includes measurement of apo B (9).

Prospective Studies of Apo B in Primary and Secondary Prevention

In a meta-analysis of apo B prospective studies, Thompson and Danesh found that apo B is a significant predictor of CHD with an overall relative risk of about 2.0 for the upper versus the lower tertile (10).

Another compelling study that supports use of apo B is the AMORIS study, which followed more than 175,000 men and women over the age of 60 for 5 years, including 864 men and 359 women who suffered a fatal MI (11). After adjustment for age and traditional lipid risk factors, including LDL-C, apo B remained a significant predictor of fatal MI, with relative risks of 1.33 (CI 1.17–1.51) and 1.53 (CI 1.25–1.88) for an increase of one standard deviation in men and women, respectively. LDL-C was an insignificant risk factor in women and only modestly associated with MI in men.

In the Quebec Cardiovascular Study of 2,039 men, ages 45–76, apo B was a strong, independent predictor of future cardiac events even after adjustment for age, smoking, systolic blood pressure, diabetes, and

medication use (12). Interestingly, the investigators found a synergistic relationship between apo B and the total cholesterol/HDL-C ratio (TC/HDL). When the TC/HDL ratio was low, an elevated apo B was associated with a 60% increased risk of CHD. But when the TC/HDL ratio was high, an elevated apo B was associated with a 2.6-fold increased risk. A 13-year follow-up of the participants also suggested a similar synergy between LDL-C and apoB (13). Among the men with elevated LDL-C but low apo B levels (<128 mg/dL), relative risk for CHD was a modest 1.5. But when both LDL-C and apo B were elevated, the relative risk was 2.2.

Among the published prospective studies of apo B in primary prevention, all but one found a statistically significant association with CHD, even after adjustment for nonlipid risk factors. Of the 13 primary prevention studies that also provided data for LDL-C, only nine reported a significant relationship between LDL-C and CHD in both men and women or all subjects combined. Among the studies reporting both apo B and LDL-C, apo B was consistently the stronger risk factor.

The secondary prevention studies reveal similar results. Baseline value of apo B was a significant predictor of recurrent cardiovascular events in all but one study, including the 4S, LIPID, THROMBO, and other studies. Neither apo B nor LDL-C was a significant predictor of recurrent events in the VAHIT study; however, subjects were selected to have relatively low LDL-C concentrations.

There is a wide variation in the reported relative risks for CHD in these epidemiologic studies, largely dependent on whether apo B levels are adjusted for other lipids and lipoproteins. Consequently, the debate about the utility of apo B for CHD risk assessment has become one of statistics rather than biological plausibility. However, as the Quebec Cardiovascular Study and AMORIS have shown, in large-scale studies with precise and standardized apo B measurement, apo B does appear to have statistical significance even when traditional lipids and lipoproteins are covariates in the regression models. This is also evident in the Health Professionals Follow-up Study. When apo B and LDL-C were simultaneously included in the model, relative risk was strongly associated with apo B, while LDL-C and non-HDL-C were no longer statistically significant (14).

Table 2

Suggested Treatment Goals in Patients with Cardio-metabolic Risk and Lipoprotein Abnormalities

	Goals (mg/dL)		
	LDL Cholesterol	Non-HDL Cholesterol	Apo B
Highest-risk patients, including those with (1) known CVD or (2) diabetes plus one or more additional major CVD risk factor*	<70	<100	<80
High-risk patients, including those with (1) no diabetes or known clinical CVD but two or more additional major CVD risk factors or (2) diabetes but not other major CVD risk factors	<100	<130	<90

*Other major risk factors (beyond dyslipoproteinemia) include smoking, hypertension, and family history of premature CAD.

From: Brunzell et al., JACC 2008;51:1512.

Monitoring LDL-lowering Therapy

Statins have proven to be highly effective in reducing serum cholesterol through inhibition of HMG-CoA reductase. Clinical trials have consistently shown that a remarkable lowering of LDL-C is associated with a substantial lowering of relative CHD risk; however, in terms of absolute risk, reduction is far less dramatic. This has led many lipid experts to conclude that LDL-C targets need to be set much lower.

However, it appears that a reduction in apo B or LDL particles may be a better target for monitoring therapeutic effectiveness and residual risk. Statins also reduce the production of both VLDL-apoB and LDL-apo B. But as shown in Table 1, the reduction in serum apo B concentration is not as dramatic as the LDL-C decrease, and levels of apo B in patients on statin therapy indicate potential residual risk associated with increased LDL particles (15).

In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) apo B at baseline and following 1 year on therapy was a strong predictor of future CVD events, whereas LDL-C failed to reach significance ($p > 0.05$ at baseline and on therapy) (16). A similar analysis in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study showed similar findings (17). The reason is appar-

ent: LDL-related risk is not captured by LDL-C measurement alone. Results from both primary and secondary statin trials suggest that on-therapy concentrations of apo B or LDL particles better predict future CHD events than does LDL-C.

New Directions

Numerous prospective epidemiologic studies show that apo B is a statistically significant predictor of future fatal and non-fatal heart disease. Apo B measurement to assess CHD risk is especially important in the large and rapidly growing subset of the population with characteristics of the metabolic syndrome and in diabetic patients. Individuals with the metabolic syndrome or diabetes tend to have an increased number of small, dense LDL particles but relatively normal LDL-C levels. Furthermore, therapy with HMG-CoA reductase inhibitors reduces LDL-C to a greater extent than LDL particle concentration, suggesting that apo B may provide a better assessment of residual risk for patients on this therapy.

Clearly, for apo B to become an important complement to the standard lipid profile, the medical community will need to accept that the number of circulating LDL particles is the major component of LDL-related CHD risk, not LDL-C. The movement towards this has already started. In a

recent review, a panel of experts concluded that CHD risk is more directly related to the number of circulating atherogenic particles than to the cholesterol content of lipoproteins, and the panel advocated apo B measurement (1). Furthermore, a consensus conference report from the American Diabetes Association and the American College of Cardiology concluded that measurement of apo B with a standardized assay is warranted in patients with metabolic syndrome, especially to assist with therapeutic monitoring (2). Table 2 gives the suggested treatment goals for these patients.

Canadian medical practice has already added apo B to guidelines for assessment of at risk patients (18), and updated guidelines from the National Cholesterol Education Program are expected in 2009 on cholesterol testing and management. The addition of apo B to these guidelines seems to be the logical next step. As laboratorians, our community will need to stay abreast of these developments, which are likely to create major changes in patient management. **CLN**

REFERENCES*

1. Barter PJ, Ballantyne CM, Carmena R, Castro Cabezas M, Chapman MJ, et al. Apo B versus cholesterol in estimating cardiovascular risk and in guiding therapy: report of the thirty person/ten-country panel. *J Intern Med* 2006;259:247-258.
2. Brunzell JD, Davidson M, Furberg CD, Goldberg RB, Howard BV, Stein JH, Wittum JL. Lipoprotein management in patients with cardiometabolic risk: conference report from the American Diabetes Association and the American College of Cardiology Foundation. *JACC* 2008;51:1512-1524.
3. Otvos JD. Measurement of triglyceride-rich lipoproteins by nuclear magnetic resonance spectroscopy. *Clin Cardiol* 1999;22(6 Suppl):II21-27.
4. Tabas I, Williams KJ, Boren J. Subendothelial lipoprotein retention as the initiating process in atherosclerosis: update and therapeutic implications. *Circulation* 2007;116:1832-1844.
5. Grundy SM. Low density lipoprotein, non-high density lipoprotein, and apolipoprotein B as targets for lipid-lowering therapy. *Circulation* 2002;106:2526-2529.
6. Stein EA, Sniderman A, Laskarzewski P. Assessment of reaching goal in patients with combined hyperlipidemias: low density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, or apolipoprotein B. *Am J Cardiol* 2005;96[suppl]:36K-43K.
7. Marcovina S, Packard CJ. Measurement and meaning of apolipoprotein B plasma levels. *J Intern Med* 2006;259:437-446.
8. Zambon A, Braun BG, Deeb SS, Brunzell JD. Genetics of apolipoprotein B and apolipoprotein AI and premature coronary artery disease. *J Intern Med* 2006;259:473-480.
9. Veerkamp MJ, de Graaf J, Hendriks JCM, Demacker PNM, Stalenhoef AFH. N-mogram to diagnose familial combined hyperlipidemia on the basis of results of a 5-year follow-up study. *Circulation* 2004;109:2980-2985.
10. Thompson A, Danesh J. Association between apolipoprotein B, apolipoprotein AI, the apolipoprotein B/AI ratio and coronary heart disease: a literature-based meta-analysis of prospective studies. *J Intern Med* 2006;259:481-492.

Editor's Note

A more comprehensive review of apo B studies and standardization issues can be found in a draft position statement that was published in the summer issue of the "Fats of Life" newsletter by the AACC Lipoproteins and Vascular Diseases Division Working Group on Best Practices. The group is soliciting comments on the draft and invites *CLN* readers to submit their thoughts. To read the statement, go to www.aacc.org and search for fats of life.

11. Walldius G, Jungner I, Holme I, Aastveit AH, Kolar W, Steiner E. High apolipoprotein B, low apolipoprotein A-1, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet* 2001;358:2026-2033.

12. Lamarche B, Moorjani S, Lupien PJ et al. Apolipoprotein A-1 and B levels and the risk of ischemic heart disease during a 5 year follow-up of men in the Quebec Cardiovascular Study. *Circulation* 1996;94:273-278.

13. St-Pierre A, Cantin B, Dagenais GR et al. Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men. 13-year follow-up data from the Quebec Cardiovascular Study. *Arterioscler Thromb Vasc Biol* 2005;25:553-559.

14. Pischon T, Girman CJ, Sacks FM, Rifai N, Stampfer MJ, Rimm EB. Non-high density lipoprotein cholesterol and apolipoprotein B in the prediction of coronary heart disease in men. *Circulation* 2005;112:3375-3383.

15. Walldius G, Jungner I. Apolipoprotein B and apolipoprotein AI: risk indicators of coronary heart disease and targets for lipid-modifying therapy. *J Intern Med* 2004;255:188-205.

16. Gotto AM, Whitney E, Stein EA, Shapiro DR, Clearfield M, Weis S. Relation between baseline and on-treatment lipid parameters and first acute major coronary events in the Air force/Texas Coronary Atherosclerosis Prevention Study (AF-CAPS/TexCAPS). *Circulation* 2000;101:477-484.

17. Simes RJ, Marschner IC, Hunt D, Colquhoun D, Sullivan D, Stewart RAH. Relationship between lipid levels and clinical outcomes in the long-term intervention with pravastatin in the ischemic disease (LIPID) trial. To what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels? *Circulation* 2002;105:1162-1169.

18. Genest J, Frolich J, Fodor G, McPherson R, the Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management of dyslipidemias and the prevention of cardiovascular disease: summary of the 2003 update. *JAMA* 2003;289:921-924.



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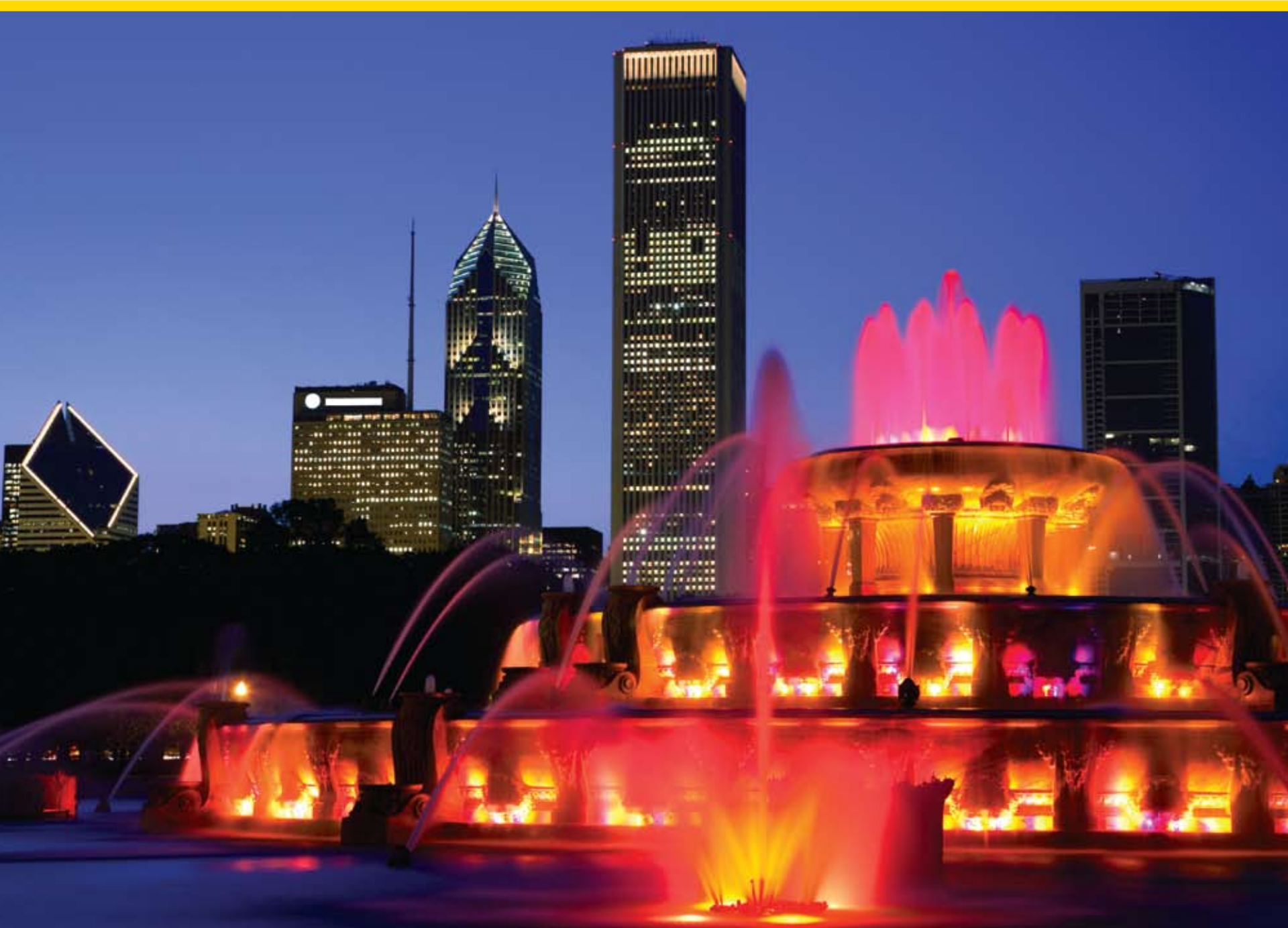


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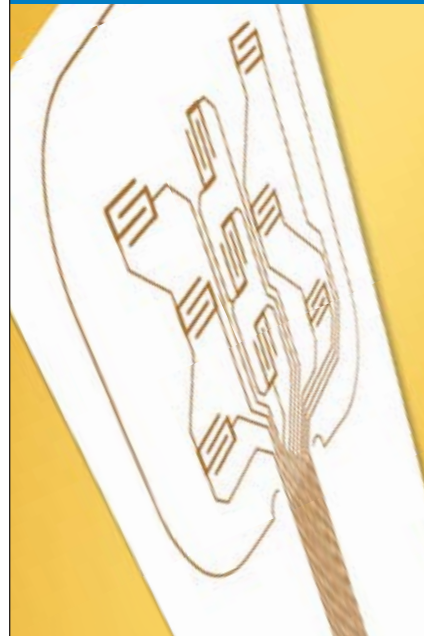
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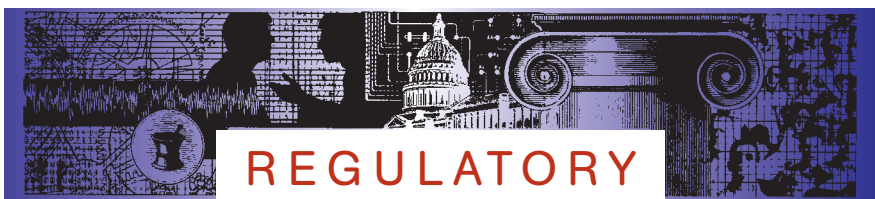


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Comparative Effectiveness Bill in Senate

A new bill introduced in the Senate would create a hub for researchers to evaluate clinical research—for drugs, devices and surgical procedures—in a bid to lower healthcare costs.

The bill, S 3408, would create the non-profit Health Care Comparative Effective-

ness Research Institute. It would work with HHS, AHRQ and NIH, as well as drug and device makers, patients, and clinicians, to deliver peer-reviewed research studies about healthcare effectiveness. A private, 21-member Board of Governors, comprising the HHS secretary, the director of AHRQ, the director of the NIH, as well as representatives of patients, physicians, public health agencies, public payers, private

payers, the pharmaceutical industry, device manufacturers, nonprofit health research organizations and quality improvement organizations, would govern the institute.

Senate Finance Committee Chair Max Baucus (D-Mont.) and Senate Budget Committee Chair Kent Conrad (D-ND) sponsored the bill. The institute would cost \$5 million starting in 2010 and be funded by taxpayer money.

House Committee Passes Health IT Bill

The House Energy and Commerce Committee unanimously approved legislation—HR 6357, sponsored by Rep.

John Dingell (D-Mich.)—designed to promote faster adoption of electronic health records (EHRs). The Protecting Records, Optimizing Treatment and easing Communication Through Healthcare Technology [PRO(TECH)T] Act of 2008 aims to promote national use of EHRs by 2014.

The Act would provide \$560 million in grants and loans for healthcare providers, particularly in small and rural practices and those serving the underserved, to acquire EHR systems. If approved, the PRO(TECH)T Act would require HHS to disclose more fully how it resolves complaints of HIPAA privacy and security violations.

The PRO(TECH)T Act also would establish a process for developing, recognizing, and harmonizing technical standards for health IT, and promote the adoption of such standards by HHS.

To view the bill, go to www.thomas.gov.

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AHRQ, AARP Join Forces for Health, Prevention Effort

The Agency for Healthcare Research and Quality (AHRQ) and the AARP have teamed up to release two new checklists designed to help men and women over the age of 50 learn what they can do to stay healthy and prevent disease.

The two organizations also released an accompanying wall chart, the Staying Healthy at 50+ timeline, which provides information about recommended preventive services. These three publications are: "Men: Stay Healthy at 50+: Checklists for Your Health; Women: Stay Healthy at 50+: Checklists for Your Health; and The Staying Healthy at 50+ Timeline. Each shows at a glance the evidence-based recommendations from the U.S. Preventive Services Task Force regarding screening tests, preventive medicines, and healthy lifestyle behaviors.

The Checklists for Health brochures, available in English and Spanish, are designed to help patients and clinicians discuss necessary preventive screening tests.

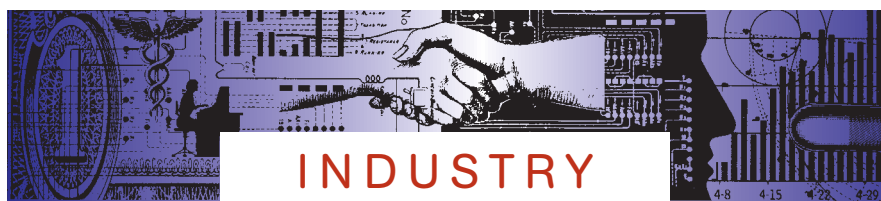
P4P Programs May Not Affect Quality of Care

A new study concludes that pay for performance programs—also known as P4P programs—offer little to no impact on quality of care. The study compared 81 Massachusetts physician groups eligible for quality incentives with 73 that lacked eligibility, and the performance of some 5,350 physicians between 2001 and 2003. The study was published in the July/August issue of *Health Affairs*.

Bonuses ranged from \$200 to \$2,500 per quality measure for an individual physician, depending on the health plan.

The researchers found that during this period overall performance improved on almost three-quarters of such preventive care measures as HbA1c testing, breast cancer screening, and well-child visits. However, the scientists observed that earning a bonus for providing guideline-based care made no difference. Statistically, the physicians' performance measures were indistinguishable.

View the abstract at <http://content.healthaffairs.org/cgi/content/abstract/27/4/1167>.



INDUSTRY

Affymetrix Boosts Portfolio with Asuragen IVT Reagent Kits

Affymetrix announced an agreement with Asuragen for in vitro transcription (IVT) reagent kits for clinical molecular diagnostics applications. Asuragen will develop and manufacture kits configured for use with Affymetrix' GeneChip System 3000Dx, the only available diagnostic microarray platform to win FDA clearance. According to Asuragen's chief scientific officer, Matt Winkler, the new reagent kits will facilitate greater adoption of Affymetrix microarray technology by improving workflow for clinical labs. Financial terms of the deal were not disclosed.

DNA Repair Company Get Exclusive Rights to Breast Cancer PGx Test

The Boston-based DNA Repair Company announced a licensing agreement with Helsinki University Central Hospital for the use of a newly discovered test that strongly predicts how women with breast cancer will respond to standard anthracycline-containing chemotherapy regimens. Researchers at the hospital discovered that the NQO1*2 enzyme, a variant that disables the production of the NQO1 protein, is a factor in breast cancer treatment response. Patients with NQO1*2 had worse survival

outcomes when treated with anthracycline-based chemotherapy than with alternatives. Researchers found that women with a double copy of NQO1*2 in their genome had only a 17% survival rate, while those who had only a single copy or did not have a variant had a survival rate of 75% (*Nature Genetics* 2008;40:844-53). "The findings of the researchers on the effect of NQO1*2 on breast cancer survival were highly significant and hold important promise for predicting clinical outcomes for cancer patients," said Daniel Paterson, CEO of the DNA Repair Company. "We are excited at the opportunity to employ this novel biomarker in our efforts to give physicians data-driven tools to identify the most beneficial treatment regimen for a particular patient." Financial terms were not disclosed.

Agencourt and Third Wave Sign Agreement on New HPV Tests

Agencourt Bioscience announced a deal with Third Wave Technologies whereby the Agencourt Genfind DNA isolation system will be integrated into Third Wave's new HPV tests, which are still under FDA premarket review. Agencourt is a subsidiary of Beckman Coulter, while Third Wave is owned by Hologic. The companies also agreed to collaborate on future products. "With the growing use of HPV testing

to screen for cervical cancer, the marketplace has been demanding improvements in diagnostic tests," said Kevin Conroy, CEO of Third Wave Technologies. "Agencourt's nucleic acid preparation technology delivers the reliable recovery of purified DNA required for both our Cervista HPV HR and Cervista HPV 16/18 tests. Agencourt Genfind is also easily automated, allowing Third Wave to attend to the needs of our medium- to high-volume customers, a key part of the overall HPV strategy for our company." Agencourt's Genfind system uses proprietary paramagnetic bead-based nucleic acid purification that requires no organic solvents, vacuum filtration, or centrifugation steps. According to Third Wave, the global market for HPV testing will reach \$250 million in 2008. Financial terms of the deal were not disclosed.

ARUP and Weber State University Team Up for Lab Tech Education

ARUP Laboratories and Weber State University (WSU) announced a collaboration aimed at tackling shortages of qualified laboratory workers. Under the

agreement, ARUP and WSU will offer ARUP clients access to Web-based courses in medical technology toward CLS bachelors' degrees and CLT associates' degrees. "According to the U.S. Bureau of Labor Statistics for the period of 2002 through 2010, 12,400 graduates will be needed annually to staff the nation's clinical laboratories. However, on a national basis, fewer than half of the necessary laboratory personnel are graduating," said ARUP president and COO Ronald Weiss, MD. "We are seeing these shortages become more critical within community health systems that are growing their outreach programs. This collaboration enables our client laboratories with an opportunity to educate laboratory personnel, without taking them away from their work sites." The program will allow students to learn and earn credit while working in their own facility with the support of their employer instead of attending offsite classes, and graduates will be able to sit for the registry exams after finishing their AAS/CLT or BS/CLS degree. More information about the program is online, at www.aruplab.com/weber.

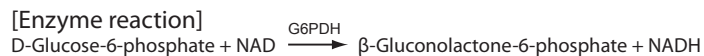
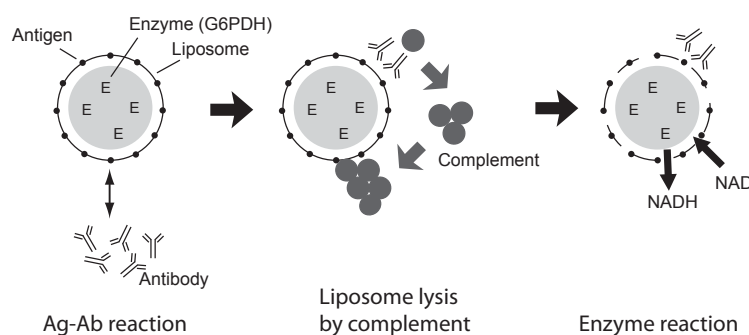
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DIAGNOSTIC

Genes Predict Survival In Lung Cancer Patients

Prognostic models for early-stage lung cancer should include both gene expression and clinical parameters such as patient age, sex, and stage of disease, new research concludes. The retrospective study, published in *Nature Medicine* (2008;14:822-7), examined the validity of the various biomarkers and gene signatures used to classify patients with non-small-cell lung cancer. Data from 442 cancer patients from six institutions were collected and analyzed based on gene expression and patient characteristics. The investigators then divided the patients into four groups, based on the degree of survival associated with each. Two sets constituted training sets for development of predictive models; the other two sets were for validation. The investigators then modeled risk profiles by scoring and classifying each case based on one of the following methods: gene cluster expression summaries, expression of individual genes, principal components of gene expression, membership in clusters defined by gene expression or a vote of single-gene classifiers. According to the researchers, only the first and last methods showed statistically significant predictive value of survival.

Fetuin-A Levels Predict Incident Diabetes in Elderly

Retrospective case-cohort study reports that among participants age 70-79 years, the rate of incident diabe-

tes was associated with higher levels of fetuin-A. The findings, reported in *JAMA* (2008;300:182-8), were based on a cohort of 3,075 participants recruited from the Health ABC Study. The researchers assessed Medicare participants for fasting blood glucose at the second, fourth, and sixth annual visits. A total of 500 patients were randomly selected for stratification by age and race. Of this group, 135 were diagnosed with incident diabetes during 6 years of follow-up. Participants in this sub-cohort were 50% female and 50% African American. Of 575 not stratified, 112 had incident diabetes. Levels of fetuin-A were divided into tertiles; tertile 1 (≤ 0.76 g/L) served as the reference range. Patients in tertile 2 (0.77-0.97 g/L), after adjustment for age, sex, race, visceral adiposity, PAI-1, adiponectin, leptin, TNF, and IL-6, had an odds ratio of 1.83 for incident diabetes. For patients in tertile 3 (> 0.97 g/L), the OR was 2.44 after adjustment for all such factors. These results suggest fetuin-A could be an important marker for detecting an increased risk for diabetes in elderly persons. In addition, "blockade of fetuin-A binding to the insulin receptor might be considered a novel therapeutic target for prevention or treatment of insulin-resistant states," the authors wrote.

Thyrotropin Levels Linked to Alzheimer's Disease in Women

According to new findings from the Framingham Study, low and high levels of thyrotropin are associated with increased risk of Alzheimer's disease (AD) in

women (*Arch Intern Med* 2008;168:1514-20). The investigators analyzed the relationship between baseline levels of thyrotropin from blood collected in 1977-1979 and the incidence of subsequent AD in 1,864 male and female participants. They found that women with the lowest (< 1.0 mU/L) and highest (> 2.1 -50.5 mU/L) levels of thyrotropin had more than double the incidence of AD compared to women with levels in the middle range (1.0-2.1 mU/L). The adjusted hazard ratio for AD in the lowest-tertile group was 2.39, compared with the middle-tertile patients, and 2.39 for the highest-tertile group. In men, however, there was no such relationship. There were 51 cases of AD among the 330 women in the low tertile, 25 cases of 313 in

the middle tertile, and 45 cases out of 305 women in the high tertile. Mean patient age at baseline was 71 years in women and 70 years in men. The authors noted that there is no clear explanation for the association between low levels of thyrotropin and susceptibility to Alzheimer's disease in women. It might be a consequence, rather than a cause, of Alzheimer's disease, they wrote, in that neurodegeneration might cause the hypothalamus to secrete less thyrotropin or cause the pituitary gland to be less responsive to thyrotropin-releasing hormone.

Performance of Rapid HIV Tests in the ED

A study of an on-site screening test for HIV in the emergency department at Brigham and Women's Hospital, Boston, found that an oral rapid test to detect the virus had a lower specificity than the investigators had expected and lower than that listed by the test's manufacturer. The researchers, who noted that this result was consistent with earlier studies of such tests when tested in actual field settings, reported findings from 849 participants in the *Annals of Internal Medicine* (2008;149:153-60). Of these patients, 810 had a nonreactive result, and 39 had a reactive result. Of those with a reactive result, 31 consented to have the result confirmed; 26 of those 31 were found not to be infected with HIV. Based on their study, the investigators estimate the HIV test sensitivity to be 96.9% (95% CI, 95.7% to 98.1%) in this ED setting. According to the manufacturer, the sensitivity is 99%. The higher rate of false-positives than that indicated by the test manufacturer points to the need for confirmation of oral tests as quickly as possible—perhaps by making HIV RNA testing part of such confirmation testing, the investigators noted. Testing for the virus's RNA by PCR amplification, which is used in blood banking, detects HIV at an earlier stage than standard antibody testing and may help catch more new infections.

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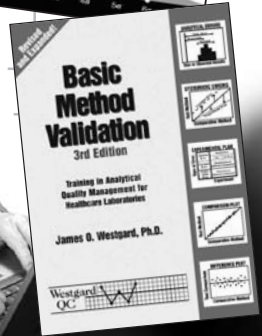
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NEWS FROM THE FDA

FDA Clears Osmetech's Warfarin Sensitivity Test and Instrument

Osmetech announced the FDA clearance of its eSensor Warfarin Sensitivity Test for use as an aid in the identification of patients at risk for increased sensitivity to warfarin. The eSensor Warfarin Sensitivity Test detects three genetic markers known to play a role in warfarin's metabolism. FDA also cleared the company's eSensor XT-8 molecular diagnostics platform, a random-access, small-footprint microarray instrument. This is the third pharmacogenomic test cleared for warfarin dosing.

FDA Clears Pathwork Tissue of Origin Test

The second in vitro diagnostic multivariate index assay (IVDMIA) cleared by the FDA, the Pathwork Tissue of Origin Test uses a microarray to analyze a malignant tumor's gene expression pattern and pinpoint the source of hard-to-identify tumors. The test looks for 15 common tumor types, including bladder, breast, and colorectal tumors, and uses the PathChip

gene expression array, a custom-designed microarray chip designed by Affymetrix. It is the first such custom chip from Affymetrix to achieve FDA clearance. According to Pathwork Diagnostics, up to 200,000 newly diagnosed cancer patients annually in the U.S. may have a tumor for which the site of origin is uncertain after the initial diagnostic workup.

Celera's VirSeq HIV-1 Genotyping System Software v2.8 Cleared

Celera announced FDA clearance for its ViroSeq HIV-1 Genotyping System software v2.8. The system detects mutations in the HIV-1 viral genome that confer drug resistance, helping monitor HIV-1 infections. The updated software includes two additions to the resistance algorithm for new drugs—etravirine and darunavir—as well as updates to the resistance algorithm for all protease and reverse transcriptase inhibitors. The system also can now run on Intel dual-processor computers. The ViroSeq system features an automated DNA sequencing platform, reagents, and dedicated software. Abbott Laboratories distributes the system.

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Response Biomedical's POCT RAMP NT-proBNP Test Cleared

Response Biomedical announced the FDA clearance of its RAMP NT-proBNP test as an aid in the rapid diagnosis of heart failure. The test, run on the RAMP200 POC analyzer, is clinically concordant with the Roche Elecsys proBNP test. In clinical trials, the test provided results comparable to those produced by its automated counterpart.

ABL80 FLEX Blood Gas Analyzer Cleared

Radiometer announced FDA clearance of its ABL80 FLEX CO-OX, a portable blood gas analyzer for POCT. The instrument measures pH, blood gases, electrolytes, glucose, and vital co-oximetry parameters. It also features an interval of 140 seconds between results, cartridge-based testing, sample size of 105 µL, self-cleaning sample inlet, automatic QC, and HIS/LIS connectivity.

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