

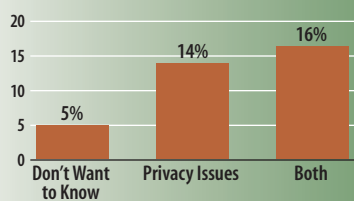
SURVEY SAYS CONSUMERS WARY OF GENETIC TESTS

As more companies enter the consumer genetic-test market, a new survey of business professionals suggests that Americans remain wary of these tests, the benefits they offer, and the personal risks users may encounter. A survey recently found that the majority of consumers are reluctant to use a genetic test in the near future to assess the hereditary risk for certain diseases, such as any type of cancer, diabetes, Alzheimer's disease, Parkinson's disease, multiple sclerosis, or asthma. The Personalized Medicine and Wellness Survey was issued by Burrill & Co., a San Francisco-based life sciences merchant bank, and ChangeWave Research, a market research firm.

The survey results are based on responses obtained from 550 business professionals to questions about several health-related issues, including personal genetic tests. Only 5% of respondents said they would be very likely to measure their genetic risk for certain diseases, while 15% said they would be likely to get a genetic test.

A key finding of the survey is that makers of genetic tests need to provide actionable information to consumers.

Snapshot: Worried about Genetic Testing



Source: Personalized Medicine and Wellness Survey, Executive Summary, 2008

Also, despite the recent signing into law of the Genetic Information Nondiscrimination Act (GINA), consumers remain concerned about their genetic privacy. Other concerns were the cost of genetic tests; that GINA protection does not include the areas of life and disability insurance; and that physicians remain the most likely source of information about genetic testing.

When asked about whom they would be willing to give access to their genetic test results, 72% said a spouse or partner, and 71% said their physician; 22% said they would share the information with research institutions for research purposes, but only 3% would share the results with insurance companies, and 2% said they would share it with their employer or a life insurance company.

Although more than half of the survey participants said that cancer and/or heart disease—the leading causes of death in the U.S.—are matters of concern, only 4% of the group said they have had a genetic test to assess disease risk. Two-thirds of those who have undergone genetic testing did so at the behest of a physician. The executive summary of the report is available online at www.burrillandco.com/survey.

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The Status of Laboratory Medicine

CDC Report Hit the Mark, But Will It Drive Change?

BY PHIL KIBAK

The 200,000-plus CLIA-certified U.S. medical laboratories conduct about 7 billion tests annually. This significant contribution to healthcare, which accounts for only 2.3% of annual U.S. healthcare costs, has an enormous impact on clinical decision-making and health outcomes. But with ever growing pressures on labs to do more with less, a comprehensive analysis of key factors affecting laboratory medicine—and the attendant identification of practices that could reduce laboratory-related error rates or optimize use of laboratory testing—was missing. Now, a 2-year effort by the CDC Division of Laboratory Systems has given stakeholders, including policymakers, a snapshot of where the field stands today. “Laboratory Medicine: A National Status Report” was unveiled in May and describes the challenges and prospects that affect clinical labs in the U.S. The purpose of the report, according to the CDC, is to lay the groundwork for transforming laboratory medicine over the next decade.

In the 384-page report, the Lewin Group, a health and human services consulting firm based in Falls Church, Va., under subcontract to Battelle Memorial Institute, compiled and analyzed data from published and unpublished literature, government databases and reports, market research reports, and input from laboratory experts and government officials. While most lab leaders praise the report as an accurate overview of key factors that affect laboratory medicine today, how the document will drive improvements is uncertain.

See **CDC Report**, continued on page 3



Saliva Tests: Ready to Spit?

Oral-based Tests Poised for Wider Array of Analytes

BY GINA ROLLINS

In Western culture, saliva has a distinctly unsavory connotation, but a wave of research involving cutting-edge technologies is changing people's opinions on the heretofore undervalued biofluid. In fact, some experts believe that analysis of saliva may be equivalent, and in some instances superior, to assessment of serum, urine, or other biofluids in diagnosing oral as well as systemic diseases. With none of the anxiety and discomfort associated with needlesticks, coupled with the micro- and nanotechnologies employed to amplify its diverse but comparatively low concentration of analytes, saliva has the potential to offer a revolutionary change in medicine.

“It's been the poor step-child of serum, yet the vast majority of proteins in serum are also present in saliva, but in minute amounts. You simply have to look harder to reveal information that's contained there,” explained John McDevitt, PhD, professor of chemistry at the University of Texas at Austin.

Two forces are driving saliva's rising currency as a diagnostic tool. One is the development of mass spectrometry and other technological advances that enable high throughput analysis and detection of concentrations of analytes that are 1,000 to 10,000 times lower than in serum. The many biological roles of saliva are well documented, such as starting the digestive process through the release of enzymes and the cleansing and diluting of detritus in the mouth. Pioneering researchers like Irwin Mandel, DDS, professor emeritus of dentistry at Columbia University, N.Y. have long maintained that saliva is a

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Report Supports Value of Lab Tests

CDC Report, continued from page 1

The report is a welcome affirmation of the struggle that lab professionals face for recognition of their contributions and value to the U.S. healthcare system, notes AACC president Larry Broussard, PhD, professor of clinical laboratory sciences at Louisiana State University Health Sciences Center in New Orleans. “The report substantiates what laboratorians have been saying. But it really is a first step and needs to be followed up with specific recommendations to address the problems identified. The critical thing is: how will the report be followed up?”

Rodney Forsman, assistant professor of laboratory medicine and pathology at the Mayo Clinic College of Medicine in Rochester, Minn. agrees and hopes that policymakers will use the data to make much needed changes in reimbursement and regulation of lab tests. “This report does not break new ground, but it gives a credible snapshot of where we are today. The relevance of the report is that we now have a government-commissioned document that supports what we in the field have been saying. And as far as those responsible for making policy, this gives them something to turn to that highlights the right areas.”

“It’s quite valuable as a resource,” added Robert Murray, JD, PhD, technical consultant with Midwest Diagnostic Pathology in Park Ridge, Ill. “The Lewin Group did its homework, and the quantitative documentation is excellent. And it appears to be very supportive of the value of laboratory testing and shows that it has a favorable cost-benefit ratio within the healthcare system.”

A Comprehensive Scope

Concern that policymakers lack a firm understanding of the field of laboratory medicine was one of the factors that prompted the CDC to initiate a national effort to identify and evaluate best practices in lab medicine. “We have felt for some time that there needed to be a document

that substantiates the scope of laboratory medicine in the United States,” explained D. Joe Boone, PhD, acting director of the CDC Division of Laboratory Systems and the administrator of the project. “Its primary focus is to help those who are not laboratory professionals—policymakers, for example—better understand the field as well as the nature of the constraints that influence or affect laboratory operations and practices. But we also hope that laboratorians find it useful.”

Boone noted that he was expecting something quite a bit smaller. “It kind of surprised me when I saw the actual magnitude of the document,” said Boone. “I was expecting something that was significantly less lengthy.” He added that the Lewin Group is still working on three additional chapters (See Box, below). Final drafts of these chapters are expected to be available for comment after August 30. The comment period for the previously finished chapters ended on June 30 with comments received from five organizations—the American Clinical Laboratory Association, the American Society of Microbiology, the College of American Pathologists, Auburn Strategies, and the Academy for Clinical Laboratory Physicians and Scientists—and two individuals. The entire report is expected to be finished by November 30.

More Specifics, Please

While many laboratorians are pleased with the report, citing words like extensive and comprehensive, others believe that there’s a need for greater depth in some of the conclusions it draws, as well as the need for more concrete recommendations.

David Mongillo, vice president for policy and medical affairs at the American Clinical Laboratory Association in Washington, D.C., remarked that “the report really touched upon a fully integrated landscape of the very complex clinical lab industry, but we view this as a first step toward any additional considerations that might

Lab Medicine: The Numbers

- ▶ Approximately 6.8 billion lab tests are performed annually in the U.S.
- ▶ Lab testing revenues in 2007 were a projected \$52 billion
- ▶ Hospital-based labs generate 54% of total testing revenue, projected at \$28.4 billion for 2007
- ▶ More than 4,000 lab tests are available for clinical use; of the 1,162 tests that are reimbursed by Medicare, about 500 are performed regularly
- ▶ The number of CLIA-certified labs exceeded 200,000 in 2007; physician office labs represent 54% of clinical labs in this sector, 80% of which are certified to perform only waived and/or provider-performed microscopy tests, such as rapid streptococcal detection

Source: *Laboratory Medicine: A National Status Report, May 2008*

include recommendations.”

One example where more definition is needed is the chapter that deals with regulatory oversight, Mongillo noted. “In a few places in the report, a statement is made that a recent FDA guidance document clarifies its oversight of IVDMIAs. But what really happened is that the FDA released a draft document which, in our opinion, did not really clarify the agency’s role regarding oversight of IVDMIAs. Instead, what it really did was provide an opportunity for comment on the FDA’s role in oversight of IVDMIAs as laboratory-developed tests.”

Mongillo said that the report also states that the FDA has statutory authority to fully regulate all LDTs but has not done so because of resource constraints. “We think that has to be fully considered. We know there are some FDA officials who make the assertion that the agency has full authority to regulate all of these LDTs, but we don’t know if that has ever been fully, legally determined. At the ACLA, we think the FDA plays an important and positive interagency role in this respect but that the responsibility for oversight of LDTs falls under CLIA and CMS.”

CDC Report, continued on page 4

Structure of Laboratory Medicine: A National Status Report

The posted report is divided into 14 sections that include eight chapters:

- ▶ The Value of Laboratory Medicine to Health Care
- ▶ Market Profile of the Laboratory Medicine Sector
- ▶ Laboratory Medicine Workforce
- ▶ Quality and the Total Testing Process
- ▶ Quality Systems and Performance Measurement
- ▶ Laboratory Information Systems
- ▶ Federal Regulatory Oversight of Laboratory Medicine
- ▶ Reimbursement for Laboratory Medicine

Three chapters still under development are:

- ▶ Patient-Centered Care And Laboratory Medicine
- ▶ Innovative Applications in Testing Technologies
- ▶ Policy Issues and Their Implications for Stakeholders in Laboratory Medicine

To view the full report of *Laboratory Medicine: A National Status Report*, go to www.futurelabmedicine.org

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AACC

Reimbursement Changes Needed

Low reimbursement rates have plagued labs for a number of years. In 2000, the Institute of Medicine issued a report, "Medicare Laboratory Payment Policy: Now and in the Future." It stated, "Existing mechanisms for keeping payments up to date are inadequate." Today, 8 years after the IOM report, the same issues still affect labs.

The IOM study took on the problem of reimbursement directly, noted Murray. "It created a flurry of interest within the lab community, but I can't think of any objective consequences that came from it."

Forsman agreed. "There was a lot of input from consultants, but what it came down to was 12 points that pretty much agreed with what everyone had been saying. For example, the IOM report indicated that the business of coding is flawed—which also was a conclusion of the new CDC report. The IOM report also said that competitive bidding wouldn't work—which also was a finding in the new CDC report. So now, we have a restatement of things we've known but now can point to."

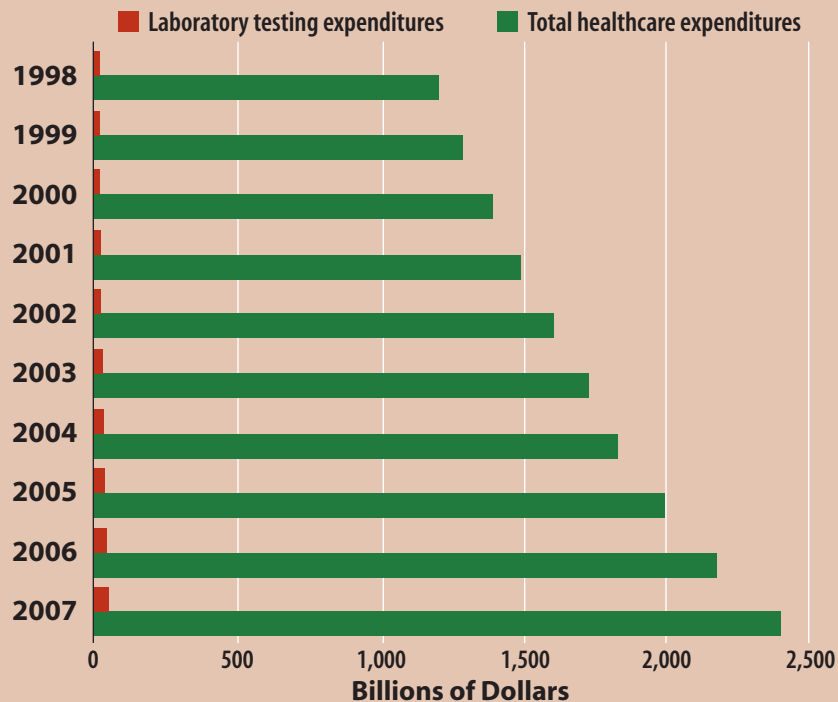
According to the CDC report, CMS is proceeding with a competitive bidding demonstration project for laboratory services, with the expectation of substantial cost savings. Supporters of the CMS competitive bidding project believe that current prices on the fee schedule have no substantial relationship to actual costs. However, the demonstration project model is highly exclusive and could have significant detrimental effects on clinical labs that lose in the bidding process, as many depend on Medicare reimbursement for a sizable portion of their revenues.

The CDC report also states that the Medicare program exerts the strongest influence on U.S. laboratory services payment. All public payers and approximately 67% of private payers use Medicare's payment methodologies as the basis for their own and as tools for negotiating discounts with providers. Redesign of the current Medicare payment system is needed to meet the growing scientific, technical, clinical, and economic challenges of the U.S. healthcare system.

For example, the report concludes that continued use of 56 different fee schedules nationwide is inefficient and unnecessarily complex. For certain commonly ordered tests, the multiple schedules result in large regional variations, while for other tests, national limitation amounts results in inadequate Medicare payments. In addition, the Medicare statute restricts payment for screening and other preventive technologies and services, unless otherwise specified by Congress. Adding these technologies and services to Medicare benefits on a case-by-case basis via legislation is cumbersome and impedes access to certain proven, beneficial tests.

"The chapter dealing with reimbursement is a reasonably fair representation of the current complexities of the payment and reimbursement system," remarked ACLA's Mongillo. "We believe that, yes, some reconsideration of payment for laboratory services, especially those that are new and sophisticated tests, may be necessary. And I think that was what the report's overall conclusion was in this area—that the fee schedule should be re-examined in terms of how it could better accommodate

Total U.S. Healthcare and Laboratory Expenditures 1998–2007



Source: *Laboratory Medicine: A National Status Report, May 2008*

some of the new diagnostic, molecular, and genetic tests that may not currently be adequately reimbursed."

Forsman noted that there seems to be some uncertainty on the part of the lab community as it looks to CMS on reimbursement issues. "A few years ago, there were recommendations of this sort, and members of the lab community said, 'Oh, they'll never listen.' But CMS did implement an open door policy and contributions were heard, and we did have the national limitations set differently for the 23 top tests."

The problem, Forsman added, is that the coding structure can be ambiguous. "We all know that certain things are favorably reimbursed. But others, like new and emerging technologies, or testing for an esoteric disease, may not be favorably reimbursed. That doesn't make the tests any less valuable. But they may not fit under current coding guidelines."

Some tests, Forsman maintained, have no clinical validity or lead to other downstream costs associated with follow-up. On the other hand, he said, there are other codes that are highly useful and offer a tremendous return on investment in terms of avoiding inpatient stays and other procedures. "If the reward system was built along those lines, I think there would be enough money in the system and we would end up with more cost-effective health care and better physician and patient satisfaction."

Laboratory Information Systems

The report notes that laboratory information systems (LIS) have evolved over the past few decades from simple systems designed to generate accurate reports to systems that can link laboratory data from one end of the total testing process to the other. However, the extent to which such systems have been adopted and their capabilities vary widely. Lack of harmonized data standards is the single greatest barrier to laboratories' ability to integrate data within the lab as well as exchange information with other health care computer systems.

These external systems may well be driving changes within LIS. "My experi-

ence is that the needs of these other systems are making the LIS fit into the jigsaw puzzle that is the electronic health record, even though labs were far and away the first to use computers," explained Murray. "Now, data from labs are reorganized by other systems. I'm in favor of anything to harmonize all these different systems, but I think it's out of our hands—it's not a lab issue now so much as an information processing issue."

Making the Transformation

The laboratorians who spoke with CLN were cautiously optimistic about how the report will affect a transformation in laboratory medicine. "It will support change, but that change will come very, very slowly," said Murray.

Boone noted that the vast amount of material covered necessitated adoption of broad conclusions as opposed to specific recommendations. "A long-term objective of the project is to see if there are particular areas where significant problems exist and how these should be addressed," he said. He added that the CDC will periodically update the report depending on the need for information, and as resources permit.

Broussard expressed his optimism that labs may fare better in the future. "This is an excellent document for presenting the facts, which are now documented, to people who are in decisionmaking capacities. For example, when people talk about cutting healthcare costs, they always look to the lab. But the report shows that the amount of money spent on lab costs as a percentage of healthcare expenditures is so small that significant cuts to the lab will not significantly affect healthcare costs overall" (See Figure above).

Forsman agreed that the time spent developing the report was time well spent, but noted that "the government will make decisions without a report. The realities are that if changes to the lab industry require statutory remedies, we will need to continue to have a presence on Capitol Hill, and this report will be helpful in terms of providing us with much needed ammunition." CLN

Spit Shines as Diagnostic Medium

Oral-based Tests, continued from page 1

window to the body. But until recently, analysis techniques were not sensitive enough to detect nano-concentrations of biomarkers in saliva.

The other factor contributing to saliva's rising star is crucial funding for two lines of investigation by the National Institute of Dental and Craniofacial Research (NIDCR) in Bethesda, Md. In 2002, NIDCR awarded grants to seven research teams to develop salivary diagnostic platforms. All focused on using microfluidics and microelectromechanical systems to detect and analyze the components of saliva, including proteins, electrolytes, DNA, and mRNA, with the goal of commercializing the products. Four of these labs received a second round of funding in 2005, and all are well on their way to developing "lab on a chip" oral-based detection systems using different platforms. Since the initiative commenced, NIDCR has funded \$43.4 million, according to a spokesperson.

On the heels of the salivary diagnostic initiative, in 2003 NIDCR funded a complementary undertaking to identify and catalogue the entire salivary proteome. It

has subsequently awarded \$24.1 million to three labs. Efforts from both NIDCR initiatives are bearing fruit in 2008.

A Mouth Full

Saliva comes primarily from three pairs of glands in the craniofacial structure: the parotid glands, located between the back of the jaw and each ear; the sublingual glands, under the floor of the mouth; and the submandibular glands, just inside the back of the jaw in the floor of the mouth. About 10% comes from minor glands clustered in the oral mucosa. Each gland, encased in a capsule of connective tissue, is composed of individual lobules supplied by a fine network of capillaries. The lobules, with serous and/or mucous cells, depending on the gland, actively take up substances from serum, such as water and salt, passively diffuse and filter others, blend them with salivary proteins, then secrete the resulting concoction—ranging from 500mL to 1.5L per day—into ducts that transport saliva to the mouth. As a result of this process of diffusion, absorption, and secretion, saliva reflects natural and artificial substances in the body, albeit at micro levels.



The Oral Fluid NanoSensor Test is a handheld, automated, integrated micro-electromechanical system that will enable simultaneous and rapid detection of multiple salivary protein and nucleic acid targets. The device was developed by a team of researchers at the UCLA School of Dentistry led by David Wong, DMD, DMSc.

Researchers distinguish between ductal saliva, which comes directly from the salivary glands, and whole saliva, which includes the entire oral fluid mix, including saliva, bacterial waste products, and serum leaked from crevicular junctures around the teeth. Ductal saliva is considered more valuable as a biofluid, so collection techniques typically use something like a Lashley cup that adheres via mild suction to the parotid duct orifices. The composition of saliva is affected by numerous factors, so some researchers also follow strict specimen protocols, such as collecting fasting early morning samples.

"Protein levels in saliva change due to medications, systemic diseases, the time of day, and whether the patient has eaten or drunk anything. There are so many variables that can impact the results," explained Brian Schmidt, DDS, MD, PhD, associate professor and an oral and maxillofacial surgeon at the University of California at San Francisco. While these types of collection techniques are important as scientists perfect their knowledge about saliva, any commercial oral diagnostic devices likely will feature simpler means of gathering samples, such as oral swabs or spitting into a tube, he said.

Saliva's Utility as a Diagnostic Fluid

Some researchers view oral-based tests as the Holy Grail of diagnostics, mainly because samples can be obtained non-invasively. Although this would appeal to squeamish people, it would be of particular importance to children and elderly patients, who typically experience the most discomfort in providing blood samples. "If the consumer is presented a choice of obtaining a sample through blood, urine, saliva, or spinal fluid and the results are equally accurate, that will drive adoption," said David Wong, DMD, DMSc, professor and associate dean of research at the UCLA School of Dentistry.

In addition, collecting saliva poses less risk to healthcare workers. Saliva samples are also easier to handle in that saliva doesn't clot like blood. In combination with micro-

and nano-technologies, oral-based diagnostics offer the possibility of condensing the full processing power of flow cytometers into low-cost, hand-held devices—an ideal solution for developing countries that lack resources and infrastructure.

But there are also advantages for industrialized countries. Oral-based diagnostics could enable speedy, low-cost POC devices that do not depend on trained phlebotomists for sample collection. And saliva-based tests could provide rapid, perhaps even field-based, results. "You can't be slower and more expensive with new diagnostics and expect economies. That's where electronics has a powerful impact for our country," said McDevitt. "We have taken advantage of the microfabrication methodologies popularized by the electronics industry to make en masse our new nano-bio-chip sensors. The

See **Oral-based Tests**, continued on page 8

Saliva-Based Tests Target Cancer

Oral-based Tests, from page 6

electronics industry has provided our society with so many examples of powerful yet affordable tools, from computers, to televisions, to cell phones. The marriage of electronics and in vitro diagnostics has the potential to change the practice of medicine by creating powerful yet affordable diagnostic aids. These devices may be mini-sized, but [could] exceed performance of refrigerator-sized instruments.”

A few oral-based diagnostics are already available commercially. Most notably, OraQuick (OraSure Technologies, Bethlehem, Pa.) was approved by the FDA in 2004 as an oral-based qualitative immunoassay for HIV-1 and HIV-2. It is a screening test only and requires a confirmatory reactive test. The same test using blood samples was approved in November 2002. There are a number of breath analyzers to detect blood alcohol concentrations using infrared spectrophotometer or electrochemical fuel cell technologies. Specimens for DNA testing used in forensics, paternity, and genealogical investigations are now commonly collected via buccal swabs. Steroid hormones, hepatitis A, B and C, and substances of abuse such as marijuana and methamphetamine also can be detected through salivary analysis.

On the Cutting Edge

Recent research seems likely to expand this relatively modest group of oral diagnostics to encompass a host of systemic and oral diseases. In addition, three NIDCR-funded

research teams from five universities are working to categorize the salivary proteome. In April 2008, the group reported that they had used different separation and fractionation technologies, along with mass spectrometry, to identify 1,166 proteins in saliva collected from 23 adults of several races and both sexes. Researchers matched their results against the plasma and tear proteomes and found that 650 salivary proteins also are in plasma and 259 are in tears. The proteome is significant in that researchers are now “empowered with a more extensive parts list than they’ve ever had before,” according to Lawrence Tabak, DDS, PhD, director of NIDCR. This initial chart of the salivary proteome will open wide the doors for further discovery, he predicts. “The challenge and exciting part is figuring out what all the parts do. I think, as with other similar efforts, how proteins work in concert will be more important than what they do individually.”

Oral-based diagnostics are being investigated actively for a number of high-impact diseases, including oral, breast, pancreatic, and lung cancer; HIV (as a combined screening and confirmatory test); as well as tuberculosis, malaria, heart disease, Sjögren’s syndrome, asthma, type 2 diabetes, COPD, and pre-eclampsia, among others.

Spotlight on Oral Cancer

Wong’s laboratory used oral cancer as a first proof-of-principle disease for salivary transcriptome diagnostics. His team found that four genes—IL-8, ornithine decarboxylase,

spermidine acetyltransferase, and IL-1 β —could discriminate and predict whether a saliva sample was from a patient with cancer or a healthy individual, with both sensitivity and specificity of 91% (ROC 0.95). The biomarkers were validated in approximately 200 subjects, and found to be consistently higher in people with oral cancer than in matched control subjects. Wong and colleagues went a step further and compared the accuracy of the salivary biomarkers with four serum RNA biomarkers for oral cancer detection and found the serum biomarkers had a sensitivity and specificity of 91% and 71%, respectively (ROC 0.88). “This demonstrates clearly that for oral cancer detection, salivary transcriptome diagnostics have a slight edge over serum,” Wong noted. “We can’t just say how good saliva is; we have to benchmark it against the gold standard—serum.”

Concurrent with its analysis of salivary biomarkers and participation in the salivary proteome project, Wong’s lab is developing an Oral Fluid NanoSensor Test (OFNA-SET), a handheld, automated, integrated microelectromechanical system that will enable simultaneous and rapid detection of multiple salivary protein and nucleic acid targets. The team is investigating the potential of using OFNA-SET in several diseases, including Sjögren’s syndrome and pancreatic and lung cancers.

Schmidt is pursuing another avenue of investigation: saliva as an indicator of oral cancer. His early work testing levels of salivary endothelin-1 (ET-1), a vasoactive peptide normally synthesized by human keratinocytes but over-produced by several cancers, found that the concentration

of ET-1 in saliva from oral cancer patients was significantly higher than in that of healthy controls. He also discovered that ET-1 mRNA was overexpressed in 80% of oral squamous cell carcinoma (OSCC) specimens. The study shows the potential of ET-1 as a discriminate marker for OSCC. In follow-up research, Schmidt is comparing pre- and post-operative ET-1 levels in patients with OSCC. “It’s very promising. We hope it might turn out to be like PSA level in prostate cancer,” he said.

Another line of investigation related to oral cancer that Schmidt is pursuing involves analyzing saliva to detect hypermethylation in the promoter region of five genes as an early indicator of the disease.

Infectious Diseases and More

Saliva-based diagnostics also have applications in infectious diseases. HIV and the viral and bacterial diseases that create opportunistic infections in HIV/AIDS patients are the research focus of a team led by Daniel Malamud, PhD, professor of basic sciences and craniofacial biology at the New York University College of Dentistry. Malamud and colleagues are developing a single microfluidic chip that will detect HIV, malaria, and tuberculosis using a detection system based on up-converting phosphor technology. In the case of HIV, the research team already has developed a chip that tests for antibodies, antigens, or nucleic acid as independent pathways on the chip, making it both a screening and confirmatory diagnostic tool. Plans are for the TB assay to detect antibodies in saliva, while the malaria test will identify nucleic acid as well as antigens.

Malamud's team is working with other labs that have already developed reagents for TB and malaria to accelerate the process of converting benchtop tests to microfluidic systems. Eventually the separate pathways will be combined into a single analytical system. "The potential is incredible," said Malamud. "No one dies of HIV; but it suppresses the immune system and makes it possible for TB and malaria to develop. If clinicians knew an HIV patient also had TB, they could start treatment right away and improve the patient's survival and quality of life."

A saliva-based test for heart disease is one of several areas of focus in McDevitt's lab at the University of Texas. The lab is adapting a miniaturized sensor based on a micro-bead array for several analyte classes. Chemically sensitized bead "micro-reactors" are populated in micro-etched pits inside a silicon wafer. When new molecular reagents are attached to the micro-reactors, they can detect different array platforms.

The lab's early efforts related to heart disease involved establishing the lowest limit of detection of CRP reported thus far, defining the physiological range of CRP in healthy, edentulous and periodontitis patients, and developing a dual platform to detect CRP and total white blood cell count. More recently it has developed a system to detect in saliva a panel of four important cardiac biomarkers: BNP, troponin I, CK-MB, and myoglobin. In a study comparing levels of the biomarkers in control subjects to those of patients with acute coronary syndrome, researchers found for the first time that all were detectable in both unstimulated and stimulated saliva samples, but the rate of

detection varied for each enzyme based on sample stimulation status. The findings suggest that salivary samples could be used to detect a standard battery of cardiac biomarkers. McDevitt envisions that the panel will help clinicians identify patients with non-ST-elevated myocardial infarction (non-STEMI) earlier and fast-track treatment for them, given that non-STEMI cardiac events often are not detected via EKG.

McDevitt's lab also has adapted a lab-on-a-chip platform to detect, from whole saliva, 12 biomarkers associated with cardiovascular disease. He hopes that one day it may be used to track patients at risk of recurrent heart attack and death after an initial coronary event. "By looking at early indicators, we think we can capture [a second event] before it happens. We project there is a unique signature here," explained McDevitt. "It's not practical or convenient for patients to give blood every day, but they can spit. That's where saliva has such a strong potential to make the transition to wellness and health promotion rather than reactive medicine."

Another area of focus for the McDevitt lab is oral-based detection systems for breast, ovarian, and cervical cancer. In addition, it has already developed a serum-based lab-on-a-chip platform for measuring CD4 lymphocyte counts (licensed to LabNow in Austin, Texas), which is being tested clinically in Africa, India, and the U.S.

Oral-based microarrays for diagnosing pulmonary diseases such as asthma, chronic obstructive pulmonary disease, and acute pneumonia are the focus of a consortium led by David Walt, PhD, professor of chemistry at Tufts University in Medford, Mass.

Walt's multi-institution team is developing a complete diagnostic system including a microfluidic chip coupled to an optical fiber microarray for detecting multiple analytes. The results will be read optically, processed using data mining and pattern recognition techniques, and reported both through a liquid crystal display and over a wireless network. In the case of asthma and COPD, "our hope is that within half an hour clinicians will be able to identify both the nature of the inflammation and the causative agents," Walt noted. For instance, patterns of protein-based inflammatory response could pinpoint whether an asthmatic exacerbation was caused by a bacterial infection or exposure to pet dander. The Walt laboratory also is exploring the use of saliva-based biomarkers to detect the onset of end-stage renal disease.

At Walt's lab, like others developing oral-based micro-diagnostics, part of the challenge in transitioning from the bench to the bedside is harnessing the passion and intelligence of a diverse team of scientists, from oral biologists and analytical chemists to engineers and computer scientists. "We have an energetic group of people with a common goal, but getting them all speaking the same language and figuring out how to work together has been challenging," he said.

How Far Off?

Just how long it will take for oral-based microfluidic diagnostic systems to be used in patient care remains to be seen. The NIDCR-funded consortia are working diligently and have had success in demonstrating proof of concept and in developing

first-generation prototypes. But as they add analytes to the platforms, integrate them into a single process, and move into larger trials, challenges are no doubt in the offing. Many of the teams are aiming for commercialization within 3 years, but whether that goal will be realized remains to be seen. "It's hard to predict, because even if the technology works, it needs to be validated in a clinical setting," said Walt. What is clear is that the emerging science of saliva-based testing is an area that laboratorians will want to keep an eye on. CLN

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ROC Curves

Uncovering the Pearls and Avoiding the Pitfalls

BY DAVID PLAUT

When clinicians order blood tests for patients, in essence they are asking for help in making a diagnosis. Their training tells them to request particular tests based on what they observe and what patients describe. However, this information often indicates several possible disorders or a cluster of similar diseases. To decide what to do next—another lab test, a radiology test, a biopsy, or even make a diagnosis—clinicians rely upon information from the lab.

It goes without saying that clinicians expect lab results to be accurate and precise; otherwise, the diagnosis could be wrong. Accuracy and precision are analytical aspects of lab tests. But frequently, these qualities are confused with the clinical efficacy of a test, which is how well the test identifies patients with a particular disease or set of diseases that share common signs and symptoms.

Many diagnostic tests performed by clinical labs are quantitative and use a cutpoint to distinguish a normal from an abnormal result. But to establish the cutpoint, researchers determine the extent to which the test results vary among people who do or do not have the diagnosis of interest. This is not a trivial exercise and requires statistical analysis. The receiver operating characteristic (ROC) curve is one such statistical analysis method that was developed in the

whether the study is blinded or not, it is at this evaluation phase that ROC curves come into play. Think of ROC curves as a trade-off between the rates of false-negative results and false-positive results—there being no “perfect test.”

In a research setting, ROC curves begin with two pieces of data on each of a series of patients; one of these is a lab result, and the other is a diagnosis provided by the clinician without regard for the result of the

While a research study of a new lab test is necessary to validate its utility, most labs accept the data cleared by the FDA, as well as data published in journals, rather than doing a ROC curve study for each test added to the menu. Take, for example, a serum glucose test or a hemoglobin method. Most hospital labs would not perform ROC curve analysis of these analytes unless their population significantly differed from that in the validation study.



1950s for evaluating radar signal detection. Today, ROC curves now are used routinely in medicine to evaluate diagnostic tests.

This article will describe how ROC curves are obtained, what they mean, and what laboratorians should understand about them.

In the Beginning

Before becoming a part of any diagnostic protocol, researchers often evaluate new tests in blinded clinical trials. However,

test being evaluated. It is in this sense that a test is referred to as blinded. The clinician can use other tests from the lab, radiology, or a biopsy, as well as the signs and symptoms she sees, but not the data from the test being evaluated as a diagnostic tool. Clearly, developing ROC curves for a lab test depends on the cooperative efforts of multiple disciplines, and laboratorians should be included when the data are reviewed and decisions are made about the test's clinical efficacy.

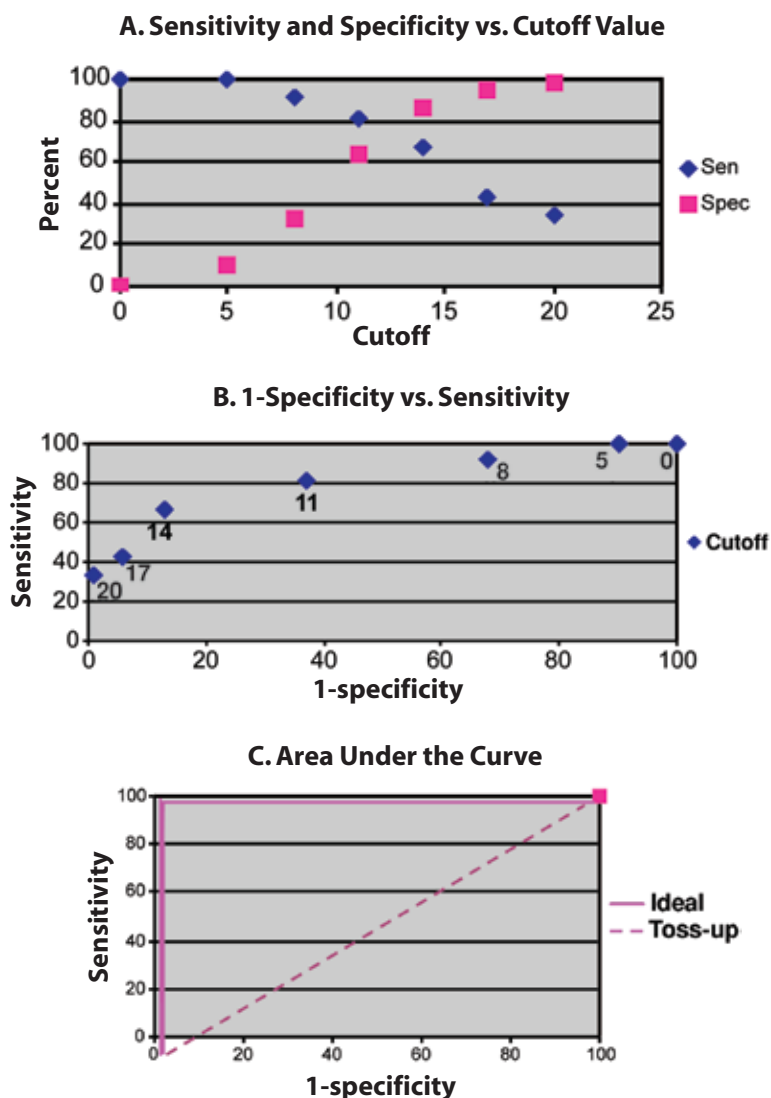
The Basics of ROC Curves

To understand how ROC curves are derived and how they are used, it's helpful to work through an example. Table 1A shows what a data collection worksheet for the ROC curve analysis might look like. In a research study, the number of patients tested could run into the hundreds, but in a community hospital, data may be collected on only a few dozen patients. There is no ideal number for the sample size, although the six data points in our example are not sufficient to determine a ROC curve.

From these data points, a 2 x 2 grid is prepared (Table 1B). In this example, a cutpoint, also referred to as a cutoff, of 15 was selected to label a test result as positive. Any value below 15 would be considered a negative result. It is important to recognize, however, that any value can be chosen as the cutoff value. In essence, the cutoff value represents a compromise between the total number of positive and negative results. If the cutoff value were set at 16 in this example, there would be no false positives.

Collecting data from dozens to hundreds of patients and varying the cutoff value allows certain test characteristics—sensitivity, specificity, positive and negative predictive value, and efficiency (Table 1)—to be determined and plotted in a variety of ways. For example, Figure 1A is the plot of some hypothetical data for the cutoff on the x-axis vs. specificity and sensitivity on the y-axis. Note that as the cutoff value increases, fewer patients with a positive diagnosis will have a positive lab result, while more patients with a negative diagnosis will yield a negative result. In other words, as

Figure 1 Examples of ROC Curves



sensitivity increases, specificity decreases and vice versa.

A second popular version of the graph in Figure 1B plots 1-specificity vs. sensitivity. In this case, each cutoff value is a point on the curve. This graphical representation of the data also allows the area under the curve to be calculated (discussed below), but some people think it is more difficult to use as a means to determine the appropriate cutoff. With currently available software, both of these types of plots are easy to produce.

Easier Said Than Done

All this seems quite straightforward. But don't be lulled into believing this is the case. While ROC curves are visually appealing and simple to read, there are many caveats that need to be considered. It is to those I wish to draw your attention and ask that you keep in mind as you read the literature, package inserts, or look at ROC curves on slides at a meeting.

Let's first look at the lab. In the example, at a cutoff value of 15, patient 436 is positive in the lab but negative to the clinician. This is considered a false-positive result. You might ask, "What went wrong?" Among the many possible answers are incorrect patient ID, analytical interference in the test, or the test simply is not specific for the disease.

To better understand the specificity of the test, it's instructive to look at its imprecision. If the test has a 5% coefficient of variation (%CV) at a level of 16, the result could

have been as low as 14.4 or as high as 17.6 ($16 \times 0.05 = 0.8$; $0.8 \times 2 = 1.6$ or 2 SDs). In other words, there's a good possibility that retesting the same sample would produce a "negative" result. This is not a trivial issue when only a handful of patient samples are tested. In this example, the specificity is 67% when the cutoff value is set at 15. However, taking into account the imprecision of the method, if the result was 14.5, the test would have a specificity of 100%.

Bear in mind that in studies of this type, the test is being performed on patients who have met certain criteria. In the emergency department, the criteria for ordering a test for troponin may include shortness of breath, chest pain, and being younger than 44 years. This is to say that the patients are selected before the test is ordered. Clearly, patient selection can have an effect on the both the diagnosis and laboratory parts of the ROC curve data sheet.

When reading a package insert or an article in a journal, make certain you understand the criteria used to select the patients studied. Then ask yourself: Is my patient population similar? Or do my physicians use other criteria to select the patients for whom they request this test? Are they perhaps looking for a different disease? It is these questions that may prompt a laboratory not engaged in a research study to do its own ROC curve study with fewer patients.

In addition to the imprecision inherent in any test are various non-analytical factors. One of these is timing. It is possible

Table 1 A. Data Collection Table for ROC Curve Study

Patient ID	Lab result	Medical diagnosis	Comment
123	9	-	
254	10	-	
436	16	-	
764	22	+	
325	34	+	
654	36	+	

B. A 2 x 2 Grid of the Data

		Diagnosis	
		Neg	Pos
Lab Result	Neg	2	0
	Pos	1	3

Definitions

Five statistics can be calculated from these diagnoses and the corresponding laboratory results.

Sensitivity = Positive result with Positive Dx/All Positive Dx

Specificity = Negative result with Negative Dx/All Negative Dx

Positive predictive value =
Positive result with Positive Dx/All Positive Results

Negative predictive value =
Negative result with Negative Dx/All Negative Results

Efficiency = Number of correct results
(Pos lab-Pos Dx) + (Neg lab-Neg Dx)/total patients

that the physician made the correct diagnosis, but the patient presented earlier, or later, in the disease continuum than the test can detect. Some examples are: a heart attack patient presenting within 30 minutes of the occurrence, a pregnant woman presenting the morning after conception, or a patient who had a thrombus in her leg a week ago and now has a negative d-Dimer result.

Another reason that the lab result and the diagnosis may differ comes down to the individual clinician. One possibility is that the clinician's diagnosis is incorrect. There are many ways for this to happen. First, the patient may not give the clinician all the information about her symptoms or the

patient may be vague about the symptoms or even evasive. In addition, many disease states have signs and symptoms—such as shortness of breath or abdominal pain—that are present in more than one disease.

Incorrect diagnosis can also be attributed to human error, and there are many opportunities for this. The clinician must interpret the patient's symptoms from visual, tactile, olfactory, and auditory input. Moreover, clinicians are frequently rushed and must establish a diagnosis within a short time, and patients are often anxious to have an immediate decision. There are any number of other explanations of how the clinician could diagnose a patient as

Table 2 Comparing Tests: Which One is Better?

Statistic	A	
	Test A	Test B
Sensitivity	82	93
Specificity	94	80

Here the cutoff value for A was selected to be highly specific for the disease, and B's cutoff value was selected to be highly sensitive for the diagnosis.

Statistic	B	
	Test A	Test B
Sensitivity	90	90
Specificity	84	85

Here data are presented for test A and B at 90% sensitivity. The tests appear to have roughly equal specificity for the diagnosis.

negative, when in fact, the patient is positive. In the data collection, only a yes or no answer is recorded, but in reality, many factors go into making diagnostic decisions. The process is not black and white.

Which Test Is Better?

ROC curve data appear in many journal articles, and sometimes only a part of the ROC curve data is published when two methods are being compared. For example, imagine two tests, A and B, are being compared for their ability to detect a given disease. The authors present the data shown in Table 2A.

Which test is better? The data do not make it easy to answer this question. Look back at Figure 1A and you will see part of the problem: as sensitivity increases, specificity decreases and vice versa. It is possible that these two tests are quite similar in their ability to detect the disease. The problem here is that it appears that the cutoff for test A selected specificity over sensitivity, whereas the cutoff for test B chose sensitivity over specificity. Had the researcher first chosen a sensitivity of, say, 90%, and then looked at the corresponding value for specificity of test A and B, the data might have appeared more like those in Table 2B.

When the authors also present the actual graph of the data, even though only

a finite number of points are plotted as in Figure 1A, more information is available to the reader. It is also helpful when authors include information about the selection of a value for either sensitivity or specificity. Then the reader can make a more informed judgment about which test is better.

Demystifying Area Under the Curve

One more aspect of the ROC curve—the area under the ROC curve (AUC)—is frequently used to describe a test's validity. Figure 1C shows two variations of AUC. In the ideal world, the data would go from 0.0 instantly up to a sensitivity of 1.00 and then horizontally across at 1.00 to a point on the specificity scale of 1.00. This gives an AUC of 1.0. On the other hand, any value less than 1.00 is less than ideal.

Figure 1C also shows a line with a 45° slope, which is an AUC of 0.5. In some respects, a diagnosis based on a test with an AUC of 0.5 is equivalent to flipping a coin. Generally, such data signify that the test is useless for diagnosing the disease or condition.

Published studies often include an estimated AUC when comparing two or more tests. Let's look at an example from a recent article on cardiac markers. "Diagnostic efficiency was compared...by AUC for three strategies: 6-h post-pain CK-MB measure-

ment; Delta CK-MB; and 6-h post-pain cTnT measurement. At 6-h post pain the respective values were: CK-MB 0.939; Delta CK-MB 0.948; and cTnT 0.989." The authors conclude that cTnT at 6 hours has high diagnostic sensitivity for AMI and is superior to CK-MB mass and Delta CK-MB even using a low cut-off value. However, one might ask if 0.989 is statistically different from 0.948.

Because most tests use only a single cutoff value and the AUC is obtained from multiple cutoffs, you may sometimes wonder about the value of the AUC. The AUC has one direct interpretation: If you sample a randomly selected healthy patient and obtain a result of x and sample a randomly selected diseased patient and obtain a value of y , the AUC is an estimate of the probability that y is greater than x , assuming that large values indicate disease.

The Take-Home Message

In general, ROC curve analysis is a set of statistical tools that helps select optimal tests and similarly helps discard suboptimal ones. The ROC curves are also helpful for selecting optimal cutoffs for a test and have become a common tool in medicine to determine the clinical accuracy of lab tests.

When you look at a ROC curve, remember there is more to the simple lines on a graph. All ROC curves are good representations of the data; it is the other factors—the lab test, the other diagnostic tests, the patients, and the clinicians—that are all imperfect. These details can explain why your clinician does not like a test or why you field callers wondering why a test is positive when it "it shouldn't be." There are many pearls in a ROC curve, but be aware of the possible pitfalls!

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CLM

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CDC Cholesterol Standardization Program Celebrates 50 Years of Service

From Modest Beginnings to Landmark Improvements in Healthcare

BY GERALD R. COOPER, MD, PHD

In September, the CDC will mark the 50th anniversary of its cholesterol standardization program. Through the efforts of many investigators, this program has developed tools to insure accuracy and has earned recognition as a quality approach to improve lab testing. Here is a look back on how this program evolved, as well as a look into the future.

From Modest Beginnings

The need for a cholesterol reference laboratory originally stemmed from the 1957 Conference on Longitudinal Cardiovascular Studies. Cardiovascular researchers had exchanged serum specimens and found disagreement among the cholesterol measurements performed in each investigator's respective laboratory. As a result, clinicians and laboratorians agreed that cholesterol measurements had to be standardized to obtain measurement results that were reproducible within and comparable between laboratories. CDC was asked to develop a cholesterol reference laboratory and serve as a neutral party to help standardize cholesterol measurements among cardiovascular epidemiologic laboratories.

By the end of that year, CDC had established a Cholesterol Methodology Development Laboratory and Standardization Office staffed by: Eloise Eavenson, PhD, chemist; A. John Schneider, MD, medical officer; Myron Willis, PhD, statistician; and Gerald R. Cooper, PhD, medical director. Their plan was to develop suitable serum-based reference materials for cholesterol and then design a program that would focus on standardizing cardiovascular epidemiologic laboratories. Among the program's major objectives were: determining whether lyophilized human serum could be used as a standard reference material for total cholesterol analyses; preparing highly purified cholesterol for use as the primary standard; and measuring and assessing the significance of differences among labs that determined total cholesterol measurements. To accomplish these objectives, the group prepared and distributed lyophilized serum specimens of different cholesterol content so that they could collect and evaluate analytical data for various labs.

The First Cooperative Cholesterol Standardization Program

In 1958, the agency initiated the first Cooperative Cholesterol Standardization Program (CCSP) with seven cardiovascular epidemiologic laboratories. The CCSP was organized in three phases for participating laboratories. During the first phase, participating laboratories used blind, randomized duplicates to measure within-laboratory precision. In phase two, a lab's techniques had to be deemed acceptable, and the lab had to produce comparable coefficients of variation (CVs). The third phase measured variability in cholesterol concentrations reported on human serum pools. Since a cholesterol reference method was not yet available, the goal was to assist the labs in maintaining their cholesterol serum

levels as determined on quality-control serum pools and on the pools of the CCSP. The average standard deviation of the first CCSP reported results was 10.6 mg/dL (0.27 mmol/L) for pools in the 150–225 mg/dL (3.88–5.82 mmol/L) range. Six of the seven laboratories used modifications of the Abell-Kendall (A-K) method. The seventh laboratory used an alcohol-ether extraction and ferric chloride-acetic acid-sulfuric acid color-developing reagent procedure.

After an extensive evaluation and comparison of five cholesterol methods was conducted, CDC selected the A-K procedure as the cholesterol reference method for the CCSP on the basis that a CV of 1% was demonstrated, the procedure and reagents appeared valid, and fewer problems were encountered in daily use.

National Heart Institute Collaboration

CDC's program got another boost when Jim Watt, MD, Director of the National Heart Institute, attributed the failure of heart disease studies to questionable cholesterol measurements. In 1961, he initiated a collaboration with CDC to expand the CCSP standardization services to all epidemiologic lipid labs supported by NHL. By 1965, the CCSP provided services to at least 65 participating cardiovascular labs in the U.S. and 18 labs in other countries.

CDC Becomes a WHO Collaborating Center

Another landmark in the cholesterol standardization program occurred in 1962 when WHO appointed CDC as a Collaborating Center for Reference and Research in Blood Lipids. The objective was to offer cholesterol standardization assistance to international research labs supporting WHO studies of CVD. This designation opened the door for CDC to broaden its standardization influence around the globe.

The Program Grows

From 1966 through 1968, CDC implemented an Experimental Triglyceride Standardization Program with 19 laboratories. The program goal was to determine the precision and accuracy that participating labs attained using different methods for measuring triglyceride concentrations. The first reference method, developed in cooperation with Hugh Lofland, MD, of Wake Forest University School of Medicine, was a method that used silicic acid-chloroform extraction, chemical hydrolysis, and color development by metaperiodate-arsenite-chromotropic acid reagent. All results were to be reported in mmol/L to prevent errors resulting from different primary standards. From the reported triglyceride values, the researchers estimated that the maximum allowable limit for reported means should be ± 0.1 mmol/L and 5% for reported analytical CV. The initial Cooperative Triglyceride Standardization Program in 1968 had 105 participating laboratories and was modeled after the CCSP. By 1974, the cholesterol and triglyceride standardization efforts were combined into a Cooperative Cholesterol and Triglyceride Standard-

Identifying CVD Risk

Today, the CDC-NHLBI Lipid Standardization Program enrolls about 100 domestic and international laboratories every year. These laboratories have supported some of the most important clinical investigations in cardiovascular medicine, including the Lipid Research Clinics-Coronary Primary Prevention Trial, the Multiple Risk Factor Intervention Trial, the Specialized Centers of Research in Atherosclerosis, the Atherosclerosis Risk in Communities Study, the US Women's Health Initiative, the West of Scotland Coronary Prevention Study, and the US National Health and Nutrition Examination Survey, to name only a few. Such studies have established a medical database that has permitted the development of public health interventions designed to identify people at increased risk for cardiovascular disease and its complications.

ization Program (CCTSP), and the same human serum pools were used for both analyses.

During the 1970s, medical interest in the role of HDL-C as a risk factor for CVD skyrocketed and the need for accurate measurement of HDL-C became apparent. In 1981, CDC added standardization for HDL-C and instituted a reference method for it. To reflect the broader emphasis on total cholesterol, triglycerides, and HDL-C, as well as the close collaboration between CDC and NHLBI, the name of the program was changed in 1984 to the CDC-NHLBI Lipid Standardization Program.

The First Reference System in Clinical Chemistry

Another milestone in the program's history occurred in 1975. That year, AACC formed a Cholesterol Reference Method Study Group to select and evaluate potential reference methods for cholesterol measurement. The group recommended that CDC study the A-K method and an enzymatic method as two candidate reference methods and that NIST develop a definitive method. After extensive studies were completed, the A-K method was selected as the reference method and isotope dilution-mass spectrometry was chosen as the definitive method. The CDC A-K reference method, the NIST ID-MS definitive method, the NIST SRM 911 pure cholesterol primary standard, and the serum reference materials prepared by CDC and

offered by NIST, became the components of the National Reference System for Cholesterol, the first officially recognized reference system in clinical chemistry.

Where to from Here?

In recent years, the number of candidate risk factors for CVD and its complications has grown considerably. These biomarkers are termed emerging or novel risk factors because they are associated with an increased risk for CVD, but their causative, independent, quantitative contributions to the disease are not yet fully documented, nor have standardized methods for measurement been developed.

Today, CDC is focusing its efforts on biomarkers that have been identified by experts as important to cardiovascular laboratory medicine. Among the leading candidates are cTn I, BNP, urine albumin, cystatin C, CRP, apo AI, and apo B. Building on a 50-year history of successful accomplishments that have made it a global leader in clinical laboratory standardization, CDC plans to pursue collaborative efforts with other agencies and organizations to develop standardization programs for these important biomarkers of the future. CLN



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Thursday, September 18 in Barcelona, Spain

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Wednesday, September 24

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Monday, October 27 in Kansas City, Mo.

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Important Erratum

The description of the ONLINE TDM Tobramycin assay marketed by Roche Diagnostics that appeared in our July New Products Review section was incorrect. CLN sincerely regrets this error. The correct description is provided here.

Introducing ONLINE TDM Tobramycin 100 test cobas c pack for cobas c 501 analyzers

The ONLINE TDM Tobramycin assay is based on a homogeneous enzyme immu-

noassay technique used for the quantitative analysis of tobramycin in human serum or plasma. The assay is based on competition between drug in the sample and drug labeled with the enzyme glucose-6-phosphate dehydrogenase (G6PDH) for antibody binding sites. Enzyme activity decreases upon binding to the antibody, so the drug concentration in the sample can be measured in terms of enzyme activity.

The 12-week, onboard stability of the cobas c pack along with calibration stability allow for a convenient and economical method for therapeutic drug measurement of



tobramycin in serum, K2 or K3 EDTA or sodium or lithium heparin plasma, sodium citrate or fluoride oxalate plasma.



Congress Overrides Veto, Repeals Competitive Bidding, Makes Medicare Bill Law

On July 15 the laboratory community achieved a major victory when members of Congress overrode a President Bush's veto of HR 6331, the Medicare Improvements for Patients and Providers Act, effectively repealing the CMS's authority to

conduct a competitive bidding demonstration project for laboratory services.

The competitive bidding demonstration project sought to force laboratories to bid competitively against one another for Medicare contracts in an effort to lower Medicare costs. Opponents of competitive bidding, such as the AACC, had concerns it would stifle laboratory innovation, reduce investment in newer technologies, and

force smaller laboratories out of business.

In December 2007, CMS invited 66 labs in the San Diego area to participate in a bidders conference and would announce participating labs in April. But in January three labs—Internist Laboratory, Sharp Healthcare, and Scripps Healthcare—filed suit in federal court to halt the project, saying it would have a negative impact on the integrated delivery of care. A federal judge at first dismissed the lawsuit and denied a temporary restraining order based on government arguments that any challenge to the project was premature because no winners or losers had been selected so none of the labs had suffered any harm. But the judge later granted an injunction that prevented CMS

from announcing winners, otherwise implementing and carrying out the project in San Diego, and disclosing any information in the bid applications. The court found that the three labs had shown that the competitive bidding measure would cause irreparable harm, including substantial economic damage to the labs, and danger to patients.

The House of Representatives had overwhelmingly passed the bill in June and the Senate passed it in July. The bill, introduced by Rep. Peter Stark (D-Calif.), also replaces the pending 10.6% cut in physician payments with a 1.1% increase.

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

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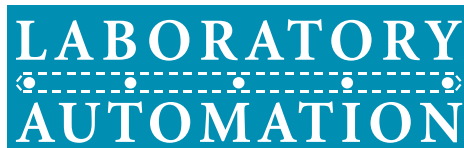
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HHS Selects 12 Communities For EHR Demonstration

HHS Secretary Mike Leavitt named 12 communities that will participate in a 5-year, national Medicare demonstration project that provides incentive payments to physicians for using certified electronic health records in patient care.

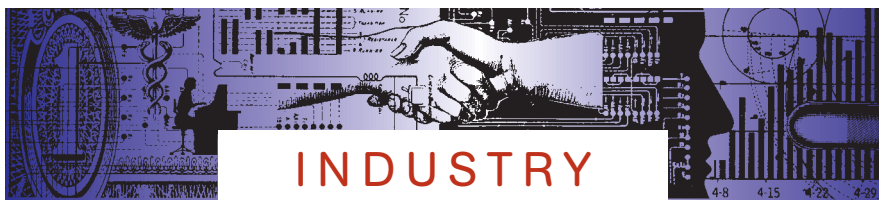
The communities range from multi-county to state level and include Alabama; Delaware; Jacksonville, Fla.; Georgia; Maine, Louisiana; Maryland and Washington, DC; Oklahoma; Pittsburgh, Pa.; South Dakota; Virginia; and Madison, Wisc.

As many as 1,200 primary care physicians in the selected communities will receive financial incentives. They also may receive bonus payments based on results of a survey measuring the number of EHR functionalities a physician group has incorporated into its practice. According to the HHS, total payments under the demonstration for all 5 years may be up to \$58,000 per physician or \$290,000 per practice. Findings from the project will help determine the role of EHRs in delivering high-quality care and reducing medical errors. For more information go to www.cms.hhs.gov/DemoProjects/EvalRpts/downloads/2008_Electronic_Health_Records_Demonstration.pdf.

NYC Launches Borough-wide HIV Testing

The New York City Department of Health has launched a project to have all residents of the Bronx between the ages of 18 and 64 learn their HIV status within the next 3 years. The initiative, called The Bronx Knows, is an effort that teams the health department with community-based organizations, hospitals, and community health clinics. Bronx residents can go to any one of 40 designated sites throughout the borough for reliable testing.

City officials say that cumbersome consent procedures required by state law have deterred doctors from offering the tests. Although officials estimate that close to 70% of Bronx adults have undergone testing for HIV at some point in their lives, about 250,000 have never been tested for the virus. According to the Health Department, Bronx residents account for nearly one-fourth of New York City's HIV infections and one-third of AIDS deaths annually. Officials also said that the Bronx's large number of AIDS deaths can be attributed to people not getting tested until it is too late to treat the virus effectively.



INDUSTRY

Hologic Scoops Up Third Wave Technologies

Hologic announced a \$580 million deal to acquire Third Wave Technologies, a developer of molecular diagnostic reagents for a wide variety of DNA and RNA analysis applications based on its proprietary Invader chemistry system. Third Wave recently submitted HPV tests for FDA approval, and Hologic said it believes the global market for HPV testing will increase to \$800 million in the next few years. "The combination of Hologic and Third Wave brings together two great companies that employ complementary technologies but share a common mission: to help save the lives of women," said Jack Cumming, Hologic's CEO.

Qiagen Gets Real-Time PCR Portfolio With Corbett Acquisition

Qiagen announced a deal worth up to \$135 million to acquire Corbett Life Science, a privately held developer, manufacturer, and distributor of life sciences instrumentation, headquartered in Sydney, Australia. Corbett is known for developing the world's first rotary, real-time PCR cyclers system, used to detect real-time PCR reactions that make specific sequences of DNA and RNA targets visible. "We are pleased to offer our customers the choice of superior platform of technologies for the entire workflow process—from sample to result," said Peer Schatz, CEO of Qiagen. "Corbett technologies are excellent complements to our portfolio of current and future molecular testing solutions. We expect this transaction to contribute significantly to our leading positions in molecular diagnostics, applied testing, pharmaceutical and clinical research, as well as academic research."

Micronics Receives NIH Grant For Rapid HIV POC Test

Micronics announced it received a \$100,000 Small Business Innovation Research grant to develop its rapid, POC diagnostic test for HIV. The Micronics test system will use a droplet of blood and small, disposable cassettes that contain all necessary reagents and control to perform a nucleic acid assay. "The overall objective of the NIH grant is to determine whether our test can provide the same kind of information as the current nucleic acid test in use today," said Karen Hedine, CEO of Micronics. "If this can be proven, we believe that our application will offer significant human health benefits, given the fact that it can be performed at reduced cost and in minutes in a doctor's office, public health lab, remote field hospital, or hospital birthing center." Hedine noted that current POC antibody-based tests for HIV cannot determine the infectious status of a newborn child for as long as 18 months, due to the presence of maternal antibodies.

J&J Unit Grabs Amic to Boost POCT Portfolio

Johnson & Johnson's Sollentuna, Sweden-based Nordic AB will acquire Amic, a privately held Swedish developer of in vitro diagnostics for POCT. Amic is developing a chip-based microfluidic platform to enable fully quantitative immunoassays in POC settings. "This acquisition is a strategic opportunity to develop a point-of-care channel," said Mark Straley, worldwide commercial president of Johnson & Johnson's Ortho-Clinical Diagnostics. "We're committed to bringing novel assays and existing tests closer to the patient and delivering information to healthcare professionals when and where they need it." Financial terms of the deal were not disclosed.

Gentag, MacroArray Technologies Collaborate on Cell Phone PSA Test

Gentag and MacroArray Technologies announced a joint development program to design a series of disposable, wireless diagnostic tests that send results via a

cell phone or PDA to the attending physician. The first will be a urine-based PSA test that uses MacroArray's proprietary reagents. Similar to pregnancy tests, the man will place a urine sample on the test strip that incorporates an embedded wireless sensor tag. When antibodies in the test react with antigens in the urine, data are sensed by the embedded electronic tag and sent to a cell phone or PDA that in turn transmits results to the man's physician. "The proprietary cell phone communication technology from Gentag combined with MacroArray's biomarkers will provide a significant level of exclusivity in this market," said John Peeters, CEO of Gentag. Financial terms of the agreement were not disclosed.

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DIAGNOSTIC

American Academy of Pediatrics Updates Guidelines for Lipids in Children

In new guidelines published in the July issue of the journal *Pediatrics*, the American Academy of Pediatrics issued and updated several recommendations for hypercholesterolemia in children: a healthful diet, including low-fat dairy products, for

children older than 2 years and, for obese children younger than 2 years; nutritional counseling and increased exercise for children and adolescents with high LDL-cholesterol; screening with a fasting lipid profile for children with CVD risk factors and/or high-risk or unknown family history; weight management as the primary treatment for obese children or those with high LDL cholesterol or low HDL cholesterol;

and for such children 8 years or older and whose LDL is 500 mg/dL or greater, considering pharmacologic therapy, with lower LDL thresholds for children who are at least 10 years old, depending on other risk factors (*Pediatrics* 2008;122:198–208).

High Homocysteine, Fibrinogen Levels Boost Risk for CKD

Elevated levels of homocysteine and fibrinogen account for 38% of the increased mortality risk associated with chronic kidney disease (CKD), according to a new report in the *American Journal of Cardiology* (2008;101:1741–46). The investigators enrolled 4,680 consecutive

new patients over a 9-year period in the observational cohort study and assessed them for various serum values. They found that CKD, defined by an eGFR of ≤ 60 mL/min/1.73m², was associated with a more than doubled incidence of death. During 22 months' follow-up, there were 278 deaths. Each patient's eGFR was calculated via the MDRD equation, which comprises serum creatinine, body weight, age, and race. There were 524 patients with an eGFR of ≤ 60 and 5,156 whose eGFR was > 60 . The investigators used a formula to account for adjusted and unadjusted hazard ratios for mortality. They also created several models including different clinical parameters. They found that when eGFR was included, the only clinical value that predicted mortality was homocysteine (adjusted HR 1.92) and fibrinogen (adjusted HR 2.99). Patients with the lowest tertile of homocysteine level also had the lowest mortality risk of all patients with CKD.

Diabetes Risk Increases Even Within Healthy Glucose Range

In a large cohort of HMO participants followed over a 3-year period, the risk of incident type 2 diabetes increased by 6% with every increase of 1 mg/dL in plasma glucose even when glucose was below the 110-mg/dL threshold previously established as impairment of fasting glucose, according to findings published in the *American Journal of Medicine* (2008;121:519–24). Of 46,578 participants, there were 1,854 who developed type 2 diabetes. Mean follow-up was 81 months for all subjects, average participant age was 57.5 years, and 40% were men. When those who developed diabetes were categorized by baseline glucose level, the portion of the total incident-diabetes subgroup was larger with each larger glucose range. Those with glucose < 85 mg/dL made up 9.4% of new cases. Those whose glucose was 65–89 mg/dL were 14.2%. Those in the range of 90–94 mg/dL were 28.1% of new cases, and those with 95–99 mg/dL were nearly half of the new diabetes cases, at 48.3%. Each increase of 1 mg/dL had a hazard ratio for incident diabetes of 1.06 after confounding factors were controlled for. Among the cohort at large, the risk of developing diabetes was 4% among participants with normal blood glucose levels and 11.3% among those with impaired fasting glucose.

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FDA Approves New Genetic Breast Cancer Test

Invitrogen announced the FDA approval of its SPOT-Light HER2 CISH test kit that determines whether a patient with breast cancer is a good candidate for treatment with Herceptin. Current medical practice requires that all patients who are considered for Herceptin treatment be tested for *HER2* amplification or overexpression. The test uses a DNA probe for the *HER2* gene that's amplified in 18%–30% of breast cancers, helping predict whether a breast cancer patient is a candidate for Herceptin treatment. Results of the test, which is based on chromogenic in situ hybridization (CISH), are visualized under a standard bright-field microscope—as opposed to FISH tests, where the results must be visualized using a fluorescent microscope.

The HER2 CISH test results are quantifiable, removing the subjectivity of tests based on immunohistochemistry (IHC) interpretation. And unlike other tests, the SPOT-Light kit allows the lab to store the tissue for future reference.

HemoCue's Albumin 201 Gets CLIA Waiver

HemoCue AB announced that the FDA granted a CLIA waiver for its Albumin 201 system, making it the first quantitative, point-of-care waived test for screening for, diagnosing, and monitoring microalbuminuria. The urine-based system is designed so that non-laboratory-trained physicians and other healthcare professionals can screen patients for microalbuminuria and begin treatment based on the test's results within a single office visit.

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The candidate must have an M.D. and/or Ph.D. degree with American Board of Pathology (CP or AP/CP) or American Board of Clinical Chemistry certification/eligibility. Eligibility for licensure in the state of California and experience as a Clinical Chemistry director are also desired. The faculty appointment will be commensurate with training and experience.

The individual will share the technical and clinical responsibilities of a high-volume automated clinical chemistry laboratory, and will also participate in teaching pathology and laboratory medicine residents. The successful candidate will also be expected to conduct clinical investigative research related to clinical chemistry or other related clinical services.

Salary and benefits packages are competitive. The David Geffen School of Medicine at UCLA is an Equal Opportunity Employer. Interested persons should send their curriculum vital, a cover letter describing clinical and research interests, and three references to:

Anthony W. Butch, Ph.D., Chair
Clinical Chemistry Faculty Search Committee
David Geffen School of Medicine at UCLA
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10833 Le Conte Avenue
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abutch@mednet.ucla.edu

Colorectal Cancer Monitoring Test Cleared

ADL announced FDA clearance of its AMDL-ELISA DR-70 (CRC) blood test for post-surgery monitoring of patients who have been previously diagnosed with colorectal cancer. According to ADL, because carcinoembryonic antigen (CEA),

the basis for the currently accepted monitoring test, can have normal values in some patients who are biopsy-positive for cancer, oncologists need an additional test for monitoring those patients who are CEA negative yet have biopsy-confirmed colorectal cancer. ADL's test is the first FDA-cleared monitoring test since the 1982 approval of CEA.