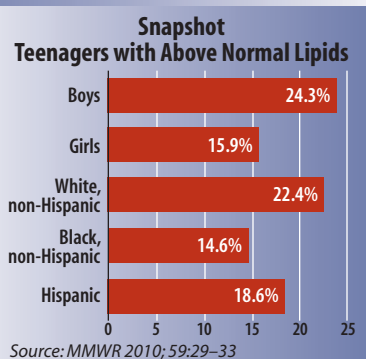


BAD NEWS: ABNORMAL LIPID LEVELS IN TEENAGERS

At least 20% of teenagers have abnormal lipid levels, placing them at risk for cardiovascular disease (CVD), according to a new study by CDC researchers (MMWR 2010; 59:29–33). Prior studies had indicated that abnormal cholesterol levels had become a problem among adolescents, but the new data documents the problem on a national level.

The researchers analyzed National Health and Nutrition Examination Survey (NHANES) data from 1999–2006. More than 3,000 youths age 12–19 participated in home interviews, had physical examinations in NHANES mobile examination centers, and provided fasting blood samples for lipid profile testing. The prevalence of abnormal lipid levels varied by body mass index (BMI), with 14.2% of normal weight individuals, 22.3% of overweight, and 42.9% of obese having at least one abnormal value, based



on cut-offs of ≥ 130 mg/dL for high LDL-C, ≤ 35 mg/dL for low HDL-C, and ≥ 150 mg/dL for triglycerides. The analysis also indicated that girls have higher HDL-C levels compared with boys after puberty, older adolescents are more likely than younger ones to have abnormal lipid levels, and that fewer non-Hispanic black youths have low HDL-C and high triglyceride levels in comparison with non-Hispanic white youths.

Recommendations vary about screening youths for lipid disorders. In 2007, the U.S. Preventive Services Task Force found insufficient evidence to recommend for or against screening, but in 2008 the American Academy of Pediatrics (AAP) called for targeted screening based on family history and other CVD risk factors. Under the AAP recommendations, 32% of study participants would have met criteria for lipid screening based solely on their weight. Approximately 22% of overweight and 43% of obese participants would have been eligible for counseling on therapeutic lifestyle changes.

Based on the study findings, the researchers suggest that clinicians be aware of lipid screening guidelines and recommended interventions for children and youth who are overweight or obese.

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Lessons from the POCT Front

How Can Labs Improve Implementation, Tackle Compliance Challenges?

BY GENNA ROLLINS

For at least a decade, point-of-care testing (POCT) has been the darling of the medical diagnostics industry, with sustained growth in testing volume and continual technological breakthroughs. The trend shows no sign of abating, as drivers such as the need for hospitals and clinics to better manage capacity and improve care, coupled with further innovations, are making POCT ever more attractive. Yet hospitals and health systems continue to experience challenges in implementing and sustaining POCT programs, at times leaving both laboratorians and clinicians frustrated and wary about the process. The reasons for less-than-satisfactory outcomes are as varied as the programs themselves, but experts cite many factors that can make or break a POCT application.

Several POCT medical directors placed the success of their programs squarely on the backs of point-of-care coordinators (POCCs), who do everything from investigating requests for new services and overseeing POCT implementations to troubleshooting problems and ensuring compliance with regulatory and quality control requirements that end users may view as onerous. “The biggest thing is not software or one machine that can operate better than another. It’s having that person who can make it happen,” explained Kent Lewandrowski, MD, associate chief of pathology and director of clinical services for anatomic and clinical pathology at Massachusetts General Hospital in Boston. “The administrator for our point-of-care program is a very competent, plain-spoken, forceful individual who makes clear what people have to do. She’s very well-organized and respected.”



See **POCT**, continued on page 2

NCI Launches National Biobank

Why High-Quality Specimens Have Researchers Excited

BY BILL MALONE

With all the bad news about the banking industry and the economy of late, the American public might not notice the emergence of a relatively new type of bank that is catching the interest of the lab community. Biobanks—also known as biorepositories—collect, store, process, and distribute biological materials and the data associated with those materials. Typically, these biological materials are human biospecimens—such as tissue or blood—and the clinical information pertaining to the donor of that biospecimen. Although individual researchers and institutions have long contended with storing their own frozen specimens, now a surge of cash from last year’s American Recovery and Reinvestment Act (ARRA) is speeding the launch of the first centralized, standardized biospecimen resource in this country.

Spearheaded by the National Cancer Institute (NCI), the new national biobank, called the cancer Human Biobank (caHUB), will at least initially have a more narrow objective than some of the independent biobanks already in the U.S., such as Mayo Clinic’s venture that began collecting specimens in April 2009. And as of yet, there are no plans to recruit and monitor massive numbers of healthy patients such as the half million-participant UK Biobank.

But while it will not replace other burgeoning efforts, caHUB will play an important role in meeting the growing demand for high-quality, well-documented biospecimens that are needed to keep

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Resources, Review Process Key Success Factors

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Investment, Administrative Support Critical

As important as POCs are, not every institution gives them the tools they need to be successful. "I have talked with so many people, and the ones who are struggling often seem not to have enough financial or staff resources to run good programs," observed Lou Ann Wyer, MS, MT(ASCP), clinical specialist for point-of-care testing and quality management at Sentara Healthcare in Norfolk, Va. "No point-of-care program can be run easily if it's not given enough administrative support." That sentiment was echoed by Deanna Bogner, MS, MT(ASCP), point-of-care testing coordinator for Christus Santa Rosa Health Care in San Antonio. "Many point-of-care coordinators are expected to run the program by themselves, because point-of-care testing is not something some organizations dedicate a lot of resources to until it's a problem," she said. Wyer and Bogner are veteran POCs and both have been recognized by AACC's Critical and Point of Care Testing Division as Point-of-Care Coordinator of the Year, Wyer in 2001 and Bogner in 2003.

Giving a program just enough to get by on can put POCs in a tough spot, particularly when they're new and learning the

ropes, according to Bogner. "They're usually plucked from the main lab and are good at project management in the sense of being told the tests they'll be doing every day and in managing that process and their time accordingly," she noted. "But with point of care, they're placed in a complex process that interfaces across several different areas of the hospital, and they have no idea what to do first." Appropriate guidance and resources enable them to make the leap out of the lab and become excellent stewards of POCT services. "Just because they've only been a bench tech doesn't mean that's all they can be," she added.

Variations on a Theme: The Role of POCT

Institutional philosophies about the role of and oversight process for POCT also are crucial in the ultimate success of any rapid testing application, experts say. NACB Laboratory Management Practice Guidelines on evidence-based practice for POCT recommend using an interdisciplinary committee to manage POCT. However, organizations appear to have quite different approaches to POCT oversight, with some erring on the side of approving new POCT requests, and others having much more structured approaches that are anything but rubber-stamp approvals. The former is a set-up

AACC Resources for Point-of-Care Coordinators

Recognizing the essential role that point-of-care coordinators (POCCs) play in the success of point-of-care testing (POCT) services, AACC's Critical and Point-of-Care Testing Division has developed numerous resources to support and enhance the skills of POCs.

In 2002, the Division held the first POC Forum at AACC's annual meeting. Over the past 7 years, this popular event has been attended by hundreds of POCs across the U.S. Each year experts address various topics of importance to POC practice. Past themes have included POCT in the emergency department, patient safety, and POCT-related quality issues. Division members also are invited to participate in the Division's online forum, where they can exchange ideas about current practice challenges with colleagues across the country.

Since 2000, the Division has also bestowed a Point of Care Coordinator of the Year award to recognize outstanding achievements in the POCT field. The honorees receive a \$500 cash award and travel allowance to attend AACC's annual meeting, where they are formally recognized.

The Division's latest offering is the POC Specialist Certificate Program, an eight-part online course designed to prepare POCs for their critical role in POCT and promote standardized best practices in near-patient testing. The program covers eight areas of POC practice, including regulations, policies and procedures, connectivity and IT, quality management, administration, instrument selection and validation, education and training, and communication. POCs who complete the eight modules and pass a multiple choice test are awarded certificates at the AACC annual meeting and also are recognized at regional POC meetings. More than 450 laboratorians have enrolled since the program's inception in 2008.

In addition to the Division's formal programs, the 2008 Point of Care Coordinator of the Year, Peggy Mann, MS, MT(ASCP), has established a POC-to-POC mentoring program. Mann, who is POC and reference lab coordinator for clinics at the University of Texas Medical Branch in Galveston, has many years' experience in the field and wanted to help newcomers deal with some of the challenges presented by POCT. The initiative pairs experienced POCs with newer POCs to guide them in developing and improving their practice. POCs interested in this program should contact Mann at pmann@utmb.edu

More information about the CPOCT Division's activities are available online at www.aacc.org/members/divisions.

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for failure, according to Brad Karon, MD, PhD, director of point-of-care testing at the Mayo Clinic. "When the process by which new tests get approved is vague or ill-defined, there can be a lot of political pressure put on the lab to support all these tests," he explained. "It becomes a political issue with the end users wanting point-of-care tests because vendors told them how great they were and lab administrators fighting it because of cost or quality concerns." Karon also is chair of AACC's Critical and Point-of-Care Testing Division.

In Bogner's discussions with colleagues across the country, this approach is surprisingly common, with predictable unsatisfactory outcomes. "A doctor goes to administration requesting a certain POC test. Administration goes to the lab director, who tells the point-of-care coordinator to do it. Later, the coordinator comes back and reports that it's not working, the quality control isn't being done, etcetera, and by then it's a big mess because no one asked the tough questions," she explained.

The bottom line is that a serious evaluation of all proposed POCT applications is crucial, whether it's accomplished via a formal standing committee or an ad hoc

group of key participants. For example, Mayo Clinic's Priorities Lab Testing Committee reviews POCT requests and oversees existing services. Conversely, Massachusetts General Hospital relies more on lab POCT staff, including the POCs, reviewing requests with clinical and administrative staff of the service in question. Both Karon and Lewandrowski believe their respective approaches are working well.

Regardless of how the POCT review and approval process is structured, labs should aim to discover the same basic information, in the context of the institution's view of the role of POCT. At Mayo Clinic, POCT is used to "support rapid decision-making and situations where rapid results lead to either improved outcomes or a more efficient disposition of the patient," Karon explained. "The key to me is, if all you're going to do with the test is have the result faster and there's very little chance that any outcome will change, then the request is unlikely to be approved."

A prime example of Mayo Clinic's philosophy in action was the recent approval of a POC lactate test in the emergency department and intensive care units. "It was part of an institutional improvement initiative

to recognize sepsis faster. This includes a sepsis response team that intervenes when a patient is suspected of having sepsis, and along with the POC lactate, the team gathers a number of other clinical parameters," said Karon. "This test was approved because we had external published data that showed this sort of approach worked in other institutions, and the protocol for it made clear that the result would be used in a process that allowed decisions to be made in real time."

Looking at Central Lab Solutions

Holding the line on POCT implementations that have the potential to cause problems down the road boils down to an open, honest dialogue with the requesting department, according to experts. Several lab directors emphasized the necessity of determining whether the lab can address the end user's request before implementing a POCT solution. "It's mainly used to decrease turnaround time, and the usual reason people want point-of-care is when the central lab can't provide results in a timely manner," noted Fred Kiechle, MD, PhD, medical director for clinical pathology at Memorial Healthcare System in Hollywood, Fla. "A great example is glucose results for diabetics with ketoacidosis who are on insulin drips. If the nursing unit needs results within the hour to adjust the drip, but we provide the result within an hour-and-a-half, we're not helping them. So my first question would be, why can't the central lab solve this problem?"

Often this type of dialogue leaves all parties satisfied with a lab-based, rather than POCT solution. "There were certain technologies where we improved the turnaround time in the central lab to such an extent that the units didn't want point-of-care because they didn't want to have to maintain it. If you adopt a point-of-care mentality in the central lab, that may be all that's needed," explained Cynthia Bowman MD, medical director of clinical laboratories at Long Island Jewish Medical Center in New Hyde Park, NY. As an example, Bowman's lab now performs fecal occult blood testing for the emergency department with a 30-minute turnaround time. "That was fine for them. It helps with their workflow and they don't have to worry about quality control issues," she added. The central lab also maintains a 5-minute turnaround time for blood gasses to meet ICU needs, and tightened serum creatinine turnarounds to screen patients for kidney injury prior to radiological interventions.

Understanding What's Really Involved

Very often, the requesting department does not have a good sense of what taking on a POCT application will require, in terms of costs, regulations, training, and quality control concerns, according to experts. Exploring these issues upfront can forestall later problems that frustrate end users and can lead to failures, where either both parties agree a point-of-care application is not working or the lab is forced to pull the service. Bogner has experienced this first hand. During her first 2 years at Christus Santa Rosa Health Care, the number of POCT applications shrank. "We started to pull the manual things like fecal occult blood testing that are so difficult to keep track of. We looked at how many tests the users were performing and went back to

the nurse managers. We told them, 'You only did 10 of these. Do you really want to keep 35 nurses competent with them?' The answer was no, and tests like that went back to the main lab," she recalled.

End users particularly may not understand the strict quality control and competency standards they'll be held to. This can become a factor in failed implementations when using sites finally realize what they have to do to offer a test. "I worry that we've sold waived tests as being so simple you can't make a mistake. But many of these devices are deceptively simple and actually very sophisticated," said Bowman. "For point-of-care testing to really mature, a number of things have to happen, and one of them is that things don't get taken for granted." To underscore that point, Bowman and her staff take pains to determine how well the site understands the nitty-gritty details of

operating the POCT device and complying with regulatory and quality assurance requirements. Temperature controls and storage issues are only two examples of the exacting standards the using site must adhere to. "I hear stories from my peers that people measure temperatures but store something up high or under a window and the kit deteriorates. So we ask if they'll be able to document that the kit was kept in proper conditions throughout the life of the instrument," she explained.

Maintaining and substantiating competency with an instrument in sites with a high number of staff members—such as the emergency department—can be the sticking point that either closes down a POCT service or prevents its approval. This also is one reason why applications that don't work in one setting can make perfect sense in another. For instance, there was a

request at Massachusetts General Hospital to perform rapid HIV testing in labor and delivery as a way to deal with the relatively small number of women who present in labor without having had prenatal care. The goal then would be to initiate antiretroviral therapy for HIV-positive mothers to prevent maternal-fetal HIV transmission. However, given the low volume of testing and the considerable size of the labor and delivery staff, the request was denied. "We set that up in the central lab where competency could be maintained. Yes, it takes a little longer, but the result is still available within 15 minutes. If we had implemented it in labor and delivery, it likely would have been a fiasco," explained Lewandrowski. On the other hand, this same application was approved for the hospital's sexually transmitted diseases clinic. "There, it made

See **POCT**, continued on page 4

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POC Coordinators, IT Work Closely

POCT, continued from page 3

sense. There's a limited number of people performing the test and the volume is such that they would be able to maintain competency."

To bring home the point about the using site's responsibility in quality control, the University of Texas Medical Branch (UTMB) in Galveston requires top-level sign-off on any new requests for service. "We require not just the nursing supervisor, but also the medical director of the site to sign-off. His or her name may not be on the CLIA certificate, but we require it so the site will know that point-of-care testing is tied to the CLIA certificate," explained Peggy Mann, MS, MT(ASCP), POC and reference lab coordinator for clinics. She was recognized in 2008 by AACC's Critical and Point of Care Testing Division as Point of Care Coordinator of the Year.

In concert with the using site's responsibility for quality control, labs need an effective means of monitoring compliance. In many cases this boils down to the POCCs' visible presence on units and in clinics. "The old 'sneakernet' is still extremely important. People trying to manage from their connectivity are not going to know the programs. They have to be out and about," said John Petersen, PhD, professor of pathology, director of point-of-care testing, and associate director of clinical chemistry at UTMB. Petersen also is treasurer of AACC's Critical and Point of Care Testing Division.

Mayo Clinic's Priorities Lab Testing Committee oversees compliance via monthly audit reports. The site's compliance with performance criteria are highlighted as red, yellow, or green. Two or more quarters with multiple red indicators requires a meeting with the committee to discuss remediation plans. If the problem continues, the site faces removal of the point-of-care method in question, according to Karon. Long Island Jewish Medical Center recently implemented a rotating system of intensive review of individual sites. "It's a constant revolving focus on different units, so it hopefully encourages them to constantly keep up with compliance," Bowman indicated.

A major consideration for Bowman is the leadership and past reliability of a site in maintaining quality control, competency, and the like. "Are these people who have a mindset to collaborate or are they indifferent or even hostile to that? We'll work much more readily with sites that have already shown they can perform, than those that have been difficult to work with or have no track record," she commented.

Clearing IT Hurdles

Although the increased sophistication of POCT devices has facilitated new testing applications and vastly improved connectivity and data collection, IT remains a major stumbling block to successful POCT services. As an example, Massachusetts General Hospital recently implemented POCT blood gas measurements in its surgical suites. The instruments, which were specially wired for use in that setting, also had middleware that enabled a direct interface with the LIS and hospital electronic health record. However, in practice, the devices weren't always docked immediately after being used, and the LIS recognized

when the data was received, not when the test was performed. "We had to pull the plug because we didn't have a way to solve that technical problem short of a very expensive IT project we didn't have the time or resources to invest in," said Lewandrowski. "We plan to revisit this."

Those types of challenges have forced POCCs to become more conversant with IT issues and work closer than ever with IT staff. "Point-of-care coordinators understand now that they'll have heavy involvement with IT and need to communicate clearly and closely with IT," observed Wyer. At Sentara, the POCC-IT connection has matured to the point that a dedicated team of IT staff works with the POCCs, and each group has developed an appreciation for issues of importance to the other. "Our worlds have meshed a little. That's why our relationship is so collaborative," said Wyer.

Analytic issues also continue to be a factor in the successful deployment of POCT. A key area of concern involves diabetes management, because blood glucose testing accounts for the majority of the POCT market. Recently an analysis of eight HbA1c POC instruments found that six did not meet CV criteria within the relevant clinical range (Clin Chem 2010; 56:44-52). In

addition, because of mounting concerns about the accuracy of blood glucose meters and their use in settings not approved as safe and effective, the FDA will hold a hearing this month on appropriate clinical and analytical requirements for the devices.

As manufacturers, users, labs, and regulators collaborate to address POCT analytical issues, labs have an important role in managing expectations and clarifying appropriate usage of POCT devices. "Sometimes we as laboratorians ask about accuracy and precision in point-of-care like we would in a lab setting, where you'd want the most accurate method," said Karon. "You often have to accept decreased accuracy or precision of the point-of-care method in exchange for the ability to improve outcomes by changing the way you use the information."

With the POCT market only expected to grow in coming years, solid lab-POCT site relationships will be essential to maintaining viable POCT services, according to Bowman. "In the lab, we're really focused on the technical process, while the clinical setting is usually focused on the patient process and outcomes. We need to bring the two perspectives together and there needs to be an appreciation that all concerns are 'our' issues so that our clinical peers understand we are not being arbitrary and obstinate and we show our willingness to work with their realities." CLN

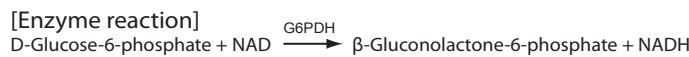
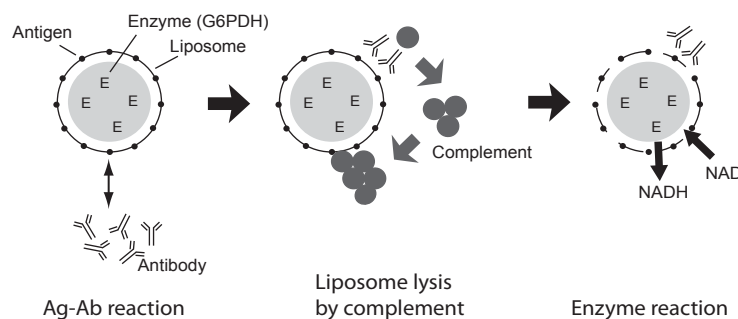
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Research, Pilot Projects Lay Groundwork

Biobank, continued from page 1

translational research moving forward, according to Stephen Thibodeau, PhD, professor of laboratory medicine at Mayo Clinic College of Medicine, co-director of molecular genetics, and co-founder of Mayo Clinic Biobank. “Biobanking is really one of the cornerstones of a translational research program. It all comes down to the quality and the availability of biospecimens,” he said. “We in lab medicine and the Mayo research community are going to be so dependent on availability of biospecimens, that I think caHUB is really an important initiative that NCI needs to continue. But it won’t be sufficient on its own, and other biobanks will continue to be important.”

Playing Catch-Up

Perhaps the most well known biobank involves an entire country. deCODE Genetics in Iceland—where some 60% of the population has given a specimen—and other such projects in other countries are matched by a patchwork of more modest independent endeavors in the U.S., a disparity that has not gone unnoticed by the scientific community here. Other countries, including Japan, Estonia, and the U.K., grappled with the shortage of high-quality, well-documented biospecimens by setting up enormous national population-based banks of specimens and data.

Why is a national biorepository so important? Some researchers have complained that progress in pharmacogenomics and other cutting-edge lab medicine areas has been exceedingly slow. The frustration, they complain, is the lack of the blood specimens for biomarker discovery and validation. A chorus of reports from the Institute of Medicine, the Department of Health and Human Services, and the President’s Council of Advisors on Science and Technology (PCAST) have also lamented the slow progress of personalized medicine and identified the critical need for high-quality biospecimen banks.

“Despite tremendous excitement about the potential value of molecular biomarkers...this potential has largely gone unfulfilled,” noted the 2008 PCAST report, *Priorities for Personalized Medicine*, with bottlenecks in validation as “the most important constraint on progress.” The report’s recommendation to address this problem includes both disease-specific biobanks and population biobanks for longitudinal health and disease studies. NCI’s caHUB will be first national project that tackles the first with an opportunity to take on the second in the future.

One of the world’s largest single biobanks, UK Biobank belongs to this second category, with a collection of nearly 500,000 sets of blood and urine samples from people age 40–69. Central to the project is a plan to annotate precisely each participant via a thorough initial questionnaire and physical workup and then to follow their health records indefinitely. Another reason that this biobank will be such a treasure chest of information is that The U.K. National Health Service treats the single largest group of people anywhere in the world and keeps detailed records on all of them from birth to death. As a result,

follow-up of UK Biobank participants through routine medical records will allow researchers to pinpoint those who develop a wide range of diseases and make studies that utilize the biobank’s samples that much more meaningful.

Key to making this large project successful was almost a decade of careful planning and pilot projects that have ensured a smooth collection process, high-quality specimens, and the necessary ethical-legal framework for an endeavor with huge implications for society at large, said UK Biobank CEO and principal investigator Rory Collins, FMed Sci, FRCP, British Heart Foundation professor of medicine & epidemiology at Oxford University. Before a single sample was collected, special working groups conducted wide consultation with the scientific community and the public. “These working groups looked at key questions to ask participants about exposure to a wide range of potential risk factors, what kinds of initial measurements to make, what kinds of samples to collect, and how to collect them in such a way that they would be usable for a range of assays, including assays that haven’t been invented yet,” Collins said. “And particularly in all of this, bearing in mind that we were trying to do a study that was a hundred times bigger than Framingham, efficiencies of scale have been critical.”

With its scale and depth of involvement with participants, UK Biobank has become a sort of proof of concept that with careful planning and technological creativity, large biobanking projects can be successful and financially feasible. Relying on a mix of public and private money has kept the project moving below budget and on schedule, with more than 80% of the 500,000 participants already recruited. In fact, Collins and his colleagues were recently invited to Washington to meet with NIH leaders and share their expertise.

A Focus on Quality

At the same time that other countries have pushed forward with national biobank schemes, researchers in the U.S. have been burdened by a surprisingly ineffective system composed of silos of samples that vary greatly in quality, according to Jim Vaught, PhD, Deputy Director of NCI’s Office of Biorepositories and Biospecimen Research (OBBR). “The rationale for caHUB is that we think the standards need to be raised across the board,” Vaught said. “Samples in U.S. biorepositories were not consistently collected, processed, and stored. So, after observing biospecimen-related quality issues in studies we’ve been a part of at NCI, we believe that the best plan is to prospectively collect samples under very carefully designed conditions, standard operating procedures, and careful quality control—all well documented and applied consistently.”

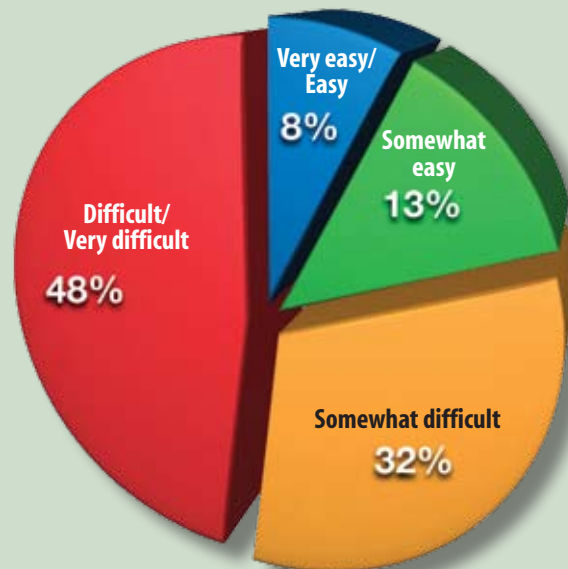
Before embarking on detailed planning for caHUB, OBBR started with an analysis to see what researchers were up against when it came to biospecimens, surveying primary investigators at NCI and other institutions. The survey showed that about 40% found it difficult or very difficult to acquire enough biospecimens, with half

See **Biobank**, continued on page 6

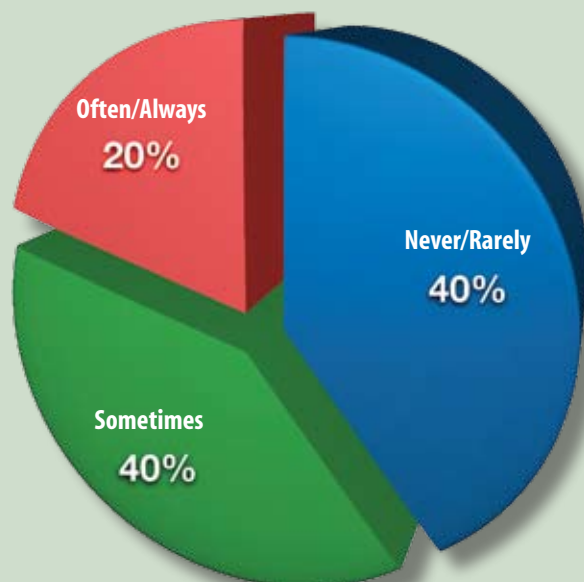
Researchers Voice Their Opinions The Critical Need for Quality Biospecimens

As part of the planning phase for the National Cancer Institute’s (NCI) new national biospecimen resource, called caHUB, the Office of Biorepositories and Biospecimen Research conducted a survey of researchers funded by NCI, as well as federal agencies, cancer centers, industry, foundations, and advocacy groups about the need for quality human biospecimens. The survey results indicated that acquiring quality biospecimens was a major barrier to progress in many research areas, including discovery and validation of new diagnostic assays.

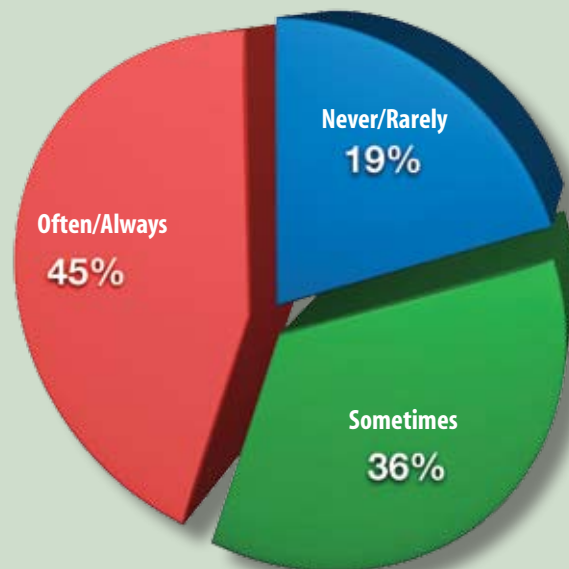
Ease of Acquiring the Quality of Biospecimens



Question Their Data Because of the Quality of Biospecimens



Limit Research Scope of Work Due to the Shortage of Quality Biospecimens



Source: Office of Biorepositories and Biospecimen Research, 2009. <http://biospecimens.cancer.gov/cahub/>

Better Specimens Mean Better Assays

Biobank, continued from page 5

of the respondents saying it was equally challenging to get the quality of biospecimens they needed. Even more disturbing, 20% said they often or always question their data because of the poor quality of biospecimens. About 40% said they at least sometimes question data.

Even with the best intentions and protocols, individual investigators face innumerable challenges trying to collect and maintain their own biospecimens, said Allison Hubel, PhD, Director of the University of Minnesota Biopreservation Core Resource (BioCoR), a knowledge base, research, and education resource for the biospecimen community. Hubel is a professor of mechanical engineering and former member of the department of laboratory medicine and pathology at the University of Minnesota. "When individual investigators store their own samples, they just can't match a biorepository's monitoring, maintenance, and database management system, which allows you to have a sense of security about the quality of your samples," she said. "In addition, a software system should be assigning identification to and tracking each sample. An individual investigator is going to have trouble justifying implementation of a laboratory information management system, while for the central repository it can be part of the infrastructure."

After its survey and other study of the issue, OBBR decided that its previous efforts at developing best practices documents and an online network among independent biobanks—while successful—were not enough. "We decided that the best way to address the problem was to develop our own procedures and then have the various clinics, hospitals, laboratories, and repositories collect samples for us in carefully prescribed ways so there is a consistent set of samples and data," explained Vaught. "This way when collaborators request specimens and data, they know what they're getting."

Commercial and other independent biobanks will continue to provide tissue and blood samples, and many do have high quality standards of their own or have adopted OBBR's Best Practices for Biospecimen Resources, Vaught said. However, caHUB will be aiming still higher. "The difference between what they do and what caHUB will do is that we'll have a much richer data set that will be collected in a longitudinal fashion, and the combination of the quality of the samples and the rich clinical, demographic, and specimen quality data set will be of a much broader and higher quality than the commercial providers."

A better quality of specimens is the link from discovery to practice in lab medicine, and especially personalized medicine, emphasized Vaught. "We are promoting the connection between caHUB and personalized medicine because we think it's really important. Sample integrity and quality are essential for the research that leads to new biomarkers and more personalized treatment. The Cancer Genome Atlas (TCGA) was a prime example that required very high quality samples and produced results." TCGA is a project working to catalogue the genetic mutations associated with cancer.

Now is the time for laboratorians to provide feedback on the caHUB project as

OBBR evaluates what kind of specimens the research community needs, Vaught said. Currently caHUB has several existing clients, including TCGA and various clinical trials under NIH, from which caHUB will collect samples, in addition to a separate "benchmark" or reference collection of tumor and normal tissues collected under contracts being solicited over the next few months. "Initially this will be a disease-based collection, but we have interest from population-based study investigators. We have to take their concerns into consideration and think about whether there are certain biomarker assays or validation studies that will require a different approach to specimen collection. We will be forming a committee to assess potential study designs," he said.

Mayo's Own Bank

The dearth of quality biospecimens has also led to other new biobank projects in the U.S., such as the Mayo Clinic Biobank. Similar to the population-based UK Biobank model, Mayo Clinic aims to recruit 20,000 participants from among the institution's own patients and then track them through their Mayo Clinic electronic medical records indefinitely. The focus of this collection will be on a generally healthy population as opposed to a disease population.

These biobanking projects have, and will continue to have, a large impact on new discoveries and their translation into clinical practice, Thibodeau stressed. "Access to well annotated, high quality material will be essential for a wide variety of studies. When I think about the use of biospecimens for these purposes, I think of lab medicine as being one of the many beneficiaries. These translational discoveries will ultimately lead to the development of a variety of novel assays—diagnostic markers, prognostic markers, predictive markers for drug response, and tests for genetic predisposition," he said. "And with the implementation of new high-throughput, high-content technologies such as next generation sequencing, along with studies that require larger and larger number of participants, the need for a substantial number of quality biospecimens will be even more important. This will be true for samples obtained from both disease as well as healthy donors."

Thibodeau also sees a trend where lab medicine and pathology are becoming more involved in the discovery of new biomarkers, especially in personalized medicine. However, this growing involvement of laboratorians will stall without the ability to properly validate novel tests before they are used clinically, he said.

Before one of these novel diagnostic assays can be implemented in a clinical laboratory, there's an important next step. "There's been a tremendous amount of work performed in both industry and research laboratories developing new markers, but what's really critical before these things can be introduced into the clinical lab is our ability to clinically validate them: to demonstrate that they're doing what they're supposed to be doing," Thibodeau explained. "And the only way that you can complete such studies is to have a large number of high-quality samples. The work

in clinical labs is fundamentally changing, and with those changes, the access and need for biospecimens has become more acute."

Pushing the Envelope with Technology

Just as breakthroughs in technology are driving trends in research and clinical labs, the biobanking community is grappling with the need to improve the technology behind preserving the high-quality specimens. Biobanks themselves are under pressure to keep up and are now drawing upon cutting-edge technology from other disciplines in science and engineering in order to collect and maintain the biospecimens that the tests of the future will demand. "Most of the technology that has been developed to actually facilitate the preservation of biospecimens is on the order of 30 to 40 years old," said Hubel. "It was really developed for systems for which a very small number of samples are preserved, which translates into very labor-intensive and operator-intensive processes." Hubel, an engineer herself, has been working on projects that will make biobanking as up-to-date as the assays researchers need them for.

One of these projects developed through Hubel's BioCoR consortium at the University of Minnesota is an innovative microfluidic device to process biospecimens and reduce the amount of labor involved. When preserving a specimen, multiple steps have to occur. For example, components like red and white cells, plasma, and serum must be separated. Then a cryopreservative solution has to be introduced into the biospecimen being preserved. In order to be used, the specimen must be thawed and the protective agent removed. A microfluidic device could be used at each one of these steps in order to handle the volume of liquid and cells in a semi-automated and controlled

fashion, thereby reducing dependence on an operator for some of the processing steps, as well as reducing loss of cells and samples to human variability.

BioCoR is also developing 3-D Raman confocal microspectroscopy techniques to understand the relationship between the state of the intracellular cryoprotective agent during cryoprocessing and the ensuing thermal and osmotic damage to cells. "The Raman study is allowing us to take the latest in molecular characterization techniques and apply that to the science of preservation for biobanking. Now that we have a tool that allows us to image down to the nanoscale, we can use it to expand our understanding of damage or stabilization, and possibly develop a new paradigm of preserving biospecimens," said Hubel.

One of the discoveries that has come out of the BioCoR Raman study is helping researchers understand why cells within a block of tissue fare so poorly compared to cells isolated in a suspension. "The conventional wisdom has been that heat and mass transfer limitations frame the freezing of a tissue versus the freezing of an isolated cell suspension. Those issues are true, but we believe there are other issues involving cell-to-cell communication that are present in a tissue versus isolated cells which play a role in long-term freezing response," Hubel explained. "Those are very exciting discoveries, in particular because we have a lot of challenges freezing tissue samples right now, whether they be normal or pathological samples."

Using more advanced technology and cutting-edge methods is, in fact, the only way that the larger projects have been successful. This strategy fits right in with the advice that the UK Biobank's Collins has for caHUB. "If you're going to do a large study, you have to be efficient. You can't



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just take what you would normally do with a few thousand people and multiply it up," he said. "It's really worthwhile having an industrial approach to the way in which the study is done and the way in which the quality is maintained. You can be a bit ad hoc if you're just studying a few thousand people. But you can't if you're studying a few hundred thousand people. I think that's the main thing. Design the study for its scale, and in particular invest in systems that manage a very large-scale study in a very efficient way in order to get much higher quality data."

The Ethical Side

Simultaneous with the unique needs of biobanks that are driving new technology and preservation science, caHUB will also have to grapple with an increasingly complex burden of ethical questions surrounding collecting samples and using them for research. Most of these questions focus on obtaining informed consent to use a person's blood or tissue in the first place. Plus, the ensuing information associated with that person's sample creates more ethical issues down the road.

"The expectation and the classical requirement in traditional research is that research participants have to be fully informed, which includes understanding the nature of the research, and knowing exactly what it is they are consenting to," explained Karen Maschke, PhD, a research scholar at The Hastings Center, an independent nonprofit bioethics research institute. Maschke also sits on caHUB's ethics subcommittee. "The problem that emerged with research involving biospecimens was that the classical approach to informed consent was not always going to be possible, especially when biospecimens are collected and stored for future use that researchers may not be able to specify at the time they're collected. So you can't always fully inform a person about all the potential types of research they're consenting to with their biospecimens."

Due to the often large leaps that science makes, such as the sequencing of the human genome, researchers and biobanks learned that to make biospecimens useful, it was important to make consent for their use wider, accommodating future advancements in science and unknown directions that researchers might take. However, having a completely open-ended consent in which a researcher or a biobank asked to be able to perform any kind of valid research, even if it wasn't yet conceived, left a lot to be desired for many observers concerned with ethics, Maschke said.

This has led to two other approaches. Closer on the spectrum to specific consent, so-called tiered or layered consent evolved from studies at the NCI where participants were given a sort of multiple choice on how their specimen might be used, with check offs for each type of research or disease like cancer, diabetes, or Alzheimer's. "The challenge with tiered consent is that the biospecimen resource that collects the samples must then maintain a database to track each combination of consent for each specimen," Maschke explained. "Some researchers have argued this is too complicated and expensive, while others don't like it because it limits the use of the biospecimens and makes it hard for people doing less common kinds of studies to get

the number and quality of specimens they need."

While tiered consent opened up the use of biospecimens beyond a single, specific type of consent, the compromise just doesn't work for the scope of a new generation of biobanking initiatives that must include as-yet unknown research possibilities. The desire of UK Biobank, Mayo Clinic, and others to be a library for future research has led to a third, hybrid approach: essentially open-ended consent, coupled with independent oversight that keeps the participants' interests in mind.

This is why going forward, caHUB and other large projects will have to put so much stress on governance by data access committees and ethics committees, Maschke emphasized. Though not without controversy, UK Biobank has been a

leader in this new model, depending on an independent committee called the UK Biobank Ethics and Governance Council to act as an autonomous guardian of the overall governance and ethical framework. The council monitors and reports publicly on the biobank's conformity to the framework and advises on the interests of research participants and the general public. This way, the biobank can use a very open-ended consent from participants and still maintain the public's trust as new uses for biospecimens develop beyond what any original participant might have imagined.

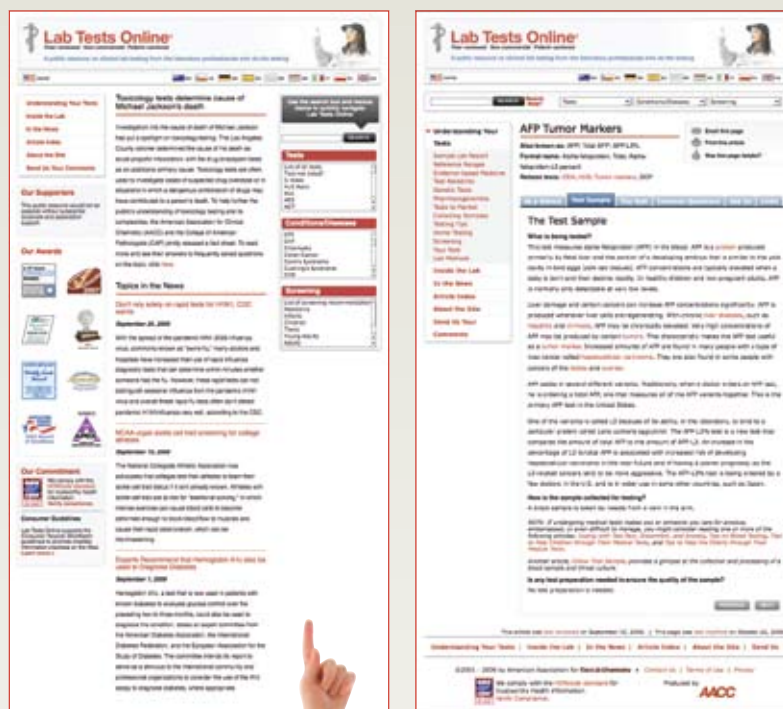
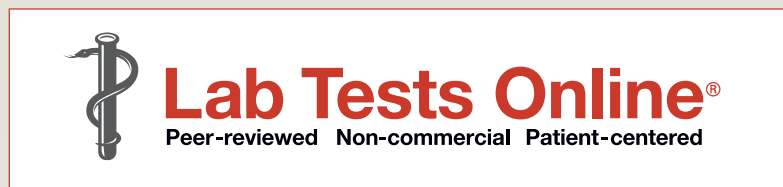
Getting Underway

As caHUB begins collecting its first samples later this year, it will have the advantage of observing larger and more complex initia-

tives in other countries, while Mayo Clinic and others continue with independent projects that have their unique features. Due to the distribution of care in the U.S., it's unlikely that caHUB will ever match the depth and breadth of a project like UK Biobank, Thibadeu predicted. Yet the Mayo Clinic initiative and others can produce good results and all deserve the support of laboratorians.

"Quality biospecimens will lead to new diagnostic, prognostic, and therapeutic markers, and that's why NIH is devoting so many resources to their own program. Downstream, it's going to mean a lot to patients," he said. "Our end goal here is to have these assays in a clinical environment, but how do we get there? These biorepositories are one of the tools, so we need to continue to invest in them." CLN

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Lead Testing

Meeting the Analytical Demands of Identifying Exposed Children

KATHLEEN L. CALDWELL, PHD, AND ROBERT L. JONES, PHD

Anaturally occurring, malleable, dense, blue-gray metal, lead has been used in commercial products such as fossil fuels, house paint, batteries, ammunition, solder, pipes, devices to shield X-rays, and craft-making products. But because of health concerns, government agencies imposed regulations that either eliminated or dramatically reduced the amount of lead added to gasoline, paints, food cans, ceramic products, caulking, and pipe solder.

Although lead reduction represents one of the best-known public health success stories, the problem is not fully resolved. Lead is particularly harmful to the developing brain and nervous system of fetuses and young children, and lead-based paint remains the most common source of lead exposure for children in the U.S. Older housing, especially pre-1978, is more likely to have leaded paint, putting millions of children who live in these homes at risk for lead exposures. Because a higher proportion of people in lower socio-economic classes tend to live in older, substandard housing, socio-economic status is a common predictor of possible lead exposure.

Less common sources of exposure also still exist, including lead-glazed ceramic pottery, plumbing systems with lead-soldered joints or lead pipes, lead-containing folk remedies, and lead-contaminated dust in indoor firing ranges. Recently, another seemingly innocent source was discovered that put children at risk of lead poisoning: inexpensive toys and trinkets. In fact, some cases of severe lead poisoning occurred in which the child swallowed and retained the toy. Children may also be exposed to lead that is brought into the home on the cloth-

central nervous system. At high levels, lead results in seizures, coma, and even death. Even at low exposure levels, lead has been documented to cause learning disabilities and behavioral problems. What constitutes a safe level of exposure to lead is still a point of debate among public health experts, but no safe blood lead level in young children has been identified.

Not only are the lives of children and their families greatly affected by lead exposure, but society also pays a high price to care for these children. In fact, even

exposure on a child's developmental status and educational achievement have significant effects throughout the child's entire life, leading to the much higher economic burden on society.

Blood: The Preferred Matrix

Even at blood lead levels that can result in neurologic damage, there may not be obvious physical symptoms, so excessive blood lead can go unrecognized and undetected. Laboratory testing of blood is the only reliable way to identify lead-exposed individuals. The concentration of lead in whole blood has gained wide acceptance as the best available measurement of cumulative exposure, because blood levels reflect both recent intake and an equilibration with stored lead in other tissues, particularly the skeleton.

Although a number of alternate matrices have been proposed and discussed, including saliva, hair, and nails, their use in measuring lead exposure remains problematic for a number of reasons. Any matrix used as a tool for biomonitoring must have certified or standard reference materials of the analyte that is being tested; however, these alternative matrices lack such materials. The alternative matrices also lack reliable reference ranges or correlations to the analyte/matrix combination for human populations. Laboratories analyzing these matrices should have matrix-matched internal quality control material and matrix-matched calibration curves so that matrix effects will not bias the analytical results. Furthermore, alternate matrices may have a high potential for pre-collection environmental contamination that cannot be effectively eliminated. Such contamination can contribute to a high analytical bias and therefore produce a false-positive clinical result. Finally, there are no proficiency testing programs established for lead testing in saliva, hair and nails. For these reasons, this article will address only the measurement of lead in whole blood.

Public Health Guidance

In 1985, the Centers for Disease Control and Prevention (CDC) established ≥ 25 $\mu\text{g}/\text{dL}$

ing of adults whose work or recreational activities involve lead.

Here we describe the advantages and disadvantages of the blood lead analysis methods, as well as why public health efforts to identify children who have been exposed to lead are so critical.

The Public Health Problem

Lead affects almost every organ system in the body, but it is especially harmful to the

though asthma affects many more children in this country, the total economic costs of asthma pale in comparison to those of lead exposure. As recently as 2002, researchers studying the contribution of environmental pollutants to the incidence, prevalence, mortality, and costs of pediatric disease in American children estimated the cost of asthma at \$2 billion annually, while that of lead exposure was \$34 billion. The negative effects of even small amounts of lead



as an elevated blood lead level in children and recommended the erythrocyte protoporphyrin assay (EPP) as a screening test for lead exposure. But in 1991, the agency lowered the level of concern for blood lead in children under age 6 years to 10 $\mu\text{g}/\text{dL}$. At this new lower level, the EPP test was no longer sensitive. Consequently, in its 1991 statement CDC also changed its recommendation concerning the best test for detecting lead exposure to direct measurement of lead in whole blood rather than the extraction method used in the EPP test.

Lead Analytical Methods

Today, labs primarily assess lead exposure with whole blood lead measurements. Although a number of human tissues and fluids also reflect lead exposure, most of the published information related to human exposure and health effects is based upon the concentration of lead in whole blood. In blood, lead binds to erythrocytes and then is distributed initially to soft tissues. Because lead has a relatively long half-life of 1–2 months, the fraction of absorbed lead not promptly excreted can become incorporated into bone and even teeth. Consequently, lead concentration in whole blood serves as a measure of recent exposure, whereas bone lead is an indicator of long-term exposure.

In cases of very high exposure, *in vivo* measurements may be necessary to reflect the exposure accurately. Lead concentration *in vivo* may be determined by non-invasive, *in vivo* X-ray fluorescence (XRF); however, XRF is still an emerging technique available only in research settings. Several research teams are working to understand the localization of lead in bone, its mode of chemical binding, and its chemical and physiologic distribution.

Typically, labs collect venous blood samples for lead assessment; however, finger-stick capillary samples may prove to be equally useful. For the latter, the sample collection process must be performed carefully to avoid external contamination. Three common analytical techniques are often used to measure lead in whole blood. These include anodic stripping voltammetry (ASV), atomic absorption spectroscopy (AAS), and inductively coupled plasma mass spectrometry (ICP-MS).

Zinc protoporphyrin (ZPP) measurements were also used for assessing lead exposure in children prior to 1991; however, the method still has utility today for cases in which blood lead levels are $\geq 25 \mu\text{g}/\text{dL}$. In cases of acute exposure, although blood lead levels decrease, according to the 1–2 month half-life, ZPP lead levels remain elevated for the lifetime of the involved red blood cells. Lead levels measured by ZPP do not reflect recent or acute lead exposure, and they do not change quickly when a person's source of lead exposure is removed. ZPP measurements may aid in detecting a person's average exposure to lead over the last 3–4 months; however, the method is not sensitive enough for use as a screening test in children.

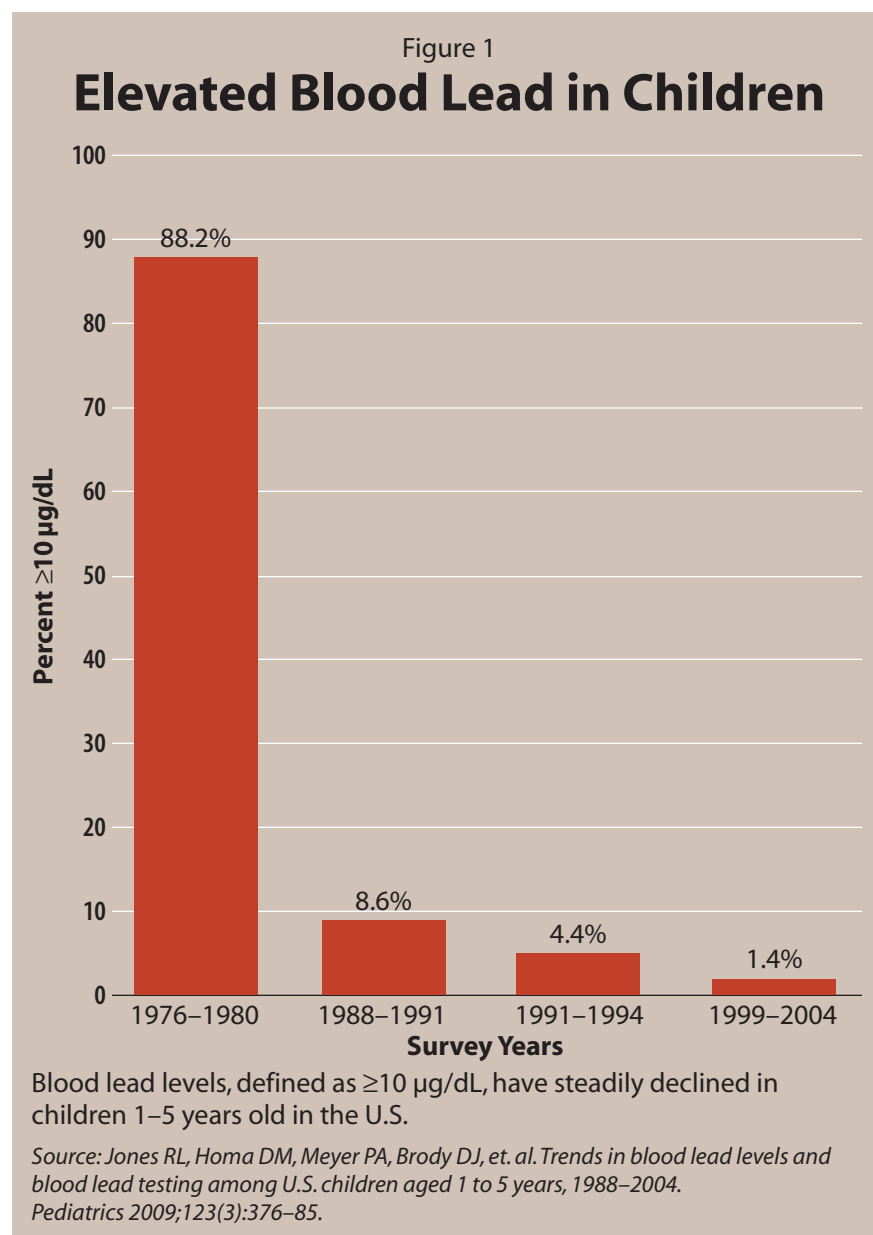
Although the AAS method, with either a flame or an electrothermal atomization furnace, is outdated technology, it is spe-

cific and sensitive and provides reliable laboratory data for lead levels. The method involves the use of graphite furnace atomic absorption spectrometry (GFAAS) and is based on the fact that free atoms will absorb light at frequencies or wavelengths characteristic of the element of interest. Measuring light absorbed at 283.3 nm by ground-state atoms of lead from either an electrodeless discharge lamp (EDL) or a hollow cathode lamp (HCL) source provides useful information: the amount of light absorbed can be linearly correlated to the concentration of analyte. Typically, 100 μL of blood is diluted with a matrix modifier and dropped onto the graphite furnace, which is a small graphite tube. When the graphite furnace is heated, the sample is vaporized and the lead is atomized. Although GFAAS has been shown to be precise and dependable, it can only measure one element at a time.

ICP-MS's multi-element analysis capability enhances lab productivity, and therefore many public health and private clinical labs use the method. ICP-MS offers a high degree of specificity, sensitivity, and selectivity, as well as the ability to analyze other toxic and essential metals from a small sample. This technique can also determine the isotope ratios of the lead in a set of samples, which is not possible with AAS. Such ratios help determine if a particular source of lead is a possible contributor to poisoning of an individual.

In a routine clinical mode that uses a whole blood sample of $<100 \mu\text{L}$ (either venous or finger-stick capillary), ICP-MS analysis provides an adequate limit of detection (often $<0.5 \mu\text{g}/\text{dL}$) that can be achieved with minimal sample preparation. This multi-element analytical technique is based on quadrupole ICP-MS technology, which couples radio frequency power into a flowing argon stream seeded with electrons, creating the plasma. The predominate species in the plasma are positive argon ions and electrons. Use of a nebulizer inserted within a spray chamber converts diluted whole blood samples into an aerosol, and a portion of the aerosol then is transported first through the spray chamber followed by the central channel of the plasma, where the temperature is 6000–8000° K. This thermal energy atomizes and ionizes the sample, and the ions, along with the argon gas, then enter the mass spectrometer through an interface that separates the ICP from the mass spectrometer. Once inside the mass spectrometer, the ions pass through the ion optics, and the mass analyzing quadrupole before they strike the surface of the detector. Electrical signals resulting from the ions are processed into digital information that is used to indicate the intensity of the ions and subsequently the concentration of the element.

Analytical methods such as GFAAS and ICP-MS work well for routine measurement of blood lead levels $<0.5 \mu\text{g}/\text{dL}$. However, as the cutoff for a blood lead level of concern drops, laboratories wishing to engage in routine biomonitoring must evaluate pre-analytic variables with care, eliminating as much background contamination as possible. The use of "lead-free" blood collection devices, alcohol wipes, laboratory reagents, and sample vials is essential.



Lead Testing at the Point of Care

Recognizing the need to add point-of-care (POC) capability to the arsenal of blood lead methodologies, CDC spearheaded development of a first-of-its-kind, portable blood lead instrument that has since been used to identify lead poisoning globally. In 1997, scientists at CDC, in collaboration with ESA Biosciences, a supplier of medical analytical instruments, developed the first portable blood lead testing device approved for field use in healthcare clinics and in targeted blood lead investigations. The LeadCare instrument uses electrochemistry with a small, screen-printed colloidal gold electrode to measure the amount of lead in whole blood by ASV. At the beginning of a blood lead measurement, the operator mixes 50 μL of fresh, whole blood with a treatment reagent. This process disrupts the red blood cells that contain most of the lead and chemically disassociates the lead from the red blood cell components. "Free" lead is then released in the treatment reagent in the form of divalent lead, which is then available for detection on the sensor electrodes. After the blood treatment reagent mixture is transferred to the sensor and the test is started, an electrical potential is applied by the analyzer, causing the lead to plate onto the test electrode. The analyzer strips the lead from the plate via a voltage shift to a more positive potential. The device measures the resultant current associated with stripping and automatically converts it into a blood lead value that is displayed on the analyzer.

The Food and Drug Administration (FDA) classified the first-generation ASV device as 'moderately complex,' a classification that limited its use in the U.S. However, design improvements eventually led to the 2007 release of a CLIA-waived device. The second-generation LeadCare II Blood Lead Test System is a fast and simple system that allows healthcare providers to detect blood lead levels in patients. It is now widely available in a variety of patient care settings, such as doctors' offices and public health clinics.

Given the public health need for lead testing, CDC funded development of the LeadCare II as a CLIA-waived device. This POC device has led to a paradigm shift in blood lead testing. Health practitioners can now perform in-office tests during a single well-child visit and avoid unnecessary delays in the detecting, counseling, and treatment of cases of lead poisoning. Where it has been implemented, the device provides a significant public health benefit, empowering parents and the public health community to help prevent future lead poisoning.

Being able to educate parents about the dangers of lead at the same time they learn of their child's lead levels has been proven to be effective in rectifying and reducing lead exposure. But given that lead poisoning is an environmental health condition, monitoring by public health officials is also crucial. Therefore, it is critically important that labs and other healthcare providers report all blood lead test results to public

health officials. Many states already mandate such reporting, and CDC has worked with ESA to develop user friendly software that supports the reporting requirement.

The Goal: Improved Public Health Outcome

In 1991, CDC defined the blood lead level of concern that should prompt public health actions as 10 µg/dL, and subsequently the U.S. Department of Health and Human Services (HHS) established a national goal to eliminate blood lead levels ≥10 µg/dL in children younger than age 6 by 2010. Remarkable progress has been made towards this goal. As a result of the reduced use of lead in commercial products and public health efforts to educate the public about the dangers of lead exposure, data from the National Health and Nutrition Examination Survey (NHANES) indicate the number of children 1–5 years with

blood lead levels ≥10 µg/dL has fallen from an estimated 8.6% during 1988–1991 to 1.4% during 1999–2004.

NHANES, a national survey of the health of the non-institutionalized U.S. population, also indicates that blood lead levels have continued to decline since 1976 (Figure 1). NHANES data from survey periods 2007–2008 indicate that approximately 1.2% (95% CI of 0.2–3.9) of 817 children tested who were representative of the U.S. population had blood lead levels ≥10 µg/dL. Of these children, 100% in the 1–5 years age group had detectable lead values, defined as CDC's 0.25 µg/dL limit of detection. For the NHANES 2007–2008 survey period, the geometric mean for children 1–5 years old was 1.24 µg/dL (95% CI of 1.18–1.29), compared with 1.57 µg/dL (95% CI of 1.5–1.7) for survey years 2003–2008.

As the blood lead levels for U.S. children steadily fall, laboratorians will need to continue to evaluate analytical methods and instruments that will enable them to provide public health officials with the best means to monitor the population. Although widespread exposure to lead sources such as leaded gasoline and paint have diminished, exposure resulting from toys and other consumer products has become a source of concern. These new exposure risks emphasize the need for laboratorians to provide analytical methods capable of detecting low levels of blood lead and to test blood lead in non-traditional settings, such as doctor's offices, walk-in clinics, or field study locations. Efforts to identify affected children and eliminate lead poisoning will require continued innovation and persistence from both public health officials and lab professionals. **CLM**

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

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Key Flu Indicators Level Off

FDA's Emergency Use Authorizations for Detecting the 2009 H1N1 Virus

In April 2009, the U.S. Secretary of Health and Human Services declared a public health emergency due to the outbreak of the 2009 H1N1 influenza virus. Now according to the most recent data from the Centers for Disease Control and Prevention, the overall cumulative hospitalization rates for the 2009-2010 influenza season have leveled off in all age groups and very few 2009 H1N1-laboratory confirmed hospitalizations were reported by states during the week ending January 30.

Nevertheless, confirming the identity of the virus responsible for influenza-like

illness remains important for administering appropriate therapy to individuals, as well as the general public health. "The need to correctly identify influenza subtypes was demonstrated during the height of the 2009 H1N1 pandemic," said Andy Shrago, senior director of sales and marketing at Gen-Probe Prodesse. "With different pharmaceutical susceptibility profiles for each of the three strains, we expect that laboratory and physician needs will be best met by products that can reliably detect and differentiate all three strains of influenza A—seasonal H1, seasonal H3, and 2009 H1N1."

To help speed identification of the virus, the Food and Drug Administration (FDA) issued 13 emergency use authorizations (EUAs), making assays available for diagnosing 2009 H1N1 influenza virus under certain circumstances (see Table). It is important to note, however, that FDA has not cleared or approved any tests for the identification of the 2009 H1N1 influenza virus. Under its authority, FDA can permit the use of unapproved and uncleared medical products in a public health emergency provided certain criteria are met. FDA can only grant EUAs for the duration of the emergency, which is currently set to expire

on April 26, 2010, unless it is terminated sooner or renewed. The agency can also revoke any EUA prior to the termination of the emergency.

In contrast to 2009, this year manufacturers will need to develop assays that are able to accurately and effectively differentiate multiple strains, says Shrago. "While the IVD community did an outstanding job serving public health needs by quickly getting 2009 H1N1-only tests to market through the FDA's EUA process, labs will demand post-pandemic, complete subtyping assays in the coming months to meet clinical requirements," Shrago predicted. **CLN**

2009 H1N1 Virus Tests with FDA Emergency Use Authorization

Test	Manufacturer/Lab	Date Authorized	Scope	Test Technology	What is Detected
2009 H1N1 Influenza A Real-time RT-PCR Test	ViraCor	Jan 2010	Use by ViraCor Reference Lab only	Real-time reverse transcriptase PCR assay	Conserved region of the matrix gene present in both seasonal and 2009 H1N1 influenza A viruses Region of the hemagglutinin gene found in the 2009 H1N1 influenza virus
Xpert Flu A Panel	Cepheid	Dec 2009	Moderate and high complexity CLIA-certified labs	Real-time reverse transcriptase PCR assay	Four forward primer sequences for detecting the matrix gene in influenza A Two forward primer sequences for detecting the hemagglutinin gene in 2009 influenza A H1
rRT-PCR Swine Flu Panel on JBAIDS	CDC	Aug 2009, amended Dec 2009	Use by Department of Defense labs only	Real-time reverse transcriptase PCR assay	Universal influenza A strains NP gene of H1N1 influenza strains HA gene specific to 2009 H1N1 influenza subtype H1
Resequencing Influenza A Microarray Detection Panel	TessArray	Dec 2009	High complexity CLIA-certified labs	Resequencing microarray assay	2009 H1N1 influenza virus gene sequences NA1av, NSav, M1hu, M3hu, and M5Av Seasonal A/H1N1 gene sequences HA1hu, NA1hu, M1hu, M3hu, and M5Av Seasonal A/H3N2 gene sequences HA3hu, NA2hu, M1hu, M3hu, and M5Av
GeneSTAT 2009 A/H1N1 Influenza Test	DxNA	Dec 2009	High complexity CLIA-certified labs	Reverse transcriptase PCR assay	Hemagglutinin and neuraminidase genes found specifically in the 2009 H1N1 influenza A virus Conserved region of the matrix gene present in both seasonal and 2009 H1N1 influenza A viruses
ELITech Molecular Diagnostics 2009 H1N1 Influenza A virus Real-Time PCR Test	Epoch Biosciences	Nov 2009	Use by ARUP Laboratories Only	Real-time reverse transcriptase PCR assay	Hemagglutinin gene found specifically in 2009 H1N1 influenza A virus Conserved region of the Matrix Protein 1 gene present in both seasonal and 2009 H1N1 influenza A viruses
RealTime ready Influenza A/H1N1 Test	Roche	Nov 2009	High complexity CLIA-certified labs	Real-time reverse transcriptase PCR assay	Hemagglutinin gene found specifically in 2009 H1N1 influenza A virus Conserved region of the Matrix Protein 2 gene present in both seasonal and 2009 H1N1 influenza A viruses
ProFlu-ST Influenza Assay	Gen-Probe Prodesse	Oct 2009	High complexity CLIA-certified labs	Multiplex real-time reverse transcriptase PCR assay	Conserved regions of the seasonal influenza A/H1 and A/H3 hemagglutinin genes Conserved regions of the 2009 H1N1 influenza nucleoprotein gene
Simplexa Influenza A H1N1 (2009) Test	Focus Diagnostics	Oct 2009, amended Dec 2009	High complexity CLIA-certified labs	Real-time PCR assay utilizing fluorescent probe-primers	Conserved region of the matrix gene present in both seasonal and 2009 H1N1 influenza A viruses Hemagglutinin gene found in the 2009 H1N1 influenza virus
H1N1-09 Influenza Test	Diatherix	Oct 2009	Use by Diatherix Reference Lab only	Multiplexed molecular diagnostic assay that performs target-enriched multiplex PCR nucleic acid amplification	Hemagglutinin and neuraminidase genes found in the 2009 H1N1 influenza virus
Influenza A H1N1 (2009) Real-Time RT-PCR	Focus Diagnostics	Jul 2009, amended Dec 2009	High complexity CLIA-certified labs	Real-time reverse transcriptase PCR assay utilizing fluorogenic hydrolysis probes	Conserved region of the matrix gene present in both seasonal and 2009 H1N1 influenza A viruses Two separate regions of the 2009 H1N1 influenza virus' HA gene
Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel	CDC	May 2009	Public health and other qualified labs	Panel of oligonucleotide primers and dual-labeled hydrolysis probes for use in a real-time reverse transcriptase PCR assay	2009 H1N1 influenza virus RNA
Swine Influenza Virus Real-time RT-PCR Detection Panel	CDC	Apr 2009, amended Dec 2009	Public health and other qualified labs	Panel of oligonucleotide primers and dual-labeled hydrolysis probes for use in a real-time reverse transcriptase PCR assay	NP and hemagglutinin genes found in the 2009 H1N1 influenza virus

Source: FDA. Available at www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm.



Gene Patent Case Underway

The first hearings in federal court have begun in a case that has broad implications for biotechnology and personalized medicine. In May of last year, The College of American Pathologists and the Association for Molecular Pathology, among others, joined in an American Civil Liberties Union (ACLU) lawsuit challenging the patents controlled by Myriad Genetics for breast cancer risk testing. Should ACLU win the case, many other patent claims would be called into question, upending strategies for companies that hold patents on genes, including those used in pharmacogenomics and other diagnostics areas.

On February 2, ACLU lawyers argued before a U.S. District Court judge in New York that medical research was being held back by the *BRCA1* and *BRCA2* patents and that these genes are “an ancient secret

of nature,” while attorneys representing Myriad Genetics and the University of Utah Research Foundation, which is also named in the lawsuit, countered that a ruling making these patents invalid would “wreck the foundation of the entire biotechnology industry,” according to the Associated Press. It could be months before the judge issues a ruling on whether the case can move forward.

Meanwhile, biotech and in vitro diagnostics companies are speaking out. The Biotechnology Industry Association (BIO), along with biotech and in vitro diagnostics companies, recently sent a letter to Secretary of Health and Human Services Kathleen Sebelius on the issue. The letter comes as a retort to recommendations laid out in the October 2009 meeting of the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS). At this meeting, SACGHS recommended that Sebelius work

to create an exemption from liability for infringement of patent claims on genes for anyone making, using, ordering, or selling a test developed under the patent for patient care purposes, as well as an exemption from patent infringement liability for those who use patent-protected genes in the pursuit of research.

In the letter, BIO warns that weakening or eliminating the current patent system for genes will threaten the “innovation collaboration” in the U.S. and “undermine the foundations of American life science innovation,” as well as lead to a loss of jobs and a competitive disadvantage to other countries.

The SACGHS report is available online at <http://oba.od.nih.gov/SACGHS/>. The BIO letter is available on the BIO website, <http://bio.org>.

Hospital Infection Control Inconsistent

Research by Consumer Reports using recently-released public data found that central line infection rates vary widely among states, cities, and even within healthcare systems. Consumer Reports also published a list praising 105 hospitals whose most recent public reports counted zero infections. Central-line infections account for approximately 15% of all hospital-acquired infections and approximately 30% of all 99,000 annual hospital-acquired infection-related deaths, according to the report.

For its analysis, Consumer Reports analyzed data from intensive care units at 926 hospitals in 43 states, using information from public state reports and from the Leapfrog Group, a nonprofit that collects voluntary hospital quality information. The investigation found “enormous variations...even within the same healthcare systems,” citing as an example Kaiser Permanente hospitals in the Los Angeles area. Kaiser's Harbor City Medical Center reported no infections in the 1,769 days its ICU patients were on central lines in 2008, but Woodland Hills Medical Center reported 13 infections in 1,937 central-line days in its medical-surgical ICU, more than four times the nationwide average.

The full report, as well as the list of hospitals with no infections, is available from the Consumer Reports website, www.consumerreports.org.

NH Bill Would Expand Patient Rights to Medical Records

Lawmakers in New Hampshire are considering a bill that would go beyond the federal Health Insurance Portability and Accountability Act (HIPPA) privacy rules to ensure that patient medical records aren't shared without permission. Under the proposed bill (HB 1649), patients could request an audit of all healthcare providers who accessed their records during the previous 3 years. The legislation would also require an organization to obtain patients' consent before disseminating electronic health record data.

New Hampshire is unique in being the only state that, under law, considers patients to be the owners of their medical records,

and has a history of strict privacy requirements. The enactment of HIPPA in 2003 actually widened what providers could do with patient records compared to existing state law, according to *Laconia Citizen*. HB 1649 aims to restore those additional protections.

The bill is available on the state legislature's website, www.gencourt.state.nh.us/house/.

President's Budget Aims To Cut Waste in Medicare

Although President Obama's 2011 budget continues to expand on the administration's priorities in healthcare—such as healthcare information technology, comparative effectiveness research, and an additional \$1 billion for National Institutes of Health research—the budget proposal also reaffirms focus on trimming waste in Medicare, closely following the predictions of observers in the clinical lab field that the Center for Medicare and Medicaid Services (CMS) will push increasing scrutiny over claims from laboratories and other providers (See *CLN*, January 2010 p.1).

To combat healthcare fraud and waste, Obama's budget requests an increase of \$250 million over the FY 2010 enacted level for this purpose at the Department of Health and Human Services. The administration's estimates indicate that these investments would generate \$9.9 billion in savings from “increased recoveries and prevention efforts.” In addition, the budget proposes legislative and administrative changes that could save \$14.7 billion in Medicare and Medicaid over 10 years.

At CMS, \$110 million in additional funds will go toward a new, comprehensive Health Care Data Improvement Initiative to transform CMS's data environment from one focused primarily on claims processing to one also focused on data analysis and information sharing. According to the administration, these changes are vital to modernizing the Medicare and Medicaid programs by making CMS a leader in value based purchasing, improving systems security, and increasing analytic capabilities and data sharing with key stakeholders.

A fact sheet covering healthcare-related elements of the President's 2011 budget is available from the White House website, www.whitehouse.gov/omb/factsheet_key_health_care.

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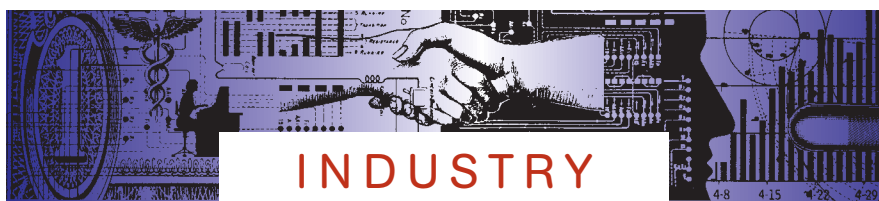
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INDUSTRY

OraSure Technologies, Roche Sign Commercialization Agreement

OraSure Technologies and Roche Diagnostics announced that the two companies have signed an agreement for worldwide commercialization of fully automated, oral fluid, drugs-of-abuse assays using OraSure's Intercept oral specimen collection device. The Intercept device is the only FDA-cleared, laboratory-based, oral fluid testing system used for detecting commonly abused drugs such as marijuana, cocaine, opiates, PCP, amphetamines, barbiturates, methadone, and benzodiazepines. The assays use Roche's KIMS technology and will be jointly developed by both companies.

"We are very pleased with our joint development effort with Roche and the finalization and execution of the commercialization agreement associated with these important drugs-of-abuse assays," said Douglas A. Michels, president and chief executive officer of OraSure Technologies. "We look forward to working with Roche to bring these new assays to market where they will have an immediate and positive impact on laboratory efficiency for drugs-of-abuse testing." The commercialization agreement is structured to capitalize on OraSure's established presence in the oral fluid testing market, and Roche's established base of analyzers and marketing capabilities. Additional terms of the agreement were not disclosed.

Quidel Announces Acquisition Of Diagnostic Hybrids

Quidel announced the signing of a definitive agreement to acquire Diagnostic Hybrids, a manufacturer of direct fluorescent in vitro diagnostic assays used in hospitals and reference labs, for approximately \$130 million in cash. "Our combined organization will have greater channel strength, and together we will provide our customers a full service offering the best-in-class diagnostic products," said David Scholl, PhD, president and chief executive officer of Diagnostic Hybrids. Quidel plans to operate Diagnostic Hybrids as a separate subsidiary. Dr. Scholl will remain as president of Diagnostic Hybrids and also become a senior vice president of Quidel. The acquisition is subject to customary closing conditions and is expected to close in the first quarter of 2010.

Life Technologies to Buy AcroMetrix

Life Technologies announced that it has signed a definitive agreement to acquire AcroMetrix, a provider of molecular and serological diagnostic quality control products used by clinical laboratories, blood screening centers, and in vitro diagnostic manufacturers. "With the growth of DNA and other molecular based tests, there is a growing need for high-quality, indepen-

dently provided controls to ensure the accuracy and integrity of laboratory test results," said Gregory T. Lucier, chairman and chief executive officer of Life Technologies. "The acquisition of AcroMetrix builds on our substantial business of providing tools and technologies into the molecular diagnostics industry." Financial terms of the agreement were not disclosed.

Predictive Biosciences to Acquire OncoDiagnostic Laboratory

Predictive Biosciences announced the acquisition of OncoDiagnostic Laboratory (ODL), a private, CLIA-certified anatomic and molecular diagnostics lab serving specialty physicians. The acquisition provides Predictive Biosciences with a fully integrated pathology laboratory through which the company plans to commercialize its molecular cancer diagnostic assays. The first in Predictive Biosciences' portfolio of non-invasive assays is a urine biomarker-based test for the detection of bladder cancer, which the company plans to make commercially available in 2010. "We look forward to leveraging ODL's urology focused sales organization to introduce our proprietary bladder cancer assay later this year," said Peter Klemm, PhD, president and chief executive officer of Predictive Biosciences. "Importantly, Predictive and ODL share a common set of values—a commitment to innovation, customer service, and patient care—and we are certain that these values will serve as a solid foundation for our merged company's growth." Financial terms of the agreement were not disclosed.

AstraZeneca, Dako to Collaborate On Personalized Medicine

AstraZeneca and Dako Denmark A/S announced that they have entered into a collaborative agreement to develop companion diagnostic tests for multiple AstraZeneca oncology projects. Under the agreement, the companies will work to develop diagnostic tests that can be used by physicians to determine the most appropriate cancer treatments. The collaboration

will combine Dako's expertise in cancer diagnostics and AstraZeneca's experience in the development and commercialization of oncology products. "We believe it is important for pharmaceutical and diagnostic companies to combine their expertise in a strong, collaborative approach to enable the development of diagnostic tests for use with drug therapies," said Lars Holmkvist, chief executive officer of Dako Denmark A/S. The financial terms of the agreement were not disclosed.

AACC's March Webinar Lineup

Customizing Quality Control for Improved Patient Safety

March 3

This program will provide strategies that will allow you to develop a quality control plan that is specific to your lab's workflow process control needs.

Mass Spec in the Clinical Lab: Is Now the Time?

March 25

Find out if mass spec has a place in your lab and learn about clinical applications where it is now routinely used.

The New ADA Guidelines: Using HbA1c in Diabetes Screening and Diagnosis

March 31

Discover what this major change to the American Diabetes Association's guidelines means for your lab.

For complete program information and to register, go to AACC.org.

AACC and AMP Present

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For additional information or to register, visit www.aacc.org/events/meetings/ or call the AACC Customer Service Department at 1-800-892-1400 or 202-857-0717



NT-proBNP, CRP Add to Risk Prediction for Perioperative Cardiovascular Events

New research indicates that both N-terminal pro-brain natriuretic peptide (NT-proBNP) and C-reactive protein (CRP) are strong and independent predictors of perioperative major cardiovascular events (PMCE) in non-cardiac surgery. The findings suggest that the two biomarkers could add significantly to the predictive value of current clinical risk evaluation methods, such as the revised cardiac risk index (RCRI) (Heart 2010; 96:56–62).

The study involved 2,054 prospectively enrolled patients who were referred to a consulting cardiologist for evaluation of preoperative cardiovascular risk. The patients were scheduled for elective non-cardiac surgery but had at least one cardiovascular risk factor such as hypertension or diabetes, or abnormal electrocardiography (ECG). NT-proBNP and CRP levels were measured within 2 weeks of surgery, and preoperative cardiovascular risk was assessed using RCRI, which assigns points to risk factors such as history of ischemic heart disease and pulmonary edema. Prior research had shown that RCRI scores of 0 to ≥ 3 corresponded to a 0.4% to 11% risk of a major cardiac event, including myocardial infarction (MI) and pulmonary edema.

The study's primary endpoint was PMCE, defined as any single or combined event of secondary endpoints including MI, onset of pulmonary edema, or primary cardiovascular death. Ultimately, PMCE developed in 14.1% of patients.

The researchers evaluated increasing RCRI score, and increasing quartiles of NT-proBNP and CRP as risk predictors of PMCE, and found that all three were associated with greater risk of PMCE. They also discovered that each variable was related to

clinical outcomes independently of each other. Each standard deviation increase in RCRI, log CRP, or log NT-proBNP was associated with a 1.3–2.2-fold increased rate of PMCE after adjustment for other risk predictors and risk factors. The researchers also found that adding NT-proBNP and CRP to RCRI increased the adjusted relative risk from 1.5 to 4.55, suggesting that the predictive power of RCRI could be strengthened significantly when used with the two biomarkers.

Low Blood Lead Levels in Adolescents Linked to Reduced Kidney Function

According to a newly published study, blood lead levels below the current CDC-designated level of concern in children are associated with lower estimated glomerular filtration rate (GFR) in adolescents (Arch Intern Med 2010;170:75–82). This analysis, which is one of the largest examining the association between lead levels and kidney function in children, suggests that more attention should be paid to the effects of low-level environmental lead exposure, even in young populations generally free of comorbidities that typical contribute to chronic kidney disease (CKD).

The study builds on a growing body of evidence in adults exploring the link between low-level lead exposure and kidney function. In 1991, CDC lowered the blood lead level of concern for children from 30 to 10 $\mu\text{g}/\text{dL}$ based on studies linking blood lead levels as low as 10 $\mu\text{g}/\text{dL}$ to neurodevelopmental effects. While subsequent research has bolstered the premise that chronic lead exposure $< 10 \mu\text{g}/\text{dL}$ negatively impacts cognitive and cardiovascular function in children and adolescents, the same type of analysis involving kidney function has been challenging due to the high vari-

ability and low sensitivity of serum creatinine measurements used to estimate GFR. Investigators in this study had the advantage of being able to use a pediatric-specific cystatin C-based eGFR equation, with serum cystatin C levels measured as part of the Third National Health and Nutrition Examination Study (NHANES III). The study population included 769 adolescents between the ages of 12 and 20 who participated in NHANES III.

The researchers found that nearly all the participants had blood lead levels $< 10 \mu\text{g}/\text{dL}$, with the median level being 1.5 $\mu\text{g}/\text{dL}$, and median cystatin C-eGFR of 112.9 mL/min/1.73m². Linear regression analysis showed that higher blood lead levels were consistently associated with lower eGFR, and that participants with lead levels in the highest quartile had a 6.6 mL/min/1.73m² eGFR compared with those in the lowest quartile. In a model adjusted fully for factors such as age, sex, and race, doubling of blood lead levels was associated with a 2.9 mL/min/1.73m²-lower eGFR. The investigators also used a creatinine-based eGFR equation, which also showed an inverse, albeit weaker, association between blood lead level and eGFR.

Combined Use of H-FABP, cTn T Leads to Misclassification of Patients with Suspected MI

An analysis comparing the usefulness of heart-type fatty acid binding protein (H-FABP) in comparison with and in addition to cardiac troponin T (cTn T) in patients with suspected acute myocardial infarction (AMI) revealed that while H-FABP had higher sensitivity than cTn T during the first 4 hours of symptoms, it had poor specificity (Am J Cardiol 2010; 105:1–9). Using both H-FABP and cTn T results also improved sensitivity and negative predictive value in detecting AMI within the first 4 hours of symptom onset, but with specificity significantly lower than for cTn T alone. The latter finding resulted in a lower combined overall test accuracy and greater misclassification of patients than when cTn T alone was used, particularly in patients with non-ST elevation MI.

Although both cTn I and T dramatically changed the workup for patients presenting with suspected AMI and lead to a redefinition of MI in 2000, a number of studies have reported low sensitivity for these biomarkers within the first 6–12 hours of symptom onset. H-FABP has been proposed as a timelier marker for AMI diagnosis because of its high sensitivity shortly after symptom onset, and studies in selected study populations have shown favorable diagnostic results with H-FABP. However, there has not been an extensive analysis of H-FABP in the setting of complex diagnostic decision-making involving unselected patients, so the researchers designed their study to evaluate the use of H-FABP in 97 consecutive unselected patients presenting to the emergency department with ischemic-type chest pain.

As expected, cTn T sensitivity for diagnosing AMI was lowest when symptom duration was < 4 hours, but increased to 100% when symptom duration was > 4 hours.

H-FABP sensitivity was higher than cTn T among patients admitted within 4 hours of symptom onset, and was greatest between 2–4 hours. However, H-FABP sensitivity declined after 8 hours, and the specificity for H-FABP was significantly lower than cTn T in all subgroups and for all periods. When evaluating use of the markers together, the researchers found a significantly greater early sensitivity compared with cTn T alone, but a much lower specificity. Consequently they concluded that “greater sensitivity for an early diagnosis of AMI using a combined test can only be achieved with a marked loss in overall diagnostic test efficiency and a greater misclassification rate.”

Serum Calcium Levels Linked to Higher Mortality in Non-Dialysis-Dependent Chronic Kidney Disease

New research indicates that both chronic hypercalcemia and acute hypocalcemia are associated with increased mortality in patients with moderate or advanced non-dialysis-dependent chronic kidney disease (NDD CKD) (Clin J Am Soc Nephrol 2010; doi:10.2215/CJN.06040809). The findings, among the first to examine the relationship between abnormal calcium levels and mortality in NDD CKD patients, suggest that while lower calcium levels can have short-term harmful effects, abnormally high levels also can be injurious over longer periods of time.

The results illustrate “calcium’s complex pathophysiologic role in humans, which varies from that of a rapidly fluctuating intracellular messenger to that of a stable component of skeletal structure,” according to the authors.

The study involved 1,259 male patients evaluated for NDD CKD with a medium of 18 calcium measurements taken during a medium follow-up of 3.2 years. The primary outcome measure was overall all-cause mortality. Baseline, time-varying, and time-averaged serum calcium levels were associated with all-cause mortality using Cox models adjusted for a variety of factors. Higher baseline calcium and time-average calcium were associated with higher mortality. However, in time-varying analyses, lower calcium levels were associated with increased mortality.

The researchers concluded that maintaining normal serum calcium levels may be beneficial in patients with NDD CKD, although they emphasized that prospective studies would be needed to determine a target range for serum calcium and how this target should be achieved to realize the greatest therapeutic potential.



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NEWS FROM THE FDA

Abaxis Receives FDA 510(k) Clearance for New CRP Test

Abaxis announced that FDA granted 510(k) marketing clearance for its new C-reactive protein (CRP) assay on the Piccolo Xpress point-of-care analyzer. The assay runs in less than 12 minutes and is suitable for detecting many types of conditions, including infections, inflammatory diseases, tissue injury, and some neoplastic processes. The test initially will be available to the U.S. market on the acute care panel MetLyte Plus CRP.

ARK Diagnostics Zonisamide Assay Cleared

The ARK Zonisamide Assay has received FDA 510(k) clearance. Manufactured by ARK Diagnostics, the assay is intended for the quantitative determination of zonisamide in human serum or plasma on automated clinical chemistry analyzers. Zonis-

amide concentrations are used to aid in the treatment of patients taking zonisamide, an anticonvulsant used to treat seizures.

FDA Clears Influenza A/B Virus ID Kit

Diagnostic Hybrids announced that FDA 510(k) clearance was granted for its D3 FastPoint L-DFA Influenza A/Influenza B Virus Identification Kit. The kit identifies influenza A and B from a patient specimen in less than 30 minutes. D3 FastPoint incorporates the same proprietary monoclonal antibodies used in other respiratory products by Diagnostic Hybrids. The kit also features the same fluorescent labeling technologies used in the company's D3 Ultra and D3 Duet products and L-DFA technology that allows for the simultaneous detection of two respiratory viruses on a single slide. The new kit is the second product in Diagnostic Hybrids' D3 FastPoint L-DFA product line.

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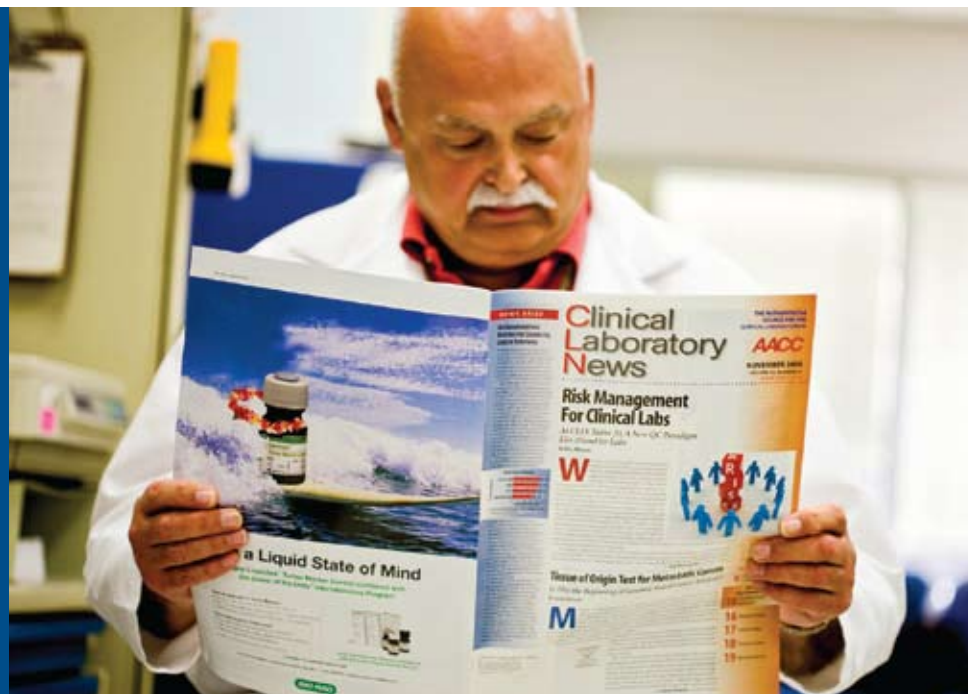
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