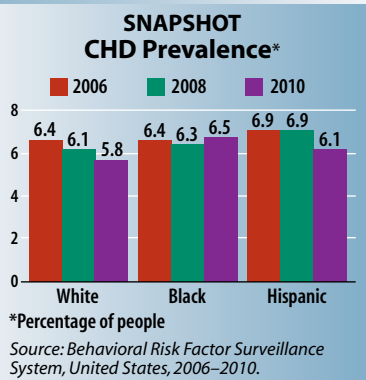


CHD PREVALENCE CONTINUES TO DECLINE

A new report in *Morbidity and Mortality Weekly* found that the number of Americans with coronary heart disease (CHD), including heart attack and angina, has continued to fall since the 1960s. While this is good news, the report also indicates disparities in the decline by state, race, and ethnicity.

From 2006 to 2010, the number of Americans who reported being diagnosed with CHD by a health professional decreased from 6.7% to 6% according to the report, "Prevalence of Coronary Heart Disease—United States, 2006-2010." The U.S. Centers for Disease Control and Prevention analyzed data from the Behavioral Risk Factor Surveillance System to examine how different genetic and socioeconomic factors affected the disease's prevalence.

The report credits the decline to reductions in the prevalence of high-risk populations for heart disease, such as smokers, patients with uncontrolled high blood pressure or high blood cholesterol, along with improvements in treatments for heart disease.



In 2010, adults age 65 and older had the highest rates of self-reported CHD, 19.8%. People age 45-64 followed at 7.1%, and individuals age 18-44 years with 1.2%. American Indians/Alaskan Natives reported the highest prevalence of the disease with 11.6%, followed by African Americans with 6.5%. CHD affected 6.1% of Hispanics and 5.8% of Caucasians.

New data from the study revealed how education affected a person's chances of developing CHD. Americans with less than a high school diploma reported the greatest prevalence of the disease with 9.2%, compared with people who graduated from high school at only 6.7%. Those with a college degree were the least affected by CHD, with a prevalence of 4.6%.

Hawaii and the District Columbia had some of the lowest percentages of reported CHD cases. West Virginia and Missouri showed a statistically significant decline in the disease. The report found West Virginia down to 8% from 10.4% and Missouri to 6.0% from 7.7%. Southern states continued to see the greatest prevalence of CHD.

The full report is available at www.cdc.org.

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Proficiency Testing: Making the Grade

When Is Just Getting by Good Enough?

BY BILL MALONE

Next year, the rules governing proficiency testing (PT) in clinical labs will turn 20 years old. Considering the advances that have occurred over the past 2 decades, federal regulators who oversee the program that requires labs to regularly evaluate their performance think it's time for a change. The Centers for Medicare and Medicaid Services (CMS) and the Centers for Disease Control and Prevention (CDC) are now working on an overhaul of PT regulations through an in-depth analysis of the list of required analytes, grading measures, and other standards.

PT experts in the lab community also are eager to see changes in the way labs use and understand PT that go beyond receiving a passing grade for regulatory requirements. They stress that while PT can be an agent for improving lab medicine, it is also a tool that is frequently misunderstood. While laboratorians have discovered that PT results can yield insights for quality management, the unknown differences between PT samples and patient samples can leave labs with questions about their true performance. PT providers must often alter samples during multiple steps of processing, preparation, and storage, so labs cannot always expect to see the same results as they would with authentic patient samples.



See **Proficiency Testing**, continued on page 3

The Challenge of Diagnosing Pulmonary Embolism

What's the Best Role for D-dimer?

BY GENNA ROLLINS

Pulmonary embolism (PE) is a diagnostically challenging condition that carries a high cost if not recognized and treated promptly. Of the estimated 650,000-900,000 individuals with PE in the U.S. each year, as many as 200,000 die from the condition. Even though physicians have a number of tools available to assess patients' risk of PE, accurate diagnosis remains a problem. Among those tools is the D-dimer test, which often is misused and misunderstood as an early rule-out test, leading to further risky, costly, and unnecessary testing and treatments.

"The consequences are very high in both directions. If you fail to diagnose pulmonary embolism, your patient can die. But if you over-diagnose it, then you're committing that individual to a lifetime of thinking they may have had a potentially fatal disease, and putting them on fairly dangerous medications," explained Jeffrey Kline, MD, interim chair of emergency medicine at Carolinas Medical Center in Charlotte, N.C. "When patients are not ruled out early, it usually requires radiation and contrast, both of which can injure the body. But emergency medicine doctors generally underestimate the value of the D-dimer test. They either don't use it or use it in a way that's not going to help them rule-out the case that's right before them."

Making the PE Diagnosis

One of the main challenges in diagnosing PE is that it presents like many other medical problems. Chest pain, dyspnea, syncope, weak-

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Matrix Effects Limit PT's Potential

Proficiency Testing, continued from page 1

As a result, laboratorians need to have a clear understanding about the potential—as well as the limits—of PT. For example, passing a PT challenge should not be confused with excellent clinical performance or accuracy for an assay, explained Gary Horowitz, MD, associate professor of pathology at Harvard Medical School and director of clinical chemistry at Beth Israel Deaconess Medical Center in Boston. “This is a basic misunderstanding about proficiency testing. In most cases, getting a passing grade doesn’t tell you whether you’re doing a great job; it just says that you’re not a statistical outlier compared to your peers. And it’s only good for patient care if your peer group is doing well,” Horowitz said. “On the other hand, if labs dig a little deeper and understand PT’s limitations, there are tremendous opportunities to generate a lot of information from PT data to improve quality.” Horowitz has worked on the College of American Pathologists (CAP) chemistry resource committee, which oversees the CAP PT program for clinical chemistry.

An Easy A?

Under the Clinical Laboratory Improvement Amendments (CLIA) that spell out the requirements for PT in the U.S., labs

must enroll in three PT events a year for each analyte listed in the regulations that the lab performs. Most events consist of five samples, and a lab needs to produce results within range in four out of five to pass. In some cases, such as immunohistochemistry, all five responses must be correct. Occasionally failing is not uncommon, and CLIA allows a lab to fail one out of three events on a rolling basis. In other words, a lab needs to pass at least two in a row after a failure, irrespective of the calendar year.

After an initial failure of two out of three events, or two consecutive events for an analyte or specialty, CMS may impose training and technical assistance if certain conditions are met. However, because CMS sees repeated failures as a possible indicator of more serious quality problems, a failure still keeps labs on edge, as CLIA penalties for repeated failures can mean testing for those analytes is halted. But apart from the stress, what does passing or failing really say about the lab?

According to Horowitz, the answer is—it depends. For many analytes, PT providers grade events based on peer groups—pooling results from a group of labs using the same instrument and reagent. With peer groups, acceptable answers must fall within range of a target value, determined

according to a formula based on the mean of all participant responses. “Less than one percent of laboratories on a statistical basis are going to have outliers, so the grading is actually designed to find laboratories that are performing very poorly,” Horowitz said.

Moreover, with a grade hinging on a group average, how a peer group happens to come together can significantly alter how difficult a particular challenge really is. “If your peer group is very imprecise, and you’re being graded by plus or minus three standard deviations, your values could be pretty far from the mean value and you’d still pass,” Horowitz explained. “On the other hand, methods that are inherently more reproducible have to meet a higher standard.”

PT providers are stuck using peer groups because the matrix effects in PT samples are, for the most part, unknown. Fresh frozen, carefully prepared human serum is hard to handle for PT providers, due to cost and logistics. As a result, PT samples are manufactured in a way that inherently alters their matrices. These alterations cause unknown biases in PT samples that render comparison to either a gold standard, or to other labs using different reagents and instruments, impossible. The behavior of such samples among methods is what’s known as commutability. A commutable sample acts like any real patient sample, something many PT samples can’t live up to.

Understanding commutability enables labs to interpret PT results wisely, emphasized W. Greg Miller, PhD, who currently serves on the CAP chemistry resource committee. Miller and Horowitz coauthored a review article about PT that appears this month in *Clinical Chemistry* (Clin Chem 2011;57:1670–1681). “PT can be a very effective tool for evaluating state-of-the-art, but only if the samples are commutable. If not, then you do not have useful information about methods and method comparison,” Miller said. “It’s important for laboratorians to recognize that you cannot predict, for a given sample, whether or not it will be commutable. So you really have to treat all the samples as if they’re non-commutable, unless you have evidence that conclusively demonstrates that they are.” Miller is a professor of pathology and director of clinical chemistry and pathology information systems at Virginia Commonwealth University in Richmond.

A lack of commutability can lead laboratorians to incorrectly assume that two methods for an assay agree. Conversely, laboratorians can also wrongly attribute discrepancies among methods to the matrix effects of the PT sample, when in fact a real bias exists, noted Robert Rej, PhD, director of clinical chemistry and hematology for the Wadsworth Center, New York State Department of Health. “If method A gives you
See **Proficiency Testing**, continued on page 4

Flaherty Stepping Down as AACC EVP Tenure Marked by Technological Change, Growth

By Genna Rollins

After 20 years at the helm of AACC, executive vice president Richard Flaherty is leaving the association effective December 31. Flaherty, who announced his retirement in February, felt that this was an opportune time to hand off the organization’s leadership mantle. “AACC’s at an inflection point where we have all this new technology, social networking, and more and more services,” he said. “I think we’re at one of those points where we’re going to look back and say this was a key time of change. So it’s probably good after 20 years for someone else with a new way of looking at things to come on board.”

Flaherty leaves AACC in a strong position to take on these new challenges, according to AACC president, Ann Gronowski, PhD. “Rich has taken the association through an amazing period of financial, technological, membership, and international growth. Together, these things have made AACC the strong and well-respected association that it is today,” she observed. “These things were made possible, in part, because Rich created an environment that has led to great trust and openness between the AACC staff and volunteers. He will be sorely missed.”

In reflecting on his tenure, Flaherty noted it was no accident that changes at AACC had mirrored trends in the field. “When we created the Program Coordinating Committee in 1999 we wanted to look at the totality of members’ needs and the totality of what we were providing in order to evaluate where we needed to do better and fill in gaps,” he recalled. “By the same token, we’ve put a lot more systems in place to get feedback from annual meeting attendees so that the organizing committee can get a better sense of what the leanings of the field are as they plan the meeting.”

Flaherty also noted how much over the years AACC has stepped up its collaboration with other organizations. “When I joined the association, there already was an initiative to reach out to other groups. Today, we’re much more outward looking. In terms of formal interactions and relationships, we’re probably tied into 35 to 40 organizations.” Likewise, AACC’s international presence, is much more prominent today through programs like Van Slyke Foundation International Travel Grants, Spanish versions of webinars, and *Clinical Chemistry* content translated into nine languages. “Even 20 years ago, we were more international than members realized. We were known as ‘American’ but in reality we had a very substantial number of international members. Over time, we’ve come to recognize that more and embrace it.”

While he hesitated to point to one milestone achieved in the past 20 years that stands out, Flaherty expressed particular pride in the success of



Thanks, Rich, for a job well done from all AACC members and staff.
Godspeed on the next leg of your journey.

Lab Tests Online, AACC’s public resource on clinical lab testing. The U.S. site launched in July 2001, and by the next year had received a laudable 1 million visitors. By February 2011, that number had soared to more than 100 million. “Not only was Lab Tests Online an outstanding accomplishment as a patient education service, but in my mind it also is very important because it reflects a change in how our members think about their relations with other healthcare groups and with patients. Historically we were in the basement laboratory hidden away. The launch of this website represented the first time we actually started talking to the public, and with that move, a very empowering attitude developed.”

Flaherty expressed appreciation to the AACC staff and board, as well as his family, for their support over the years. For now, he plans to enjoy some down time with his wife, Ellie, and their four children and grandchild, before plotting the next chapter in his professional life. “I’m too young to stop contributing, but I don’t know yet what my next contribution will be. I’m very grateful to the field for the opportunity I’ve had, and I’m going to miss it.”

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AACC

PT Data Essential for Quality

Proficiency Testing, continued from page 3

a value of 100 and method B a value of 120, the initial presumption is often that this is a difficulty with the PT samples, rather than necessarily with the analytical system, even though that might not be the case” Rej said. “Unfortunately, with the huge number of samples needed by each PT provider, and with manufacturers constantly upgrading and changing their methods, it’s just not possible to systematically research every PT fluid and every method for every analyte to discern whether the problem lies with the PT material or with the actual method.”

Near Misses and Fruitful Failures

Even though the dearth of commutable PT samples makes it difficult to compare methods or assess true accuracy, PT data remains a treasure trove for quality management at the level of the individual lab, Miller and his coauthors emphasized in their *Clinical Chemistry* review. “Peer group evaluation provides valuable information to assess quality, verifying that a laboratory is using a measurement procedure in conformance to the manufacturer’s specifications and with other laboratories using the same technology,” the authors wrote.

Speaking at an October 12 AACC webinar, Making Proficiency Testing Work for

You, Horowitz described how PT reports can offer a glimpse of impending quality problems even when the lab is passing its PT challenges. “Even though PT was only designed to identify outliers, that doesn’t preclude us as laboratorians from saying, ‘yes, we had no PT exceptions on this report, but I don’t like being at 1.9 standard deviations. What are we doing differently?’” Horowitz said. “At that point, you graduate from using PT only as a regulatory tool and move into using it as a quality management tool.”

Horowitz offered an illustration from his lab, consecutive PT surveys that all showed passing results. In one example, the surveys boosted his confidence in the lab’s calcium results. The surveys showed that in each challenge, the lab’s results came close to the mean of the peer group—on both sides of the mean—indicating a lack of bias. For bilirubin, however, the surveys picked up a potential problem. Horowitz noticed that in all of the past three surveys, his lab had fallen on the negative side versus his peer group. “I can use this as a warning signal that we haven’t failed yet, but we’re on the verge of failing because there is something going on that’s not quite right,” he said. “Good performance would not have a bias that continues to be on one side of the mean.”

In such situations, Horowitz recommends taking advantage of troubleshooting guides from the lab’s PT provider. He especially likes those from CAP because they display charts representative of various trends of bias and how to investigate them. “Troubleshooting should not be reserved only for when a PT failure occurs,” Horowitz said. “Labs should be examining all of their PT data, even in the absence of failures.” For example, a trend of consistent bias on PT surveys could indicate that the lab has been storing a calibrator improperly. In that case, if the lab doesn’t catch it, results will be consistently off the mark without the lab knowing about it.

When a lab does fail a PT challenge, deliberate and thoughtful troubleshooting is more than helpful. It’s required by CLIA and lab accreditors. Also speaking at the AACC webinar, Judith Yost, MA, MT (ASCP), director of the CMS Division of Laboratory Services, appealed to labs to carefully investigate and document all PT failures. “With an unsuccessful performance, you really need to do a root cause analysis and be sure to document the details of your investigation determining what actually happened,” she said. “Sometimes it can be just an aberration, a random error, but usually not. Something in the laboratory’s systems and processes caused that error to occur.”

After a failure, Horowitz encouraged labs to use a good troubleshooting check-

Time to Tackle Proficiency Testing Regulations What Can Labs Expect from the New Rules?

Lab medicine has changed a lot since 1992. However, the rules for proficiency testing (PT) in the Clinical Laboratory Improvement Amendments (CLIA) have not. Regulators are now in the data-crunching phase of a project to review and revise the CLIA PT regulation based on recommendations from the Clinical Laboratory Improvement Advisory Committee (CLIAC). They are aiming to have the draft proposed rule ready for Department of Health and Human Services clearance next year. Following clearance, the proposed rule soliciting public comment will be published in the *Federal Register*.

Speaking at an October 12 AACC webinar, Making Proficiency Testing Work for You, Judith Yost, MA, MT (ASCP), director of the Division of Laboratory Services at the Centers for Medicare and Medicaid Services (CMS), acknowledged that parts of the regulations are outdated or confusing to labs. For example, the regulations instruct labs to treat PT samples just like patient samples, but labs can get in serious trouble if they refer a PT sample to another lab for confirmatory testing, a common procedure for certain tests. For example, in the case of HIV antibody testing, many labs perform immunoassay screening in house and refer reproducibly reactive samples to reference labs for Western Blot confirmation. In addition to clarifying the language in the regulation for such issues, CMS plans to tackle adding new analytes to the list that require PT and a review of the grading criteria labs must meet.

CLIA lists 83 analytes, but PT providers offer PT for many more than these, and accreditors often require labs to participate. For example, based on a lab’s test menu, the College of American Pathologists (CAP) requires PT enrollment for close to 400 analytes. About 600 others are available, but optional.

CMS is working together with the Centers for Disease Control and Prevention (CDC) to develop an updated list of analytes and a related grading system. “CLIAC has recommended that we look at four things: availability of PT, testing volume for different analytes, clinical relevance, and cost,” said Nancy Anderson, chief of the Laboratory Practice Standards Branch in the Division of Laboratory Science and Standards at CDC. “We came up with a scheme for looking at those criteria in a logical way, so we started by looking at the availability of PT,

and programs that might offer it, even if it’s not already regulated. We considered analytes that are now offered by multiple PT programs, because we’ll be working with them to get data when we get to the point of setting the scoring criteria.”

CDC also examined testing volumes, based on data from Medicare, Medicaid, and private payers. To evaluate clinical relevance of an analyte—the most challenging element, according to Anderson—CDC is reviewing clinical practice guidelines, CDC’s own *Morbidity and Mortality Weekly Report*, as well as FDA risk classification and other data.

Molecular tests will also be on the table when CDC and CMS collaborate to pen draft regulation. “Under CLIA, PT is based on the analyte and is method-neutral,” Anderson explained. “There are some molecular methods that already have required PT in microbiology.”

CDC and CMS will meet with PT providers and other experts for input on how grading criteria should change, according to Anderson. They’ll discuss what the limits should be around the target value for each analyte. Both new analytes being added to the list, as well as those currently in the regulation, will be considered. “We realize that the grading criteria need to be adjusted, because for some analytes they’re too wide, and for others too narrow,” Yost commented.

According to Robert Rej, PhD, director of clinical chemistry and hematology for the Wadsworth Center, New York State Department of Health, federal regulators face a tough challenge to update PT regulation when the field is constantly changing. Rej has served on both CDC and CLIAC groups that have advised regulators on PT. “There have to be a certain minimum number of labs to make it worthwhile to mount a PT program, and the tests themselves must demonstrate clinical utility,” he said. “A test that is highly useful and of critical clinical importance, even though it may not be performed by a large number of laboratories, might be included over a test that is less clinically important, but offered by a larger number of labs. Laboratory medicine is a dynamic field, with tests going in and out of favor, but the total number of tests appears to be increasing at a steady rate. Maintaining such a list for regulatory purposes is certainly not easy.”

list to make sure no stone is left unturned and that the lab documents each investigation consistently. Accreditors often make such checklists available to labs, or labs can develop their own. The December review article in *Clinical Chemistry* offers one example. In addition, Horowitz recommended that labs not only pay attention to the sample deemed unacceptable, but go further and review all five samples for that particular challenge. Often they will display a bias that can give clues as to what went wrong. Even in the case of a truly random error, where no serious systematic underlying problem comes to light, faithful adherence to a troubleshooting checklist will demonstrate to accreditors that the lab took the failure seriously.

PT Without the PT

Even for those analytes for which no formal PT survey is available, CLIA still requires a biannual accuracy check, referred to as alternative assessment. According to Yost, CMS surveyors cite labs 6% of the time for failure to properly perform and document alternative assessment. "That is a pretty significant number," she said. "Labs need to meticulously compare their test menu to their PT enrollment on a regular basis and make sure that those analytes for which no PT is available have that accuracy check documented."

Sometimes even when a PT provider does have samples available for an analyte, not enough labs participate using the same instruments and reagents to meet the 10-participant minimum for a proper peer group. However, even in such cases, a PT provider's data can still be mined for a useful quality check, Horowitz maintained. For example, if the PT provider returns results that are ungradeable due to a lack of participants, a lab can perform an alternative assessment by comparing to another peer group. "Too few participants doesn't necessarily mean that the game is over," he said. "What we've done is go back through the participant summary report and find another method that we thought was comparable because it was an almost identical instrument using the same reagents. Then we did our own evaluation of our results versus those results: our value, minus the mean for the other group, divided by the standard deviation. That is perfectly acceptable on the inspection list as alternative assessment. Of course, what you can't do is look through the surveys and select something just because it agrees with your value so that you look good."

If no survey exists for an analyte, a lab must consider other options. For example, Horowitz's lab offers a qualitative Watson-Schwartz test, used to screen for acute intermittent porphyria. In the absence of any PT surveys, the lab performs an alternative assessment by sending out some of their samples every 6 months to a reference lab and comparing results. For detailed advice on alternative assessment, Miller recommended labs refer to a guideline from the Clinical Laboratory and Standards Institute, GP29-A2: Assessment of Laboratory Tests When Proficiency Testing Is Not Available.

New Approaches for Molecular Dx PT?

The burgeoning field of molecular diagnostics presents unique problems for PT that challenge both regulators and labs.

CLIA regulates PT by analyte, not by method, so regulators would not add molecular methods per se, but are considering adding genetic mutations and other analytes (See Box, p. 4).

Particularly in the area of molecular oncology, PT providers have hit a wall with traditional PT schemes. Providers can send out samples of purified DNA to assess the analytical phase of testing for many molecular tests. However, when it comes to oncology assays like KRAS mutation testing, selection and handling of the tumor specimen is just as critical as the analytic step of identifying the genetic mutation, noted Jeffrey Kant, MD, PhD, past chair of the CAP/American College of Medical Genetics Biochemical and Molecular Genetics Resource Committee. "When you're working with tissue specimens, the samples themselves are much more challenging," he said. "They may have been fixed and embedded in paraffin previously, requiring the lab to go back and rehydrate the tissue and get the nucleic acid out to test it. Others may have a heterogeneity of tumor spread, or necrosis that has set in with poor blood supply." Kant is professor of pathology and human genetics at the University of Pittsburgh Medical Center.

Providing enough high quality, standardized specimens for this kind of testing is a formidable undertaking. And the lack of uniformity of tissue specimens can make it appear there are problems with an assay when there are not, according to Kant. "It may be that in your hospital situation, everything is working great," he said. "But if specimens in a PT survey are suboptimal for reasons the provider can't always control, the overall performance on a survey can actually be poorer than what the general experience is in the community, and so it misrepresents the true quality of testing. Potentially, regulators could look at this and say we're doing a terrible job."

The unique difficulties of tissue specimens also limit the kinds of questions a PT survey can answer, Kant explained. "You really can't test the sensitivity of someone's assay, because you can't reproducibly provide a sample to dozens of labs where you know the percent of the tumor mutation is 10 percent from tissue," he said. "That just isn't going to be possible, biologically."

Until these problems get worked out, Kant sees potential in PT providers breaking out the preanalytical, analytical, and reporting phases of testing to assess the whole as accurately as possible. Although it might not satisfy purists who prefer a more holistic assessment, a piecemeal method currently offers the greatest flexibility, reliability, and utility for a PT program, Kant said.

As powerful molecular tests for oncology increasingly draw the attention of regulators, payers, and the public, PT providers and labs will be under pressure to get it right, Kant commented. "I think this area is going to get more and more visibility because it's a rapidly growing area, and certainly in the case of companion diagnostic tests, there are critical clinical decisions and a significant amount of money riding on decisions to give these therapies or not. That's why my bias is to make sure people can get the right analytic results out of standardized materials, and I know that the molecular oncology committee in CAP has been making efforts in that direction."

When the Truth Is Not Relative

The cost and limited availability of high-quality patient samples means that for the foreseeable future, PT providers and labs will have to continue to make due with materials of unknown commutability for most PT surveys. In the mean time, labs that want to go the extra mile can take advantage of optional, accuracy-based PT surveys for certain analytes. Accuracy-based surveys use validated commutable samples that labs can compare to a gold standard reference method. This way, labs can compare their PT results to a true value and not solely among themselves via a peer-group mean.

At the level of the individual lab, accuracy-based PT demonstrates the real-world performance of an assay for patient care, Horowitz emphasized during the webinar. On a wider scale, since accuracy-based PT does away with matrix-related bias, such programs can reveal the real state of agreement, harmonization, and accuracy across methods.

For this reason, despite the fact that PT providers can only offer accuracy-based surveys on a limited basis, the lab community should take advantage of these programs to power harmonization efforts, Miller said. In their *Clinical Chemistry* paper he, Horowitz, and their coauthors set out several ways in which this could occur.

They encouraged PT providers to share commutable samples in order to reduce costs, and share global summary reports of accuracy-based surveys to advance the field. Manufacturers have a role to play as well. For example, companies could exploit residual commutable samples to calibrate their instruments. "PT/External Quality Assessment providers are in a unique position to add substantial value to the practice of laboratory medicine by identifying analytes that are in need of standardization or harmonization, and by stimulating and sustaining global standardization and harmonization initiatives that are needed to support clinical practice guidelines," the authors wrote.

In October 2010, when AACC convened a conference of stakeholders from around the world on the issue of harmonization, using commutable samples for PT was a central theme (CLN 2010;36:12). PT will continue to have this crucial role, according to Miller. "As the AACC harmonization initiative takes shape over the next several years, the role of accuracy-based PT becomes quite important in assessing the success of any given harmonization activity," he said. "I hope that as our profession understands better the importance of and develops the tools to achieve harmonization, that accuracy-based PT becomes more a part of our usual practice." CLN

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Interpretation of D-dimer Problematic

D-dimer, continued from page 1

ness, and hypotension can be present in PE as well as a great many other conditions. Yet emergency physicians hear the diagnosis clock ticking loudly: the majority of PE-related deaths occur within the first hour, so they want to discern PE from non-PE patients with all due haste.

Various clinical prediction rules have been developed to help physicians risk-stratify patients with suspected PE, including the Geneva Score, revised Geneva Score, Wells Score, and Pisa Model. In general, these schemas assign points to predisposing factors, symptoms, and clinical signs to yield low-, intermediate-, and high-risk probabilities of PE. Depending on where a patient falls in these risk groups, clinical guidelines recommend a range of further diagnostic tests and interventions.

The gold standard PE diagnostic is contrast CT scan of the chest, which has its own downsides and incentivizes physicians to rule-out patients before ordering the test, according to Wesley Self, MD, MPH, assistant professor of emergency medicine at Vanderbilt University School of Medicine in Nashville. “Contrast CT is expensive and involves exposure to radiation and iodine, which can cause renal failure or allergic reactions, so it’s not completely benign,” he explained. “And we’re talking about tens of thousands of people across the country who may be taking these scans, so you’re going to have some complications.”

While some physicians and hospitals adhere strictly to algorithms using one of the risk models, others take a more informal approach that relies on the physician’s judgment. Recently updated American College of Emergency Physicians (ACEP) guidelines found either objective criteria or gestalt clinical assessment appropriate in evaluating suspected PE. The guideline found insufficient evidence to support use of one method over the other (See Figure, p. 7, for a suggested algorithm).

What’s the Pre-test Probability?

Whether one employs formal or informal risk assessment, use of D-dimer hinges on the physician’s determination of a patient’s pre-test probability of having PE. The ACEP guidelines and others, including the American College of Physicians (ACP)/American Academy of Family Physicians (AAFP) and the European Society of Cardiology (ESC), all recommend that a negative D-dimer result in patients with a low pre-test probability of the disease can be used to exclude patients from further PE work-up (See Box, above).

The guidelines diverge somewhat in their recommendations surrounding

patients deemed to be at intermediate pre-test probability. ACEP specified that a negative quantitative D-dimer assay may be used to exclude PE, but did not find strong evidence for this approach. The ESC guideline qualified its endorsement of D-dimer testing in intermediate risk patients to be performed only when using a highly, as opposed to moderately, sensitive assay. The ACP/AAFP extended its D-dimer recommendations only to low-risk patients.

What Does a Positive Result Mean?

Given D-dimer’s crucial place in excluding low- and intermediate-risk patients, physicians’ understanding of the test is paramount, but unfortunately problematic. D-dimer is a product of the degradation of fibrin clots caused by the action of three enzymes, thrombin, activated factor XIII, and plasmin. D-dimer levels rise in the presence of an active clot, so a negative or normal test suggests that either PE or its venous thromboembolism cousin, deep vein thrombosis (DVT), are unlikely. This means the D-dimer test has a high negative-predictive value for ruling-out a clot. However, since D-dimer is very specific for fibrin, it can be elevated in quite a number of conditions besides PE or DVT, including cancer, stroke, infection, liver or renal disease, and aortic dissection, to name a few. This gives the test a poor positive-predictive value, and therein lies the interpretation challenge for physicians.

“People always think that a positive test result means disease is present, but that’s not the case with D-dimer and pulmonary embolism,” said Jeff Ginsberg, MD, FRCPC, professor of medicine in the department of hematology and thromboembolism at McMaster University in Hamilton, Ontario, Canada. “A positive result has no meaning in this situation. It doesn’t make a diagnosis of pulmonary embolism. That’s where people sometimes get confused.”

Because of its specificity for fibrin, none of the guidelines recommend using D-dimer in patients with a high pre-test probability of PE. “The reason we don’t order it in high risk patients is because the test is positive in three-quarters to 80 percent of them. It’s just a waste of time, and in emergency medicine, time is everything,” said Kline.

How to Use D-dimer

Some physicians also tend to view the test as having a dynamic range so that higher concentrations suggest greater risk. Although D-dimer levels have been associated with the severity of PE, most studies have used a 500 ng/L cutoff, with values above that level considered positive. Therefore, most, but apparently not all, clinicians use even

Pulmonary Embolism Guidelines

Several professional organizations have issued guidelines for diagnosing and managing pulmonary embolism (PE), including the American College of Emergency Physicians (ACEP), the American College of Physicians (ACP)/American Academy of Family Physicians (AAFP) and the European Society of Cardiology (ESC).

ACEP

In patients with a low pretest probability for PE, a negative quantitative D-dimer assay result can be used to exclude PE.

In patients with an intermediate pretest probability for PE, a negative quantitative D-dimer assay result may be used to exclude PE.

Fesmire FM, Brown MD, Espinosa JA, Shih RD, et al. **Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department with Suspected Pulmonary Embolism.** *Ann Emerg Med* 2011;57:628–52.

ACP/AAFP

In appropriately selected patients with low pretest probability of deep venous thromboembolism or PE, obtaining a high-sensitivity D-dimer is a reasonable option, and if negative indicates a low likelihood of venous thromboembolism.

Qaseem A, Snow V, Barry P, Hornbake ER, et al. **Current Diagnosis of Venous Thromboembolism in Primary Care: A Clinical Practice Guideline from the American Academy of Family Physicians and the American College of Physicians.** *Ann Intern Med* 2007;146:454–58.

ESC

A negative D-dimer result in a highly sensitive assay safely excludes PE in patients with a low or moderate clinical probability, while a moderately sensitive assay excludes PE only in patients with a low clinical probability. When using a recently introduced two-level clinical probability assessment scheme, a negative D-dimer result excludes PE safely in PE-unlikely patients either by a highly sensitive or moderately sensitive assay.

Torbicki A, Perrier A, Konstantinides S, Agnelli G, et al. **Guidelines on the diagnosis and management of acute pulmonary embolism.** *Eur Heart J* 2008;29:2276–2315.

quantitative enzyme-linked immunosorbent assays (ELISA) and latex-based automated assays with immunoturbidimetric readings as if they were qualitative tests. “My impression is that some doctors think that the higher the D-dimer is, the more likely the patient has PE, without realizing all the studies are just dichotomous—either positive or negative,” explained Francis Fesmire, MD, medical director of the Chest Pain Center at Erlanger Medical Center and professor and clinical research director of the department of emergency medicine at the University of Tennessee College of Medicine in Chattanooga. “I’ve seen doctors order the test and let’s say the result is 510 ng/L, and they’ll say, ‘Oh, it’s minimally elevated, so I’ll ignore it. But that’s not how you utilize the test. It’s either positive or negative.’”

To quell this kind of misunderstanding, and in recognition of the analytical characteristics of the D-dimer test, Massachusetts General Hospital (MGH) in Boston has implemented a third category of test results, according to Kent Lewandrowski, MD, associate chief of pathology and director of laboratory medicine at MGH and associate professor of pathology at Harvard Medical School. “If the cutoff is 500 ng/L, you can get a 490 on one measurement and call it negative, but the next measurement can be 510, and it would be called positive. That’s just due to imprecision of the assay around the cutpoint. So to get rid of that problem, we created a borderline category which spans the cutoff on both sides.”

Physicians also go astray by ordering D-dimer in situations where it is not

needed, or worse, likely to muddle rather than clarify their clinical decision-making. “Probably the biggest problem I see is indiscriminate ordering of D-dimer,” said Fesmire. “It’s pretty routine that in smaller hospitals that transfer patients to us, they will have D-dimer on their cardiac profiles, but that’s doing a disservice to the patient. It’s going to lead to so many false positives in patients who shouldn’t have had the test to begin with.” He suggested that labs that currently include D-dimer in their cardiac panels consider removing the test so that it will have to be ordered separately.

Fesmire applies a Golden Rule for ordering D-dimer tests in suspected PE: “I try to take a step back and ask myself, if I didn’t have this assay would I be ordering a CT scan? If the answer is no, then I don’t order the test,” he explained. While Lewandrowski lauded that attitude, he cautioned that it is unlikely to be widely adopted. “It takes a very mature physician to be able to take that approach. It reflects a lot of experience and introspection; however, I think given the high stakes involved in diagnosing pulmonary embolism and the level of risk aversion of doctors, not many will do that,” he predicted.

Kline actually would like to see more D-dimer tests performed in the work-up of PE, in a bid to reduce the number of low-risk patients sent for CT scan. “A normal D-dimer is stronger evidence of the absence of PE than a normal CT scan. If you compare patients with negative CT scans against those who have quantitative D-dimer results less than 500 ng/L and follow them for three months, fewer of the people with

Considerations for Choosing a D-dimer Test

- ▶ Cutoff determined by clinical studies
- ▶ High diagnostic sensitivity (high negative-predictive value)
- ▶ Acceptable diagnostic specificity
- ▶ Easily performed with rapid availability of results (within 30 min)
- ▶ Good reproducibility around cutoff
- ▶ Quantitative results

Source: *Clin Chem* 2011;57:1256–62. Reprinted with permission.

low D-dimer levels will manifest certain PE than people with negative CT scan," he said. Kline also has proposed a model, the Pulmonary Embolism Rule Out Criteria (PERC), to help deal with low-risk patients. Unlike the aforementioned clinical prediction rules that help doctors risk-stratify patients, PERC, which does not involve D-dimer testing, is aimed at ruling out risk of PE in patients who've already been categorized as low-risk. The ACEP guidelines recommended that physicians consider using PERC in patients with a low pretest probability of PE to exclude diagnosis based on history and physical examination alone.

Overcoming Testing Challenges

Kline suggested that a few bad experiences using D-dimer will sour physicians on the test. "That's because they over-estimate the false-positive rate, and they sort of have this non-scientific, non-quantitative approach that it's positive enough times in patients whom they don't want it to be positive in, that they quit ordering it." He outlined a worst-case scenario that he says has played out in too many emergency departments. The physician orders a D-dimer test in a patient being worked up for PE whom he suspects would not do well in a CT scan. The first blood sample is lost, so he has to reorder the test. "Now, 210 minutes after you ordered the first test and at the end of your shift, the D-dimer comes back above the threshold. So you have to look your partner in the eye and say, yes, we've had this guy here four hours waiting around for the D-dimer, but since it came back positive, you're going to have to follow him through the CT scan."

Both Kline and Lewandrowski suggested that laboratorians could help physicians avoid this type of problem by reminding them that in the majority of emergency patients, D-dimer results will be negative. Lewandrowski also recommended setting up an emergency department-laboratory working group that meets routinely to hash-out issues. "Oftentimes people in healthcare will get furious with another department, but they don't say anything. They'll just say, I'm never ordering that test again," he said. "Left to themselves, they're going to hate you, and the only way you can cure that problem is to form an ongoing collaborative relationship."

Lewandrowski also encouraged laboratorians to work with the emergency department in tightening turnaround times as much as possible. With the exception of Kline, who uses a point-of-care (POC) assay, the other clinicians who spoke with CLN rely on lab-based D-dimer tests, and none are thrilled with the turnaround time, generally reported at 1-1½ hours. However,

they also emphasized that if they are suspicious enough of PE or believe a patient's pre-test probability of PE is on the high end of intermediate, they will not wait on the D-dimer results, but proceed to other diagnostic tests or treatments.

A couple of years ago MGH converted to a POC D-dimer assay and found that it cut turnaround time dramatically, to 25 minutes from about 2 hours (Am J Clin Pathol 2009;132:326-331). The entire hospital has since implemented this assay. "One doesn't like to have two different methods used for the same problem in the same hospital," Lewandrowski observed.

If turnaround time is a serious concern of clinicians, labs might want to look again at the type of assay they're using, Lewandrowski suggested. "If you use a quantitative, whole-blood method, you don't have to spin the sample down and make plasma and you can have the result in 15 to 20 minutes. Whereas, if you have to make plasma, it will take 45 minutes as a minimum turnaround time," he said. Other considerations include the cutoff determined by clinical studies, high sensitivity, and acceptable specificity (See Box, p. 6).

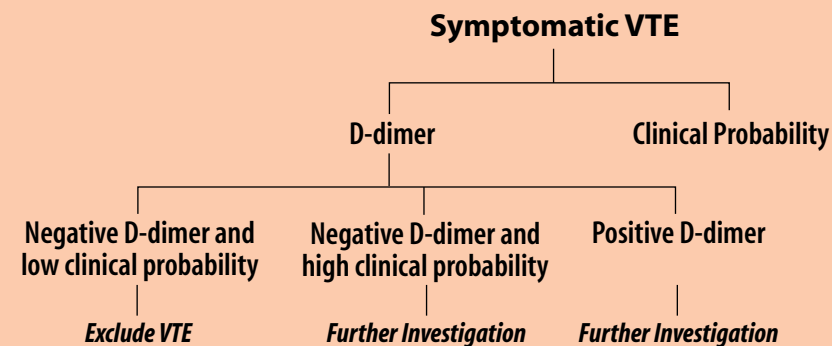
Lewandrowski also suggested that labs collaborate with emergency departments on pre-analytical bottlenecks. Sometimes delays attributed to the lab actually occur in the emergency department. Given the hectic and highly variable workflow there, drawing blood or dispatching tubes to the lab may not always take priority. "Nurses are multitasking and have multiple patients. If a nurse is drawing blood for a D-dimer and the patient next door starts crashing, he's not going to say, I've got to get this sample to the lab. He's going to drop that for the moment and deal with the problem," he observed.

Ginsburg advised that clear interpretive comments would remind physicians to put D-dimer results in the context of patients' clinical presentation. "Even if the test result is off-the-map sky-high, then a comment should be made that this can be seen not only in pulmonary embolism but also a variety of other non-thrombotic conditions, so in-and-of-itself does not make a diagnosis of pulmonary embolism." He also recommended that labs inform clinicians of the type of D-dimer assays they're using as well as how sensitive the assay is, and keep the medical staff apprised of any changes in methods.

Kline also encouraged labs to evaluate D-dimer thresholds in several specific populations, including pregnant women, patients with cancer, and those older than age 70 or who have a low pre-test probability of PE. "The threshold really needs to be examined. In fact, I think it could

An Algorithm for Investigating Suspected Pulmonary Embolism

Numerous algorithms have been proposed for assessing the clinical probability of pulmonary embolism (PE) and using D-dimer results to rule-out PE or pursue further diagnostic work-up. This example for venous thromboembolism (VTE), which encompasses both PE and deep venous thromboembolism, was proposed by Armando Tripodi, PhD.



Source: *Clin Chem* 2011;57:1256-62. Reprinted with permission.

be doubled in all those populations," he said. In a 2005 study published in *Clinical Chemistry*, he demonstrated a progressive increase in circulating D-dimer levels during normal pregnancy, and called for a large management study to establish new thresholds during each trimester (Clin Chem 2005;51:825-829). For now, the ACEP, ACP/AAFP, and ESC guidelines all note the rising D-dimer levels or decreased

specificity of the test in these populations, but none call for revised thresholds.

Kline and others urged laboratorians to collaborate with clinicians to make the best use of D-dimer testing. "They need to be part of the conversation, because we as emergency doctors have an obligation not to subject our patients to the toxicity of CT scanning when we don't need to. Working together we can accomplish that." **CLN**

For Further Information

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Glomerular Filtration Rate

The Importance of Standardized Serum Creatinine in Detecting Kidney Disease

BY W. GREG MILLER, PHD

The Centers for Disease Control and Prevention estimates that more than 20 million Americans age 20 and older may have chronic kidney disease (CKD), a type of kidney disease most commonly caused by diabetes and high blood pressure (1). Despite its high prevalence, many people go undiagnosed because the disease has no symptoms. Furthermore, healthcare providers often fail to identify CKD because patients' serum or plasma creatinine concentrations appear normal even when they have lost significant kidney function. One of the most important indicators of early disease is glomerular filtration rate (GFR), an indicator of how well the kidneys filter waste products from blood. Early detection is important because effective treatments exist that can delay or even avoid the costly progression of the disease to kidney failure.

An equation developed 13 years ago to estimate GFR from the Modification of Diet in Renal Disease (MDRD) Study provided a simple clinical tool to better identify and monitor people with CKD (2) (Table 1). The equation relates creatinine concentration to filtration rate by the kidneys. Because measuring serum or plasma creatinine is a standard component of the basic metabolic profile performed during many routine healthcare visits, the hope was that routine reporting of eGFR would raise awareness of CKD among patients and providers and improve early intervention efforts.

However, the prevalence of the disease continued to soar and place a substantial burden on the healthcare system. In 2000, the National Institute of Diabetes and Di-

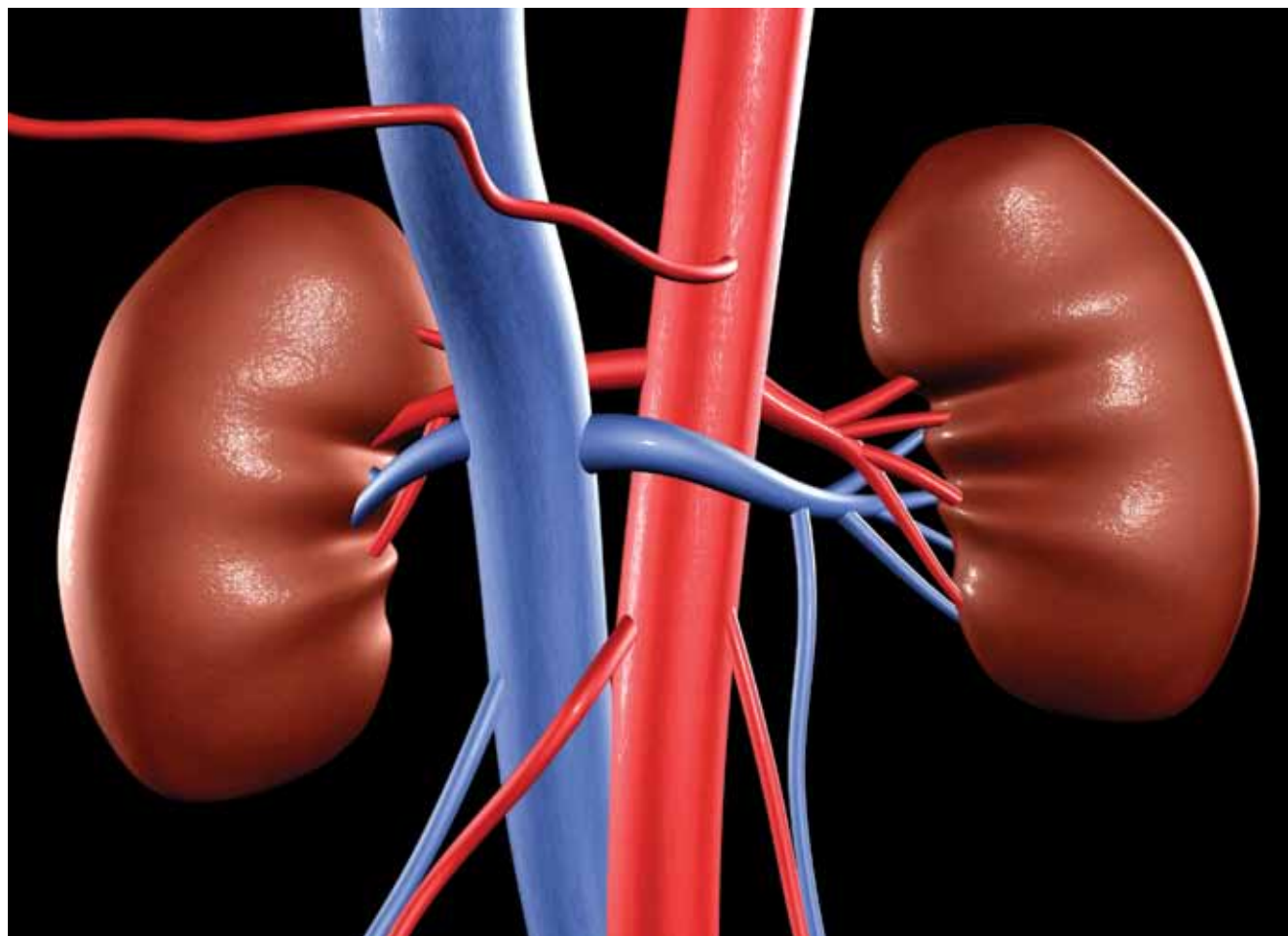
to reduce variability among the different measurement procedures used by laboratories and therefore reduce the variability in eGFR results.

Measuring creatinine and reporting eGFR are critical to promoting early detection and management of CKD. This article will describe the steps laboratories should take to ensure that they are reporting eGFRs according to the most current NKDEP recommendations.

How Sensitive is Creatinine?

One obstacle to using eGFR as an indicator of early kidney disease is that some medical professionals are not convinced that creatinine is a sensitive biomarker for the disease. The National Health and Nutrition Examination Survey (NHANES) data from 1999–2000 showed that 80% of adults with an eGFR <60 mL/min/1.73m² were not identified as having CKD (6). Physicians likely failed to recognize patients' creatinine concentration as an indicator of early kidney disease because the value fell within the so called "normal range." Creatinine reference intervals are based on the central 95% of results for a presumably healthy group of people. This group is likely to include some that have non-symptomatic CKD, as well as a wide range of muscle masses. Consequently, eGFR at the upper limit of a given reference interval is consistent with loss of approximately half of the normal kidney function for many individuals.

Researchers have shown that creatinine, as well as cystatin C and beta-trace protein, are sensitive biomarkers for GFR and that changes in their concentrations have equivalent abilities to reflect deteriorating kidney function and to predict risk for progression of CKD (7,8). The NKDEP recommends that laboratories report eGFR along with creatinine concentrations to provide a better assessment of kidney function. The equations used to calculate the eGFR include age, gender, and race factors that partially compensate for changes in muscle mass and therefore the rate of creatinine production. In comparison to creatinine



gestive and Kidney Diseases established the National Kidney Disease Education Program (NKDEP) to educate providers and the public about CKD. The goal of the program was to improve identification of people with CKD and to promote evidence-based interventions. The NKDEP formed a Laboratory Working Group (LWG) in 2002 to promote routine reporting of eGFR by laboratories and to standardize creatinine measurements. The goal of this group was

AACC, the College of American Pathologists (CAP), and other laboratory and nephrology organizations around the world endorsed reporting eGFR (3), although some individuals expressed opposing opinions (4,5). Based on a May 2011 CAP survey of predominantly North American laboratories, 84% of participants now report eGFR, and of those, 82% report eGFR whenever they provide serum creatinine results.

Table 1

Equations Used to Calculate Glomerular Filtration Rate Using Standardized Creatinine Results

► Modification of Diet in Renal Disease (MDRD) Study Equation (for adults ≥18 years)

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 175 \times (\text{Creatinine})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if Female}) \times (1.212 \text{ if African American})$$

This equation is for creatinine in mg/dL. Numeric values should not be reported above 60 mL/min/1.73 m² because they are excessively biased to lower values.

► Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Study Equation*

eGFR is in mL/min/1.73 m²

Non-African American Female creatinine ≤0.7 mg/dL	$\text{eGFR} = 144 \times (\text{Scr}/0.7)^{-0.329} \times (0.993)^{\text{Age}}$
Non-African American Female creatinine >0.7 mg/dL	$\text{eGFR} = 144 \times (\text{Scr}/0.7)^{-1.209} \times (0.993)^{\text{Age}}$
African American Female creatinine ≤0.7 mg/dL	$\text{eGFR} = 166 \times (\text{Scr}/0.7)^{-0.329} \times (0.993)^{\text{Age}}$
African American Female creatinine >0.7 mg/dL	$\text{eGFR} = 166 \times (\text{Scr}/0.7)^{-1.209} \times (0.993)^{\text{Age}}$
Non-African American Male creatinine ≤0.9 mg/dL	$\text{eGFR} = 141 \times (\text{Scr}/0.9)^{-0.411} \times (0.993)^{\text{Age}}$
Non-African American Male creatinine >0.9 mg/dL	$\text{eGFR} = 141 \times (\text{Scr}/0.9)^{-1.209} \times (0.993)^{\text{Age}}$
African American Male creatinine ≤0.9 mg/dL	$\text{eGFR} = 163 \times (\text{Scr}/0.9)^{-0.411} \times (0.993)^{\text{Age}}$
African American Male creatinine >0.9 mg/dL	$\text{eGFR} = 163 \times (\text{Scr}/0.9)^{-1.209} \times (0.993)^{\text{Age}}$

*for adults ≥18 years

► Modified Schwartz Equation⁺

$$\text{eGFR (mL/min/1.73m}^2\text{)} = 0.41 \times (\text{height / serum creatinine})$$

Height is in cm and creatinine is in mg/dL. eGFR is applicable from 15–80 mL/min/1.73m².

⁺ for children <18 years

concentrations, physicians more easily recognize eGFR as a continuous variable that reflects kidney function.

Limitations in Estimating GFR from Creatinine

Although eGFR is valuable in detecting early kidney disease, creatinine concentration in blood is influenced by factors other than the GFR. In particular, muscle mass, diet, and differences in the rate of kidney tubular secretion all can affect creatinine concentration.

It is important to recognize that eGFR is not the patient's actual GFR. Rather, eGFR is an estimate based on an equation that captures the average GFR for a large number of persons. An individual's eGFR can be different from their actual GFR based on differences between that individual's age, gender, race, or weight and the average for the persons used to generate the equation. In addition, the relationship between creatinine and GFR only is reliable for patients in a stable metabolic state. In other words, eGFR is less useful in pregnant women, hospitalized patients, and in individuals with acute or prolonged illnesses.

Furthermore, any condition that affects

muscle mass or muscle metabolism will decrease the reliability of creatinine to assess kidney function. For example, frail elderly, critically ill, obese, and cancer patients will be affected, as well as people who have had an amputation, are immobile, or participate in strenuous exercise or bodybuilding. Creatinine also is a less useful biomarker in individuals with vegan diets or who take creatinine supplements. In addition, creatinine concentration increases following consumption of meat. Finally, creatinine is poorly correlated with GFR in conditions associated with increased tubular secretion or extra-renal elimination of creatinine, such as severe CKD.

New Equations for eGFR

Five years ago, the NKDEP LWG published recommendations for laboratories reporting eGFR and for standardizing creatinine measurements (9). All large, global in vitro diagnostic companies have now recalibrated their routine creatinine measurement procedures to be traceable to an isotope dilution mass spectrometry (IDMS) reference measurement procedure. Most whole-blood measurement systems also have been calibrated to IDMS. With this standardiza-

Table 2

NKDEP Recommendations for Dosing Medications

The following recommendations are for adults and are based on standardized creatinine measurements.

- Use eGFR or eCrCl for drug dosing.
- If using eGFR in very large or very small patients, multiply the reported eGFR by the estimated body surface area (BSA) in order to obtain eGFR in units of mL/min:

$$\text{eGFR (mL/min/1.73m}^2\text{)} \times \text{estimated BSA} = \text{eGFR (mL/min)} \text{ for drug dosing}$$

Note: BSA can be obtained from a standard nomogram or can be calculated using equations such as:

$$\text{m}^2 = \sqrt{\frac{\text{Height (in)} \times \text{Weight (lb)}}{3131}}$$

IMPORTANT CAUTION: Physicians should assess kidney function using alternative methods, such as measured CrCl or measured GFR when prescribing drugs with narrow therapeutic or toxic indices, when eGFR and eCrCl provide different estimates of kidney function, or for individuals in whom any estimates based on creatinine are likely to be inaccurate. (See section on Limitations in Estimating GFR from Creatinine).

tion, the need for new equations for calculating eGFR became clear for reasons described below, and the LWG has recently focused on this area for both adult and pediatric populations.

Adult equations. The authors of the original MDRD Study equation for adults age 18 or older developed it using a routine creatinine measurement procedure that had a positive bias compared to the IDMS reference measurement procedure. In fact, at the time, all routine creatinine measurement procedures had positive biases of varying magnitudes compared to the IDMS procedure. Not unexpectedly, this variability in bias produced variability in patients' eGFRs. When the NKDEP LWG standardized creatinine measurement procedures, the results were typically 5–30% lower (10), causing a positive bias in eGFR calculated using the original MDRD Study equation or any other older equation. Following publication of the LWG's recommendations, researchers re-expressed the four-variable MDRD Study equation for eGFR using serum creatinine standardized to the reference measurement procedure (11) (Table 1).

Of note, the NKDEP recommends against laboratories reporting MDRD equation values >60 mL/min/1.73m², because these values are negatively biased and have increased variability. This variability is related to the proportionally larger influence of small calibration biases and the

poorer precision of creatinine methods at lower concentrations, as well as to greater imprecision in the measured GFRs in the population used to develop the equation.

The Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration has published a new equation to estimate GFR in adults using standardized creatinine measurements and the other variables in the four-parameter MDRD equation (12) (Table 1). The CKD-EPI equation was developed from a much larger cohort of patients, including healthy and CKD individuals, but still relatively few elderly people. eGFRs calculated from the CKD-EPI equation show consistent performance across studies and subgroups defined by age, gender, race, diabetes, transplant status, and body mass index. The equation also has improved accuracy, particularly for GFRs >60 mL/min/1.73m², making it suitable for reporting numeric values in this higher GFR range. The variability of results at higher eGFR values is slightly better for the CKD-EPI equation than for the MDRD equations, but it remains a factor when interpreting results. It is not clear if an upper limit for numeric values should be used for the CKD-EPI equation. However, the influence of imprecision at lower creatinine concentrations corresponding to more normal GFRs will contribute to increased imprecision in the eGFR value and needs further investigation. Additional information on both equations is available

Table 3

Calvert Equation

$$\text{Total Drug Dose (mg)} = \text{Target AUC} \times \text{GFR (mL/min)} + 25$$

This is the most common method for calculating dosage of the chemotherapeutic agent, carboplatin. The total drug dose is based on the area under the desired concentration versus time curve (AUC) for the drug. The value for GFR should not exceed 125 mL/min irrespective of the equation used for its estimation.

on the NKDEP website under the Laboratory Professionals section.

Pediatric equations. Investigators from the Chronic Kidney Disease in Children (CKID) group developed a revised Schwartz equation (13) for use with standardized creatinine results (Table 1). As with the adult equations, all older pediatric equations for estimating GFR give erroneously high values and should not be used with standardized creatinine results. The CKID investigators also are developing other equations that will likely use creatinine and cystatin C values; however, the NKDEP LWP cannot recommend laboratories use these equations until cystatin C calibration standardization has been accomplished. (See section on Cystatin C: An Alternative to Creatinine).

Using eGFR to Estimate Drug Dose

eGFR values also are important for dosing medications that are excreted by the kidneys, especially in patients with impaired kidney function. Labeling guidelines from the Food and Drug Administration (FDA) provide adjustments of drug dosages for these patients. Current FDA labeling recommends either creatinine, measured GFR, or estimated creatinine clearance (eCrCl) calculated from the Cockcroft and Gault (C-G) equation for most dosages of these drugs. However, the creatinine measurement procedures used by pharmaceutical companies to develop recommendations for drug dosing were likely calibrated differently than the one used to develop the C-G equation in 1976. Furthermore, the C-G equation estimates creatinine clearance, not GFR, and researchers have shown that the MDRD Study equation gives results that are closer to a measured GFR than does the C-G equation (2).

Clearly, FDA's labeling recommendations for dosing these medications need to be updated to take into account standardized creatinine measurements. Resolution of this discrepancy is still ongoing. The basic issue is that standardized creatinine results today are typically 5–30% lower than older methods. The recommendations included in drug product labeling are based on older equations and non-standardized creatinine measurement procedures that had a positive calibration bias, as well as variability in the bias itself among different measurement procedures. Consequently, the NKDEP LWG recommends not using an equation to back calculate a value that could be used in the C-G or other older estimating equations.

A recent report simulated dose determinations for 15 drugs using both the re-expressed four-variable MDRD and the C-G equations to estimate eGFR and eCrCl, respectively (14). In the study, the researchers compared dosages of the drugs based on standardized creatinine results to those calculated from measured GFRs in 5,504 adult patients. For most patients and drugs examined, there was little difference in the drug dose that patients would receive using either equation to estimate kidney function; however, the discordance rates increased for drugs with dose adjustments based on narrower intervals of kidney function. Based on these results, as well as the difficulty establishing the calibration condition of creatinine measurement procedures used to develop the labeling for drug-dose recommendations, the NKDEP

recommends that either equation may be used to determine drug dosing in patients with impaired kidney function unless the drug has a narrow index for kidney toxicity or the patient's condition is such that creatinine is not a reliable measure of kidney function (Table 2). More details are available on the NKDEP website.

Of particular note, however, is an FDA advisory on the chemotherapeutic agent carboplatin. The FDA in October 2010 notified the oncology community of a potential safety issue related to the dosing of this drug, which is used to treat advanced ovarian and other cancers and has a narrow index for kidney toxicity (15). The most common method for calculating dosage for this drug is the Calvert equation (Table 3), in which the drug dose is based on the area under the desired concentration of drug versus time curve (AUC). In its advisory, FDA warned oncologists that GFR estimated from a standardized creatinine result should not exceed 125 mL/min, irrespective of the equation used to calculate the value. This eGFR limit is intended to prevent excessive doses of the drug, and consequently kidney damage, for people with relatively normal kidney function.

Specificity of Creatinine Measurement Procedures

While standardization of serum creatinine measurement procedures has improved the quality of eGFR calculations, it does not address limitations of a measurement procedure caused by interfering substances. To gain a better understanding of the influence of interfering substances on creatinine measurement, the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) Working Group on Glomerular Filtration Rate Assessment and the NKDEP LWG investigated potentially interfering substances in a panel of 365 individual clinical samples, representing 19 different disease categories and a healthy control group. The study also included sera supplemented with acetoacetate, acetone, ascorbate, and pyruvate. Investigators measured serum creatinine by four enzymatic and three Jaffe procedures, as well as an IDMS measurement procedure that was used to determine biases for each method. The results showed differences in both magnitude and direction of bias among measurement procedures, whether enzymatic or Jaffe. Furthermore, although the influence of interfering substances was less frequent with the enzymatic procedures, no procedure was unaffected (16).

Cystatin C: An Alternative to Creatinine

Another excellent biomarker for kidney disease is cystatin C, which also is a risk factor for cardiovascular disease, one of the major complications of CKD (17). Nucleated cells throughout the body produce the protein; however, it is unaffected by muscle mass and age > 1 year. The primary limitation to using cystatin C in clinical practice has been lack of standardized measurement procedures (18,19). Consequently, equations that have been developed to estimate GFR from cystatin C are only suitable for that specific measurement procedure and a population similar to that used to develop the equation.

The IFCC Working Group on Standardization of Cystatin C has developed a reference material that is now available

from the Institute for Reference Materials and Measurements in Belgium (20). This serum-based reference material is in the process of being characterized for commutability among commercial measurement procedures with the goal of enabling manufacturers to standardize calibration traceability to this reference material. The working group also is developing a new, more universal equation using a large and diverse population to estimate GFR from standardized cystatin C results.

When these standardization activities are complete, cystatin C will be a valuable addition to the tests available to monitor kidney disease. It will be particularly useful for pediatric and elderly patients and those in whom the relationship between creatinine and kidney function is compromised.

Strides in CKD Detection

The economic burden of CKD on the healthcare system will continue to grow, especially from the increasing prevalence of diabetes in the U.S. population. The improvements resulting from standardization of creatinine have made the equations used to calculate eGFR better clinical tools. While there are still imperfections in these tools, the laboratory has an essential role in improving detection of early kidney disease in at risk patients. **CLN**

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Next Month
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A Look
Ahead
for 2012

Clinical Significance of Analytes in Non-standard Body Fluids

Each month, AACC's Expert Access Live Online Program features a different hot topic. Visit AACC's website for more information and an archive of past presentations.



The following is an excerpt from the October 2011 presentation by Deanna Franke, PhD, DABCC, MT (ASCP), a clinical scientist at Pathology Consultants of South Broward, LLP in Hollywood, Fla.

We get a lot of requests for electrolytes in various non-standard body fluids. Is there clinical utility?

According to CLSI Guideline C49-A, there is limited, documented evidence for measuring various electrolytes, including sodium, potassium, chloride, bicarbonate, calcium, and magnesium in non-standard body fluids (NSBF). Fluid concentrations generally are similar to ionic activity in plasma and add little to diagnostic evaluation, patient management, and prognosis. As laboratorians, we also need to be keenly aware of issues related to how electrolytes, as water soluble substances, are distributed in body water and how they are measured, such as by direct versus indirect ion selective electrodes. High protein and lipid content reduces the content of water in a sample, thereby distributing electrolytes in a smaller volume. This exclusion effect can result in falsely low values and does not reflect true electrolyte physiologic activity.

So for this example, measuring electrolytes in a chylous effusion makes it difficult to accurately assess the true patient picture and limits clinical utility of NSBF electrolyte measurements. Using indirect ion selective electrode methods to measure electrolytes in samples with high protein/lipid content can also lead to potentially low values, because it requires sample dilutions. Other points to consider include: 1) Asking about sweat chloride. Quantitation of chloride in sweat for cystic fibrosis using chloridometer is well-developed and standardized. In my opinion, by definition, sweat would not be considered a NSBF for electrolyte (chloride) measurement. 2) Quantitating sodium, potassium, and further osmolality in liquid stool. Using liquid supernatant without dilution is essential in differential diagnosis of diarrhea to distinguish between osmotic versus secretory causes. After measurement of osmolality and electrolytes, calculation of stool osmotic gap can be a significant clinical tool in proper diagnosis and clinical management. 3) Referencing published works on research use-only applications for electrolyte measurements in body fluids. Within our healthcare institution, we discontinued NSBF electrolyte testing for regulatory and clinical reasons. When we followed-up with doctors who ordered the test, we found there was no clear clinical benefit for measuring electrolytes.

What is the role for molecular markers such as KRAS and LOH with respect to the diagnosis of pancreatic cystic lesion on cyst fluid aspiration? Is this role likely to expand? What data would be

needed to support that expansion?

From what I understand, KRAS and LOH (loss of heterozygosity) molecular testing can be ordered on pancreatic cyst fluid to assist in differentiating benign and potentially malignant cysts. Personally, I have not had the time to adequately investigate pancreatic cyst fluid molecular testing, but I did come across a recent, well-written review that discusses diagnostic utility of imaging, biochemical marker (CEA, CA 19-9, CA 15-3, amylase, lipase) and DNA molecular analysis (J Gastrointest Liver Dis 2011;20:175-180). I am in complete agreement with this review that the role for these tests in clinical diagnosis of malignant cysts will expand. However, further studies need to be conducted to validate biochemical and molecular testing, determine useful cutoffs, and develop a best practice testing algorithm for diagnosis and management.

Most tests that you presented are measured on routine chemistry analyzers or immunoassay platforms. For tests performed on routine chemistry analyzers, which preliminary studies would be required to ensure the fluid is within the linearity range?

Here is an example situation. You get a request for Alpha-fetoprotein (AFP) in cerebrospinal fluid (CSF). Two questions come to mind: 1) How do I know if my method can accurately measure AFP in CSF matrix and 2) Can I use the same AMR used for serum? Although this presentation did not cover method validation studies, in this example, I would suggest starting with CSF and measure AFP (background). Using a serum sample with a high/elevated measured AFP, you then can perform serum/CSF mixing studies. This allows you to determine background (CSF only) and get a sense of how AFP in serum (FDA-approved matrix) is recovered when diluted with CSF (non-FDA approved = NSBF). You may also be able to try and spike in AFP calibrators or known standards into CSF and determine if AFP is recoverable within the linearity range of the assay. This exercise can be duplicated on routine chemistry analyzers as well.

Does your lab perform most of this testing with manufactured reagents on common analyzers, or do you perform a lot of LDTs for the non-standard fluids?

Yes and Yes. In general, methods and analyzers used for blood, plasma, and urine can be validated for use with NSBFs. Measuring analytes in NSBF are lab-developed tests (LDTs) and require validation. By definition, you are not following FDA-

approved manufacturers' recommendations and are using a body fluid not validated by the vendor. This leaves the laboratory responsible for ensuring assays can be used for alternative sample matrices.

How do you handle proficiency testing for the various fluid components since a number of analytes are not commercially available in matrix-specific samples?

A number of national reference laboratories offer NSBF testing. Sample exchanges with reference laboratories or with a laboratory that has validated the NSBF is the only other option besides using commercially prepared proficiency testing materials. It is important to understand and know the comparative method. Ideally, you want to exchange with a lab that is using the same method. Recognized commercially prepared proficiency testing materials are not matrix specific but are sufficient to meet regulatory standards and requirements for ongoing proficiency testing. If national reference laboratories are not offering this test, you may want to consider collaborating with physicians who are ordering the test to understand how they use

the information and determine if the test/result is even clinically useful.

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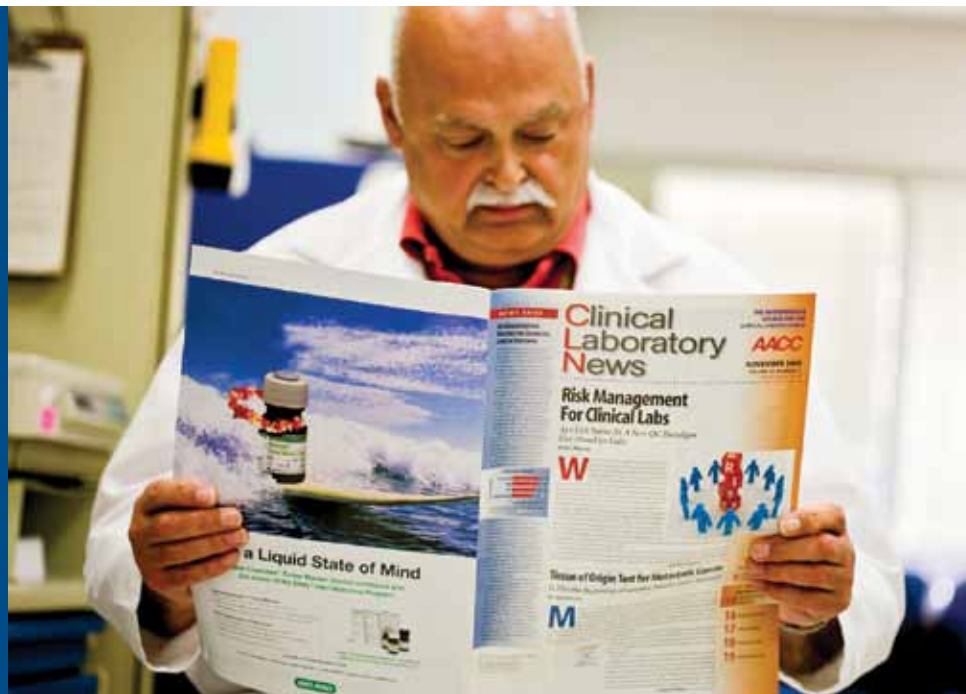
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Congress Ponders Lab Cuts To Pay Docs, Trim Deficit

More cuts to the lab fee schedule are once again on the table, this time as part of a strategy to fix the much maligned sustainable growth rate (SGR) system, Medicare's formula for paying physicians, as well as in response to the July \$1.5 trillion deficit-reduction law that raised the nation's debt ceiling.

Established in 1996, the SGR formula is widely recognized as deeply flawed, and Congress has had to act each year to intervene to prevent massive cuts to physicians under Medicare. Now Congress wants a permanent fix to the SGR problem, but needs to come up with money elsewhere to keep physician payment at a reasonable level. The Medicare Payment Advisory Commission (MedPAC), an advisory group to Congress on Medicare payment, offered several scenarios to Congress. Under one proposal, cuts in lab reimbursement would account for 9% of the required offset savings. It would also cut payments for laboratory services that are included in the Medicare physician fee schedule. The proposal would mean a 10% cut to labs for 10 years, totaling \$21 billion.

The American Clinical Laboratory Association (ACLA) wrote to MedPAC Chairman Glenn Hackbarth to protest the recommendation, noting that lab tests account for only 1.6% of Medicare spending, making the industry a poor target for cuts. "Payments have been reduced by about 40% in inflation-adjusted terms over the past 20 years. In addition, the Affordable Care Act cut Medicare reimbursement for

laboratory services by an additional 19% over the next 10 years," wrote ACLA President Alan Mertz.

Mertz also noted that lab fee schedule cuts are being considered by the so-called super-committee, the Joint Select Committee on Deficit Reduction. The super-committee must identify trillions of dollars in cuts under a last-minute deal cut by President Obama and Congress that allowed an increase in the U.S. debt ceiling. At *CLN's* press time, the super-committee had not yet met its December 2 deadline to submit a report and legislative language to the president and Congress. Once the super-committee submits its report, Congress has until December 23 for both houses to vote on a common bill. If Congress fails, \$1.2 trillion in automatic cuts kick in, affecting discretionary spending across the board, and including defense and Medicare providers.

FDA, CMS Launch Parallel Review Initiative

In an effort to reduce the time between Food and Drug Administration (FDA) approval of a device and a Medicare payment decision on the same device, FDA and the Centers for Medicare and Medicaid Services (CMS) have launched a pilot parallel review program.

The FDA and CMS are now accepting submissions for concurrent review and have issued procedures for voluntary participation and guiding principles that the agencies will follow during product review.

Often, device sponsors focus solely on obtaining FDA approval, only to find that

Medicare coverage is not automatically forthcoming. Both agencies rely on clinical data in reaching their decisions, and while they have distinctly different regulatory responsibilities, parallel review can reduce the time between FDA approval and Medicare national coverage determinations, according to the FDA.

The voluntary pilot program, which will last for up to 2 years with the possibility for extension, will not change the existing separate and distinct review standards for FDA device approval and CMS coverage determination. It is only available for qualifying new medical device technologies and will only accept five devices per year.

In September 2010, FDA and CMS announced their intention to implement a parallel review process, and received 37 public comments, which can be found in the public docket.

More information is available in the *Federal Register* notice, www.gpoaccess.gov/fr/.

Accountable Care Organization Final Rule Released

The Department of Health and Human Services (HHS) released final rules for its Shared Savings Program, part of the Patient Protection and Affordable Care Act. The final rule explains how healthcare providers can form voluntary Accountable Care Organizations (ACO) that cooperatively manage care for Medicare patients beginning next year. Providers that form ACOs will get to share in financial savings with Medicare as long as they also meet quality of care performance standards. Financial savings are benchmarked against what Medicare would usually pay for an episode of care. Inspired by models such as Mayo Clinic and Geisinger Health System, the idea is that providers can hold down costs and improve quality at the same time due to the inherent benefits of coordinated care.

The final rule made several concessions to healthcare providers after some 1,300 comments that followed a draft rule issued in March 2011. Among other concerns, providers were worried that while they could keep up to 60% of the money they saved Medicare, substantial penalties would be levied for failure.

According to the Kaiser Foundation, key changes in the final rule made to appease providers include: providers will be able to participate in an ACO without risk of losing money; quality measures that ACOs will have to meet to qualify for performance bonuses were reduced from 65 to 33; community health centers and rural health clinics will be allowed to lead ACOs; and groups may now apply throughout the 2012 calendar year.

Federal savings from this initiative could be up to \$940 million over 4 years, according to HHS, and to get things started, the government will advance up to \$170 million to physician-owned and rural providers to help them start ACOs.

The Shared Savings Program final rule is available from HealthCare.gov, www.HealthCare.gov/law/resources/regulations/index.html.

States, Vendors Agree on Standards to Connect EHRs

Aiming for plug-and-play connectivity among electronic health records (EHR) and health information exchanges (HIE), a collaborative of state governments and EHR vendors issued an initial set of technical specifications to standardize connections between healthcare providers, health information exchanges (HIE), and other data-sharing partners. The EHR/HIE Interoperability Workgroup built upon existing published standards for interoperability from the Office of the National Coordinator (ONC) in the Department of Health and Human Services. The group's new specifications describe how encrypted health information can be transmitted over the Internet and how clinicians can query an HIE for relevant data on a specific patient.

The New York eHealth Collaborative helped form the group, which is comprised of its federally designated counterparts in seven states—California, Colorado, Maryland, Massachusetts, New Jersey, New York, and Oregon—and eight EHR vendor members, including Allscripts, eClinicalWorks, e-MDs, Greenway Medical Technologies, McKesson Physician Practice Solutions, NextGen Healthcare, Sage Healthcare Division, and Siemens Healthcare. In addition, there are three HIE services vendors participating, including Axolotl, InterSystems, and Medicity.

The new specifications are available at the organization's website, www.interopwg.org.

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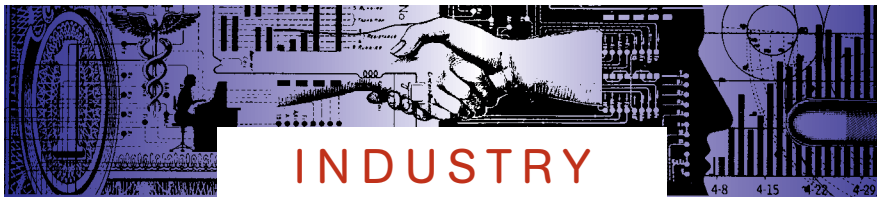
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INDUSTRY

Abbott to Split into Separate Companies

In a major announcement, Abbott announced it will split into two separate, publicly-traded companies. One company will concentrate on diversified medical products, and the other will focus on research-based pharmaceuticals. The diversified medical products business, which includes the branded generic pharmaceutical, medical devices, molecular diagnostics, and nutritional businesses, will keep the Abbott name. The research-based pharmaceutical company, which includes the firm's current portfolio of proprietary pharmaceuticals and biologics, will be named at a later date. "Today's news is a significant event for Abbott, and reflects another dynamic change in our company's 123-year history, strengthening our outlook for strong and sustainable growth and shareholder returns," said Miles White, CEO and chairman of Abbott. The split will take the form of a tax-free distribution to Abbott shareholders of new, publicly-traded stock for the new pharmaceutical company. The stock distribution ratio will be determined later. Abbot has not confirmed when the split will take place.

Siemens, Illumina Team on Infectious Disease Testing

Siemens Healthcare Diagnostics and Illumina have joined forces to use next-generation sequencing for identifying infectious diseases and potential treatment paths. The companies also hope to make Siemens molecular HIV tests compatible with Illumina's recently launched MiSeq next-generation sequencing platform. "Next-generation sequencing is a transformational technology that we believe will significantly impact clinical diagnostics over the next five years," said Michael Reitermann, CEO of Siemens Healthcare Diagnostics. "Our partnership with Illumina brings together two innovation leaders to set a new standard of care in the next wave of clinical diagnostics and personalized medicine."

Bristol Myers-Squibb, Saladax add Ortho-Clinical Diagnostics To Companion Dx Deal

Bristol Myers-Squibb and Saladax Biomedical have expanded an agreement covering companion diagnostics by adding Johnson & Johnson's Ortho-Clinical Diagnostics. The three partners will work together to develop and obtain regulatory approval of certain diagnostic assays. Saladax and Ortho-Clinical have a separate agreement to commercialize assays resulting from the deal. Saladax and Bristol-Myers Squibb originally teamed in May 2010 to develop clinical diagnostic tests for certain drug compounds in Bristol Myers-Squibb's pipeline.

Oasis Licenses Technology To Develop Alzheimer's, Parkinson's POC Tests

Oasis Diagnostics has licensed technology from two researchers in an effort to develop saliva-based point-of-care (POC) diagnostics for Alzheimer's and Parkinson's diseases. Oasis will develop POC tests using

eight proprietary biomarkers found in saliva for the diagnosis, prognosis, and monitoring of patients with Alzheimer's and/or Parkinson's. The company will develop the tests on its Verofy POC platform that uses immunochromatographic test strips.

Roche Licenses Technology to Develop New Sequencing Platform

In an effort to develop a new DNA sequencing system, Roche has licensed technology from the Biodesign Institute at Arizona State University (ASU) and the Columbia University Nanoscience Center. Stuart Lindsay at the Biodesign Insti-

tute and Colin Nuckolls from Columbia University developed the technology being licensed, which features "specialized approaches" for DNA base sensing and reading. According to Roche and Arizona Technology Enterprises, the tech transfer arm of ASU, the technologies decode the DNA bases as they pass through a chip containing semiconductor-based nanopores. The licensing deal also builds on an ongoing relationship between Roche, its sequencing technologies subsidiary 454 Life Sciences, and IBM to develop a single-molecule, nanopore-based technology that will directly read and sequence human DNA.

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DIAGNOSTIC

Ovarian Cancer Outcomes, BRCA1/2 Expression Linked

An analysis of outcomes tied to *BRCA1* and *BRCA2* mutations in women with ovarian cancer found that *BRCA2* mutation, but not *BRCA1* deficiency, was independently associated with improved survival, improved chemotherapy response, and genome instability, compared with *BRCA* wild-type (JAMA 2011;306:1557–65). The authors conducted the study because there is conflicting data about the outcome of *BRCA*-deficient patients after ovarian cancer develops. Some investigators have reported that patients with *BRCA1/2* germ line mutations typically have a better clinical course, but others have found the opposite. The authors also wanted to elucidate more thoroughly the effect of *BRCA1/2* mutations on platinum-based chemotherapy response.

The observational study, conducted by an international consortium of researchers, involved analysis of genomic and clinical data from 316 high-grade serous ovarian cancer patients in The Cancer Genome Atlas (TCGA) project. All the cancer specimens reported in the TCGA database had been surgically resected before treatment started and were high-grade, and 96% were stage III or IV. The researchers looked at both primary response to chemotherapy and platinum-free duration after treatment. Cases were considered primary sensitive if the patient had a complete or partial response to adjuvant chemotherapy as notated in the TCGA database. Patients with stable or progressive disease were categorized as primary resistant.

Overall, 225 cases were classified as primary sensitive and 36 were primary resistant. The researchers excluded another 55 cases that lacked data on primary response to adjuvant therapy. *BRCA2* mutation carriers

had a 5-year survival rate of 61%, in comparison to 25% in wild-type *BRCA* cases. In contrast, there was a nonsignificant difference in survival between *BRCA1* and wild-type *BRCA* cases. In comparing *BRCA1* and *BRCA2* mutation carriers, the researchers found that 44% of *BRCA2*-mutated cases remained progression free 3 years after surgical resection, compared with just 22% of *BRCA1*-mutated cases. *BRCA2*-mutated cases also had significantly longer platinum-free duration following chemotherapy versus those with *BRCA1*.

Using whole-exome deep-sequencing data, the researchers found *BRCA2*-mutated cases were highly enriched with hypermutated samples in comparison to *BRCA1* cases. They also identified 51 genes that were differentially mutated between *BRCA2* and wild-type cases.

S. gallolyticus Linked To Colorectal Cancer

A meta-analysis by Dutch researchers indicates that *Streptococcus gallolyticus*—also known as *S. bovis*—infection is strongly associated with colorectal cancer (CRC), with a reported prevalence from 30–77% that markedly exceeds estimated CRC prevalence in the general population of 20–25% (Clin Infect Dis 2011;53:870–78). Based on this finding, the authors urged further research into this gram-positive bacterium as a means of detecting occult CRC.

The investigators also called for consistent use of a nomenclature first proposed in 2003 for the *S. bovis* species. Historically, this bacterium had been considered a single species, *S. bovis*, associated with infective endocarditis in humans. However, over time, three phenotypic designations, *S. bovis I, II/1*, and *II/2* had been described. Then in 2003 a proposal was made for a new nomenclature, with *S. bovis I* and *II/2* reclassi-

fied as *S. gallolyticus* subspecies *gallolyticus* and *pasteurianus*, respectively, and *S. bovis II/1* reclassified as *S. infantarius* subspecies *infantarius* and *coli*, respectively.

The meta-analysis indicated that *S. gallolyticus* has an “unambiguous association” with CRC, with a pooled odds ratio of 7.26 among infected patients. In addition, CRC was more prevalent in patients with *S. gallolyticus* infective endocarditis than infection at other sites, with a pooled odds ratio of 3.72. The researchers speculated that superior binding to collagen I on heart valves could be the mechanism behind the increased rate of infective endocarditis and that *S. gallolyticus* strains may have a competitive advantage in colonizing collagen-rich premalignant or malignant sites in the intestine.

Homocysteine Improves Cardiovascular Risk Prediction

New research suggests that elevated homocysteine levels predict future cardiovascular disease (CVD) and coronary heart disease (CHD) events in disparate adult populations, and that adding homocysteine levels to the Framingham risk score (FRS) significantly improves risk

prediction, particularly in individuals at intermediate risk for CHD events (J Am Coll Cardiol 2011;58:1025–33). Although the authors called for more research involving homocysteine and CVD risk, they suggested that elevated homocysteine levels should be considered a biomarker for elevated CVD risk, rather than a causally related modifiable risk factor.

The findings come from a post hoc analysis of data sets from two studies, the Multi-Ethnic Study of Atherosclerosis (MESA) and the National Health and Nutrition Examination Survey III (NHANES III). Homocysteine levels >15 μmol/L significantly predicted CVD and CHD events in the MESA trial, and CVD and CHD mortality in NHANES III, after adjustments for traditional risk factors and C-reactive protein. Addition of homocysteine level to MESA significantly reclassified both the overall and intermediate risk populations from both MESA and NHANES III.

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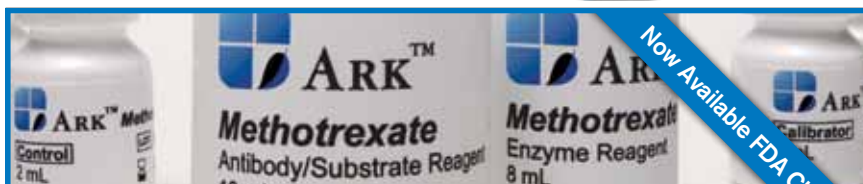
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NEWS FROM THE FDA

Acute Myeloid Leukemia Test Cleared

Abbott has received FDA clearance for its new test that helps predict prognosis of patients with acute myeloid leukemia (AML). The Vysis EGR1 FISH Probe Kit is based on FISH technology and detects a chromosomal deletion in bone marrow that is usually associated with an unfavorable prognosis for AML patients.

Siemens Fully Automated Vitamin D Total Assay Gets Nod

FDA has cleared Siemens Healthcare Diagnostics vitamin D total assay for use on the ADVIA Centaur/XP Immunoassay Systems. Siemens ADVIA Centaur Vitamin D Total assay measures the total level of 25-hydroxyvitamin D in serum and plasma to aid in assessment of vitamin D sufficiency. The assay allows labs to consolidate vitamin D testing with routine testing on a single, fully automated immunoassay platform.

Gen-Probe's HPV Assay Approved

FDA has approved Gen-Probe's APTIMA HPV Assay, an amplified nucleic acid test that identifies high-risk strains of human papillomavirus (HPV) that are associated with cervical cancer and precancerous lesions. The test detects 14 high-risk HPV types associated with cervical cancer and precancerous lesions and is approved to operate on Gen-Probe's fully automated, high-throughput TIGRIS instrument system.

Green Light for BioHelix's HSV Assay

BioHelix has received FDA clearance to market its IsoAmp HSV Assay. The assay is designed to detect the herpes simplex

virus and identifies the virus in genital and oral lesion specimens from symptomatic patients.

Approval for Acute Hepatitis B Test

FDA has granted Roche premarket approval for its IgM antibody to hepatitis B core antigen assay that runs on the cobas e 601 analyzer. The Anti-HBc IgM assay is used for qualitative determination of IgM antibodies to hepatitis B core antigen (anti-HBc IgM) in human serum or plasma. The presence of anti-HBc IgM in conjunction with other laboratory results and clinical information is indicative of an acute or recent HBV infection.

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