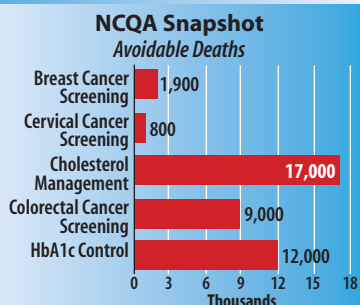


NCQA REPORT: REFORM MUST TACKLE UNEVEN CARE

While quality of healthcare in the U.S. continues to improve overall for the 9th consecutive year, Congress and the new administration must make the persistent variation in care a primary target of healthcare reform, according to the 2008 State of Health Care Quality report by the National Committee for Quality Assurance (NCQA). The report urges the new administration to set regional targets for both quality and efficiency and recommends that payments to both plans and physicians be tied to achieving these goals.

Despite some problem areas, the report shows a steady overall improvement in quality. NCQA applauded the surge of health plans that reported HEDIS measures of care, including a total of 240 PPO plans, up from 141 in 2006. Today, one in three Americans is enrolled in a health plan reporting quality measures, a 29% increase in the last year alone. The report emphasized that reporting HEDIS data has been shown to boost quality of care. In fact, taking into account the improvements in core measures since NCQA began monitoring data in 1996, more than 125,000 lives have been saved through more consistent delivery of care in



accordance with evidence-based guidelines.

But NCQA notes that the rate of improvement has not been consistent across the country, and uneven quality of care is causing many avoidable deaths and leaving large swaths of the nation behind. The report points out that if all healthcare plans improved performance in key areas to match the quality of the top performing plans, many deaths could be avoided.

Looking at quality geographically, commercial health plans in New England exceeded the national HEDIS average by 4.7 percentage points, while plans in the Mid-Atlantic scored an average of 1.3 percentage points above the national average. Lagging behind, plans in the South Central region reported scores that average 4.0 points below the national HEDIS rate. The prevalence of quality reporting varies widely as well. In a broad area that cuts through the middle of the nation, roughly from Idaho down to Alabama, quality reporting is scarce or nonexistent, compared to much higher rates of reporting in the Northeast and West Coast. The report is available free from www.ncqa.org.

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A New Role for Hemoglobin A1c

Should It Be Used to Screen for Diabetes?

BY GINA ROLLINS

Over the past two decades hemoglobin A1c has become an accepted and reliable measure of long-term glycemic control in diabetics. In fact, venerable organizations like the American Diabetes Association (ADA) recommend that diabetics have their HbA1c levels checked routinely as part of continuing care. Today, the growing epidemic of diabetes has focused attention on early identification of the disease before the multiple complications set in. Recent strides in standardizing the HbA1c test, along with the medical community's desire to identify and intervene earlier in the continuum between normal glycemic levels and frank diabetes, has focused attention on a broader role for HbA1c. Now an independent panel of diabetes experts has proposed using HbA1c as both a screening and diagnostic tool for diabetes, placing it alongside the two principal diagnostic measures, the oral glucose tolerance test (OGTT)—considered the gold standard—and fasting plasma glucose test (FPG).

While many clinicians welcome the use of HbA1c for this purpose, the idea is not without controversy, mainly due to ongoing concerns about the test's sensitivity and the lack of a definitive randomized controlled trial demonstrating that early intervention based on HbA1c levels improves long term outcomes for at-risk individuals. David Sacks, MD, associate professor of pathology at Harvard Medical School and one of the authors of the proposal published in the *Journal of Clinical Endocrinology Metabolism* (2008:2447–2453), said the group's intent was to “generate discussion in the community, get people

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Proprietary Lab-Developed Tests

Responding to Innovation or Skirting Regulation?

BY BILL MALONE

When FDA published the 2006 draft guidance on in vitro diagnostic multivariate index assays (IVDMIA), the agency caught the lab community by surprise. While FDA maintains that the IVDMIA guidance covers only a narrow category of tests that falls under its regulatory authority, many in the lab community saw the document as a warning flag for future FDA regulation of lab-developed tests (LDT). Now 2 years later, in the absence of a final IVDMIA guidance document, a resurgent business model is keeping LDTs in the spotlight, ramping up pressure on FDA to look more closely at the innovative test services companies are bringing to market. In fact, the agency recently called out LabCorp for its OvaSure test, a controversial move that made headlines in the New York Times and other national news media (See p. 15).

Despite the uncertain times for LDTs, a recently released report, “Diagnostic Test Service Commercialization: A Roadmap to Diagnostics in the 21st Century,” published by Kalorama Information, identifies a growing market for test services in which reference labs and companies offer proprietary tests out of their own CLIA-registered labs. Although these test services are offered under an established regulatory path, FDA and members of Congress remain concerned that CLIA oversight might not be enough to ensure consumers are protected from tests that do not meet FDA's stringent standards.

“I have no doubt that some of these lab-developed tests are very high in quality,” said Steven Gutman, MD, director of FDA's Office of

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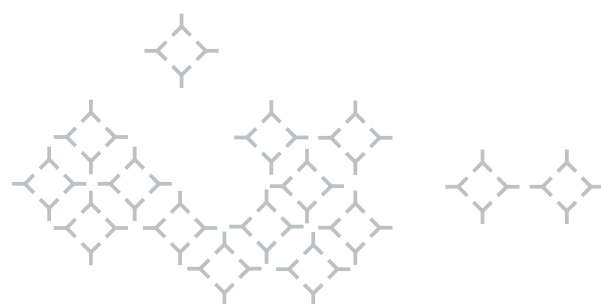
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Current Screening Methods Not Perfect

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to look objectively at the published data and see if there is a role for HbA1c.”

Among the reasons the authors cite to consider HbA1c as a screening and diagnostic tool are the rising incidence and substantial disease burden of diabetes, the significant numbers of undiagnosed diabetics and people at risk for diabetes, and evidence that early intervention can slow or forestall diabetic complications. At the same time, both OGTT and FPG have limitations as tests, and both present practical challenges in performing the tests, primarily because patients must fast for at least 8 hours prior to the exam.

The Scope of the Problem

Diabetes is a gripping worldwide health problem. Fueled by a pandemic of obesity, the incidence of the disease is growing rapidly, as is its burden on society through increased healthcare costs and decreased quality of life. CDC estimates that in the U.S. there are 24.1 million people with the disease, up by more than 3 million in just 2 years, with an associated \$174 billion annual cost of care. On a global basis, WHO projects that by 2030 there will be at least 350 million people with diabetes, about double the current number.

The picture is even more serious in light of the number of people who have frank diabetes but have not been diagnosed, and the considerable number of so-called pre-diabetics. The latter includes people who have impaired fasting glucose (IFG) with fasting glucose levels between 100 and 125 mg/dL, impaired glucose tolerance (IGT) with a 2-hour post glucose load between 140 and 125 mg/dL, or both IFG and IGT. Approximately 25% of diabetics in the U.S.—about 6 million people—have not been diagnosed, and another estimated 57 million are considered pre-diabetics, according to CDC. Although the natural history of IFG and IGT varies, approximately one-third of people with either condition will go on to develop diabetes, one-third will remain pre-diabetics, and another third will return to normal glycemic levels.

Since there is a long asymptomatic period during which many undiagnosed diabetics and pre-diabetics are likely to develop micro- and macrovascular complications, the concept of a screening and diagnostic program to identify those at risk is quite appealing.

Existing Guidelines

Longstanding guidelines of the ADA call for screening and diagnosing diabetes by one of three methods, including FPG, OGTT, or symptoms of hyperglycemia (See Box below) combined with a casual plasma glucose (CPG) test, with a repeat test on another day in the absence of unequivocal hyperglycemia. During the last major review of its screening and diagnostic criteria in 2003, ADA did not recommend using HbA1c for such purposes, citing a "lack of evidence on [its] prognostic significance and diagnostic thresholds."

FPG, OGTT, and CPG have screening and diagnostic cutoffs that are the same for each respective test. A diagnosis of diabetes requires an FPG level ≥ 126 mg/dL (7.0 mmol/L), 2-hour plasma glucose level of at least 200 mg/dL (11.1 mmol/L), or a casual plasma glucose level ≥ 200 mg/dL (11.1 mmol/L) and symptoms of hyperglycemia.

ADA recommends screening adults for diabetes starting at age 45, or at an earlier age if they are overweight or obese and have one or more additional risk factors, such as being physically inactive, having hypertension, or a first-degree relative with diabetes.

A Gold Standard?

FPG and OGTT have been used for decades to diagnose diabetes, and most studies have used OGTT levels to demonstrate the efficacy of primary prevention efforts. However, both tests have varying degrees of sensitivity, with OGTT considered the more sensitive, and both suffer from weak reproducibility. "OGTT is the Fool's Gold of a gold standard because the intra-subject variability is very high," said David McCulloch, MD, FRCP, clinical professor of medicine at the University of Washington and medical director for clinical improve-

ment at Group Health Cooperative in Seattle. "It depends on how long the person has been fasting, if they exercised the day before, how stressed they are, and other factors."

Other drawbacks of the tests include the requirement for patients to fast at least 8 hours beforehand and the need for a confirmatory test on another day. "If a doctor sees a patient and tells them they need to come back for an OGTT or FPG, it's often inconvenient and many simply don't come back. The time to do a screening is when they're in the office for a routine physical," explained Sacks.

Perhaps the greatest arguments in favor of HbA1c as a screening and diagnostic test are that it can be performed at any time, involves a simple blood draw, and is highly reproducible. The test also reflects long-term glycemic levels and is not as subject to short-term lifestyle changes as OGTT or FPG. Since the average erythrocyte lifespan is about 120 days, the HbA1c value represents a weighted average of ambient glucose levels and will not be affected by what the patient has eaten the day of or days before the test.

Anecdotal information and some published data indicates that clinicians already are using HbA1c as a defacto screening and diagnostic test, according to Sacks. McCulloch, for one, uses it as an unofficial screening test in his practice. "If a patient comes in and I have a high suspicion that he might have diabetes, I will run a HbA1c. If it's above 7 percent, it's virtually certain that he has diabetes. But because of insurance requirements and medical-legal issues, I still will verify it with two FBGs," he explained. A survey cited by the authors of the recommendation found that 93% of physician respondents reported routinely screening for diabetes, with 49% using HbA1c for screening and 58% for diagnosis.

The Variability Factor

If HbA1c has the advantage of ease-of-use and little intra-subject variability, it is not without limitations. Most notably, HbA1c varies considerably between individuals. For instance, one study found that inter-individual variance accounted for 85% of the index of individuality, versus only 6%

for intra-individual variability (Diabetes Care 1998; 21: 261–4).

HbA1c also does not produce valid results for all populations. "If a patient has any condition involving altered red blood cell turnover, it can't be used for monitoring or screening for glycemic levels," said Sacks. Examples include hemolytic anemia, aplastic anemia, and lack of a spleen, which slows red cell clearance. In addition, HbA1c is higher for African Americans and certain other ethnic groups. Other hemoglobin proteins, including HbS, HbC, and possibly HbE may interfere with certain assays. However, as of mid-2008 only about 5% of labs use assay methods with clinically significant HbS and HbC interference, according to the authors of the new recommendation.

While standardization of HbA1c was a significant problem at the time the landmark Diabetes Control and Complications Trial (DCCT) was published in 1993, the National Glycohemoglobin Standardization Program (NGSP) has been instrumental in standardizing and establishing a true reference method for HbA1c. Today, more than 99% of labs that measure HbA1c in the U.S. use NGSP-certified methods. In addition, CAP proficiency testing criteria will be steadily tightened over the next 4 years with a reduction from the current $\pm 12\%$ to $\pm 6\%$. Further, based on results of the A1c-Derived Average Glucose (ADAG) study, which demonstrated a linear relationship between estimated average daily glucose (eAG) and HbA1c, ADA now recommends that laboratories provide physicians with both eAG and HbA1c (CLN, October 2008).

One of the most controversial aspects of using HbA1c as a screening and diagnostic tool, however, is the body of evidence surrounding its utility for those purposes. The DCCT demonstrated that tight glycemic control, measured by decreases in HbA1c levels, lowered the risk of microvascular disease in type 1 diabetics, and the United Kingdom Prospective Diabetes Study (UKPDS) found a similar relationship in type 2 diabetes. These seminal studies imply that lowering HbA1c levels would yield similar results for prediabetics, but a definitive randomized controlled trial demon-

See **HbA1c**, continued on page 4

Current ADA Criteria for Testing for Diabetes and Pre-Diabetes in Asymptomatic Adults

1. Testing should be considered in all adults who are overweight (BMI ≥ 25 kg/m²) and have additional risk factors:
 - ▶ physical inactivity
 - ▶ 1st degree relative with diabetes
 - ▶ being of high-risk ethnic populations
 - ▶ women who delivered a baby weighing > 9 lb or were diagnosed with GDM
 - ▶ hypertension
 - ▶ HDL-C < 35 mg/dL and/or triglyceride > 250 mg/dL
 - ▶ women with polycystic ovarian syndrome
 - ▶ IGT or IFG on previous testing
 - ▶ other clinical conditions associated with insulin resistance, such as severe obesity
 - ▶ history of CVD
2. In the absence of the above criteria, age 45
3. If results are normal, testing should be repeated at least at 3-year intervals, with more frequent testing considered depending on initial test results and risk status.

Current ADA Criteria for the Diagnosis of Diabetes

1. FPG ≥ 126 mg/dL
2. Symptoms of hyperglycemia and a casual plasma glucose ≥ 200 mg/dL
3. 2-h plasma glucose by OGTT ≥ 200 mg/dL

Proposed Criteria for Screening and Diagnosis of Diabetes*

- ### Screening
- ▶ FPG ≥ 100 mg/dL
 - ▶ HbA1c $> 6.0\%$
 - ▶ RPG ≥ 130 mg/dL
 - ▶ if result is negative, screen again in 3 years.
 - ▶ if result is positive but below the diagnostic threshold, test again using a different method.
 - ▶ if result is above the diagnostic threshold but a 2nd test doesn't reach the threshold, test again in 1 year.
- ### Diagnosis
- ▶ FPG ≥ 126 mg/dL
 - ▶ HbA1c $\geq 6.5\%$
 - ▶ RPG ≥ 200 mg/dL
 - ▶ diagnosis requires confirmation unless there are unequivocal symptoms of diabetes
 - ▶ diagnosis through HbA1c requires confirmation using FPG or OGTT, or if 1st HbA1c is $\geq 7.0\%$, by a 2nd HbA1c $\geq 6.5\%$
 - ▶ in asymptomatic individuals with HbA1c $\geq 6.5\%$, if FPG ≥ 126 mg/dL or RPG ≥ 200 mg/dL, diagnosis is confirmed
 - ▶ if screening is positive but $<$ diagnostic threshold, 2 tests must meet the diagnostic threshold

* proposed by an independent panel of diabetes experts (J Clin Endocrinol Metab 2008; 93:2447–2453)

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Controversy Around Screening, Cutoffs

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strating it unequivocally has not been conducted. "The reasoning is not flawed and one would intuitively find it acceptable, but there is not that much data around interventions in the IGT or IFG population," noted Gojka Roglic, MD, medical officer for the WHO diabetes program.

Published research presents a complicated picture of the efficacy of HbA1c in at-risk populations. For instance, one recent analysis found that addition of HbA1c to the Framingham Risk Score in the EPIC-Norfolk Study cohort made a small but statistically significant improvement to discrimination of coronary heart disease events in men but not in women (Arch Intern Med 2008;168:1209-1216). Another involving the same population found that in both men and women, the relationship between HbA1c and both cardiovascular disease and all-cause mortality was continuous and significant throughout the whole distribution. The relationship was apparent in persons without known diabetes (Ann Intern Med 2004; 141:413-20).

Another controversy surrounding HbA1c is establishing screening and diagnostic cutoffs with adequate sensitivity and specificity. Sacks and his coauthors saw their proposal as a two-step process, first with agreement in the medical community that HbA1c is an appropriate screening and diagnostic test, followed by further analysis of cutpoints. However, they did put forth suggested cutpoints, based on "available literature, but it wasn't an independent analysis of all papers on HbA1c," noted Sacks. For screening, the panel recommended a cutpoint of 6.0%, which is 2 standard deviations above the population mean, as described in the National Health and Nutrition Examination Survey (NHANES) II and III. Based on the NHANES data, that cutpoint would yield a 63% to 67% sensitivity and 97% to 98% specificity, which "would avoid an undue burden of false-positive tests," according to the authors.

Also based on NHANES II and III data, the authors recommended HbA1c of 6.5% as a baseline diagnostic threshold, which would yield a sensitivity of 43% to 44% and a specificity of 99.6%. They suggested that at levels between 6.5% and 6.9%, the diagnosis should be confirmed with either FPG or OGTT. However, if the initial test is 7.0% or higher, a confirmatory test could be done with HbA1c because interference with the assay would be unlikely.

Other analyses have found HbA1c not to be as robust a diagnostic measure. One review of primary cross-sectional studies found a cutpoint of 6.1% with a sensitivity ranging from 78% to 81% and specificity from 79% to 84%, and that HbA1c and FPG both had low sensitivity for the detection of IGT (Diabet Med 2007 24:333-43).

Given the mixed picture of HbA1c, some professional organizations believe it is premature to endorse the test as a screening and diagnostic tool. One such group is the American College of Endocrinology (ACE). The ACE task force on pre-diabetes consensus statement on the diagnosis and management of pre-diabetes pointedly did not address the possibility of adopting HbA1c for such a purpose, and indeed, did not include further evaluation of HbA1c in

its recommendations for further research needed. "There are no data to judge HbA1c as a predictor of diabetes risk and no known utility of the measure for prediabetes assessment," noted Alan Garber, MD, PhD, chair of the ACE task force and professor of medicine, biochemistry and molecular biology at Baylor College of Medicine in Houston.

WHO also has no immediate plan to reassess its HbA1c-related recommendations, according to Roglic. During the last revision of its diagnostic guidelines in 2006, HbA1c "was not even discussed," she said. Aside from a concern about insufficient data in support of HbA1c's predictive value, WHO faces practical considerations in making any HbA1c-related recommendations. "The consensus paper was written from the position of the U.S., which has resources, populations, and needs that are not quite the same as the WHO clientele," Roglic explained. "Many countries in sub-Saharan Africa don't have a lab infrastructure even to measure blood glucose, so practices there won't change as a result of any updated screening or diagnosis guidelines." Nonetheless, WHO does intend to revisit diagnostic or screening criteria or

possibly both, perhaps in late 2009.

Meanwhile, ADA, the International Diabetes Foundation, and the European Association for the Study of Diabetes are towards the end of a major review of available data, including an extensive meta-analysis, according to Richard Kahn, PhD, chief scientific and medical officer of ADA. "My guess is that we will recommend that HbA1c is an appropriate diagnostic tool for some patients," he said. "We've tentatively said it's a pretty good test, sensitive, precise, and reproducible." He indicated that an announcement should be forthcoming early next year.

With data and opinions falling on both sides of the utility of HbA1c as a screening and diagnostic tool, the debate will no doubt continue. At its core is the importance of chronic hyperglycemia and HbA1c as an effective bellwether of the condition, said William Winter, MD, professor of pathology and laboratory medicine at the University of Florida in Gainesville. "The issue is, is an elevated HbA1c a suitable marker of chronic hyperglycemia that should either supplement or even replace blood glucose testing as a diagnostic criteria for diabetes? One can argue that diabetes is a disease of chronic hyperglycemia and an elevated A1c-emia alone is a laboratory finding and not a disease unto itself." CLN

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Old Idea Making a Comeback

LDTs, continued from page 1

In Vitro Diagnostic Device Evaluation and Safety. "I also have no doubt that some of them are not so high in quality. What I don't know is how it will all sort out and whether tests of less value will in fact produce a branding issue that might come back to haunt labs. If poor quality tests enter the market, then people could lose confidence in tests more generally."

What's Old is New

Although the number of LDTs commercialized as proprietary test services is on the rise, with some 70 tests already available or near market, the test service model is not a new one, according to the Kalorama Report. In the 1980s, IVD companies like Roche, Beckman, and Corning had their

own CLIA-registered labs through which they could market their tests. But by the late 1990s, these company labs were sold off to create the current reference lab giants of LabCorp and Quest, which since then have bought up many smaller, independent reference labs.

In the midst of this consolidation phase, companies like Myriad Genetics with its BRCA test for inherited breast cancer risk and Athena Diagnostics with its ApoE test for risk of Alzheimer's disease were making a name for themselves with novel tests that looked for links between genes and disease risk. These and a handful of other companies became the predecessors of the current boom in the proprietary test service market, explained Shara Rosen, RT, MBA, author of the report and a senior consultant with

Kalorama Information. At first, the high cost of these early test services raised eyebrows. Take Myriad Genetics for example. When the company first began marketing its BRCA test for hereditary breast cancer, they charged more than \$3,000. "That was unheard of then," said Rosen. "It seemed like a fortune. Now people don't even blink. The insurers don't even blink."

Today, after what Rosen describes as a 10-year lull since Myriad's and other companies' test services hit the market, both small IVD companies and the large reference labs are trying to capitalize on research from the Human Genome Project and advances in molecular biology, pushing the envelope with highly complex tests for cancer and other diseases. According to the Kalorama report, the esoteric test segment into which these tests services fall will continue to grow at a rate of 10%–15% per year, compared to 6% for the rest of the

IVD market. In 2007, esoteric test service revenues reached almost \$4 billion, about 12% of the wider lab market worth more than \$40 billion (See Graph, p. 9).

Gutman agrees that the business model for proprietary tests is not new. "I would say that it's actually an old practice, but that it may have new life because of the interesting new technologies that are entering the marketplace through that regulatory route," said Gutman. "And I guess there's good news and bad news. The good news is that it does certainly create what one might characterize as the least burdensome route to market, and the bad news is that there's a certain non-parity between that route and the more established FDA route. And there is less transparency than in the FDA route."

Two Paths to Market

The Medical Device Amendments of 1976 and CLIA 1988 outline two distinct paths for companies to commercialize lab tests. A company can choose to market a test as a kit through FDA's risk-based review process, or it can set up its own lab and market a proprietary LDT as a test service, with its lab falling under CLIA regulation, explained Paul Radensky, MD, JD, a partner with the law firm of McDermott, Will & Emery in Washington, D.C. that represents the Coalition for 21st Century Medicine and several companies that market unique test services. "When we're looking at today's environment, tests that tend to follow the CLIA pathway, rather than the FDA pathway, are a number of highly advanced, high-complexity genetic or genomic assays where there is a lot of concern about the transferability of the method from one lab to another and about what it would take to put these in kit form while maintaining the accuracy and validity of the tests," said Radensky. "There's also a lot of concern about whether FDA can find a truly least burdensome pathway to clear clinically meaningful claims."

Gregory Critchfield, MD, president of Myriad Genetic Laboratories, Inc., said he believes that the test service model is the only way Myriad's BRCAAnalysis test could ever have entered the market. "In our business, when the BRCA genes were discovered and the clinical service was launched in 1996, as today, there was no easy way to put this in to a kit form. So, of necessity, it had to be developed by a laboratory offering a service," said Critchfield. "The test involves sequencing a very large number of DNA bases, looking at structural rearrangements in the gene, and interpreting the data because there are a number of variants that can be found, all making for a test that is best made available in a the laboratory environment." Critchfield pointed out that because Myriad has the patents and exclusive license to perform BRCA1 and BRCA2 testing, the company has invested heavily in research to support the test, as well as in educating physicians and working with third-party payers to make sure that the service is covered. He credits the company's efforts to get widespread insurance reimbursement with boosting access to the test.

Rather than a way to skirt the FDA regulatory path, it's the nature of the technology behind these tests that put companies in a position to choose the CLIA-regulated test service model over the FDA route, Critchfield emphasized. "With the development

See LDTs, continued on page 8

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Figure (a): Glucose 54 mg/dL

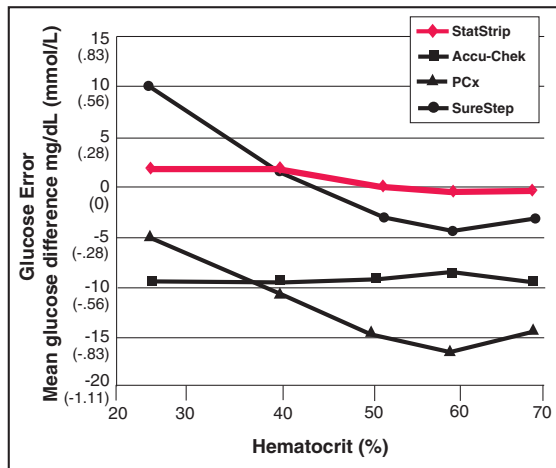


Figure (b): Glucose 247 mg/dL

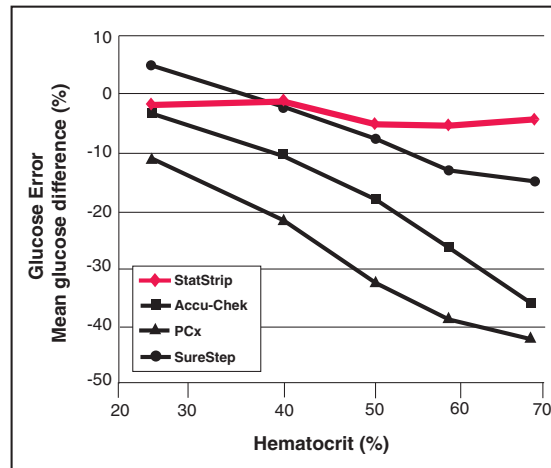
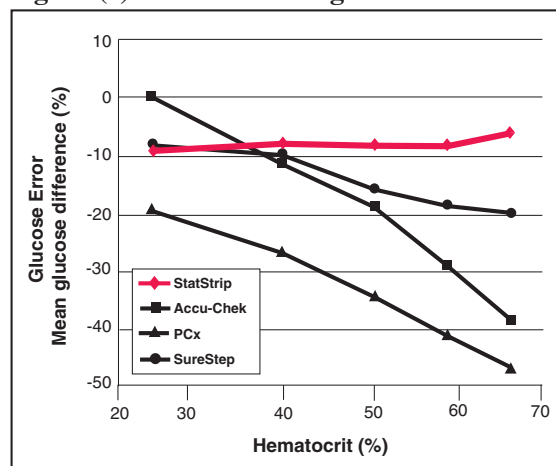


Figure (c): Glucose 483 mg/dL



Figures:

(a) Mean glucose difference (meter glucose minus reference glucose) and (b) and (c) mean glucose percent difference [(meter glucose minus reference glucose)/reference glucose x 100] as a function of hematocrit at glucose concentrations of (a) 54 mg/dL, (b) 247 mg/dL, and (c) 483 mg/dL. Each point represents the mean ± standard deviation of the mean glucose difference or mean glucose percent difference (n=6).

¹Karon BS et al (Mayo Clinic) Evaluation of the Impact of Hematocrit and Other Interference on the Accuracy of Hospital Based Glucose Meters. Diabetes Technology and Therapeutics, April 2008

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LDTs Face Economic, Regulatory Hurdles

LDTs, from page 6

of new ways of interrogating biologic systems, things like gene sequencing, expression arrays, and real-time PCR to look at messenger RNA levels, there are a variety of new technologies that have come forward and are developed to the point that we're beginning to get a better clue of what's going on in the underlying biology of disease," Critchfield said. "As a result, these are very complex tests compared to some predecessor tests. It's not like running a serum glucose."

An Economic Philosophy

However, not everyone agrees that the proprietary test service model is the best, as a business strategy or a lab medicine practice. While Myriad and other companies that offer test services argue that the huge investments they put into developing a test, marketing it, and working with insurance companies allow them to offer wider access and more tightly controlled quality, others are not so sure. "It's an interesting strategy, but I think it's a flawed one," said Edward Ashwood, MD, a senior vice president and director of laboratories at ARUP. He is also a professor of pathology at the University of Utah School of Medicine.

Ashwood supports a middle path for these kinds of tests in which companies offer the test themselves, but also license it out to other labs if they're not going to market it via the FDA route. "As you look at lab test usage, it's widely driven by market demand. And market demand stems from knowledge about the test, people in the know

advocating for tests. And when there's only one company advocating for a test, it gets stifled. So I think that holding a test tightly is not only bad for medicine, but it's bad for business."

He thinks that a better business strategy would be to loosen the hold on intellectual property and license it to anybody that wants it. "I think it's a short term perspective—how do we get the most money out of this the quickest, where we force everybody to send to us. What do you really do long term? You encourage other people to figure out ways to get around you." Ashwood also argues that when only one company is running a test, there's less motivation to improve it. "No test is perfect when it first comes out," he said. "They can all stand to be improved. And to improve a test, you need competition." When a company licenses a test to other labs, it encourages others to find a way to do better, and in turn it pushes the company to keep improving their method to stay competitive, Ashwood concluded.

But testing advancements is an area where Myriad and other companies running exclusive test services feel they've really made their mark. Critchfield contends that because Myriad is the exclusive provider of the BRCA proprietary test, the company must invest heavily in research and improvements to remain on the cutting edge. "Again, if you come back to the question, 'How can you best improve the test?' we believe that concentrated efforts on test improvement, concentrated efforts on de-

veloping the market, concentrated efforts in developing data with research, all those things that are made possible by having an exclusive license really increase the availability of the test and increase the quality of the test," said Critchfield.

The Kalorama report highlights how some companies in the business of offering proprietary tests services have experienced phenomenal growth. Myriad's diagnostics unit has had nearly 50% compounded annual growth over the past 7 years. Genomic Health, which the report calls the most successful of the test service firms by far, saw a more than 10-fold increase since 2004 in the number of its Oncotype DX tests for breast cancer recurrence performed.

However, for both of these companies, success could have been a very different story if it weren't for important favorable assessments included in guidelines from major professional societies and cancer organizations. For Myriad's BRCA analysis test, organizations like the American Society of Clinical Oncologists, the American College of Medical Genetics, the Society of Gynecological Oncologists, and the American Society of Breast Surgeons issued guidelines on appropriate evaluation of patients that would be candidates for BRCA testing. Similarly, the U.S. National Comprehensive Cancer Network 2008 Breast Cancer Treatment Guidelines and the 2007 update to the ASCO Recommendations for the Use of Tumor Markers in Breast Cancer included information on Genomic Health's Oncotype DX testing service. It's difficult to say how these tests would have fared without such backing from well-known organizations. Rosen noted that the choice to

market a test as an exclusive service, license it out to other labs, or turn it into a kit to be sold via the FDA route often comes down to how much faith a company has in itself. "It just depends on how the company sees itself, how much money it has, and what its resources and competencies are," said Rosen. "And in not licensing out a test, the company feels confident that they can offer a test service on their own."

For many of the new proprietary test services coming to market now, success may arrive even more quickly, Rosen maintained. Many of these are tissue-based and feature more actionable results. This held true in 2007, when many of the most successful tests in the esoteric segment employed immunohistochemical stains, in situ hybridization, and PCR analysis of biopsied tissue, the Kalorama report found. "The tests that are coming out now, the tissue-based tests, they tell you straight up if the tumor is going to metastasize or not, or what type of drug it will respond to," said Rosen. "They're much more actionable, and they make a huge difference in how patients are treated and in the outlay by the insurance company for follow-up treatment."

Regulation versus Innovation?

Up to this point, FDA has used its discretion in overlooking regulation of LDTs, Gutman noted, and labs and IVD companies have gotten used to considering LDTs as essentially off-limits to FDA. However, as early as 2004, it was clear that the agency viewed some of the newer, more complex LDTs differently.

Companies like Genomic Health and Correllogic, with its OvaCheck test for de-

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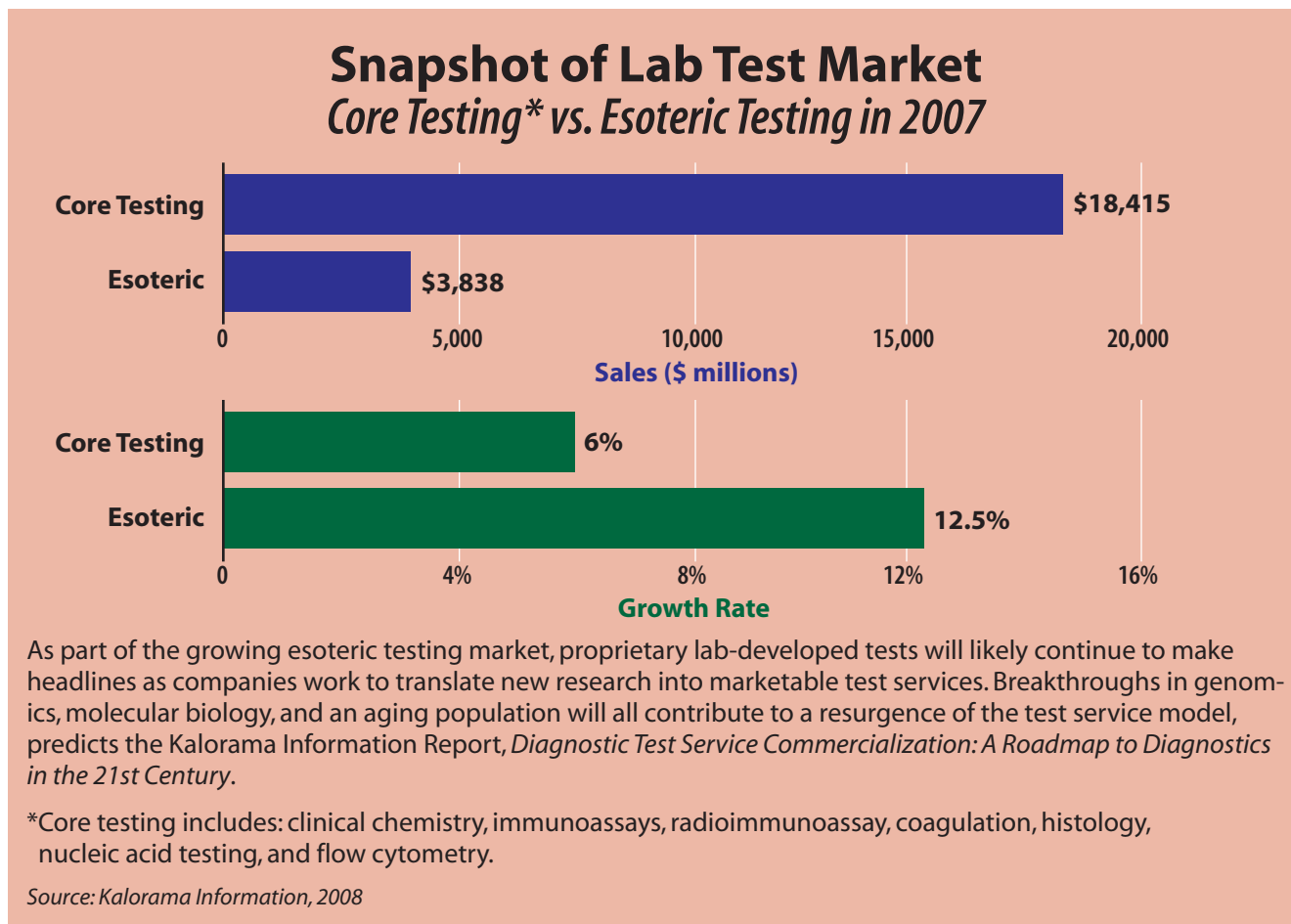
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etecting early-stage ovarian cancer, started employing proteomics and genomics to predict the course of a disease or to catch the disease earlier. Significantly, many of the new test services used software to interpret the raw data generated from looking at multiple proteins or multiple genes. In Correlogic's case, the company says it uses "artificial intelligence-based computer technology to identify hidden patterns" when looking at multiple proteins, protein fragments, and metabolites in blood.

This level of complexity, as well as the high-profile use of software for patient-specific interpretation, caught the FDA's attention. "The IVDMA guidance really reflected a major change in FDA policy with respect to laboratory-developed tests. Many of us who have worked in this area for several years were quite confident that the tests which FDA is now calling IVDMIAs fit squarely under FDA's enforcement discretion policy for LDTs because these were performed by laboratories that developed these tests in-house without distribution by the laboratory of anything other than a box to collect samples and a report of results," said Radensky.

Even though the FDA issued a revised draft guidance in 2007, many questions still remain unanswered, Radensky noted. "The revised guidance changed the definition, but it's still a very subjective definition in that it really relies on concepts like transparency, and it's not clear what is required for an interpretation function to be considered transparent."

As more companies work to create innovative tests that take advantage of developments in proteomics and genomics,



As part of the growing esoteric testing market, proprietary lab-developed tests will likely continue to make headlines as companies work to translate new research into marketable test services. Breakthroughs in genomics, molecular biology, and an aging population will all contribute to a resurgence of the test service model, predicts the Kalorama Information Report, *Diagnostic Test Service Commercialization: A Roadmap to Diagnostics in the 21st Century*.

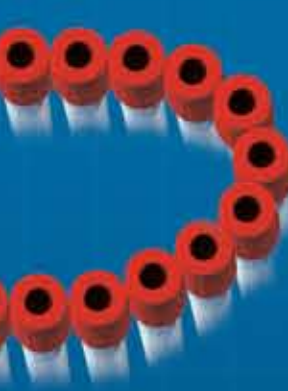
*Core testing includes: clinical chemistry, immunoassays, radioimmunoassay, coagulation, histology, nucleic acid testing, and flow cytometry.

Source: Kalorama Information, 2008

Radensky said that it's an open question whether or not FDA will confine its extension of medical device regulation to those tests that use software for multivariate analysis, or whether this might be the first step toward FDA oversight of other LDTs as well. "Once FDA—by guidance—begins to regulate LDTs, it's not clear that they won't move to other laboratory-developed tests by the same mechanism."

Radensky predicts that as technology progresses, FDA and Congress will have to come to terms with the fact that many of these complex tests do not fit well under medical device laws and regulations put into place 30 years ago. "I think that as we look to a new administration and a new Congress, and considering that science is advancing at a rapid pace, it is critically important that whatever regulatory frame-

work is developed be one that can assure the public health while at the same time encourage and not hinder scientific innovation that can improve health outcomes," said Radensky. "Any new regulatory framework must acknowledge the fact that these technologies really are very different from what Congress was considering when it passed the medical device amendments in 1976." CLN



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Endocrine Testing

Improving Patient Care with Tandem Mass Spectrometry

BY RAVINDER JIT SINGH, PHD

The current focus on patient safety has increased emphasis on the need for accurate and precise lab test results. To deliver high quality results for steroids in a timely manner, labs use a wide array of technologies, including competitive radio-immunoassay (RIA), chemiluminescence immunoassay (CLIA), and fluorimetric immunoassay (FIA). Although these immunoassays are well suited for small-molecular-weight compounds, sandwich immunoassays, such as ELISAs, are the preferred methods for proteins and small peptide hormones. Most of these assay formats have been adapted to commercial platforms, which are highly automated and allow labs to process many patient specimens per hour.

But FDA-cleared immunoassays are not available for all endocrine analytes that labs need to measure, for example catecholamines and metanephrines. For these analytes, large labs commonly use gas (GC) or high-pressure liquid chromatographic (HPLC) techniques coupled with various detection methods, such as flame ionization, ultraviolet light, electrochemical or mass spectrometry. In the past decade, HPLC coupled with tandem mass spectrometry (LC-MS/MS) has revolutionized measurement of endocrine analytes. In addition, LC-MS/MS allows labs to conveniently measure new biomarkers for which no commercial assays exist.

The most significant advance in MS technology that has facilitated routine analyses in clinical labs is the invention of an electrospray source by Nobel laureate John B. Fenn, PhD. This technology facilitates ionization of the analytes present in

method for tests related to endocrine disorders, some labs and accrediting agencies now use LC-MS/MS as a reference method. This article examines diagnostic applications of the technology for several endocrine disorders.

tumor or a cortisol-secreting tumor in the adrenal gland. A small molecular weight molecule, cortisol's structure is very similar to other endogenous and exogenous steroids, resulting in artificially high values in immunoassays.

Analysis of urinary-free cortisol (UFC) is most commonly used for the diagnosis of Cushing's syndrome; however, physicians also order plasma cortisol, plasma-free cortisol, midnight plasma cortisol, and midnight salivary cortisol tests to confirm the diagnosis. Measurements of UFC and its metabolite, cortisone, are useful in evaluating apparent mineral-corticoid excess, congenital adrenal hyperplasia, and adrenal insufficiency.

Historically, labs have used RIA for analysis of UFC and plasma cortisol. Today, labs have replaced RIA with automated non-radioactive CLIA. Even with an extraction step to eliminate polar compounds, these assays are prone to interferences from other endogenous steroid metabolites and exogenous synthetic glucocorticoids and can produce false-positive results (Figure 1).

Comparisons between immunoassay and chromatographic methods have been reported for UFC measurements, and researchers have concluded that UFC immunoassays are not highly precise or accurate. Therefore, more specific methods have been developed using LC-UV, LC-MS and GC-MS. These chromatographic methods have reduced interference for cortisol quantification and allow quantification of cortisone, an endogenous metabolite of UFC.

The LC-UV method for cortisol and cortisone however, require a lengthy analysis time to obtain resolution between cortisol and cortisone. The analysis must also ensure that the commonly used synthetic corticosteroids and the more hydrophilic cortisol metabolites do not interfere with the cortisol and cortisone peaks (2).

Despite its superiority to immunoassays, LC-UV analysis is still prone to interferences, most notably from carbamazepine and

liquid droplets and sprays the molecules directly into the mass spectrometer from the HPLC. With this advancement, labs can achieve greater throughput of patient samples compared to GC-MS. Now considered the gold standard for measuring steroid hormones, LC-MS/MS analysis offers improved precision and accuracy (1).

Over the last few years, we have implemented this technology at the Mayo Clinic for routine analysis of steroids and now perform more than a million endocrine tests per year. In addition to being a reliable

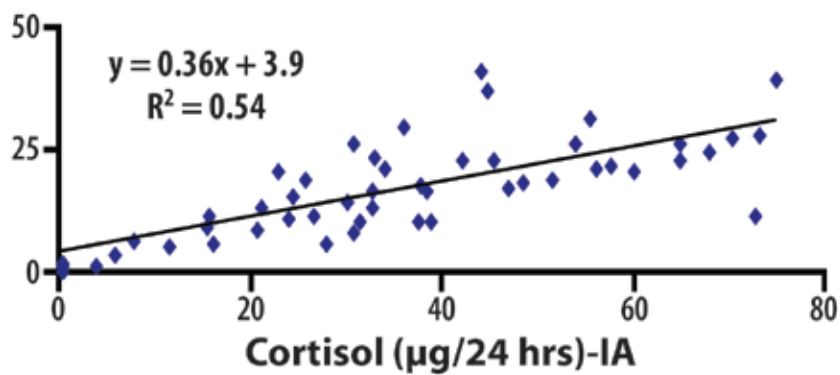
Cushing's Syndrome

Cortisol, a glucocorticoid hormone, plays an essential role in adaptation to stress, regulation of metabolism, and inflammatory responses. Hypercortisolism is associated with the rare condition known as Cushing's syndrome and has been linked to hypertension, diabetes, and obesity. It is frequently difficult to distinguish mild or moderate hypercortisolism, so called pseudo-Cushing's syndrome, from full blown Cushing's.

Endogenous hypercortisolism can result from either an ACTH-secreting pituitary



Figure 1
**Correlation Between
 Cortisol Assay Methods**



Urinary-free cortisol data from 24-hour urine specimen of different patients. IA = immunoassay

its hydroxy metabolites. To resolve carbamazepine interference, some labs have turned to LC-MS or GC-MS analysis. Although chromatographic methods with a single MS detector provide specific quantitation of cortisol, these methods have not been widely implemented due to low throughput and higher instrument cost. However, triple-quad, tandem mass detectors have provided exponentially better throughput for endocrine testing, and the cost per sample is now comparable to commercial immunoassays.

Sex Steroids

In vivo formation of cortisol, aldosterone, and sex steroids involves cleavage of cholesterol, followed by minor oxidations and reductions at various carbon sites, which results in various steroid intermediates. These steroid intermediates are very similar in structure and chemical properties, presenting an analytical challenge for various methods used in clinical labs.

Inherited defects in steroid biosynthesis, in particular 21-hydroxylase deficiency, results in a disease known as congenital adrenal hyperplasia (CAH). This enzyme deficiency increases levels of an intermediate steroid, 17 α -hydroxyprogesterone (17-OHP), a precursor for androgens (testosterone) and a cause of virilization of females.

Steroid intermediates and metabolites have been reported to cross-react with the immunoassay reagents, and in particular, labs have reported calibration issues for 17-OHP immunoassays. Chromatographic separation and detection using tandem mass spec, however, eliminates cross reactants and allows for specific determination of sex steroids.

To confirm the diagnosis of CAH, it is critical to determine multiple steroid intermediates in a single blood sample collected from the patient. Analysis of individual analytes by RIA or CIA can be very time consuming and expensive, but with LC-MS/MS, labs can measure multiple steroids in small-volume serum samples, which is particularly advantageous for pediatric samples. (Figure 2) (3).

Estrogen immunoassays also present analytical issues for labs, and recently the quality of the epidemiologic data collected

from estrogen immunoassays has been questioned. Using these assays, researchers have reported variable 17 β -estradiol serum levels in postmenopausal women, and median normal values by these methodologies differ by approximately 6-fold (4). Therefore, some labs have developed tandem MS based assays to increase sensitivity and specificity of these assays. Because these analyses require expensive instruments and highly trained personnel, only large reference labs currently offer this type of analysis.

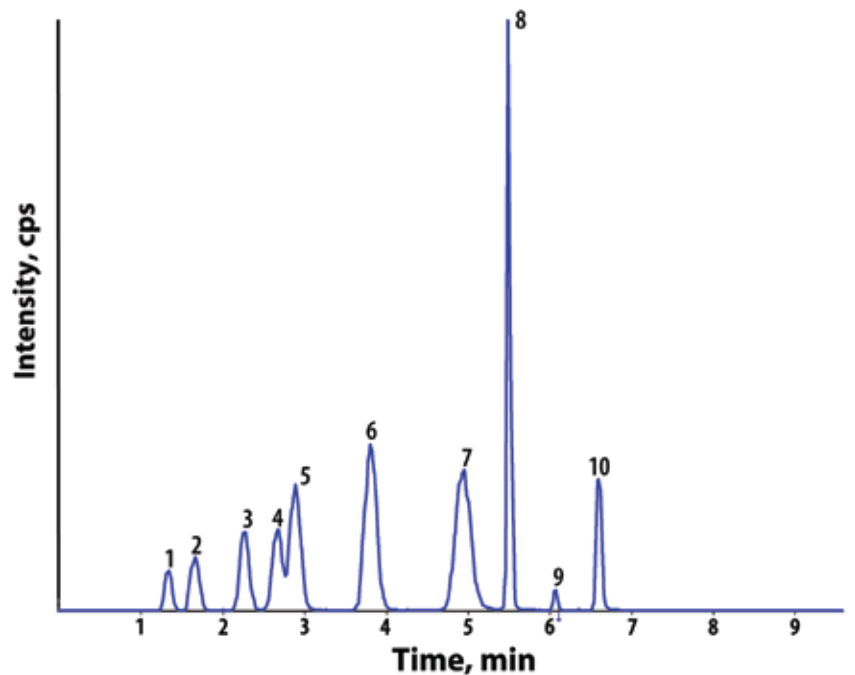
Similar issues exist for testosterone testing, especially for results from women and children (5, 6). Current assays lack accuracy and precision, and they have large interlaboratory variation in these patient populations. Large reference labs have adopted the LC-MS/MS methodology to address some of these concerns. Although the LC-MS/MS assays provide testosterone results with good precision and accuracy, improvements need to be made to increase the sensitivity and precision at the lowest detection limits for children and women.

Labs typically develop in-house LC-MS/MS assays for steroid hormones. These assays have labor-intensive, manual steps that can produce interlaboratory variations. Some reference labs also claim their procedures are proprietary. To maintain assay quality, CAP and the New York State Department of Health offer proficiency programs for sex steroids. In a recent survey, the New York State Department of Health reported the CVs to be >20% among the labs performing testosterone analysis by MS/MS methods (7). They concluded that although LC-MS/MS instruments are readily available, improvements in comparability are needed, and a high-level reference-method protocol should be developed through formal interlaboratory collaboration. In a recent position statement, endocrine experts also cited problems in proficiency testing for testosterone (8).

Pheochromocytoma

Pheochromocytoma is a rare but potentially fatal tumor arising from chromaffin cells. It can produce episodic secondary hypertension, along with headaches, sweating, and palpitations. Screening for pheochromocytoma is typically part of an evaluation

Figure 2
**Multiple Steroid Analysis
 by LC-MS/MS**



A 100- μ L serum sample was processed using solid-phase extraction and injected into an LC-MS/MS. The steroid peaks are cortisone (1), cortisol (2), 21-dexycortisol (3), cortiscosterone (4), 11-deoxycortisol (5), androstenedione (6), dexycorticosterone (7), 17-hydroxy progesterone (8), progesterone (9), and pregnenolone (10).

for secondary causes of hypertension, unexplained fainting spells, incidental adrenal masses, or less commonly, for patients with a family history of pheochromocytoma. Patients with pheochromocytoma can present with adrenal incidentaloma, hypertensive paroxysms, sustained apparent polygenic hypertension, hypertension in pregnancy, and hypertensive crisis induced by anesthesia. Although pheochromocytoma is lethal, it can usually be cured with surgery.

Biochemical testing for pheochromocytoma typically has included measurements of metanephrines and catecholamines. But analysis of plasma concentrations of free metanephrines is challenging, since less than 5% exist in an unconjugated state. Researchers recently reported that measurement of fractionated, plasma-free metanephrines by HPLC with electrochemical detection (HPLC-EC) had 100% sensitivity and 89% specificity for detecting pheochromocytoma (9).

Other methods for analysis of metanephrine and normetanephrine include colorimetric assays, immunoassays, HPLC, and GC-MS. Drug interferences and the lack of an internal standard limit the utility of the colorimetric assay. Although new immunoassays for metanephrines have been shown to be free of drug interference, they still lack an internal standard to monitor recovery through the extraction process. Recent modifications in HPLC methods have resolved known drug interferences for metanephrines, but analytical run times have been increased. To overcome drug interferences, researchers have also developed an isotope-dilution GC-MS method, which is specific but requires a time-consuming derivatization step and takes longer to run. Alternatively, some labs have successfully

implemented LC-MS/MS methods that use stable deuterium-labeled isotopes of metanephrines and normetanephrine and have good throughput.

The LC-MS/MS assay has several advantages. It is sensitive and offers automated on-line extraction and high-throughput processing of samples. In addition, the method can measure the dopamine metabolite, methoxytyramine, an added utility for detection of dopamine-producing paragangliomas. The capability to detect all three O-methylated metabolites in as little as 50 μ L of plasma or urine also makes the assay suitable for diagnosis of other neuroendocrine tumors—particularly neuroblastomas (10).

Vitamin D

Experts now project a vitamin D deficiency epidemic in North America. Labs most often measure serum 25-hydroxy vitamin D (25-OH-D), an accepted marker for vitamin D nutritional status. With this increased interest, more than 5 million 25-OH-D tests are expected to be performed in the U.S. this year.

The methods currently used for 25-OH-D include low-throughput assays, such as HPLC-UV and RIA, or high-throughput automated CLIA and LC-MS/MS assays. Although various methods are available for measuring circulating concentrations of 25-OH-D, none of these assays are standardized against a common calibrator. Surveys from CAP and the UK-based Vitamin D External Quality Assessment Scheme provide independent approaches to monitor the performance of laboratories that use various methods for testing of 25-OH-D. Based on this data, the CV for the same method has been reported to be

>20% among labs. Recent CAP data also indicate that labs performing immunoassays report results ranging from 41 to 96 µg/L for a survey sample with a value of 75 µg/L determined by LC-MS/MS (Figure 3). There could be many reasons for these variations, including drifts in calibrator reagents. Regardless of the reason, there is a clear and urgent need for harmonization and standardization (11).

Calcium homeostasis is also frequently monitored in vitamin D deficient patients. Fortunately, the performance of calcium tests by most manufacturers is very good and has a CV of <1%. In order to deliver high quality vitamin D results, however, labs need to have vitamin D tests with similar precision. NIST is currently developing quality control materials (human serum, SRM 972) to deal with this problem. The control material will contain 25-OH-D₂, 25-OH-D₃, and the metabolite 3-epi-25-OH-D at four different concentrations, as characterized by LC-MS/MS. Preparation of this SRM is especially important for immunoassays for which the cross-reactivity with 25-OH-D₂ and 25-OH-D₃ is not well defined.

Endocrine Testing: Future Challenges

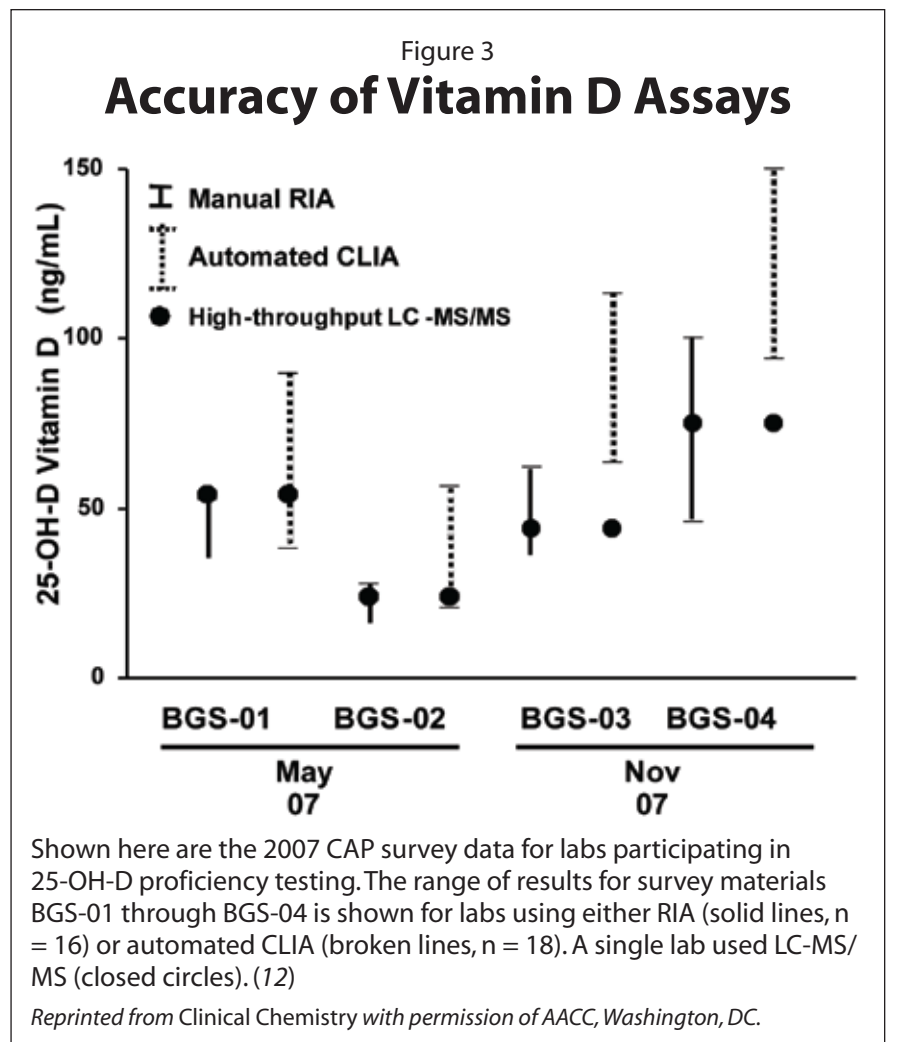
Immunoassays allow for the sensitive detection of a wide range of endocrine hormones. They are very precise, come in a wide range of formats, and most importantly, are highly automated. This familiar assay format has been used to establish reference ranges for a variety of endocrine analytes, and the problems and limitations of the reagents used in these assay formats are also widely understood in clinical labs. As labs have gained experience with MS analysis, investigators have reported discrepancies between results for this method and those of immunoassays, especially at the low end of the concentration range for steroid hormones, creating a heightened awareness of the limitations of immunoassays.

But LC-MS/MS technology is relatively new to clinical labs. Its problems and chal-

lenges are not as well understood for routine clinical analysis, and only a small number of labs have adopted this highly specific technology. Recently, CDC, in partnership with NIST and the Endocrine Society, initiated a project to standardize assays for endocrine hormones. The goal of this effort is not only to help clinicians and laboratorians better understand MS analysis, but also to work with the industry to standardize and improve endocrine immunoassays. These efforts are clearly worthwhile and will undoubtedly help improve the quality of these lab tests. CLN

REFERENCES

1. Kinter M. Toward broader inclusion of liquid chromatography-mass spectrometry in the clinical laboratory. *Clin Chem* 2004;50:1500-1502.
2. Taylor RL, Machacek D, Singh RJ. Validation of a high-throughput liquid chromatography-tandem mass spectrometry method for urinary cortisol and cortisone. *Clin Chem* 2002;48:1511-1519.
3. Guo TD, Taylor RL, Singh RJ, et al. Simultaneous determination of 12 steroids by isotope dilution liquid chromatography-photo spray ionization tandem mass spectrometry. *Clin Chim Acta* 2006;372:76-82.
4. Nelson RE, Grebe SK, O'Kane DJ, et al. Liquid chromatography-tandem mass spectrometry assay for simultaneous measurement of estradiol and estrone in human plasma. *Clin Chem* 2004;50:373-384.
5. Albrecht L, Styne D. Laboratory testing of gonadal steroids in children. *Pediatr Endocrinol Rev* 2007;5 Suppl 1:599-607.
6. Kane J, Middle J, Cawood M. Measurement of serum testosterone in women; what should we do? *Ann Clin Biochem* 2007;44:5-15.
7. Cao Z, Soldin S, Rej R. Poor interlaboratory agreement of testosterone measurements using HPLC-tandem mass spectrometry. *Clin Chem* 2008;54 Suppl S:A113.
8. Rosner W, Auchus RJ, Azziz R, Sluss PM, Raff H. Position statement: Utility, limita-



- tions, and pitfalls in measuring testosterone: An endocrine society position statement. *J Clin Endocrinol Metab* 2007;92:405-413.
9. Taylor RL, Singh RJ. Validation of liquid chromatography-tandem mass spectrometry method for analysis of urinary conjugated metanephrine and normetanephrine for screening of pheochromocytoma. *Clin Chem* 2002;48:533-539.
10. Singh RJ, Eisenhofer G. High-throughput, automated, and accurate biochemical screening for pheochromocytoma: are we there yet? *Clinical Chemistry* 2007;53:1565-7.
11. Carter GD, Carter R, Jones J, Berry J. How accurate are assays for 25-hydroxyvi-

- tamin D? Data from the international vitamin D external quality assessment scheme. *Clin Chem* 2004;50:2195-2197.
12. Singh RJ. Are clinical laboratories prepared for accurate testing of 25-Hydroxy vitamin D? *Clin Chem* 2008;54:221-223.



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LabCorp Withdraws Ovarian Cancer Test

Warning Letter Ads New Twist to FDA's Approach to LDTs

BY BILL MALONE

In response to a September FDA warning letter, LabCorp recently cut the OvaSure test for ovarian cancer from the company's menu. The warning letter came after the agency asked to discuss the test's performance characteristics with LabCorp. FDA ultimately determined that the test could not be marketed under the rubric of lab-developed tests (LDT), pushing regulation of LDTs back into the spotlight for another reason.

In the warning letter, FDA asserts that because Yale researchers developed the test, it doesn't count as the type of in-house test that FDA allows to skip premarket review or 510(k) clearance. The letter states that OvaSure was "designed, developed, and validated" by Yale researchers, and so is "not within the scope of laboratory-developed devices over which the agency has traditionally exercised enforcement discretion."

In reply to the warning letter, LabCorp made the case that OvaSure is no different from other tests based on know-how from

academic researchers. In an SEC filing that officially announced the withdrawal of OvaSure from the market, LabCorp states that OvaSure was "rigorously validated pursuant to CLIA requirements" and that it disagrees with FDA that its interactions with Yale "provide FDA any basis for exercising jurisdiction over the test. LabCorp licensed intellectual property from Yale University; we did not purchase any products or materials from Yale." The letter goes on to argue that labs frequently offer tests which originate in academic research centers, a practice that can "permit this research to be translated into innovative diagnostic test services."

The Fine Print: All LDTs are Devices

While FDA has maintained for over a decade that LDTs are devices subject to FDA jurisdiction, the agency has generally declined to regulate them (CLN, November 2006). Instead, the agency regulates the building blocks of LDTs—analyte-specific reagents (ASR), which encompass the anti-

bodies, nucleic acid sequences, and other reagents that are the primary ingredients.

FDA laid out its view on LDTs in its final rule on ASRs published in 1997. This rule classified low-risk ASRs as class I devices exempt from premarket 510(k) requirements, and moderate and high-risk ASRs as class II and III devices, respectively. The purpose was to regulate all ASRs in a consistent way.

Some stakeholders had asked for a more strict approach, arguing that even labs that are qualified to perform high-complexity testing don't necessarily have expertise in developing tests themselves. Another argument for stricter oversight of ASRs was that CLIA regulation of labs does not require LDTs—which are made up of ASRs—to be validated in rigorously controlled clinical trials to establish expected values and performance characteristics. Such clinical trials are only required under FDA-cleared products. However, in the final rule, FDA stated that it "recognizes that the use of in-house developed tests has contributed

to enhanced standards of care in many circumstances and that significant regulatory changes in this area could have negative effects on the public health." Even at that time, FDA made its view clear that LDTs are still devices under its purview: "FDA believes that clinical laboratories that develop such tests are acting as manufacturers of medical devices and are subject to FDA jurisdiction." But the agency asserted that its oversight, as explained in the ASR final rule, was sufficient to assure quality of LDTs.

Ironically, LabCorp's OvaSure seems to have been fated to run into the same problems as a similarly named test that also worried FDA—Correlogic's OvaCheck test, which also identifies early-stage ovarian cancer. In Correlogic's case, FDA took issue in 2004 with the test's sophisticated interpretation software, a new element in test interpretation. Two years later, FDA released its controversial IVDMA draft guidance that deals with software that interprets data from multiple analytes. **CLN**

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NHGRI Supports Study Of DTC Genetic Testing

The Genetics and Public Policy Center at Johns Hopkins University received a 2-year, \$589,318 grant to study the field of direct-to-consumer (DTC) genetic testing. The study will look at how companies offer tests and test interpretation to consumers while bypassing the traditional healthcare

model. The study will also investigate who orders the tests, how they use the information, and how the ordering and testing processes are regulated. Genetic tests for more than 1,300 diseases or conditions are now available, with the number climbing rapidly. Theoretically, almost any genetic test could be offered directly to consumers, and more than 30 companies have tests on the market, explained the study's principal investigator,

Gail Javitt, JD, MPH, who is also the center's law and policy director. She also noted that while a lot of anxiety exists about DTC genetic testing, there's a paucity of information about the industry or consumers who purchase the tests. More information about the study is available on the center's website, <http://www.dnapolicy.org/>.

AdvaMed, AHA, AHIMA Support Move to ICD-10

Urging the Department of Health and Human Services (HHS) not to delay the switch to the new ICD-10 coding system, AdvaMed, AHA, and AHIMA voiced their support of ICD-10 in a letter to Con-

gress (CLN November, 2008). The three associations argue that Congress's goals of improving quality, reducing medical errors and infections, and modernizing health IT won't move forward without the switch. "The time for moving forward is long overdue," the letter reads. "The ICD-9 code set was never designed to provide the increased level of detail required to support emerging needs such as biosurveillance, quality reporting, and development for pay-for-performance programs. The National Committee on Vital and Health Statistics concluded in 2003 that we were ready to transition to ICD-10. Now is the time to act on that recommendation." The letter also argues that vendors will continue buying and building products for the old ICD-9 system until the switch takes place, and that those systems will be expensive to retrofit in the future. The letter is available online, http://www.ahima.org/icd10/documents/2008_AHA-AHIMA-AdvaMedICD-10SenLetterOct28.pdf.

Audit Finds Slack Enforcement Of HIPAA Security Rule

A recent audit by the HHS Office of Inspector General found that CMS had done too little to make sure that healthcare providers and insurers followed the HIPAA security rule, a law that requires all electronically transmitted health information be kept confidential and protected from unauthorized use. CMS did not have effective mechanisms to make sure that healthcare entities were complying with HIPAA or that electronic information was being protected, although CMS did have a good process for receiving and processing complaints, according to the report. In response, CMS has moved ahead with a plan to conduct compliance reviews of covered entities. The report is available on the HHS Office of Inspector General's website, <http://www.oig.hhs.gov/>.

Presidential Advisory Council Urges Support of Personalized Medicine

The President's Council of Advisors on Science and Technology (PCAST) issued a report outlining priority areas and policy recommendations for personalized medicine, including a call for a greater role for the federal government to provide funding, coordinate research, and eliminate regulatory hurdles. Applauded by the Personalized Medicine Coalition (PMC), of which AACC is a member, the PCAST report lays out a blueprint for pushing more widespread adoption of personalized medicine by healthcare providers. The report also recommends that government work with industry to facilitate research by putting together a collection of high-quality biological specimens accompanied by comprehensive disease annotations. The report's authors also note reimbursement problems with genomics-based molecular diagnostics. Currently reimbursed at the same rate as other laboratory tests, these molecular tests should be reimbursed based on their value in patient care, the report concluded. The report is available on the PCAST website, <http://ostp.gov/cs/pcast>.

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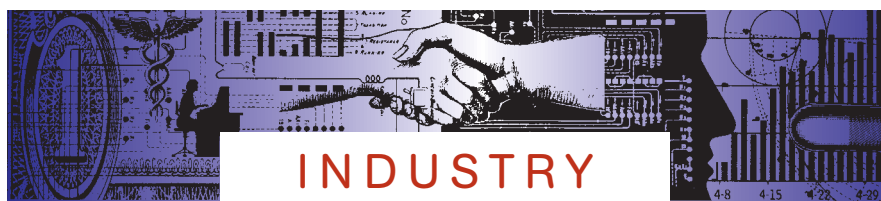
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INDUSTRY

Study to Assess Influence Of Personal Genetic Testing

Four healthcare, technology, and research organizations have teamed up to assess the behavioral consequences of personal genetic testing. The study, led by Scripps Translational Science Institute and co-sponsored by Navigenics, Affymetrix, and Microsoft, will examine whether personal genetic scans inspire people to make lifestyle changes or seek further medical evaluation. "Genome scans give people considerable information about their DNA and risk of disease, yet questions have been raised if these tests are ready for widespread public use," said Eric Topol, MD, director of Scripps Translational Research Institute and principal investigator of the study. "Our study will prospectively evaluate the effect that state-of-the-art gene scans have on people's lifestyles, behaviors, diets, and psyches."

The study will offer genetic scans to up to 10,000 employees, family members, and friends of the Scripps Health System in San Diego and will monitor changes in participants' behavior over 20 years. Affymetrix will scan participants' genomes and Navigenics will interpret results and give personalized guidance on ways to mitigate the risk of disease. Then each participant will be able to enter and store clinical and lifestyle

information in an individual, online Microsoft HealthVault account. Participants can use the HealthVault account to manage their health information and share it with healthcare providers. As part of the study, researchers will use the genetic variations found in participants as a tool to examine how genes are linked to disease.

Cypress Bioscience Launches Test Services for RA

Cypress Bioscience announced two new personalized medicine test services aimed at rheumatologists treating patients with rheumatoid arthritis. The Avise PG test supports dose optimization and therapeutic decision making for patients taking methotrexate, a common first-line therapy for RA, by measuring levels of the active metabolites of the drug. Traditionally, physicians have had to depend on a patient's clinical signs and symptoms to optimize methotrexate therapy. The other test, Avise MCV, aids in the diagnosis and prognosis of RA. This test measures antibodies to mutated citrullinated vimentin, a protein found in the inflamed joints of patients with RA. Both are available exclusively from Cypress Bioscience and performed at the company's CLIA-certified lab in San Diego, Calif. "To date, rheumatology has not benefited from advances in personalized medicine to the

same extent as fields such as oncology," said R. Michael Gendreau, MD, PhD, chief medical officer at Cypress Bioscience. "Cypress Bioscience is committed to developing personalized medicine tools to help rheumatologists individualize patient care with the goal of improving both the diagnosis and treatment of rheumatologic disease."

Northfield Labs Submits Blood Substitute for Priority Review

Northfield Laboratories announced it has submitted a Biologics License Application (BLA) to the FDA for PolyHeme, the company's experimental human hemoglobin-based red cell substitute. PolyHeme is intended for use for treatment in life-threatening blood loss when red blood cells are not available. Northfield also requested Priority Review from FDA, which means a 6-month review timeline instead of the usual 10 months. Northfield has been working on PolyHeme for two decades and incurred over \$200 million in losses. Last year, the company reported clinical trial results that showed more trauma patients died within 30 days of receiving PolyHeme

than those who received traditional care; however, the company remains optimistic. "This submission is the culmination of the development of PolyHeme for its initial clinical indication," said Steven Gould, MD, CEO of Northfield. "We firmly believe in PolyHeme's potential to save the lives of patients for whom blood transfusion is not an option." By regulation, FDA has two months to review the company's BLA and decide whether it merits Priority Review.

Aetna Gives In-Network Coverage To PGxHealth Genetic Tests

PgxHealth, a division of Clinical Data, announced that it has become an in-network provider for Aetna, gaining full coverage for its FAMILION genetic tests. These tests detect genetic mutations that recognize inherited forms of cardiac channelopathies, such as long QT syndrome, as well as cardiomyopathies. With the new in-network coverage for Aetna patients, PgxHealth now has reimbursement for the tests for an estimated 155 million people. The company is also an approved Medicare provider for its genetic testing services.

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Survey Shows Labs Struggle With Critical Value Reporting

Being able to report critical values for outpatient-related tests is the single greatest obstacle faced by laboratorians in accomplishing this important patient safety function, according to a survey of more than 350 hospitals and hospital systems (Arch Pathol Lab Med 2008;132:1666–1671). Three-quarters of respondents reported experiencing difficulty in getting outpatient providers to return calls or pages. New strategies for making contact with the covering provider are needed in this population particularly, because the patients are not necessarily easy to reach or in close proximity to medical services. Authors of the study also report how some labs have investigated ways to reduce false-positive results for outpatient values. For example, a case study at one institution found that plasma potassium drawn at the same time and being placed in ice with HbA1c samples had a high number of critical values, which on resampling were determined to be within normal limits. The lab subsequently eliminated the send-on-ice requirement and experienced a 20% to 40% drop in potassium critical values. Researchers also found considerable variability in other aspects of critical value reporting. For instance, about 18% of labs indicated they use customer service centers to handle critical value callbacks, but the majority still rely on the technologist who performed the test to do so. Approximately 22% reported not having compared their critical value lists with national norms, while 24% indicated

they have not measured the time between a critical result becoming available and being relayed to the responsible clinician. While the majority of labs used a combination of calling the ordering location, the patient's physician, or a nurse or nurse manager, 8.6% reported using wireless technology, such as pagers, to notify the caregiver. The authors believe the survey findings fill a void in the literature about improving critical value responses at a time when critical values have become more prominent in patient safety initiatives.

PSA Assay Standardization Bias Could Affect Clinical Decision-Making

The two most common PSA assays yield discordant results and could have negative consequences for clinical decision-making, according to findings from a recent prospective study (Journal of Urology 2008; 180:1959–1963). The findings are of particular import because many physicians and patients are not aware of the assay used for any individual PSA test. Researchers tested 1,916 samples using both the Hybritech Access assay with Hybritech standardization and the ADVIA Centaur assay with WHO 90:10 standardization, the two most common commercial PSA assays. They found 17% and 38% differences in the median and mean PSAs, respectively, with the Centaur assay lower in both instances. Using a PSA threshold of 2.5 ng/mL, 5% of subjects would have been recommended for a prostate biopsy with one assay but not the other. The study also revealed that if the tests were used sequentially, differences in the assays

Clarification: Lab Credentialing Agencies

We wish to acknowledge a letter to the editor from Christopher A. Damon, Executive Director of American Medical Technologists regarding the article in the October issue of *CLN*, "Lab Credentialing Agencies Merging: Unification Aims to Simplify Hiring Qualified Lab Personnel." The article suggests that there are only two credentialing agencies for laboratory personnel. In fact, as Mr. Damon points out, there are four: AMT (American Medical Technologists), ASCP (American Society for Clinical Pathology), NCA (National Credentialing Agency for Laboratory Personnel), and AAB (American Association of Bioanalysts). Also unclear in the article was the relative size of these programs. ASCP issues the most MT/CLS certifications, followed by AMT, then NCA. We appreciate Mr. Damon's comments and regret any misrepresentation. You can read the letter at www.aacc.org. It is posted along with the October article on the *CLN* section of the website.

could either over- or understate PSA velocity, a key factor in predicting prognosis. In fact, 26%, 14.5%, and 4.5% of subjects had a potentially misleading PSA difference between the tests of greater than 0.4, 0.75, and 2.0 ng/mL, respectively. The researchers concluded that there is a need for greater awareness of PSA assay standardization discrepancies and called for manufacturers and clinical labs to provide information about which assay their test is based on, and for lab reports to clearly state the assay manufacturer.

CRP, Troponin Predict Significant Increase in Risk of Death after AMI

Patients with CRP and troponin positivity have a two times greater risk of dying within 28 days after an AMI, and both troponin and CRP were independent predictors of 28-day case fatalities, according to a recent prospective study (Am J Cardiol 2008; 1125–2230). The study involved 1,646 patients who had experienced fatal coronary events or non-fatal AMIs and were consecutively enrolled in the WHO Monitoring Trends and Determinants on Cardiovascular Diseases (MONICA) project. In investigating the prognostic role of

CRP and troponin for both ST-elevation MI (STEMI) and non-STEMI, researchers found that in patients with STEMI, troponin positivity but not CRP positivity independently predicted 28-day fatality. The situation was reversed in non-STEMI patients: CRP positivity but not troponin positivity predicted 28-day mortality. The latter finding is incongruent with other studies; however, those studies included a significant number of patients with unstable angina only and not increased myocardial necrosis factors, according to the authors. In contrast, this analysis excluded patients with unstable angina and had only a "negligible" number of patients with no increase in myocardial necrosis markers. Researchers called for further studies to determine whether strategies such as immediate adoption of high-dose statins or very early interventional therapies might be beneficial for higher-risk patients identified by increased CRP levels upon hospital admission.

Statin Treatment, PSA Declines Linked

PSA levels declined significantly after initiation of statin treatment, and the reduction was greatest among men with larger decreases in LDL-C, higher statin doses, and higher pre-statin PSA levels, new research shows (J Natl Cancer Inst 2008; 1511–1518). This longitudinal study included 1,214 men who were free of prostatitis and prostate cancer, had not undergone prostate surgery or taken medications known to alter androgen levels, and for whom there was at least one PSA value within 2 years before and at least one PSA value within 1 year after starting statin therapy. Researchers found that after starting a statin, median LDL-C decline was 27.5% and the median PSA decline was 4.1%. Changes in PSA levels were strongly associated with statin dose and changes in LDL-C levels. For every 10% drop in LDL-C after starting a statin, PSA levels declined by 1.64%. Doses of at least 20 mg simvastatin were associated with a 8.5% greater decrease in PSA than doses less than 20 mg. Researchers conclude that if confirmed through other studies, their findings would justify further investigation into the relationship between statins and PSA, and whether statins directly influence prostate biology. They also caution that additional study is needed to assess the influence statin-mediated PSA reductions could have on cancer detection protocols.

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NEWS FROM THE FDA

FDA Clears Ikonisys HER2 Test

Ikonisys announced 510(k) clearance for its oncoFISH HER2 test, a fully automated microscopy-based application for determining HER2 status in human breast cancer specimens. Labs process the specimens with Abbott's PathVysion HER2 DNA Probe kit and run the test on Ikonisys's automated CellOptics platform that uses a high-throughput digital microscope. Increased quantities of HER2 protein can cause rapid tumor growth, resistance to certain types of treatment, decreased disease-free periods, and short overall survival in breast cancer patients.

Automated HVC Viral Load Test Approved

Roche Molecular Diagnostics announced the FDA approval of its COBAS AmpliPrep/COBAS TaqMan HCV test. The test uses proprietary real-time PCR to quantify the amount of HVC RNA in a patient's blood. The test offers a broad dynamic range, down to the "undetectable" low levels of viremia, and is calibrated to

WHO traceable standards, with a lower detection limit of 18 IU/mL. Designed for use with Roche's AmpliPrep sample preparation instrument and TaqMan analyzer, the test is the third Roche COBAS TaqMan real-time PCR test approved by FDA in that last 18 months.

FDA Clears Sysmex IG And RET-He Parameters

Sysmex announced the FDA clearance of its Immature Granulocyte (IG) parameter and Reticulocyte Hemoglobin Equivalent (RET-He) parameter for use on the company's XT-Series automated hematology analyzers. The IG parameter provides a quantitative immature granulocyte count for metamyelocytes, myelocytes, and promyelocytes using the XT-Series instrument's fluorescent flow cytometry. Identification of immature granulocytes is primarily of importance in diagnosing infectious and inflammatory diseases. The RET-He parameter provides a direct measurement of the mean reticulocyte hemoglobin content, assisting physicians with diagnosing iron deficiency.

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Molecular MRSA Test Gets Moderate Complexity Categorization

Cepheid announced that its Xpert MRSA/SA blood culture test has received a moderate complexity categorization from FDA, allowing the test to be performed in a wider range of settings. The test is designed for on-demand detection of

MRSA and SA in positive blood cultures. Cleared for marketing in October, the test is the first molecular diagnostic test for positive blood cultures to receive the moderate complexity CLIA categorization. The test runs on Cepheid's GeneXpert system, a platform designed for detecting healthcare-acquired infections.

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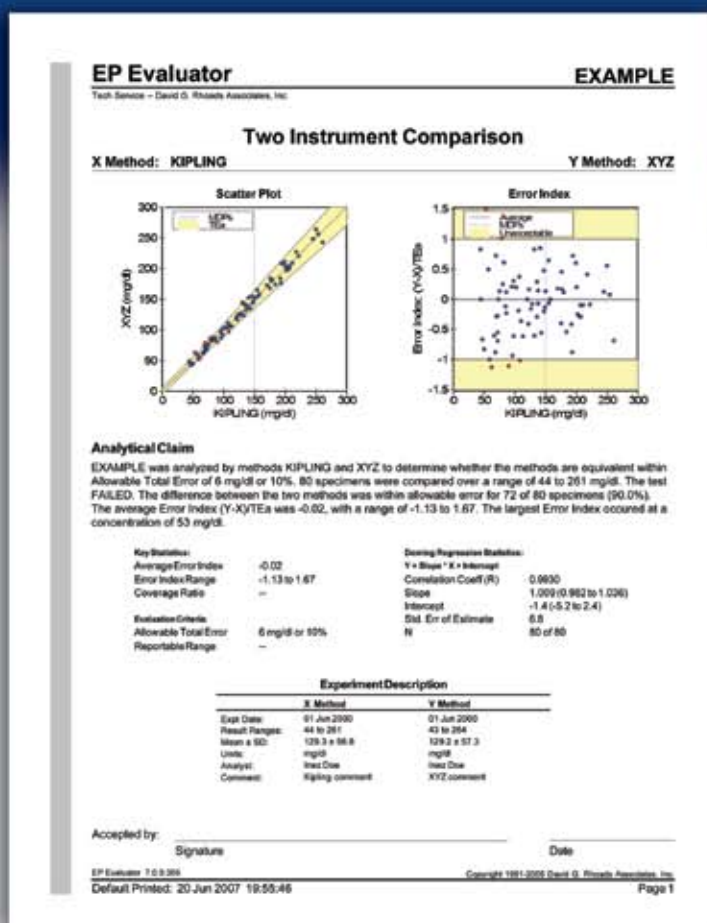
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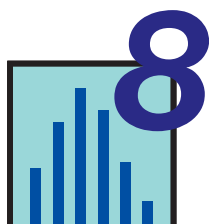
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