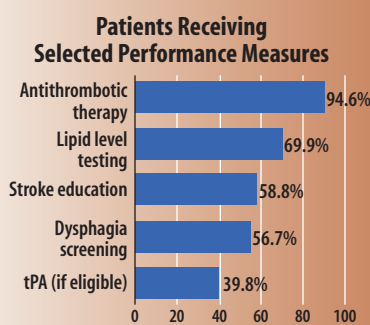


**REPORT: STROKE CARE  
NEEDS IMPROVEMENT**

A new report on stroke registry data from four states indicates that although stroke care has improved, further advances need to be made at both the healthcare system and institution levels (MMWR 2009;58:1–23). The information comes from the Paul Coverdell National Acute Stroke Registry (PCNASR), a U.S. Centers for Disease Control and Prevention-sponsored initiative to track and improve hospital-based acute stroke care.

From 2005 to 2007, PCNASR tracked 10 care performance measures involving 195 hospitals and nearly 57,000 patients in Georgia, Illinois, Massachusetts, and North Carolina through registries maintained by state health departments. A separate prototype phase took place between 2001 and 2004, with the registries led by CDC-sponsored investigators in academic and medical institutions.

Patients included in PCNASR were at least 18 years old and had a clinical diagnosis of acute ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, transient ischemic attack (TIA) or an ICD-9-CM code indicative of stroke or TIA. Ischemic stroke was



the most common diagnosis accounting for 53.3% of cases.

Lab testing was among the performance measures with the most improvement. During the prototype phase, only one-third of patients had lipid levels measured either after hospitalization for stroke or within 30 days before the stroke with the results available in the medical record. However, in the 2005–2007 timeframe, this indicator was recorded for nearly 70% of patients. Other measures with significant improvements included dysphagia screening, smoking cessation counseling, and antithrombotic therapy prescribed at discharge.

At the healthcare system level, the report emphasizes the need for greater public awareness about the symptoms of stroke and the importance of seeking care immediately. About half of patients with ischemic stroke lacked documented information on time of symptom onset, and an additional 25% arrived too late to receive tissue plasminogen activator therapy, a level that was unchanged between the prototype and 2005–2007 timeframes.

# Clinical Laboratory News

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## New Heparin Standards

*Will the Change Make a Discernable Difference  
In Coagulation Monitoring?*

BY GENNA ROLLINS

**H**eparin's essential role in the prevention and treatment of thrombosis has been recognized for decades, yet keeping the dosage in a therapeutic range always has been a delicate balancing act. Too little drug, and the patient will be inadequately anticoagulated and at-risk for clots; too much drug, and hemorrhage is possible. Although clinicians rely on tests such as activated partial thromboplastin time (aPTT) and activated clotting time (ACT) to monitor the effects of the drug, properly titrating the dose is challenging due to the heterogeneity of unfractionated heparin and patients' individualized dose-response. Now, a recent update to the U.S. Pharmacopeia (USP) heparin monograph has added another potential confounding factor in dosing and monitoring, leaving coagulation experts wondering about the ultimate impact of the change. The update, which became effective October 1, 2009, resulted in an approximate 10% reduction in heparin potency in the U.S. and brought U.S. and international units of unfractionated heparin in line with each other.

Many coagulation experts recommend a watch-and-wait approach for now. "The question is, what, if any, clinical implications this change in potency will have," said Jawed Fareed, PhD, clinical professor of pathology and pharmacology at Loyola University Medical Center in Maywood, Ill. "At this stage, all that's called for is extra caution and monitoring of patients, and watching at the bedside if any changes would be noted."

### Addressing Safety Concerns

USP updated the monograph in response to more than 200 deaths worldwide associated with adulterated heparin. In the U.S. the problem was first publicized in January 2008 when Baxter International, one of the

See **Heparin**, continued on page 3



## Interpretive Comments on Tests Results

*How Far Should Labs Go?*

BY BILL MALONE

**W**ith today's focus on patient safety, diagnostic errors have been put in the spotlight. Whether the result of systemic mistakes by an organization or those of individual clinicians, some reports have noted clinicians' failure to correctly interpret diagnostic tests, pushing the problem uncomfortably close to the walls of the lab. One explanation put forward for missed diagnoses is the sheer volume of information clinicians need to process in order to do their jobs. With PubMed adding about 670,000 new entries per year to its cache of some 18,782,970 citations, clinicians face a huge challenge to stay on top of new treatments, trends, and standards, let alone simultaneously keep an eye on developments in lab medicine.

In order to help clinicians understand test results, some labs have turned to including interpretive comments on their lab reports. Although information technology has made it easier to add interpretive comments, laboratorians have debated exactly when, how much, and what kind of commenting really works. Those labs experimenting with interpretive comments say they tread a fine line between helping physicians assimilate information from the lab without contributing to the information overload so pervasive in medicine. In fact, a recent survey suggests that physicians do want and depend on interpretive comments: general practitioners in the U.K. reported that in at least 75% of cases, the lab's interpretation influenced patient management.

As laboratorians try to figure out how best to exploit their expertise in test interpretation, they must also find the right balance when

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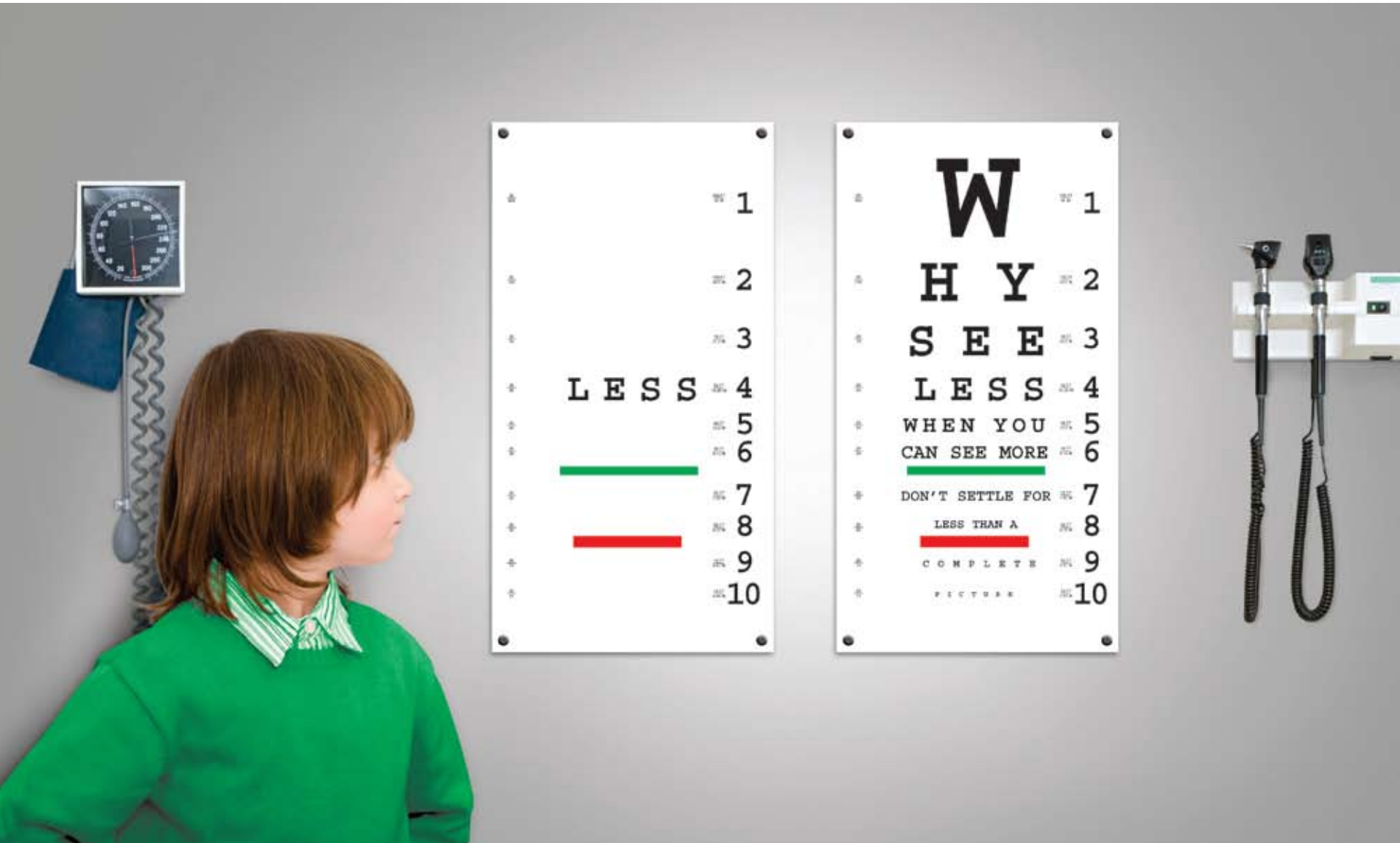
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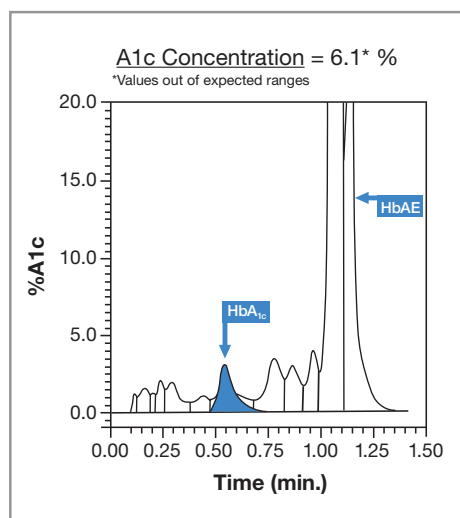
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# Experts Surprised By Heparin Change

Heparin, continued from page 1

major suppliers of heparin, noted a spike in deaths among patients taking the drug and recalled certain lots. Baxter subsequently recalled all remaining lots and the U.S. Food and Drug Administration (FDA) found the source of the problem to be contamination with over-sulfated chondroitin sulfate, which comes from the dietary supplement chondroitin and can mimic heparin's blood-thinning actions. The problem subsequently was linked to a Baxter contractor's plant in China.

Apparently the over-sulfated chondroitin sulfate passed existing quality tests, so USP first revised its heparin monograph standards in June 2008 to include new tests manufacturers must use to detect the contaminant. The second phase of USP's update included a new potency assay for heparin, the chromogenic anti-Factor IIa test, along with a new potency reference standard. This new standard is calibrated to WHO's international standard for unfractionated heparin. According to USP, there had been an estimated 10% drift over the past three decades between USP's heparin unit and WHO's international unit. Since the new USP heparin sodium for assays reference standard is directly traceable to the 5th international standard for unfractionated heparin, the disparity between U.S. and international units has been eliminated. In the long run, this harmonization of standards is a positive development, but in the meantime, laboratorians, pharmacists, and physicians will need to monitor the transition closely.

## A Divergence of Opinion

When phase two of the monograph became effective, USP indicated that it did not anticipate the change would have clinical significance. However, FDA issued a public health

alert on October 1 advising that the change in heparin potency could have clinical significance in some situations, such as when the drug is administered via bolus and "an immediate anticoagulant effect is clinically important." FDA urged providers to consider the change in potency when making decisions about what dose to administer. In addition, the agency advised that new and old lots of heparin might be available at the same time, that the potency change might require more frequent or intensive aPTT or ACT monitoring, and that clinical judgment would be essential in determining the dose of heparin for individual patients.

Although the new monograph went into effect October 1, FDA asked manufacturers to wait until at least October 8 to start shipping products manufactured and tested in accordance with the new monograph. The delay was designed to give providers and pharmacies "time to make the necessary adjustments in their prescribing and dispensing practices," according to John Jenkins, director of FDA's Office of New Drugs. "Although the FDA-approved labeling for heparin has not changed, including the recommended doses, it is essential that healthcare professionals be aware of the potential difference in potency between the old and new vials of heparin when administering the drug."

Even though the heparin contamination problems were well-known, the change in USP's monograph and the FDA alert came as surprises to many in the field, according to Charles Eby, MD, associate professor of pathology and immunology at Washington University School of Medicine in St. Louis. Likewise, many healthcare providers were unaware of the potency drift between USP and WHO standards that had taken place over the years. As a result, initially there was some alarm in the coagulation field, but as experts had time to contemplate the impact, the concerns have diminished, he said.

A key consideration for many hospitals has been whether therapeutic ranges for PTT would be invalidated by the change in potency. In his networking with colleagues, Eby found "unanimous consensus that no, the therapeutic ranges would not be impacted." However, since both PTT and antifactor Xa assays are used to develop heparin sensitivity curves, a second issue centered on the calibrations for antifactor Xa assays, which use heparin. "We were concerned about how our industry colleagues were calibrating the antifactor Xa assays and whether they were using the same USP heparin activity that had just changed or had been calibrating with an international heparin unit that's related back to the WHO standard," Eby explained. As it turns out, all of the major manufacturers of antifactor Xa assay kits contacted by Eby and his colleagues already had been calibrating their tests to the international standard. Still, labs will do well to verify manufacturers' standards for the various assays, according to Michael Laposata, MD, PhD, pathologist-in-chief and professor of pathology and medicine at Vanderbilt University Hospital in Nashville. "We have a call in to the company that makes our reagents, and we're asking them whether they plan to change their standard in light of the planned changes to unfractionated heparin."

With USP suggesting the potency change will have little importance clinically and FDA warning that it could have a significant impact, at least in certain populations, exactly what effect it actually will have remains to be seen. The picture is murky for several reasons, most notably because of the well-known, highly variable dose-response to unfractionated heparin. For instance, one study found that even when the aPTT reached a therapeutic range of 55 to 85 seconds, the next two consecutive measurements remained in that range in less than one-third of patients (Arch Intern Med 2003; 163:621-627). In addition, patients received an average of four different heparin doses over the first 3 days of treatment, and only 7% maintained the therapeutic range on each of 4 sequential days. Similarly, a 2003 CAP Q-Probe study found that 20% of patients were not in the therapeutic anticoagulation range within 24 hours of starting therapy. On the flip side, one-third of patients were considered in the supra-therapeutic range on at least two occasions during their first 72 hours on heparin, putting them at risk for hemorrhagic complications. The study also reported a wide variation in therapeutic aPTT times.

## Patient Populations of Concern

Laposata believes any effect will be most noticeable in patients at the borderline therapeutic range after an initial bolus in-

jection of heparin. "My guess is that if it is 10 percent less potent, the potential danger would be for the person who is right at the edge of the therapeutic range. So you may be shooting for a 60 second aPTT and come out several seconds lower," he explained. "I'm guessing that people will do as they have in the past, and that is to give a bolus, and if the aPTT isn't in the therapeutic range, they'll give some more." For example, Laposata noted, a standard heparin bolus dose is 80 units/kg of patient weight and a standard maintenance dose is 18 units/kg/hour. If a patient either wasn't in or was borderline for the therapeutic range after the bolus, the maintenance dose might be increased slightly.

Obese patients are another population that deserves special scrutiny, according to Fareed. "If you give 7,500 units to a 70 kilogram patient, a 10 percent change in potency may not make that much of a difference. But in giving 7,500 units to a 100 kilogram patient, a 10 percent potency difference might have a considerable therapeutic impact," he explained.

Another expert believes that the greatest potential impact of the potency change could be in two situations where heparin bioavailability is not always closely monitored. One is when heparin is given twice daily to prevent blood clots in high-risk patients. The other is in circumstances in

See **Heparin**, continued on page 4

## For Further Information

**American College of Chest Physicians Antithrombotic and Thrombolytic Therapy: Evidence-Based Clinical Practice Guidelines (8th Edition)**, Hirsh J, Guyatt G, Albers G, Harrington R, et al, Chest 2008; 133:71-105S. A letter advising ACCP members about the new heparin monograph as well as the recommendations of an expert panel convened to evaluate the changes is available online at [www.chestnet.org](http://www.chestnet.org).

**U.S. Pharmacopeia.** A series of documents and background materials about the updated USP heparin monograph are available on the USP website, [www.usp.org](http://www.usp.org). Go to Hot Topics: USP Heparin Information.

**U.S. Food and Drug Administration.** The FDA Public Health Alert regarding the updated USP monograph is available on the FDA website at [www.fda.gov](http://www.fda.gov). Go to drugs, drug safety and availability, postmarket drug safety information for patients and providers.

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# AACC

## Clinicians, Labs Take Watchful Approach

Heparin, continued from page 3

which patients receive much higher doses of heparin, such as those undergoing kidney dialysis or cardiac procedures involving cardio-pulmonary bypass. “In those settings a 10 percent potency decrease is more likely to have clinical significance because if you’re giving X and in the past it didn’t cause clotting of the circuit, what we don’t know is if we give 10 percent less, are we crossing a threshold at which clotting becomes more frequent,” explained Mark Crowther, MD, MSc, FRCPC, acting chief of laboratory medicine at St. Joseph’s Healthcare and Hamilton Health Sciences Corporation and professor of Medicine and Pathology and Molecular Medicine at McMaster University in Hamilton, Ontario, Canada. However, he emphasized, “we don’t truly understand the implications of this change.” Crowther also serves as vice chair of the thrombosis section of American College of Chest Physicians (ACCP) guidelines on antithrombotic therapy and was part of a panel of experts convened by ACCP to evaluate the USP changes.

### Institutional-Level Monitoring a Must

Because of the highly variable dose-response to heparin, any impact may not be detectable in individual patients, so institutional-level monitoring will be critical. “Where institutions are going to see an impact is whereas last year they had 35 clots in their dialysis circuits, this year they might have 40. In an individual patient it’s going to be completely impossible to tease out,” Crowther predicted. St. Joseph’s is not alone in planning a systematic evaluation of any changes in thrombotic events. Eby explained that Barnes-Jewish Hospital in St. Louis also will be looking closely at event rates and changes in aPTT. “We’ll be looking at this as a case-control study, with controls being a retrospective review and cases being patients who receive heparin based on the new USP potency. We’ll need months of data. It’s not the kind of comparison that can be done in a week,” he noted.

ACCP indicated that it will reassess any guideline changes after its panel of experts has had an opportunity to review monitoring data. Meanwhile, the American Society of Hematology issued a notice alerting its members to the change, but has no plans to release additional guidance for now, according to Stephanie Kart, government relations manager.

In keeping with the need to monitor the impact of the potency change, lab testing will take on more importance, and some facilities may reconsider their testing strategies, predicts Paula Santrach, MD, co-director of point-of-care testing and associate professor of laboratory medicine and pathology at Mayo Clinic in Rochester, Minn. “In patients on low-dose heparin therapy, there’s been a back-and-forth lately. We used to follow them with aPTT, which is a measure of the function, the clotting time,” she explained. “But people are moving more and more to the antifactor Xa assay, which gives you results in units/mL. With the change in potency, you may not get the same kind of correlation between the concentration and the effect. So I think understanding your antifactor Xa assay and your nomograms will be important in relation to this change.”

Laboratorians may want to refer to ACCP and CAP guidelines, which recommend calibrating aPTT ranges based on antifactor Xa activity of 0.3 to 0.7 units/mL. The antifactor Xa assay has the advantage of less interlaboratory variability than aPTT assays. However, both markers have their challenges due to lack of robust data correlating them to efficacy and safety outcomes, according to Edith Nutescu, PharmD, FCCP, clinical professor in the department of pharmacy practice and center for pharmaco-economic research and director of the antithrombosis center at the University of Illinois at Chicago Medical Center. “That’s why the guidelines don’t mandate or suggest going to antifactor Xa assay,” she said. Fareed believes the aPTT assay will remain the standard of care for heparin dose-response monitoring.

When the new monograph was issued, some organizations questioned whether they should proactively update their dosing nomograms to increase the rate of heparin infusion by 10%. Eby thinks it would be premature to do so based on his discussions with colleagues. “I think the answer to that will be retrospective after we’ve accumulated data,” he predicted.

Another concern brought forward by FDA was that lots of “old” and “new” po-

tency heparin might be available at the same time, so providers would need to be able to distinguish between the two. Hospira reportedly is using lot numbers starting with 82 or higher, while the three other companies that market heparin in the U.S., APP, Baxter, and B. Braun, will denote new lots with the letter “N”. However, in early November several hospitals consulted for this article had not received any lots of the new potency heparin. The University of Illinois at Chicago Medical Center is one example. “We don’t have a firm date for receiving the new lots, but what we’re planning to do is roll them out so that practitioners are alerted that the new lots are going into effect,” explained Nutescu. “Ideally, there’ll be time in weaning out of the old and rolling in of the new lots that we can target it systematically so a given patient won’t be going back-and-forth between the old and new drug.”

As lots of the new heparin formulation make their way into hospitals across the country, laboratorians should be on the front lines of developing communication and monitoring plans with their pharmacist and physician colleagues, according to Santrach. “You have to talk about it so everyone is aware and there’s a plan,” she suggested. “Heparin monitoring isn’t necessarily standardized so you have to look at your own situation and determine what the potential impact could be and how you would mitigate that.”

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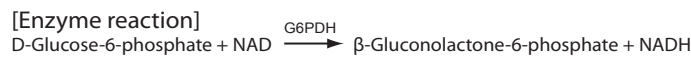
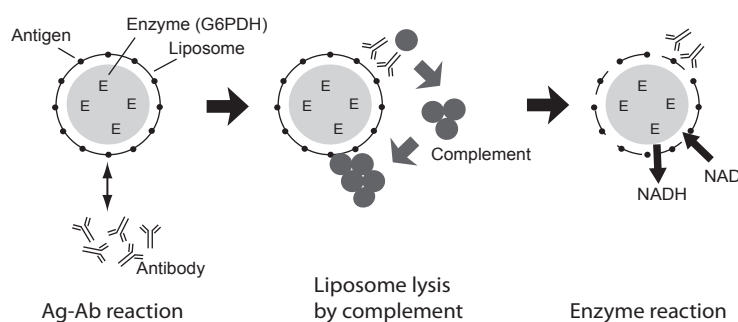
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# Interpretations Help Prevent Misdiagnoses

Interpretive Comments, from page 1

it comes to helping clinicians, said Anand Dighe, MD, PhD, director of the core laboratory at Massachusetts General Hospital, and an assistant professor of pathology at Harvard Medical School who has studied how clinicians use interpretations from his lab. "There is a very narrow view of lab medicine among clinicians. Now that is being broken down. Lab medicine doesn't just happen within the walls of the laboratory. In fact, it's much broader than that," Dighe said. "Our job description is not just to turn out ten million test results per year. Our job is to help clinicians order and interpret tests. The test result is just the starting point."

## What's In a Comment?

Interpretive comments on lab reports span a wide range, from a basic decision limit, to delta checks for serial results, to a definitive clinical diagnosis, noted Mario Plebani, MD, professor of clinical biochemistry and clinical molecular biology at the University of Padova School of Medicine and chief of the department of laboratory medicine at the University-Hospital of Padova, Italy. As a general definition, Plebani suggests that interpretive comments include "any

additional information on the lab report that may help a clinician to better interpret information from the lab." This spectrum contains everything from a canned single-sentence comment attached automatically to every result of a particular test, to individualized paragraphs that describe the clinical situation in a detailed, narrative style, as in anatomic pathology.

**"Our job description is not just to turn out ten million test results per year. Our job is to help clinicians order and interpret tests. The test result is just the starting point."**

Anand Dighe, MD, PhD, director of the core laboratory at Massachusetts General Hospital and assistant professor of pathology at Harvard Medical School

Dighe and his colleagues at Massachusetts General Hospital found that the lab's interpretive comments on coagulation results were particularly successful. They surveyed physicians when the lab first included the interpretive comments. The response was resoundingly positive: physicians said the interpretations had prevented a misdiagnosis in 71% of the cases. "Anecdotally, physicians told us that they wouldn't even look at the results of the test until the in-

terpretation was back because it just wasn't worth their time without it," Dighe explained. "With coagulation tests, there are a lot of causes of false positives and false negatives, and it was much better to have a lab expert examine the results before the physician did."

Under the Massachusetts General Hospital program, specimens arrive in the morning or the day before, and the lab performs all the tests during the day. Reflex testing is also performed if something is ab-

normal, allowing the lab to produce an answer by the end of the day. Special software packages gather all the results, and pathology residents work with the attending clinician who is in charge that week. They go into the software with all the data in front of them, write an interpretive paragraph, and put cases in pre-sign status. Finally, at the end of the day, residents sit down with the attending clinician, review the cases, and the attending clinician officially signs them out. With this system improving the efficiency of information flow, the Massachusetts General Hospital coagulation lab routinely performs 50 complex interpretations per day.

Using interpretive rounds for coagulation results inspired Dighe and his colleagues to work on similar systems for toxicology, hemoglobin, blood transfusion, protein electrophoresis, molecular diagnostics, and autoimmune disorders. The approach has been very well received by clinicians, but also underscores one of the boundaries laboratorians face in beefing up interpretations: only an MD can bill his or her time for such an in-depth service under current Medicare rules.

Outside the U.S., test interpretations are not billed separately but considered a routine part of the service a lab provides. For example, in Plebani's lab in Italy, both MDs and PhDs record interpretive comments according to each person's specific competence and training. "In particular, in the fields of hematology, coagulation and autoimmunology, MDs are very involved, while in the areas of protein and specialized clinical chemistry, PhDs are more active," explained Plebani. "However, the main difference is the individual level of competence and responsibility achieved during and after post-graduate courses. We consider this activity a fundamental job of laboratory professionals and that time for interpretive commenting has to be considered when discussing the number and qualifications of laboratory staff with administrators." His lab does not receive additional fees for interpretations, but the reimbursement is considered a part of the whole laboratory service.

Similarly, in the U.K., interpretations are "taken as a given," said Danielle Freedman, MB, ChB, consultant chemical pathologist and associate physician in clinical endocrinology at Luton and Dunstable Hospital NHS Foundation Trust in Luton. "This is just part of the service we offer. We

have clinical scientists who also give advice, which I know is a contentious issue in the states. We may be different here, but in the U.K, we see this as a high priority of our job. There is more and more testing going on, and it's more complex, so in particular you're not going to expect primary care physicians to always understand the clinical utilization of those tests." Freedman also noted that it seems new doctors coming out of medical school know less and less pathophysiology and less about lab testing.

Despite the hurdles inherent in the U.S. payment system, it's still no excuse for laboratorians not to play a role in interpretation, said Dighe. "We get the lab staff involved and they have input because they have a lot of knowledge," he said. "I think they work best when it's the technologist working with the pathologist figuring out what a result really means and what the next steps are for the patient. But how to compensate them for that time is challenging. It's really extra time. But I think you just call that part of the cost of doing business and providing a service to your customer."

## Walking the Line

Beyond economics, laboratorians face a frustrating dilemma even with basic comments that the laboratory information system (LIS) includes automatically. The fear is always that even if backed by thoughtful editing and literature references, interpretive comments can become just so much background noise to clinicians as they slog through myriads of other details throughout the day, said Corinne Fantz, PhD, codirector of the core laboratory at Emory Crawford Long Hospital and assistant professor of pathology and laboratory medicine at Emory University School of Medicine in Atlanta. "Sometimes when we talk to physicians they don't even see the comments or know that they're there," she said.

Ironically, part of the predicament lies with the electronic systems that made ubiquitous automatic interpretive comments possible in the first place. For example, in Emory's LIS, abnormal results are bolded on the electronic report the clinician sees. Interpretive comments reside in footnotes, called out by an asterisk next to the result. Due to the nature of the system, the clinician then has to click through two more pages before seeing the added information. Unfortunately, some clinicians don't get that far.

Even when getting to an interpretive comment means just a few more mouse clicks, when it becomes routine, clinicians often see it as a hassle or waste of time, explained Jay Jones, PhD, director of the chemistry and toxicology laboratories at Geisinger Medical Laboratories in Danville, Pa. "We've found that here with our electronic health record, since we use it so extensively, physicians don't want a lot of extra text, they just want a quick answer," he said. "They don't like reminders or pop up boxes, they basically say, 'get them out of my face.'"

In fact, Jones and his colleagues found that clinicians don't want to go beyond about seven mouse clicks to produce an order. "They are very sensitive to that because it's repetitive clicks, especially in primary care, where they see the same patients in the same sequence, and if they can find a shortcut, if they can do an encounter in five

See **Interpretive Comments**, on page 8



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# Collaboration Fosters Useful Lab Reports

Interpretive Comments, from page 6

clicks instead of seven clicks, they see that as a big gain," Jones explained. "It really becomes automatic after a while. They don't like slow screens and additional information that comes up that they can blow right by anyway."

The secret ingredient to making sure clinicians read interpretive comments is in the quality and utility of the information, according to Dighe. "If it's useful content physicians will find it and look at it," he said. "If you save them time, if you help them not make a mistake based on the result, then they'll look at it." Canned comments have their place, he emphasized. For example, a comment appended to every tumor marker result can help make sure clinicians understand the limitations of the lab's method. While some of the oncologists who see these results every day might not look at it, for those who are unfamiliar with the false positives and false negatives, interpretation is essential. "For some tests, the fact that 90% of clinicians don't look at a comment doesn't mean it's not valuable. There is a core of clinicians who would be lost with that result without the comment," he added.

At the same time, Dighe stresses that there is a difference between making sure that doctors unfamiliar with a test don't

struggle to interpret the results and adding comments that will not likely be useful to anyone. "Just a comment appended to every hepatitis result that explains what the difference is between IgM and IgA in hepatitis A—clinicians aren't going to look at that. It's got to be something they either don't know or aren't confident in to really add value."

Trying too hard can also cause problems. "If we don't know exactly why a physician is sending the test, we are relatively vague in the interpretation," Dighe said. "I think that's the art of doing a good interpretation. If you have all the information, give a great interpretation. If you don't, back off and give them just enough to help guide the next set of tests or convey that level of uncertainty."

## Reflex Testing

To go beyond the barest of basic comments, labs have found that reflex testing and enhanced interpretations go hand-in-hand. Reports have already demonstrated that reflex testing can both reduce costs and lead to better outcomes for labs, noted Plebani. The aim should be to substitute many individual tests with a clinical question. Reflex testing has become much more standard practice in the U.K. as well, according to

## To Comment or Not to Comment? That is the Question

Should every lab result on every report carry an interpretive comment? Probably not, say experts who have studied this issue. Physicians have little time to comb through comments that do not add value to the lab report, and in many situations the lab does not have enough patient data to provide a true interpretation.

However, for some testing areas, particularly new tests or complex panels of tests, physicians say a lab's interpretation makes a big difference in patient care, said Mario Plebani, MD, professor of clinical biochemistry and clinical molecular biology at the University of Padova School of Medicine and chief of the department of laboratory medicine at the University-Hospital of Padova, Italy. "The extensive development of specialized sectors in clinical laboratories and the correlated increase in the number of tests and their complexity have highlighted the difficulties in data interpretation encountered by general practitioners and physicians receiving laboratory tests, particularly outside their own specialty area," he said. "The autoimmunology laboratory represents a prototype for interpretive comments. It has undergone considerable growth in recent years thanks to new discoveries in physiopathology, target antigens, and diagnostic tests." Plebani also noted that the literature on the subject shows that physicians have difficulties interpreting new cardiac makers, such as cardiac troponins, hs-CRP, and in vitro allergy tests with recombinant antigens.

Freedman. For example, on a total protein that comes in at the upper limits of normal, Freedman's lab would automatically perform a serum electrophoresis to look for multiple myeloma. "Really, the ideal scenario would be for us to decide which test to perform," she said. "We have the expertise and should select, based on evidence-based medicine, what the best tests are for each condition."

Due to the complexity of any given case, reflex testing is really essential to offer true interpretations, Dighe emphasized. "It's hard to do real interpretations on single values. You really have to have the reflex algorithms in place that let you get to the bottom of why a value is elevated or low. And those require going to your medical policy committee and telling them that whenever a patient has a certain abnormality that the lab needs to do certain tests in order to give a more complete picture of a patient's status. Even if you're not going to do an interpretation, it's the right thing to do in many cases," he said. At his institution, Dighe said he's never had a problem with clinicians accepting a reflex algorithm, as long as it's something that saves them time and adds value. "They're happy to have the decision out of the clinician's hands, so if there is an abnormality on a serum protein electrophoresis, automatically free light chains get ordered on the same specimen," he said. "The patient doesn't have to come back in, we don't need another specimen, and the workup gets done. We've never had any pushback on that."

## A Collaborative Effort

Crucial in making any level of interpretation work is getting outside of the lab and collaborating with clinicians. This is the best way to ensure that comments get read and make a difference, stressed Plebani. "Because a full knowledge of, and expertise in, all aspects of lab testing cannot be realized by any individual, the interpretation of results is the paradigm of a collaborative activity with inputs both from clinicians and laboratory professionals," he said. "In addi-

tion, because of the increasing complexity of laboratory tests, even a single laboratory professional cannot achieve expertise in all fields of the discipline. Therefore, interpretive comments should be conceived as a collective responsibility of an individual laboratory service that should be managed through a common policy. However, lab professionals who have been trained and have achieved specialized knowledge in a particular field of activity should participate in developing comments related to their expertise."

Even when crafting basic comments for individual tests, it's important to consult with clinicians with expertise in that particular area, said Fantz. "We get the physicians involved when we're making those comments for their respective services. So for example, if we're making a coagulation comment, we'll refer to hematology and get their input, to make sure that everyone who knows and understands the literature is comfortable with what's being said." Similarly, if a new guideline comes out on an area of testing, Fantz will discuss the issue with physicians in that specialty and ask what should be included in the interpretive comment.

"What happens is that if you have too much written in the chart, it can be a lot of information if the test is ordered frequently on somebody that's staying in the hospital for a long time, and if they print this out, there is a lot of that comment that they have to scroll through," said Fantz.

For Freedman in the U.K., working closely with clinicians is what lab medicine is all about. "I think some people don't understand what lab medicine is supposed to be. It's not just about analyzing a sample—it's about advising the clinician, whether it be a primary care physician or a hospital clinician, both prior to an investigation and after it's been analyzed with an interpretation. So beforehand there needs to be a dialogue with the clinicians, or in regard to written protocols, what investigations are appropriate in certain clinical condition." **CLN**

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The Diagnostic Specialist

# Vitamin D Testing

## How Will We Get it Right?

BY ROSEMARY L. SCHLEICHER, PHD, AND CHRISTINE M. PFEIFFER, PHD

**D**uring the last 10 years, researchers have made a number of exciting discoveries about vitamin D. The prohormone is thought to play a role in a host of conditions, including certain cancers, type 1 diabetes, multiple sclerosis, tuberculosis, Alzheimer's disease, psoriasis, and all-cause mortality. With all the media attention on vitamin D's purported superpowers, the demand for vitamin D testing has soared and physicians and patients are now paying serious attention to vitamin D status.

Most people are aware that vitamin D can be obtained by exposing skin to sunlight, eating certain foods, or taking vitamin supplements. However, vitamin D itself is biologically inert and must undergo two hydroxylation reactions to be activated. The first step is catalyzed by a liver enzyme, producing 25-hydroxyvitamin D (25(OH)D), a longer-lived metabolite that is a suitable marker of vitamin D status (1). For the past three decades, clinicians have relied primarily on immunoassay measurements of this metabolite to determine a patient's vitamin D status.

Today, new technology has emerged for measuring vitamin D status, including high performance liquid chromatography (HPLC) coupled to tandem mass spectrometry (LC-MS/MS). Our lab at the Centers for Disease Control and Prevention (CDC) has measured 25(OH)D for the National Health and Nutrition Examination Surveys from NHANES III (1988–1994) through NHANES 2005–2006. Here we present our experience with the analytical quality of a commercially available vita-

later <sup>125</sup>I-labeled 25(OH)D (3). For nearly as long as competitive binding assays have been used in clinical labs, research scientists have used chemistry-based methods such as HPLC with UV detection or gas or liquid chromatography coupled to mass spectrometry (MS) to measure or confirm serum concentrations of 25(OH)D (4–6).

Chromatographic methods are less susceptible to sample matrix effects than immunoassays (7). In particular, LC-MS/MS first resolves compounds chromato-

potential analyte loss and behaving virtually identically to the compound of interest during chromatography and detection.

In contrast, specificity is less assured when analytes are measured using immunoassays that rely upon binding to an antibody. Cross-reactivity with nonspecific compounds is a well known issue in immunoassays. Even though extensive cross-reactivity testing may be performed for validation of immunoassays, it is never exhaustive.

Based on data from the largest survey of its kind, Vitamin D External Quality Assessment Scheme (DEQAS, [www.deqas.org](http://www.deqas.org)), most participating labs use immunoassays to measure 25(OH)D (Figure 1, p. 11). While the number of DEQAS participants has nearly doubled in the past 2 years, the number using LC-MS/MS has remained at 9%–10%. The four most commonly used tests in the summer 2009 DEQAS exercise were DiaSorin Liaison Total (36%), IDS enzyme-linked immunoassay (19%), automated IDS enzyme-linked immunoassay (11%), and LC-MS/MS (10%) (Figure 2, p. 11).

### NHANES Studies with a Commercial 25(OH)D Assay

The Nutrition Laboratory at CDC has measured 25(OH)D in more than 60,000 NHANES specimens using the DiaSorin RIA. Typically, CDC uses chromatography-based analytical methods to measure nutritional indicators; therefore, the use of an RIA to assess vitamin D status has been an exception to the rule. Generally, unless assay features such as accuracy, precision, or specificity are in doubt, CDC chemists and epidemiologists are reluctant to change assay methods because each change complicates the assessment of long-term population trends for NHANES and requires extensive cross-over studies to relate the new method to the old.

In 2004, however, the CDC laboratory began to develop an LC-MS/MS method for measuring 25(OH)D. CDC pursued this initiative because we found that the 25(OH)D immunoassay lacked the precision necessary for our studies. Furthermore, in the late 1990s, the manufacturer

min D immunoassay and a newer analytical method developed at CDC, as well as a description of our experience with a newly available standard reference material.

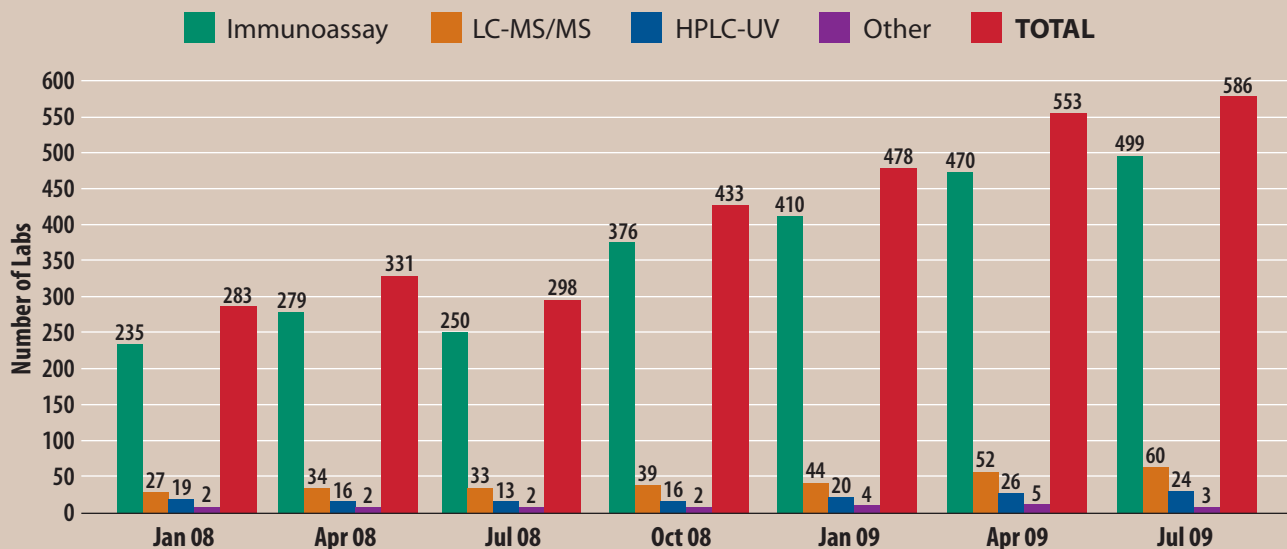
### History of Vitamin D Assays

The first method for measuring 25(OH)D was a competitive protein-binding assay that used a rat vitamin D binding protein and <sup>3</sup>H-labeled 25(OH)D<sub>3</sub> (2). This assay was subsequently replaced with a simpler radioimmunoassay (RIA) using <sup>3</sup>H- and

graphically and then detects them at specific masses. This methodology provides a high probability that a molecule of interest will be correctly identified and quantitated because it is detected as a specific transition from one mass fragment to another. In other words, it is a highly specific method. Furthermore, in isotope dilution LC-MS/MS, a stable isotope-labeled analog of the compound of interest is added during the first step of sample preparation and carried throughout the assay, correcting for any



## Figure 1 DEQAS Proficiency Testing Program for 25(OH)D



The number of laboratories participating in this survey has steadily grown in the most recent seven quarterly exercises.

made changes to the assay that affected performance and therefore the results of our long-term study. In the reformulated assay, DiaSorin incorporated a higher affinity antibody that improved precision and sensitivity by reducing non-specific binding.

As shown in later studies, the reformulated DiaSorin assay used during NHANES 2000–2006 measured approximately 12% lower than the original assay used for NHANES 1988–1994 (8, 9). One explanation for this result is that the higher specificity of the new antibody measured fewer cross reactants. Furthermore, we observed certain shifts in QC values as a result of reagent lot variation, complicating interpretation of time trend data for NHANES (10). Understandably, from time-to-time manufacturers need to change lot numbers for various components of their kits such as calibrators, tracers, or antibodies. These changes should not cause systematic shifts. However, we noticed several times during analyses of the NHANES 2000–2006 specimens that the assay performed predominantly on one side or the other of the mean

for a certain period.

Based on an 11.3% intra-individual coefficient of variation (CV) for 25(OH)D (11), quality goals for analytical imprecision, should be: 2.8% (optimal); 5.6% (desirable); and 8.5% (minimal) (12). Because manufacturer QC materials are characterized by wide QC limits (18%–20%), we generated and characterized large batches of in-house QC materials that lasted for several years and produced narrower QC limits (9%–14%). But with the assay shifts noted above, the overall CV for 25(OH)D for NHANES 2000–2006 was 13%–15%. This amount of imprecision does not meet the minimal quality goal for good precision; therefore, for our long-term study of vitamin D status, we decided to pursue an alternative analytical method.

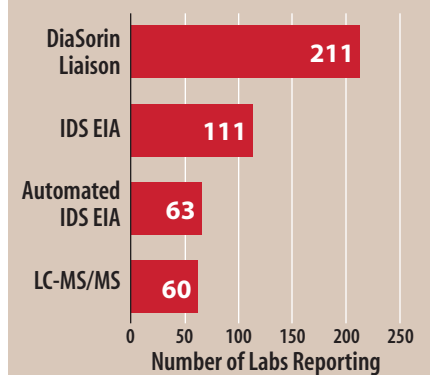
### Developing an LC-MS/MS Assay

Developing an assay for 25(OH)D was not a straightforward task for the CDC laboratory. The method of Vogeser et al. (13) was a convenient starting point because we had access to a MicroMass Quattro LC TMS

system as used in this candidate reference method. But from the beginning, we were unable to confirm that mass to charge ratio (m/z) 159 is the major product ion for 25(OH)D3. Instead, we found m/z 383 to be the major product ion, which represents loss of water as shown by others (14, 15). In addition, we wanted to measure 25(OH)D2, which was not addressed by Vogeser et al. (13). As we explored various aspects of the method while optimizing the instrument, we noted that the matrix in which the calibrators were prepared had a major impact on detector response, a finding generally not reported in other publications as an analytical issue (16).

For comparison purposes, we prepared calibrators in 85% methanol, 4% albumin in PBS, or serum. Over the range of 10–100 ng/mL, the signal intensities for both analytes in 85% methanol were about 40% lower than those in serum and 15% lower than those in 4% albumin. The lowest concentration calibrators for 25(OH)D2 and 25(OH)D3 were not detectable in 85% methanol. Although the internal standard compensated for the differences among different matrices, lower responses would be expected to decrease assay precision and accuracy, particularly at low analyte concentrations. Calibration solutions prepared in a serum-like matrix would be optimal, but the use of serum or

## Figure 2 Vitamin D Assay Methods



Source: DEQAS July 2009 exercise

plasma containing endogenous 25(OH)D requires a calibration correction that adds error to the calibration curve. We therefore opted to use 4% albumin in PBS to provide a background-free protein matrix.

Throughout our calibration efforts, the hydrophobic nature of 25(OH)D was a concern. We were worried about adsorption of the analyte to the walls of tubes and therefore designed an experiment in which we looked at repeated transfer of solutions into fresh containers (16). Contrary to our expectation, we found a positive interference at m/z 383 for 25(OH)D3 when a certain brand of polypropylene container was used. The interference nearly doubled the signal in the medium QC pool. Adsorptive losses were nil.

After several years of work, we finally settled on a chromatographic separation method that we believed would help ensure consistent results for the NHANES analyses (16). Although this method is less than ideal, it does have improved precision compared with the DiaSorin RIA (CV ≤11% and ≤16% for 25(OH)D3 and 25(OH)D2, respectively).

### Further Improvements

Although most specimens gave reproducible results using our first LC-MS/MS method, low concentrations of 25(OH)D2 in some specimens were not reproducibly measurable due to a baseline interference peak eluting in the proximity of 25(OH)D2. In an effort to further improve the assay, we set out to obtain better chromatographic resolution along with automated

Table 1

## Features of LC-MS/MS Method for 25(OH)D2 and 25(OH)D3

<b>Format</b>	96-well plate
<b>Instrument</b>	Thermo Quantum Ultra
<b>25(OH)D2 &amp; 25(OH)D3 calibration ranges</b>	6–125 and 13–250 nmol/L
<b>Internal standards (deuterium-labeled)</b>	D6-25(OH)D3 & D3-25(OH)D2
<b>Sample preparation</b>	Hamilton Starlet robot
<b>Serum volume</b>	100 µL
<b>Mobile phase</b>	Gradient – methanol/water
<b>Run time</b>	10 minutes
<b>Throughput</b>	80 patient samples per day
Improvements include better chromatographic resolution, automated sample processing, smaller volume of serum per test, and addition of a second internal standard, isotopically labeled 25(OH)D2.	

Table 2

## Performance Characteristics of LC-MS/MS Method for Measuring 25(OH)D

<b>Specificity</b>	25(OH)D2 separately quantitated from 25(OH)D3, but 25(OH)D3 not separated from 3-epi-25(OH)D3
<b>Accuracy (using NIST SRM 972)</b>	25(OH)D3 (+1% to +4%); 25(OH)D2 (–8% to +30%)
<b>Recovery (± SD)</b>	25(OH)D3 (95% ± 3%); 25(OH)D2 (97% ± 3%)
<b>Precision (CV)</b>	25(OH)D3 (5%–8%); 25(OH)D2 (6%–10% at ≥7.5 nmol/L)
<b>Sensitivity</b>	25(OH)D3 (<1 nmol/L); 25(OH)D2 (<1 nmol/L)

Table 3

## Method Comparison with SRM 972

Level	NIST certificate of analysis values from LC-MS/MS (nmol/L)			CDC DiaSorin RIA (nmol/L)
	25(OH)D3	25(OH)D2	Total 25(OH)D	Total 25(OH)D
1	59.6 ± 2.1	1.46 ± 0.49	61.1	60.5 ± 4.9
2	30.8 ± 1.5	4.14 ± 0.19	34.9	39.0 ± 4.5
3	46.2 ± 2.8	64.1 ± 4.8	110.3	72.4 ± 8.0

Levels 1, 2, and 3 using the DiaSorin RIA compared with NIST-certified (blue) or reference (green) values. Means ± U95 (expanded uncertainty) for NIST data and mean ± SD for CDC data are displayed.

sample processing (Table 1). We recently concluded validation of a new automated method in which the chromatographic separation of 25(OH)D2 and 25(OH)D3 from interfering peaks is optimal, yet quick (10 minutes). The method uses a 96-well plate format and can easily handle 80 patient samples per day by using a robot to facilitate reproducible pipetting. Other improvements include testing smaller volumes of serum (100 µL) and including isotopically labeled 25(OH)D2 as a second internal standard. Table 2 (p. 11) lists the performance characteristics of this assay method.

However, this is not the end of the story. When we set out to develop an LC-MS/MS method for monitoring 25(OH)D2 and 25(OH)D3 in NHANES, separating and measuring the C-3-epimer of 25(OH)D3 was not an objective because this compound was reported to be present only in infants less than 1 year old (14), an age group not monitored for 25(OH)D in NHANES. More recently, however, the National Institute of Standards and Technology (NIST) confirmed the presence of the epimer in serum materials from adults using their LC-MS/MS reference method. This epimer, not captured by the DiaSorin RIA (14, 17), adds bias to conventional chromatographic assays because it is not chromatographically resolved from 25(OH)D3 using the typical C18 HPLC columns.

Cyanopropyl-bonded HPLC columns and longer run times may be necessary to ensure a baseline separation of the epimer from 25(OH)D3 (18). To achieve bias-free monitoring of the vitamin D status of the U.S. population, we revised our LC-MS/MS method to separate the epimer from 25(OH)D3 and are now in the process of validating the method.

### Vitamin D Reference Materials: NIST's Role

Labs also need a reference material to ensure accurate 25(OH)D assessments. In 2005, the National Institutes of Health, Office of Dietary Supplements contracted with NIST to prepare matrix-based standard reference materials (SRM) for 25(OH)D (19). SRM 972 was released in July 2009 and is now available to labs. Only one of the materials is native serum (level 1). The others are either diluted with horse serum (level 2), or spiked with 25(OH)D2 (level 3) or 3-epi-25(OH)D3 (level 4).

The CDC Nutrition Laboratory worked with NIST to measure 25(OH)D in these materials using our automated LC-MS/MS method before a second internal standard (D3-25(OH)D2) was added to the procedure. To test the materials, we prepared

duplicate preparations per vial, two vials per day over 4 days. Our LC-MS/MS values were 1%–4% higher than NIST values for 25(OH)D3 using their LC-MS/MS reference method procedure, which has an analytical coefficient of variation of 2%–3%. The agreement between CDC and NIST values for 25(OH)D2 was good for levels 3 and 4—6% and 11% higher, respectively—but worse for levels 1 and 2—8% lower and 30% higher, respectively—where 25(OH)D2 values were low (<5 nmol/L). NIST has incorporated the CDC LC-MS/MS data into the certificate of analysis for SRM 972 (see [www-s.nist.gov/srmors/view\\_cert.cfm?srm=972](http://www-s.nist.gov/srmors/view_cert.cfm?srm=972)).

### Relating Immunoassay Values To LC/MS-MS Values

The long history of working with the DiaSorin RIA and NHANES samples prompted us to investigate the relationship of those values to the LC-MS/MS method. Therefore, we also characterized 25(OH)D values in SRM 972 with the DiaSorin RIA using the same protocol (duplicate measurements using eight vials over 4 days) for levels 1, 2, and 3; level 4 was not available at the time (Table 3). Levels 1 and 2 were within 12% of the expected values when 25(OH)D2 and 25(OH)D3 were summed together. Level 3, which was spiked with 25(OH)D2, showed about two-thirds of the target value, possibly because the vitamin D metabolite was spiked.

These data raise the issue of commutability of the reference materials, defined as the equivalence of the mathematical relationships between different measurement procedures for a reference material and for representative unaltered samples from healthy and diseased individuals (20). Commutability is assay-specific and therefore not all levels of SRM 972 are likely or need to be commutable for every assay. Formal studies using the different methods are underway to measure 25(OH)D in SRM 972 to identify which levels are commutable for which assay methods.

### Getting It Right

The ultimate goal of the CDC Nutrition Laboratory is to obtain accurate 25(OH)D values. Consequently, precise methods and traceable reference materials are essential to establishing an individual's vitamin D status. The availability of standard reference materials is a key element of getting vitamin D assessments right.

How will we use SRM materials to improve 25(OH)D testing? The CDC Nutrition Laboratory will incorporate these materials into value assignment of daily

calibration materials and into calibration verification procedures performed at least semiannually. When preparing in-house calibration materials, we will use SRM 972 to assign values to the new lot.

NIST also plans to release SRM 2972, a set of two materials containing 25(OH)D2 or 25(OH)D3 at known concentrations diluted in solvent. These materials are suitable for further dilution to use in linearity testing and for calibration verification. Ultimately, the availability of these tools will allow the CDC Nutrition Laboratory to be able to produce reliable estimates of vitamin D levels in the U.S. population.

For clinical labs, using standard reference materials and regularly participating in a proficiency testing program are essential to keeping laboratory assays on target. **CLM**

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**2010 AACC  
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# H1N1 Spreads Across the United States

## Tips on Handling the Spike in Demand for Testing

As of early November all indications were that the 2009 H1N1 influenza outbreak was still gaining steam and labs were continuing to do yeoman's work in handling a huge spike in testing demand.

To explore how labs might find some relief from the testing onslaught in a climate of tight economic circumstances and limited staff resources, *CLN* spoke recently with efficiency expert Ron Wince, president and CEO of Guidon Performance Solutions, a Phoenix-based management consulting firm specializing in business performance improvement. Wince's clients include major health systems and diagnostic manufacturers.

**Q** The H1N1 outbreak started last spring, slowed somewhat during the summer, and came back with full force this fall. What feedback are you hearing from labs about how they are dealing with it?

**A** The feedback probably mirrors what happened in the spring. Labs are feeling taxed and perceive that they don't have enough staff. At times they're running 20 to 25 percent overtime to keep up, and when you're paying someone time-and-a-half, the cost is significant.

**Q** What are some steps labs can take to ease the pressure, since most aren't able to add new staff to deal with the outbreak?

**A** In our work with labs, we've found that about 80 percent of technologists' time is consumed doing things that don't add value to the outcome of the sample. They're spending time filling out paperwork, tracking things down, walking around. So we've found three areas where labs working creatively over a couple of days may be able to eliminate 20 to 30 percent of that waste.

**Q** What specifically are the three areas of opportunity?

**A** One way is to look at how samples flow through the lab. They tend to get moved a lot without anything really happening to them. So we suggest co-locating equipment in a layout that enables things to happen more sequentially, thereby minimizing the amount of walking around staff have to do. With the equipment closer together, the technologists can work more on processing samples and getting results out.

Another area is inventory management and storage. Things technologists need from a consumables perspective often are poorly placed, so we encourage labs to think about technologists as if they were surgeons. When a surgeon is performing surgery, he stands in one place and has people bring things to him so he can do the surgery. We want that same mentality around lab staff. Reconfiguring the bench so technologists have what they need right around them can take out as much as 10 to 20 percent of cycle time on a per-sample basis.

The third area is that technologists spend a lot of time doing paperwork or working in the LIS. We had one client where

they had to go through 32 screens for each sample. If you multiply that by hundreds of samples that's a lot of time each day. So we recommend changing the way lab staff do paperwork or interface with the computer.

**Q** Changing the LIS sounds complicated and not something that could be done in a timeframe that would help labs deal with the H1N1 crunch. How could this be done quickly?

**A** If you make IT staff part of the team addressing this issue, they're usually pretty creative at figuring out how to do work-

arounds quickly. It may involve temporarily using a replacement template or sheet until the LIS can be updated. The goal is to have an immediate impact and not let the LIS be a roadblock to finding efficiencies.

**Q** If labs are struggling to keep up with testing demand, how will they be able to step back and look at these areas?

**A** The vast majority of hospitals have some kind of internal improvement team; it's just that they haven't been focused on labs. But let's say the hospital either doesn't have a team or it can't be freed up

to solve this problem. This is just like any other investment that you make. There's no good time to fix a process, but if you don't, the problem will persist. But if you can do it quickly and within a week have the whole process changed so it's working better, you're making a positive investment. So we suggest organizing a small team of technologists, lab management, and IT staff and look at it as if they were on vacation for a few days. You're freeing them to address the work flow and within a few days they can have a solution that will make a measurable impact. CLN

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# Newborn Screening for Cystic Fibrosis and Its Impact on the Clinical Lab



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 August 2008 presentation by Stanley Lo, PhD, DABCC, FACB, associate professor of pathology and associate director of Clinical Laboratories at Children's Hospital of Wisconsin.

**Q** What are the newest developments in CF testing? Could you provide some scientific references?

**A** The newest development is the change in reference intervals for infants less than 6 months in age, extending the "possible CF" range to 30-59 mmol/L. Check out: *J Pediatr* 2008;153:S4-S14; *J Pediatr* 2007;151:85-89; and CLSI document A34-A2 from 2009.

**Q** Is there a "gold standard method" for analysis of sodium chloride in sweat? I use the Nanoduct system and I want to be sure about its performance.

**A** The "gold standard" method for CF diagnosis is the sweat test using pilocarpine iontophoresis to stimulate sweat; collection of sweat onto gauze or filter paper; and the determination of chloride concentration using coulometric titration.

**Q** We perform sweat iontophoresis with pilocarpine. Have you ever heard of a negative sweat iontophoresis on a patient, but positive diagnosis for CF?

**A** Yes! Sweat chloride testing can identify up to 99% of patients with CF. We've also had cases where the newborn screen did not pick up on CF patients, but were diagnosed at a later date.

**Q** Do you see newborn screening for CF becoming part of state regulated testing in the future?

**A** I don't have a good answer for you. All I can say is that newborn screening will need to continue to follow CLIA regulations. How the regulations are interpreted and what it means for testing are a different matter.

**Q** What is IRT versus IRT/IRT?

**A** These are different screening strategies. The IRT strategy performs an IRT measurement on the initial blood spot. If it is elevated, a sweat test is done. The pros of this strategy are good specificity with no detection of carriers. The cons of this strategy are poor sensitivity, or a high false-positive rate, and a high sweat test rate. The IRT/IRT strategy obtains an IRT on the initial blood spot. If this is elevated, then another sample is collected and a second IRT is done. If this is also elevated, then a sweat test is done. The pros of this strategy are good specificity and sensitivity with no detection of carriers. The cons are that the first test has poor sensitivity and families are likely to have more anxiety.

**Q** Why does it take a couple of weeks to confirm an IRT for CF in newborns?

**A** The turnaround time for testing is dependent on the processes for screen-

ing newborns, i.e. how long does it take for the sample to get to the lab? When does the lab perform IRT testing? If a second sample needs to be collected from a patient, as in IRT/IRT screenings, it could easily extend time necessary for confirmatory results.

**Q** Several years ago at an AACC meeting, one of your co-collaborators on the Wisconsin CF Neonatal Screening Study Group said that every child born in the state could be screened for about \$3 per birth. Do you think this number is still accurate, and would it hold in other locales?

**A** I believe that the \$3 per birth cost continues to be true in Wisconsin. Though I am not part of the Wisconsin CF Neonatal Screening Study Group, I believe that most of the cost will depend on the laboratory methods used for screening, the processes used for transporting specimens

and providing results, as well as how much the state government is willing to assist in newborn screening efforts. Therefore, the cost per birth is highly dependent on the status of testing within each state or locale.

**Disclaimer**—The opinions and information are the sole responsibility of the presenter. AACC reviews the presentations for overall appropriateness, but this should not be construed as an endorsement by the association of its employees of the opinions and information offered here.

*Supported in part by an education grant from Siemens Healthcare Diagnostics.*



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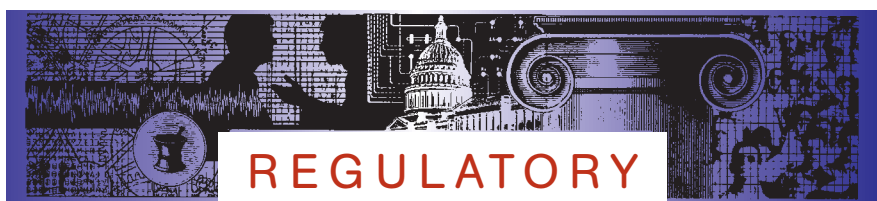
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Accepted abstracts and meeting proceedings will be published in *Point of Care: The Journal of Near-Patient Testing & Technology*.

**For abstract specifications and the electronic abstract submission form, visit: <http://www.aacc.org/events/meetings>**



## Joint Commission Changing ID Rules for Phlebotomy

Sparking an outcry from the phlebotomy community, the Joint Commission will no longer require patient involvement when identifying patients before a phlebotomist collects a lab sample, according to a pre-publication draft of the Joint Commission's 2010 National Patient Safety Goals (NPSG). The requirement for patient involvement, which included asking the patient's name, first became part of the lab NPSG in 2009.

The 2010 NPSGs require using at least two patient identifiers, but would allow both identifiers to come from the patient's ID bracelet. "By permitting those two identifiers to come from the same identification bracelet without requiring active patient involvement to confirm the bracelet was attached to the right person, patients could be misidentified without any devia-

tion from the Joint Commission's requirements...to remove that critical provision is dangerous and ill-advised," wrote Dennis Ernst, MT(ASCP), director of the Center for Phlebotomy Education, in a letter to the Joint Commission.

The Joint Commission defended the change, pointing out that the intent was not to discourage patient involvement, but that requiring it would be difficult to enforce and could raise problems with patients not able to interact. More information about the NPSGs is available on the Joint Commission's website, [www.jointcommission.org](http://www.jointcommission.org). The Center for Phlebotomy Education letter is posted at [www.phlebotomy.com](http://www.phlebotomy.com).

## GINA Provisions Take Effect

Beginning December 7, elements of the 2008 Genetic Information Non-discrimination Act (GINA) go into effect,

barring insurers from denying coverage based on genetic information. The Department of Health and Human Services published an interim final rule in the Federal Register that limits how insurers use and access a person's genetic information. The rule permits insurers "to obtain and use the results of a genetic test to make a determination regarding payment." However, plans and insurers must request the minimum amount of information needed to make such a determination. The interim final rule is available on the Federal Register website, [www.gpoaccess.gov/fr](http://www.gpoaccess.gov/fr). Search for pages 51664-51697.

## House Health Bill Covers Testing But Reduces Payment

On November 7, the House of Representatives narrowly passed its version of a healthcare reform bill that would extend lab testing to the newly insured. The bill also promotes preventive care and comparative effectiveness research. However, similar to the Senate version, the House bill spells bad news for reimbursement. The change in payment to labs would take the form of a reduction in the laboratory consumer price index (CPI) update. Starting in 2010, the bill would reduce the update by a "productivity factor," typically ranging from 1%-1.4% a year, potentially reducing payments to labs by \$5 billion over the next 5 years.

For diagnostics manufacturers, the bill would levy a 2.5% tax at the point of sale for medical devices, or about \$20 billion over 7 years. The Senate version of the healthcare reform bill taxes manufacturers \$40 billion over 10 years, based on the business's market share.

To increase the number of insured in the U.S., the bill would, among other things: ban insurance companies from denying coverage to anyone with a pre-existing condition or charging higher premiums based on sex or medical history; create a national Health Insurance Exchange as well as a government-run insurance plan that provides the means to negotiate rates with providers; expand Medicaid to all families up to 150% of the federal poverty level;

mandate that employers purchase insurance for their employees or be subject to an 8% payroll tax; mandate that all individuals obtain health insurance or be subject to a 2.5% fine of their adjusted gross income; and levy a 5.4% surtax on individuals earning more than \$500,000 annually or married couples earning more than \$1 million. According to the Congressional Budget Office, the bill would guarantee coverage for 96% of Americans.

The next step is for the Senate to pass its version of a healthcare reform bill, after which the two bills will be reconciled for differences and sent to both houses of Congress for final approval before heading to the President's desk. At CLN press time, the timeline for these events extended into 2010.

## Senate Bill Includes Workaround For 14-Day Rule

Offered by Senators Ron Wyden (D-Wash.) and Tom Carper (D-Del.), an amendment to the Senate Finance Committee healthcare reform plan would allow independent labs to bill Medicare directly for certain esoteric genetic tests even when the specimen is collected at a hospital. Under current Medicare regulation, the date of service for a test ordered less than 14 days after a patient's discharge from a hospital is considered the date on which the specimen was collected, and must be covered under the hospital diagnostic-related group (DRG) payment for that stay. Essentially, the rule treats tests ordered less than 14 days after a patient is discharged as having been performed when the patient was actually in the hospital, even if the testing takes place somewhere else.

The amendment would allow clinical laboratories to bill Medicare directly at a higher reimbursement rate if the test is not furnished by the hospital where the sample was collected, and if the test is performed only by the laboratory offering the test. The amendment is similar to legislation introduced by Jason Altmire (D-Pa.), H.R. 1699. The amendment is available on the Senate Finance Committee website, <http://finance.senate.gov>.

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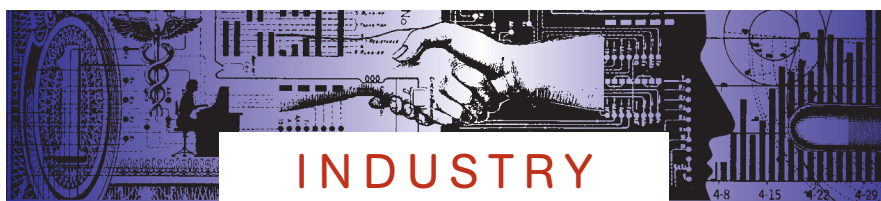
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## INDUSTRY

### GE Announces \$250 Million to Support Health IT, Diagnostics

General Electric (GE) announced the formation of the GE Healthymagination Fund, a new equity fund that will invest in promising healthcare technology companies. The fund will primarily focus on innovative companies pioneering research in diagnostic, IT, and life science technologies, as well as healthcare companies developing unique business models and services. Diagnostic technologies specifically highlighted for investment include home health, patient monitoring, molecular diagnostics, pathology, and novel imaging agents. The fund is part of GE's \$6 billion Healthymagination initiative.

### BD Acquires HandyLab

Becton Dickinson (BD) signed a definitive agreement to acquire HandyLab, a manufacturer of diagnostic assays and automation platforms. Building upon a previously announced development and distribution agreement between BD and HandyLab from 2009, the acquisition will support BD's molecular diagnostics strategy. "HandyLab has developed and commercialized a flexible automated platform for performing molecular diagnostics that is an ideal complement to our molecular diagnostics offerings," said Vincent A. Forlenza, BD president. BD plans to place its BD GeneOhm molecular assays for Methicillin-resistant *Staphylococcus aureus* (MRSA), *Clostridium difficile*, and Vancomycin-resistant *Enterococcus* (VRE) onto the HandyLab platform and market them as the BD MAX system. The acquisition is expected to close in the first quarter of 2010. Financial terms of the agreement were not disclosed.

### Myriad Acquires Rights to Pancreatic Cancer Gene Patents

Myriad Genetics acquired the exclusive license to patents covering mutations in the *PALB2* gene from Johns Hopkins University (JHU). The mutations have been linked to increases in an individual's risk for developing pancreatic cancer. The *PALB2* gene is a tumor suppressor gene that serves as a binding partner with *BRCA2*, allowing both genes to work together to repair DNA damage. Scientists at the Sol Goldman Pancreatic Cancer Research center at JHU identified the traits of the *PALB2* gene and published their findings earlier this year. Combined with Myriad's already extensive catalog of additional genes for pancreatic cancer, Myriad hopes to develop a novel molecular diagnostic test to assess the risk for hereditary pancreatic cancer by 2010. "At the present time, pancreatic cancer is difficult to diagnose early, resulting in few options to help improve patient survival," said Gregory C. Critchfield, MD, president

of Myriad Genetic Laboratories. "Knowing who is at higher risk of pancreatic cancer will allow for the development of strategies for early detection and possible prevention of this deadly disease, giving doctors and patients tools to better address this cancer."

### Exact Sciences Licenses Invader Technology from Hologic

Exact Science obtained a worldwide license from Hologic for the company's Invader, Invader plus, and real-time Invader detection technologies used for colorectal cancer screening. The Invader chemistry series is a molecular detection platform that Exact Science plans to combine with digital PCR technology exclusively licensed from Johns Hopkins University. The license agreement gives Exact Science an edge in the stool-based DNA (sDNA) screening market. The company's intellectual property portfolio now includes detection technologies, sDNA testing methods, and important biomarkers that can be used to develop colorectal screening tests. Financial terms of the license agreement were not disclosed.

### ZyGEM, Phthisis Join to Produce Pathogen Detection Devices

ZyGEM and Phthisis Diagnostics announced that they have entered into an agreement to develop devices for the detection of infectious pathogens in complex samples, such as stool, blood, and water. The collaboration will bring together ZyGEM's nucleic acid extraction technology and Phthisis Diagnostics' molecular diagnostic expertise in obtaining DNA samples from infectious pathogens. The companies' first task will be extracting pathogen DNA from stool. "We are committed to developing innovative technologies that provide researchers and clinicians with products to accurately, simply, and cost-effectively perform molecular detection assays, and we believe that access to ZyGEM's distinctive temperature-controlled nucleic acid extraction technology will help advance that goal," said Crystal R. Icenhour, PhD, president and director of research of Phthisis Diagnostics. Additional terms of the agreement were not disclosed.

### Qiagen to Purchase SABiosciences for \$90 Million

Qiagen announced that it has signed a definitive agreement to acquire SABiosciences, a manufacturer of PCR assay panels. SABiosciences' product line includes more than 100 real-time PCR assay panels for high performance analysis of DNA, RNA, and microRNA targets associated with cancer, diabetes, and immune and cardiovascular diseases, as well as pathways for apoptosis, signal transduction, and toxicology. "The addition of SABiosciences

will boost our biological content engine significantly by adding to our position as a premium partner for the pharmaceutical industry and to the use of this position to yield diagnostic content for prevention, profiling, and, most significantly, personalized healthcare," said Peter Schatz, CEO of Qiagen. The deal is valued at \$90 million and expected to close at the end of December, following approval by SABiosciences' stockholders.

### Satoris Awarded Foundation Grant to Develop Parkinson's Disease Markers

Satoris announced that it has received a grant from the Michael J. Fox Foundation to study plasma protein panels from patients with Parkinson's disease. The study, which is being performed in collaboration with Bernard Ravina, MD, associate professor of neurology at the University of Rochester School of Medicine, will compare the relative amounts of 500 plasma proteins from 25 Parkinson's disease patients with those from 25 healthy individuals. "We will use proprietary antibody arrays to measure over 500 distinct plasma proteins and at-

tempt to identify a cellular signal for the disease," said Cris McReynolds, president and CEO of Satoris. "If we're successful, the next step will be further studies using larger number of samples. Ultimately, we hope to develop and commercialize a diagnostic blood test."

### Epigenomics, Quest Complete Development of Colorectal Cancer Test

Epigenomics announced that Quest Diagnostics completed clinical validation of its Septin9 laboratory-developed blood test for the detection of colorectal cancer. "Validation of our Septin9 laboratory-developed test is an important step forward in providing a test that physicians can use to help them identify patients with colorectal cancer," said Jay G. Wohlgenuth, MD, vice president of Science and Innovation at Quest Diagnostics. "We intend to release the test in the U.S. later this year." Under terms of the licensing agreement Epigenomics will receive a milestone payment from Quest for the completion of this validation, however the amount of the payment was not disclosed.

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## Treatment in New-Onset Diabetes Does Not Reduce Inflammatory Biomarkers

New research indicates that in patients with recent-onset type 2 diabetes, treatment with insulin or metformin compared with placebo does not reduce inflammatory biomarker levels despite substantially improving glucose control (JAMA 2009;302:1186–1194). The findings may provide insight into the outcomes of three other studies in which intensive glycemic control did not lower the risk of incident cardiovascular disease (CVD), according to the authors.

The Lantus for C-reactive Protein Reduction in Early Treatment of Type 2 Diabetes (LANCET) trial involved 500 adult patients who had recently developed type 2 diabetes, with a median time since diagnosis of 2 years. The patients, who were recruited at 73 office practices, had suboptimal glycemic control, defined as HbA1c levels of 7%–10%, and elevated levels of high sensitivity C-reactive Protein (hsCRP)  $\geq 2$  mg/L. The study had four arms, with one-quarter of patients randomized respectively to placebo alone, placebo and insulin glargine, metformin alone, or metformin and insulin

glargine. The primary endpoint was change in hsCRP level from baseline to 14 weeks. Secondary endpoints included change in HbA1c, interleukin-6 (IL-6) and soluble tumor necrosis factor receptor 2 (sTNFr2) levels, change in weight, and occurrence of marked hypoglycemia.

The researchers found significant reductions in glucose and HbA1c levels among patients who received active treatment versus placebo, with the greatest reductions in glycemic parameters among those allocated to combination therapy. HbA1c levels were almost normalized among patients in the active treatment groups, and all groups except patients who received insulin alone achieved modest weight loss. However, while all four treatment arms had lower hsCRP levels compared with baseline, there was no significant difference in the reductions and no active treatment arm achieved incremental benefits from reductions in hsCRP levels compared with placebo alone. Results were similar for IL-6 and sTNFr2 levels.

According to the authors, the findings offer a potential explanation for other recent studies which did not observe a link between intensive glycemic control and lower risk of incident CVD despite epidemiologic

evidence of a graded association between hyperglycemia and future CVD events. The authors speculate that the mechanisms of weight loss may have differed among the groups. Prior studies have found visceral fat to be more closely linked to subclinical inflammation than subcutaneous fat. The authors call for further investigation of the association between various diabetes treatments and change in weight and body fat distribution.

## BNP, cTn Predictors of Adverse Outcomes in Acute Pulmonary Embolism

A recent meta-analysis found that raised levels of B-type natriuretic peptides (BNP) identified a subset of patients with acute pulmonary embolism (APE) who were at higher risk of adverse outcomes, and that among patients with elevated BNP levels, raised troponin (cTn) levels were an independent prognostic indicator (Thorax 2009; 64:869–875). The findings could have important implications for management of APE, according to the authors. Increases in BNP and NT-proBNP presumably are related to enhanced right ventricular shear stress and right ventricular dysfunction in patients with APE, while raised cTn T and I have been associated with higher mortality in APE. The goals of the analysis were to assess both the prognostic significance of BNP and NT-proBNP alone or in conjunction with cTn and the diagnostic accuracy of BNP in detecting right ventricular dysfunction in patients with APE.

The researchers analyzed 23 studies with 1,127 patients. They found that raised BNP levels were significantly associated with all-cause mortality, APE-related mortality, and serious adverse events. Among patients with elevated BNP levels, 46% also had raised cTn levels, and in these patients, the increased cTn levels were associated with increased risk for all-cause and APE-related mortality and serious adverse events. In contrast, patients with low BNP and cTn levels were at very low risk of complications.

Overall, 52% of patients with APE had raised BNP levels. About two-thirds of the studies assessed BNP levels using four different assays, while the others assessed NT-proBNP using the same assay. The various studies reported different thresholds, so in the meta-analysis, researchers used a range of thresholds to facilitate between-study comparisons. For BNP, the thresholds were 80–100 ng/mL with the Biosite Diagnostics assay, and 35–75 ng/mL for the Shionogi assay. In the case of NT-proBNP, the thresholds ranged from 600–1,000 ng/mL for the Roche assays. Four studies assessed cTn I levels, and two assessed cTn T levels. Three different assays were used with different thresholds ranging from 0.01–0.1  $\mu$ g/L.

The researchers' analysis of the link between BNP levels and risk of right ventricular dysfunction were limited due to significant heterogeneity among the studies evaluated. However, BNP appeared to have better sensitivity and specificity than NT-proBNP. Similar findings have been reported in a recent meta-analysis for the

diagnosis of heart failure, according to the researchers.

The findings have implications for the management of APE in enabling risk stratification of APE patients. Those with increased BNP levels on admission are at higher risk, and those with raised levels of both BNP and cTn are "at particularly high risk of adverse outcomes," according to the authors.

## New Prediction Model Improves Diagnosis of Acute Heart Failure

A newly described and validated prediction model incorporating clinical assessment and N-terminal pro B-type natriuretic peptide (NT-pro BNP) levels has robust accuracy in diagnosing acute heart failure (AHF) (J Am Coll Cardiol 2009;54:1515–21). In patients with undifferentiated shortness of breath, the model "appears to quickly and reliably redirect the undecided clinician for diagnosing AHF," according to the authors. The model also underscores the utility of measuring NT-proBNP as a continuous, rather than discrete, variable.

To develop the model, the researchers used data from a prior study that involved 534 patients who presented to the emergency department with undifferentiated shortness of breath, and who did not have acute myocardial infarction, renal failure, malignancy, or dyspnea that clearly was not AHF. After initial examination and review of chest x-ray and electrocardiogram, the emergency physician assigned a probability of AHF without having knowledge of NT-pro BNP levels and pursued standard clinical management. Two cardiologists subsequently judged the cases for AHF with full access to medical records but were blinded to NT-pro BNP results. The study population was then divided into low, intermediate, and high pre-test probability of AHF, and the clinicians' impressions were compared with NT-pro BNP values. The researchers then calculated likelihood ratios for the diagnosis of AHF over a number of discrete and continuous NT-pro BNP ranges, with the likelihood ratio computed as the proportion of patients with AHF who had a result in the range divided by the proportion of patients without AHF who had a result in the range.

The investigators used an external data set from the N-Terminal Pro-BNP Investigation of Dyspnea in the Emergency Department (PRIDE) study to validate the model. They found that likelihood ratios for AHF with NT-pro BNP were 0.11 for cut-points  $< 300$  pg/mL, increasing to 3.43 for values 2,700 to 8,099 pg/mL, and 12.8 for values  $\geq 8,100$  pg/mL. When applied to data from the PRIDE study, the model appropriately reclassified 44% of patients with intermediate clinical probability to either low or high probability of AHF, with a minor (2%) inappropriate redirection. The authors suggest the findings demonstrate that the model can be used to appropriately direct physicians in a "significant number" of indeterminate cases.

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# NEWS FROM THE FDA

## FDA Publishes Guidance On H1N1 Diagnostics Tests

FDA published a guidance document intended to help manufacturers develop diagnostics tests and submit requests for emergency use authorizations (EUAs) for the 2009 H1N1 influenza virus. Currently, no FDA approved or cleared tests are available to diagnose this strain of flu virus. EUAs allow authorized tests to be used during declared public health emergencies. The guidance document contains information the FDA recommends be included in EUA requests. A full copy of the guidance is available at [www.fda.gov](http://www.fda.gov). Search for UCM188679.

## FDA Grants Second Authorization for Focus Diagnostics' H1N1 Test

FDA issued a second emergency use authorization (EUA) to Focus Diagnostics for its 2009 H1N1 influenza virus test. The new EUA authorizes Focus Diagnostics to market its Simplexa Influenza A H1N1 (2009) test for use on the 3M Integrated Cycler to CLIA high-complexity laboratories for the duration of the emergency. With this EUA, Focus Diagnostics is the only company in the U.S. to offer test kits for detecting the 2009 H1N1 virus authorized by FDA for use in CLIA high-complexity labs. The Simplexa Influenza A H1N1 (2009) test uses real-time PCR to qualitatively detect RNA of the 2009 H1N1 flu virus in nasal or nasopharyngeal specimens. The test detects a specific region of the hemagglutinin gene of the 2009 H1N1 influenza virus to differentiate samples from seasonal human influenza A virus.

## Gen-Probe Granted FDA EUA for Flu Test

Gen-Probe was granted an FDA emergency use authorization (EUA) for its Prodesse ProFlu-ST test to be used in CLIA high-complexity labs for diagnosis of the 2009 H1N1 influenza virus. Aided by an algorithm that relies on seasonal A/H1 virus and seasonal influenza A/H3 virus results, ProFlu-ST is the first commercially available RT-PCR test that can identify the H1N1 virus from a single sample. Because the three influenza A subtypes have different susceptibilities to antiviral drugs, the capability to distinguish among viruses is important for clinicians and patients this flu season. The EUA will remain in place for the duration of the declared public health emergency.

## Response Biomedical Cleared to Add Analytical Reactivity Info to Assay

Response Biomedical received a special 510(k) FDA clearance for an update to the company's RAMP Influenza A/B Assay package insert to include analytical reactivity information for a strain of the 2009 H1N1 virus. Although the assay has shown the ability to detect the 2009 H1N1 virus in cultured isolates, the performance characteristics of this device with clinical specimens has not been established. The assay

can distinguish between influenza A and B viruses, but cannot differentiate influenza subtypes. The RAMP Influenza A/B Assay is marketed in the U.S. by 3M Health Care as the 3M Rapid Detection Flu A+B Test and is used to identify influenza A and B in human samples.

## Ortho Clinical's HBsAg Assay Approved

FDA approved Ortho Clinical Diagnostics' VITROS Hepatitis B Surface Antigen (HBsAg) Assay for use on the VITROS 5600 Integrated and VITROS 3600 Immunodiagnostic Systems. The VITROS HBsAg Assay is designed for the qualitative detection of the hepatitis B surface antigen in human serum and plasma. The assay can be used as a quick and reliable test for HBV, or to screen for HBV infection in pregnant women to identify neonates at high-risk of acquiring HBV during the perinatal period.

## SQI Diagnostics Platform, IgXPlex Arthritis Assay Receive Clearance

SQI Diagnostics announced FDA clearance for its automated SQiDworks Diagnostics Platform and the multiplexed IgXPlex rheumatoid arthritis (RA) assay. The fully automated platform enables labs to measure multiple biomarkers from a single sample and incorporates SQI's IgXPlex technology to facilitate multiplexed measurement of multiple biomarkers. The IgXPlex RA assay provides analysis of several biomarkers commonly used in the diagnosis of rheumatoid arthritis, including RF-IgA, RF-IgM, and anti-CCP-IgG.

## PerkinElmer Cleared for Newborn Screening Platform, TSH Assay

PerkinElmer received FDA 510(k) clearance for its automated Genetic Screening Processor (GSP), which is used by public health labs for newborn screening programs. The processor allows labs to run multiple tests for irregularities associated with metabolic diseases on very low volume blood samples from newborns. The processor also enables both multi-analyte screening and traditional or enzymatic assays. The GSP Neonatal TSH assay is the first assay to receive clearance for the GSP, though additional newborn screening assays are currently in development.

## AdvanDx Bloodstream Pathogen Test 510(k) Cleared

AdvanDx obtained FDA 510(k) clearance for a 90-minute protocol for its *E.faecalis*/OE PNA FISH test. The new protocol reduces the turnaround time from 2.5 hours to approximately 90 minutes by reducing the peptide nucleic acid (PNA) probe hybridization from 90 to 30 minutes. The test has been available since 2003 and uses PNA probes to target species-specific ribosomal RNA in live bacteria and yeast. bioMérieux distributes the *E.faecalis*/OE PNA FISH test in the U.S.

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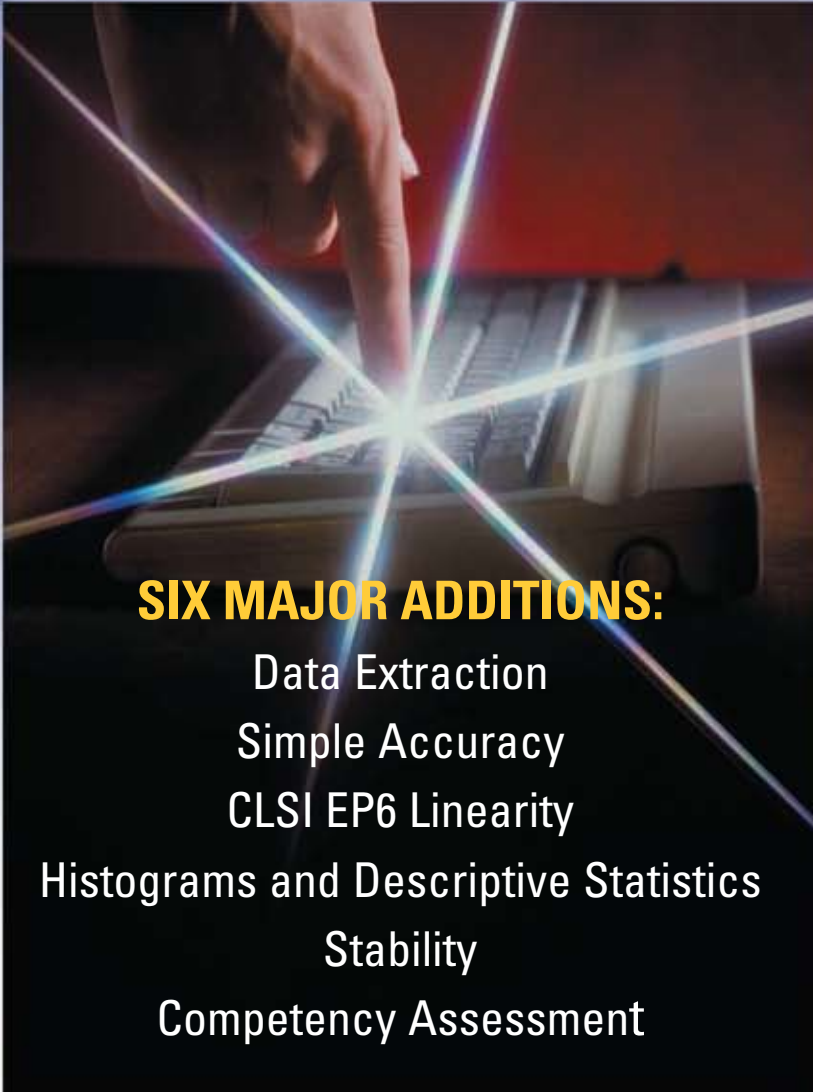
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