

## DIAGNOSTIC TESTS REMAIN UNDERVALUED

With strong opinions on both sides about whether healthcare reform will reduce costs, a new report prepared by the Lewin Group underscores why diagnostic screening tests are essential to reducing costs in the U.S. healthcare system. Commissioned by the American Clinical Laboratory Association and the Advanced Medical Technology Association, the report describes how specific screening tests provide opportunities for cost savings, as well as improved healthcare quality and patient outcomes.

The comprehensive report analyzes four case studies: methicillin-resistant *Staphylococcus aureus* testing for identifying healthcare-acquired infections; HbA1c testing for screening diabetes; KRAS gene mutation testing for targeted treatment of colorectal cancer; and human papillomavirus DNA testing for the diagnosis of cervical cancer. These case studies highlight different health problems, risk groups, and testing technologies valuable to many aspects of patient care. Overall, testing programs for these conditions have resulted in better health outcomes

### Contribution of Selected Diagnostic Tests to Avoidable Costs

Disease	Diagnostic Test	Avoidable Costs
Diabetes	HbA1c level	\$573 million
Colorectal cancer	Fecal occult blood test	\$191 million
Heart disease	Cholesterol test	\$87 million

Source: The Lewin Group. *The value of diagnostics, innovation, adoption and diffusion into health care.* July 2005.

for patients while providing cost savings and efficiencies to the healthcare system, according to the report.

However, the report also stresses that several barriers currently limit the full benefits of laboratory testing from being realized. Examples include: healthcare providers' ignorance of when to use tests; insufficient evidence regarding clinical utility of tests for specific subgroups of patients; inconsistencies in clinical practice guidelines; conflicting or inadequate coverage and payment policies; and the need for additional evidence to determine the full economic impact of laboratory testing.

The Lewin Group, a health care research and consulting firm, provides analyses to public agencies, nonprofit organizations, industry associations, and private companies, has previously conducted analyses of the value of lab testing. The firm is based in Falls Church, Va., and is an Ingenix company, a wholly-owned subsidiary of UnitedHealth Group.

A full copy of the report is available online at: [www.clinical-labs.org](http://www.clinical-labs.org).

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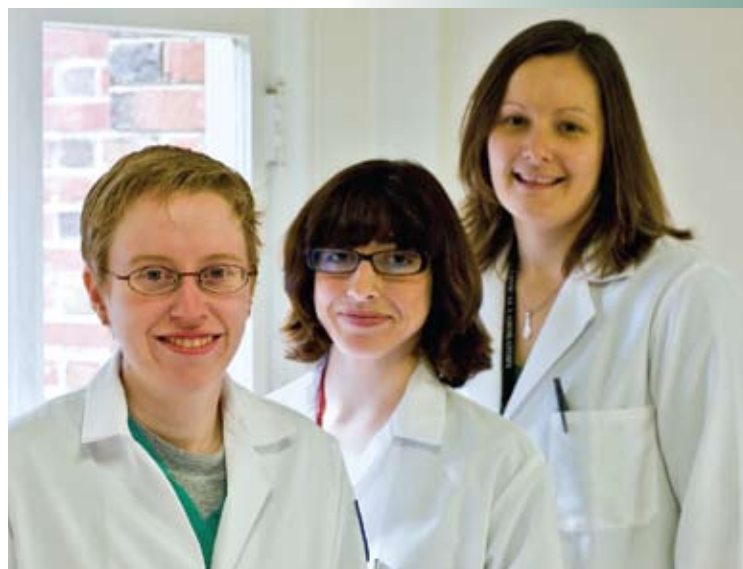
## The Workforce Challenge

### Will Simplified Credentialing Speed Change?

BY BILL MALONE

The recently-completed U.S. American Community Survey shows that the recession is having a profound impact on housing, property values, immigration, and of course, household income. But the woes of the recession might turn out to be an opportunity in disguise for the long-lamented lab workforce shortage. Working as a medical technologist (MT) or medical laboratory technician (MLT) is becoming a more attractive career option as college students take a hard look at which careers can offer job security and a good chance of finding an opening, especially considering the common perception that healthcare is recession-proof. However, even with interest in healthcare careers getting a boost from the struggling economy, educators who have been cultivating enthusiasm for lab training programs say it's now the labs' turn to proactively help tackle the shortage they struggle with daily, and avoid a worse crisis down the road.

Though many training programs have closed over the last 30 years, in fact the most urgent "limiting factor" in producing more trained lab scientists is the lack of clinical labs willing to train students during their clinical internship, explained Susan Gross MT(ASCP), chair of the Coordinating Council on the Clinical Laboratory Workforce (CCCLW). CCCLW is a coalition of 17 lab organizations working together to ensure a high quality workforce. "I know many training programs could handle more students, but there aren't clinical sites for them. It's frustrating because we're getting students interested in the lab field, but some programs can only take them if they can place them in a clinical lab for their clinical training," said Gross. "My biggest fear is that labs are taking less qualified people to fill the gap—that they're lowering their expectations instead of putting their efforts into training the next generation."



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## Differential Anemia Diagnosis

### What's the Best Marker of Iron Status?

BY GENNA ROLLINS

Anemia compromises quality of life through fatigue and impaired cognitive function and has been linked to cardiovascular disease morbidity, increased hospitalization, and mortality. Despite the significant health consequences associated with the condition, anemia remains one of the most prevalent conditions worldwide and is the most common nutritional deficiency, affecting an estimated one-quarter of the world's population. Even with such a profound disease burden, iron deficiency anemia (IDA) and anemia of chronic disease (ACD) often receive sub-optimal clinical management. Strategies to definitively diagnose and treat the conditions have not been widely implemented, and there is disagreement about the best combination of tests and cutoff points to distinguish between the two. At the same time, research advances have enhanced the field's understanding of iron homeostasis, and ushered in a new generation of analytical tools with their own set of challenges.

"There needs to be some kind of better systematic approach to differentiating between IDA and ACD. We need evidence-based guidelines to help direct diagnosis and treatment, but they just don't exist right now," said Susan Clark, RD, PhD, associate professor of human nutrition, foods and exercise at Virginia Tech University in Blacksburg. "Until we do that we're not going to help patients as much as possible and their outcomes will be more negative than positive."

#### Lacking Attention to Anemia

The prevalence of anemia and iron deficiency varies according to demographic groups, but is most common in young children, women

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# Certification Agencies Merge

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Despite hiring freezes, shrinking budgets, high vacancy rates, and other headaches labs are facing, stakeholders are cautiously optimistic that the extensive efforts of lab groups to promote lab careers are starting to pay off, with more interest in the profession and increasing numbers of students registering for educational programs and taking certification exams. On top of these accomplishments, the merger of two top credentialing agencies is raising hopes that a more coherent and unified image for lab professionals will emerge to draw potential students and more respect from the public.

## A Delayed Crisis

As bad as the workforce shortage looks now, with a vacancy rate for MTs at about 10% according to the latest American Society for Clinical Pathology (ASCP) Wage and Vacancy Report, the workforce shortage predicament could potentially be exaggerated when the economy begins to recover. The recession has caused many lab scientists to delay retirement because their investment accounts got hit by Wall Street losses, explained Kay Doyle, PhD, MT(ASCP), chair of the department of clinical laboratory and nutritional sciences at the University of Massachusetts Lowell and director of the medical technology program for more than 25 years.

"If this is the case, it delays the bulk of the retirements that are coming, because clinical labs, like nursing and teaching, had large numbers from the baby boom generation that are now looking at retirement," said Doyle. "Now things have changed. The country is only producing about one-third to one-half of what the projections say we'll need. So people work overtime, or work two jobs, and labs say they can't find the people to do the work." Currently, many labs are actually not looking to hire as many people, but not because they don't need them. The economy has made them more cautious about hiring, or has forced them to freeze hiring altogether. However, the job market for lab scientists is still exceptional, despite the cutbacks, said Doyle.

Laboratorians nearing retirement—or perhaps delaying retirement—are the mentors that young laboratorians need most for their clinical training, Gross emphasized. "The current laboratorians who are going to retire in the next 5 to 10 years are saying, 'we don't have the staff to train interns,' or 'we don't have an empty position, why should we train them now?' You can't look at it like that, as these are the labs that will be needing staff after retirements. Even if you hire one in every four you train, you can still break even financially because of the cost of turnover and hiring."

In the same way that labs expect quality to remain high despite staffing, budgets, or other factors, Gross wants labs to think about training new laboratorians as part of succession and retention planning. This includes training interns as well as developing the leadership skills of their current staff. "When budgets get tight and people aren't there, it's not an excuse to lower educational expectations or reduce quality in the lab," said Gross.

Though some schools that educate MTs and MLTs say they can now draw larger

numbers of students, the loss of clinical sites for internships during tough times has essentially put a lid on more rapid growth for the programs that are doing well. "We're being told that in some areas of the country, people are filling their classes, which they hadn't been doing for a while. But the point they make in the next breath is that their classes are not as large as they could be, because when there was a shortage, they lost clinical sites," said Elissa Passiment, CLS(NCA), executive vice president of the American Society for Clinical Laboratory Science (ASCLS). "So while the good news is that they're filling their programs, the programs' capacity is smaller than it should be. So there's an uptick, but the capacity is still not large enough to fix the problem that we're having with the shortage." ASCLS participates in the CCCLW.

Passiment believes that the profession is starting to see the fruits of some of the public relations campaigns that lab groups have put together to try and attract more people to the profession. Educators also report that the popularity of television shows like CSI and NCIS drives more students to explore careers in science, even beyond forensics. Another encouraging trend for labs is interest from immigrants to the U.S. who see jobs in healthcare as a practical career choice to steer their children into. "Healthcare tends to be one of the first places that the first or second generation looks to for educating their children," said Passiment. "So if you talk to educators in states with a large immigrant population, there is a significant influx of minority students. So that's another positive that is working for us."

## What's in a Name?

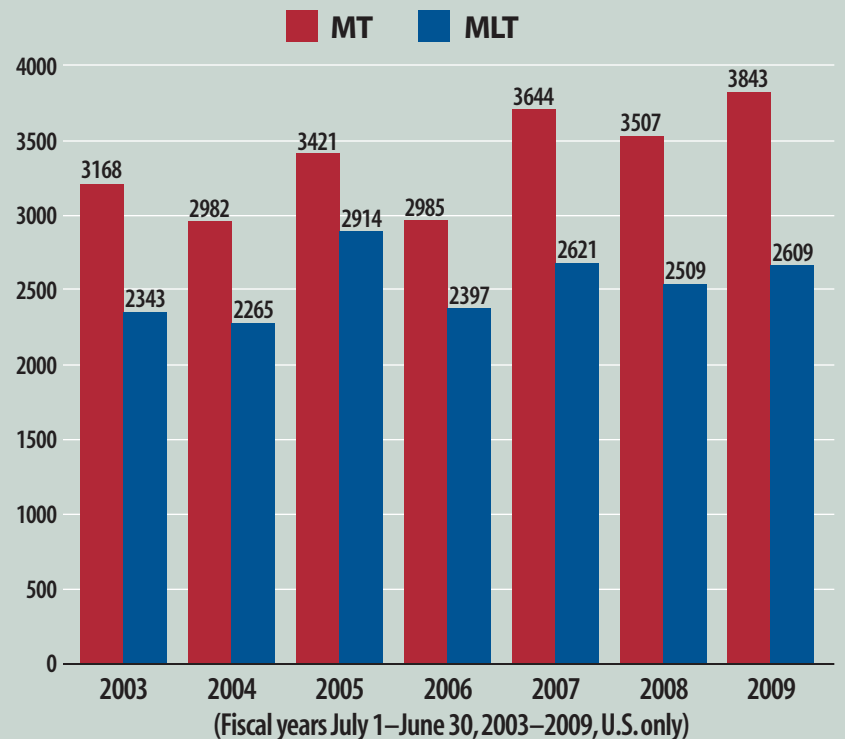
On the certification front, one challenge has been that with so many agencies offering MT and MLT credentials, students were unsure which test to take and lab managers have struggled to set standards for employment. MT and MLT designations are offered by several organizations, including American Medical Technologists (AMT), the American Society for Clinical Pathology Board of Registry (ASCP-BOR), and the National Credentialing Agency for Laboratory Personnel (NCA). Beginning in October, two of these certification organizations have merged—ASCP-BOR and NCA (See *CLN*, October 2008). Leaders from ASCP-BOR and NCA hope that the new organization, called the ASCP Board of Certification (BOC), will simplify the credentialing process for students and empower the profession with a more unified voice.

"Having a standard credential instead of having two different ones is going to increase credibility and recognition by other healthcare professionals, as well as the public," said Kathleen Becan-McBride, EdD, MT(ASCP)<sup>cm</sup>, chair of ASCP-BOR. "There was so much alphabet soup beforehand. Now we're down to unification in one credential that will also help students and employers." Even though they were both closely in line for entry level competency, there still were some differences between ASCP and NCA. To be on the safe side, students would routinely sign up for both the ASCP and NCA exams, not knowing whether once they graduated, a hiring

See *Workforce*, continued on page 4

# Education Trends for Lab Scientists

## Applicants for ASCP Board of Registry Certification Examinations



With more students taking certification exams and many educators reporting their classes filling up, more pressure is now on labs to offer needed clinical internships.

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# AACC

# Labs Benefit from Interns

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manager might be more attuned to one board or another.

Forming a larger certification agency will also help strengthen the image and reach of lab professionals, said Becan-McBride. “I think it says something about the profession coming together and becoming more unified, knowing that for patient advocacy, we have to become unified in the future with the way healthcare is changing so dramatically. It really shows the unification through the new board structure too, enabling us to work within a larger expanse of the public and profession.” The BOC Board of Governors will be composed of five ASCP Fellows (pathologists), five ASCP laboratory professionals, four representatives of ASCLS, two representatives of the Association of Genetic Technologists (AGT), and eight representatives from eight other participating societies, including AACC. There will also be one public representative on the board.

The ASCP suffix will be attached to all BOC certifications. Current and active certifications will be transferred to the ASCP BOC, but no examination will be required for the transfer. Medical technologists (MT) and clinical laboratory scientists (CLS) will be called medical laboratory scientists (MLS), with the designation MLS(ASCP).

Changing the name of the designation became significant in the process because lab professionals have always struggled for recognition and status among other healthcare professions. Medical technologist is the original and most common designation, with clinical laboratory scientist being introduced more recently by NCA. “We have found that clinical laboratory scientist has definitely been more descriptive than medical technologist. Medical technology in this country has for a while now really stood for the devices, so when you tell somebody that you’re a medical technologist, it didn’t really help, especially when recruiting in to the profession,” explained Passiment. “If you tell somebody that you are a laboratory scientist, it meant more to young people, because ‘scientist’ is something they get.” The newest iteration was conceived as part of the unification of NCA and ASCP, with the logic that ‘medical’ gets even more traction with the public than ‘clinical.’ In addition, most other countries use the word ‘biomedical’ or ‘medical’ to describe lab professionals.

In the short term, these name changes might lead to more confusion, said Kathy Cilia, MT, director of marketing at AMT, which also participates in the CCCLW. “AMT will likely stay with the MT designation for now because that is how the profession is currently known in the industry, and what employers accept,” she said. “Even with the new designation, the MT name will be in use for the foreseeable future.”

## An Example of What Works

One of the most remarkable success stories in taking on the workforce shortage comes out of Minnesota via the state’s Healthcare Education Industry Partnership (HEIP). Created by the Minnesota State Colleges and Universities with funding from the Minnesota legislature in 1998, the effort includes a clinical laboratory workgroup that has met monthly since the program’s in-

ception to talk about lab workforce needs. The group includes lab managers from the state’s larger healthcare systems, as well as rural lab managers, educators, recruiting agencies, reference labs, the state hospital association, and department of health. “It’s truly an amazing group of people who come together with no other goal than to make sure that we’re doing the right things to adequately meet the staffing needs in the future,” said Valerie DeFor, HEIP director. “There’s no competition, and it’s very open, supportive, and collaborative.”

One of the group’s recent achievements was helping secure a \$2 million U.S. Department of Labor grant for St. Paul College. The money will go toward creating an online program for lab staff without Bachelor’s degrees so they can earn degrees online while performing their clinical experience requirements at work. HEIP is also applying for money from the stimulus package, the American Recovery and Reinvestment Act.

One of HEIP’s primary areas of focus has been building awareness and interest among students. HEIP and the lab workgroup created a tool kit for lab professionals to visit K–12 classrooms and explain what laboratorians do. “One HEIP staff member focuses on the K–12 program, getting the message out that healthcare is the job of the future, there is a job for anyone in healthcare, and getting them to think beyond a doctor and a nurse,” said DeFor. “We also do a lot of work helping schools advance the curriculum and stressing math and science so that they are prepared to be successful in health career education at the post-secondary level. So they know about the lab, and hopefully they are more prepared to chose a lab field and be successful when they do that in college.”

But HEIP has done more than just get laboratorians involved. The group also has seen concrete results from its efforts. Minnesota, unlike most every other state, has seen an expansion in educational capacity for the clinical lab. The University of Minnesota program—although threatened with closure in 2003—essentially doubled its numbers. Two other state schools are pursuing NAACLS accreditation and are planning to expand, and the state’s 2-year MLT programs have had increases in students. “I think that’s a testament to HEIP’s work, and especially that clinical laboratory work group that is so committed. Without that group, we wouldn’t have the synergies that it brings. And so while one person may need to be advocating for lab issues, it makes a difference when it’s everyone sending the same message. And they know they have the support of other people to move things forward,” said DeFor. “Simply the fact that in the middle of a staffing shortage for almost every lab, I have these people to come every month and give up half a day to work on these issues—they wouldn’t do that if it wasn’t valuable and if we weren’t making a difference for them.”

With its educational programs in full swing, HEIP’s major challenge remains a lack of clinical sites for students to complete their internships. “Our message now is that, while Minnesota has done a fabulous job on the educational side with maintaining and expanding lab programs, we need help from the provider community in

getting additional clinical sites for students because we’re really, really struggling with that right now,” said DeFor. “Some of the labs say, ‘well, we’re short-staffed.’ They are, but they’re always going to be short-staffed if they don’t take students.”

To that end, an HEIP member developed a concept called preceptor training that helps labs accommodate students and be more confident in training them. Preceptor training is a short class that explains what it takes to train students, what a lab can expect of them, and how they can help them learn. “What we heard from a lot of our provider partners is that ‘we probably could take a student, but we don’t know if we can teach,’” said DeFor. “The preceptor training helps alleviate any fears that the staff would have helping a student along.”

## What’s In It for Labs?

While educators and other advocates for lab science students hope laboratorians get involved in workforce efforts because they care about their profession, they also underscore the fact that labs have a lot to gain from taking interns, including previewing prospective employees and pushing incumbents to keep up their knowledge and skills.

Since most interns find jobs at their clinical sites, lab managers are able to see their work ethic and how they fit with the rest of the staff well before they have to make a decision about hiring the person, explained Passiment. “For those labs that take on multiple students, they will tell you that it works really well for them because they have their choice of who they want to fill any empty spots they have,” she said. “The other advantage is that, for you to be able to train, your own staff really has to be up-to-date. So you get this additional benefit, and it doesn’t cost you very much.” There is also a financial benefit. Advertising for an open position can cost much more than \$20,000, well below the cost of spending some extra time with a student.

Once the laboratorians who actually train students get over the fear of a new responsibility, often they find it’s an enjoyable and rewarding experience, said Gross. “It makes it more than just a job, and both sides learn from the experience. It’s just the idea that there is something new to do that is scary.”

Doyle hears much of the same sentiment from labs in Massachusetts. “People enjoy having students because they feel it keeps them on their toes. It works out really well for both students and the clinical site, because the students have already been working there, they know the people, they know how the place operates, and if they take the job there it’s because they really want it,” she said. “Plus, they’ve already had some employee training.” At the University of Massachusetts, Doyle is also able to entice labs with vouchers for course tuition at the university if they take lab students, as well as offering access to audioconferences to help the labs with continuing education.

Whether or not labs, educators, and other stakeholders can work together to prevent a worse workforce crisis will make a huge difference to the future of the profession, said AMT’s Cilia. “However, as labs struggle with cost containment, we may see a new model emerge that includes fewer, more specialized MTs working alongside of MLTs that do the majority of lab testing,” she said. “That may be the reality we need to face in the future.”

CLN

# Inflammation Confounds Anemia Work-Up

Anemia, continued from page 1

of childbearing age, racial and ethnic minorities, and in individuals with various chronic conditions. Prevalence increases with age and is quite common in chronic diseases like cancer and autoimmune disorders. For example, anemia occurs in an estimated 30% to 60% of rheumatoid arthritis patients and anywhere from 30% to 80% of patients with inflammatory bowel disease (IBD). IDA is the most common form of anemia, accounting for about half of all cases, while ACD is the second most common type with about 30% of all cases. Although they originate from different pathways, IDA and ACD both are readily treatable. Yet both tend to receive short shrift by clinicians. “The management of IDA is often sub-optimal with most patients being incompletely investigated if not at all,” according to the British Society of Gastroenterology guidelines for the management of IDA. Essentially the same has been said of ACD.

Some experts have argued that clinicians paradoxically may be less likely to intervene in patients with chronic diseases who are the most likely to have both IDA and ACD. “Gastroenterologists tend to tolerate reduced hemoglobin levels better than their patients. It is important to consider that anemia impairs quality of life even in the absence of specific symptoms and that its treatment leads to improvement in the quality of life. These simple facts are often unrecognized or neglected by gastroenterologists caring for patients with IBD,” according to recently published guidelines on the diagnosis and management of iron deficiency and anemia in IBD (*Inflamm Bowel Dis* 2007;13:1545–1553). Christophe Gasche, MD, led the guideline effort because of the lack of attention to anemia in IBD patients. In the many extant IBD-related guidelines, “I’m not aware of a single word on anemia in any of them,” he explained. “So this is a huge problem that’s not being considered as a problem. Our goal was to make an awakening among our peers.” Gasche is professor of medicine and director of the Christian Doppler Labora-

tory on Molecular Cancer Chemoprevention at the Medical University of Vienna in Austria.

Gasche is not alone in advocating for better recognition and treatment of IDA and ACD. “There’s a sentiment that we think we can treat anemia by using the old standards, but if that’s the case, then why do we still have the problem?” said Clark. “It can take quite a while for someone with iron deficiency to become blatantly anemic. If the anemia is compounded by a chronic disease, then by the time you’re trying to discern what’s going on, you’ve got a really sick person on your hands, and sometimes that can be a comorbidity in their outcome.” Conversely, others have argued that ACD is a “beneficial and adaptive response to an underlying disease state” and that treatment of it poses distinct risks (*CMAJ* 2008;179:333–337).

## A Tightly Regulated System

Iron homeostasis is a complicated, tightly regulated system centered around the rate of erythropoiesis and the level of iron stores. Iron absorbed through the intestine binds to transferrin, a blood protein that transports iron to target cells, attaching to those cells via transferrin receptors (see figure, p. 7). In healthy adults, most transferrin receptors are connected to erythroid progenitor cells in bone marrow, and this is where most iron is used as a component of hemoglobin. When cells need iron, transferrin receptor production rises, making more iron uptake possible. At the end of their typical 120 day life, red blood cells are destroyed by macrophages that recycle iron from hemoglobin. In non-erythroid cells, iron is stored as ferritin in hepatocytes and macrophages as part of the reticuloendothelial system.

With discovery of the peptide hormone hepcidin in 2000, a more nuanced understanding of iron homeostasis has emerged. Secreted primarily by hepatocytes, hepcidin negatively regulates two essential aspects of iron homeostasis, intestinal absorption and macrophage recycling. The level of iron stores influences the release of hepcidin:

when stores are low, hepcidin expression decreases to facilitate iron absorption, and when they are replete, it increases to forestall iron overload. Hepcidin expression also is influenced by inflammatory cytokines, and its increase has been implicated in the development of ACD.

IDA occurs when there is not enough iron to maintain normal physiological functions, and is manifested on a continuum from negative iron balance to iron depletion, iron-deficiency erythropoiesis, and finally, full-blown anemia. Serum iron levels fall only when iron stores become depleted. As this happens, transferrin levels rise and transferrin saturation declines. Iron depletion exists when iron stores are low or empty but the tissues that need iron are maintaining normal function. The causes of IDA are increased iron demand, such as in pregnancy or lactation, inadequate dietary intake—most commonly through malabsorption—or as a result of intestinal bleeding.

In contrast, ACD involves immune and inflammatory mechanisms that cause disruptions in iron metabolism, erythropoiesis, and erythrocyte survival. Iron may be retained in the reticular-endothelial cells, there may be inadequate erythropoietin production, or inhibited proliferation of erythroid progenitor cells in bone marrow. In ACD, the iron supply depends on its rate of mobilization, so if the mechanisms for transporting iron to tissue are disrupted there can be a functional iron deficiency even though iron stores are adequate.

## The Diagnostic Work-up

Regardless of the type of anemia involved, labs play an essential role in pinpointing the exact problem. “It is unusual for patients to present with anemia so advanced that the clinical manifestations predominate,” according to a monograph by the National Anemia Action Council. “Anemia is almost always discovered through abnormal laboratory screening test results.” The first tip-off often is a low hemoglobin level. The World Health Organization (WHO) defines anemia as hemoglobin <13 g/dL for men, <12 g/dL for women, and <11 g/dL in pregnant women.

The conventional work-up for IDA is

fairly clear-cut and typically involves assessing erythrocyte morphology along with serum ferritin, serum iron, and total iron binding capacity (see table, below). IDA morphology is microcytic, hypochromic, and all three serum markers are low. However, the picture is murkier when it comes to diagnosing ACD or the combined state of IDA and ACD, which occurs in an estimated 20% to 30% of patients who also have ACD. One of the key issues is that ferritin is an acute phase reactant with levels determined not only by iron stores but also by the degree of cytokine activation. So values can rise in the presence of inflammation, even when iron stores are depleted from IDA. Most clinicians would agree that high and low ferritin values argue for inflammation and iron deficiency, respectively, but the middle ground leaves room for confusion and misinterpretation.

“In a person who is healthy with no active inflammation, diagnosing iron deficiency is pretty straightforward,” explained Robert Means, Jr., MD, a hematologist, professor and senior associate chair of internal medicine at the University of Kentucky College of Medicine in Lexington. “The difficulty is in a person who is sick from other reasons. Their iron and transferrin levels may be depressed as a result of the inflammation, and the ferritin may be falsely elevated.” While ferritin concentrations of ≤15 µg/L are indicative of iron deficiency, when inflammation is present, levels can rise to as much as 100 µg/L even when iron stores are depleted. In the IBD guidelines, Gasche and his colleagues recommended serum ferritin <30 µg/L as an indicator of depleted iron stores in patients with inactive IBD, and <100 µg/L in patients with active disease.

Since ferritin can confound a clear diagnosis in the presence of inflammation, many clinicians simply interpret ferritin levels in the context of inflammatory markers like C-reactive protein (CRP) or erythrocyte sedimentation rate. WHO has suggested that α-1-antichymotrypsin may better reflect change in ferritin concentration during infection (*Assessing the Iron Status of Populations*, WHO, 2007, Second Edition).

Another way around equivocal ferritin results in the presence of inflammation is measurement of soluble transferrin receptor (sTfR), a truncated fragment of transferrin receptor that reflects erythropoiesis and is not affected by inflammation. sTfR is increased in patients with either IDA or both IDA and ACD but not ACD alone. Recent unpublished research found that the combination of ferritin, sTfR and the sTfR/log ferritin index (sTfR index) improved the detection of IDA and aided in the differential diagnosis of IDA and ACD in comparison to ferritin or sTfR alone. However, one of the study’s authors, Kari Punnonen, MD, PhD, cautioned about the instrumentation used with these biomarkers. “In order to use both sTfR and the sTfR index, one needs both assays run on the same platform. Otherwise, because of the different reference units one might not be able to determine proper cut-off values,” he explained, adding that the study in question used the Beckman Coulter automated Access sTfR assay. Punnonen is general manager and medical director of Eastern Finland Laboratory Center in Kuopio.

See **Anemia**, continued on page 6

## Selected Biochemical Indicators of Iron Status

Measurement	Commonly Used Methods	Indicator of
Reticulocyte hemoglobin concentration	Automated flow cytometry	Concentration of hemoglobin in new RBCs
Serum or plasma iron	Colorimetry	Iron bound to transferrin in blood
Ferritin	Immunoassay, e.g. ELISA or immunoturbidometry	Size of iron stores
Total iron binding capacity (TIBC)	Colorimetric assay of amount of iron that can be bound to unsaturated transferrin <i>in vitro</i> ; determination from transferrin concentration measured immunologically	Total capacity of circulating transferrin bound to iron
Transferrin saturation	Calculated from: Serum iron/TIBC	Saturation of <15% with high TIBC indicates iron deficiency
Transferrin receptor	Immunoassay, e.g. ELISA or immunoturbidometry	Reflects balance between cellular iron requirements and iron supply
Body iron stores	Ratio of transferrin receptor to ferritin –[log(TfR/ferritin ratio)–2.8229]/0.1207	Measure of body iron status including iron deficits, status of storage iron and iron overload
Hepcidin	Immunoassay; mass spectrometry	Regulator of iron absorption from gut

Adapted from “Assessing the Iron Status of Populations,” WHO/CDC Technical Consultation, 2007, Second Edition.

# New Iron Status Markers Emerging

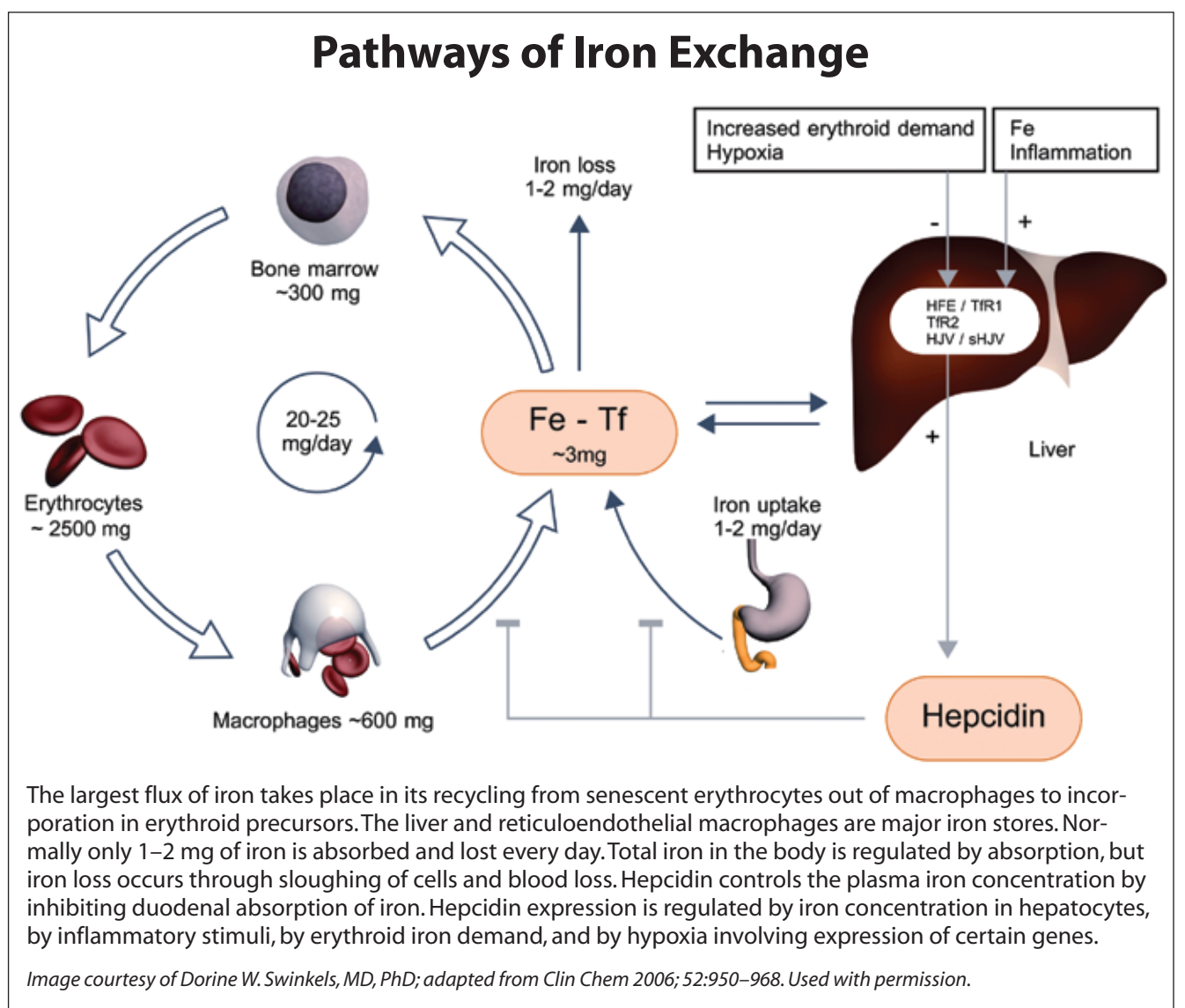
Anemia, continued from page 5

sTfR assays have not been standardized, and that may be one reason why the test has not been implemented widely, even though it has been available for a decade or more. However, a standardization effort is underway. Scientists at the British Health Protection Agency (HPA) have evaluated a lyophilized preparation of recombinant sTfR (rsTfR) in a sTfR-depleted serum matrix, coded 07/202, and in October were expected to present to the WHO Expert Committee on Biological Standardisation a study that had been carried out with manufacturers of sTfR kits. The study suggested that use of rsTfR 07/202 as a reference reagent would significantly reduce inter-method variability if manufacturers would adopt it, according to Susan Thorpe, PhD, principal scientist in the parenterals section of the biotherapeutics group at HPA.

Whether standardization will boost the use of sTfR remains to be seen. Although Punnonen has been a leading researcher in the field and his lab now performs about 6,000 sTfR assays per year versus 8,000 of ferritin, getting to that point has been a slow process. "I'm happy to see that sTfR is ordered in almost the same numbers as ferritin, but it's taken 10 years. It takes a long time to change any clinical process," he observed. An algorithm incorporating the use of transferrin, ferritin, sTfR and sTfR index has been proposed (NEJM 2005;352:1011-23).

## Newer Measures of Iron Status

Still other researchers argue that better measures of IDA and ACD are the reticulocyte hemoglobin content (CHr) and proportion of hypochromic red cells (HYPO) in combination with the sTfR index. "Typical biomarkers are only indicators of iron supply but not of iron demand. These markers give no information about whether the cell really uses the iron for the synthesis of hemoglobin or enzymes of the respiratory chain," explained Lothar Thomas, MD, professor of medicine at University Hospital Northwest in Frankfurt, Germany. "The only proof is an increase in the hemoglobin value in the CBC. But this will last several



The largest flux of iron takes place in its recycling from senescent erythrocytes out of macrophages to incorporation in erythroid precursors. The liver and reticuloendothelial macrophages are major iron stores. Normally only 1-2 mg of iron is absorbed and lost every day. Total iron in the body is regulated by absorption, but iron loss occurs through sloughing of cells and blood loss. Hepcidin controls the plasma iron concentration by inhibiting duodenal absorption of iron. Hepcidin expression is regulated by iron concentration in hepatocytes, by inflammatory stimuli, by erythroid iron demand, and by hypoxia involving expression of certain genes.

Image courtesy of Dorine W. Swinkels, MD, PhD; adapted from *Clin Chem* 2006; 52:950-968. Used with permission.

weeks. The CHr is a real time parameter that indicates changes in iron demand of the cell within a week. Therefore I feel that CHr and HYPO are better parameters than the typical biomarkers of iron metabolism." Thomas reported in 2002 that use of a diagnostic plot of CHr and sTfR index demonstrates the progressive stages of iron deficiency, regardless of whether inflammation is present (*Clin Chem* 2002;48:1066-1076). His lab uses the plot and an accompanying explanation to guide physicians in diagnosing and treating anemia.

While Punnonen agreed that use of CHr and HYPO is a viable strategy for assessing iron demand, he cautioned that the two parameters can be produced only by one type of analyzer, the Siemens Advia 120. "There are other systems which provide what they call comparable measures,

but they're based on more or less different concepts. So there's no way one could compare the results between manufacturers or analyzers," he said.

Even as researchers and laboratorians debate the merits of various iron status biomarkers, they are in agreement that

**"Typical biomarkers are only indicators of iron supply but not of iron demand. These markers give no information about whether the cell really uses the iron for the synthesis of hemoglobin or enzymes of the respiratory chain."**

Lothar Thomas, MD, professor of medicine at University Hospital Northwest in Frankfurt, Germany.

development of robust and reliable commercial hepcidin assays could transform the diagnostic landscape. "The field is moving to hepcidin. It may be as popular in three to five years as ferritin is now," predicted Thomas. However, he cautioned that values reported by immunoassay and mass spectrometry methods vary considerably. A recent review article bore this out: the seven methods examined used a wide range of normal values and had variable intra-assay precision and lower limits of detection (*J Prot* 2009 doi:10.1916/j.jprot.2009.08.003). Meanwhile, Dutch researchers have proposed an algorithm using transferrin saturation, sTfR and CRP to predict measured hepcidin levels (*Blood Cells Mol Dis* 2008;40:339-346).

Whether or not hepcidin assays hit the mainstream, experts suggested that laboratorians can do much to improve the work-up of anemia. Clark would like to see overall evidence-based guidelines for the diagnosis and treatment of IDA, ACD, and concomitant IDA and ACD. Means suggested that lab directors put on their educator hats. "Labs could be helpful by explaining that low serum iron is not necessarily diagnostic of iron deficiency and by indicating that

in the setting of inflammation ferritin can be raised even in the absence of iron," he said. "They could also help when clinicians come to them with cases they believe may be iron deficient but with indeterminate results. In such cases, the clinician needs help deciding what additional tests to do."

Both Means and Gasche urged labs to re-evaluate the normal values reported for ferritin. "There's no reason why women should have lower ferritin levels than men, but in most labs there is a difference in the normal ranges for men and women," Gasche explained. For his part, Punnonen worked to reduce the use of iron and transferrin measurements in the differential diagnosis between IDA and ACD, and saw the number of tests drop by about one-third. "It used to be routine here to measure serum transferrin and iron in patients who had anemia, but iron is low in both IDA and ACD, so it's of no use to measure iron," he explained. "When someone has to decide if a patient has iron deficiency, one should use sTfR and ferritin and forget iron and transferrin."

The many indicators of iron status, combined with changing analytical challenges, underscore the need for laboratorians to keep abreast of new developments and maintain an active dialogue with clinicians.

Dr. Means is a consultant to Beckman Coulter, and Dr. Punnonen has conducted research funded by Beckman Coulter.

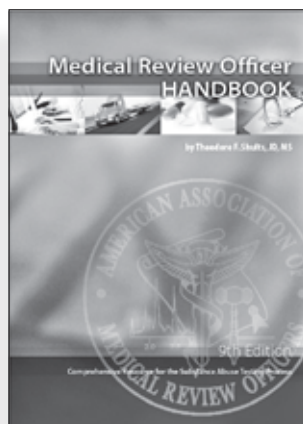
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# Contemporary Issues in Thyroid Disease Measurements



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 July 2009 presentation by Carole A. Spencer, MT, PhD, FACB, director of the University of Southern California Endocrine Laboratories.

**Q** If TSH value is trending towards the high end of the reference value, would you consider repeat testing to see if the assay is good without any interference from circulating anti-mouse antibodies? After confirming everything is in order as far as the TSH test result is concerned would you further investigate other causes of slight elevation trend in successive TSH assay results?

**A** When the TSH is trending  $>3.0$  mIU/L the first check should be for TPO antibodies (TPOAb) and an autoimmune etiology. Family history is also important. Measuring TSH on a blood specimen drawn 2 months or so later would establish that the TSH abnormality is persistent and not related to TSH lability or nonthyroidal illness. Measuring the TSH using a different manufacturer's method is a good first step to checking for human anti-mouse antibodies. FT<sub>4</sub> is unlikely to be helpful unless the TSH is grossly abnormal,  $>10$  mIU/L or  $<0.05$  mIU/L. Note: not all high TSH levels are abnormal. There can be inactivating polymorphisms of the TSH receptor requiring a higher TSH to maintain euthyroidism. Judgments regarding any treatment or follow-up interval should relate to patient-specific factors.

**Q** What should be taken into account in a study designed to assess the TSH reference range in a population 60–80 years old? Does the NACB guideline approach for TSH reference intervals apply? Do we need 120 euthyroid volunteers for each decade if we also want to know the TSH reference intervals for each decade of life?

**A** The NHANES population found a TSH upper limit of 7.5 mIU/L for 80+ year olds (JCEM 2007;92:4575 and JCEM 2009;94:1251). I do not believe we need a TSH population reference range for every decade, but we do need to educate physicians to expect higher TSH in older patients. The question to treat or not to treat ultimately depends on symptoms, TPOAb, medications, and other patient-specific factors. I think we need to abandon the concept of a fixed reference range for TSH or tailoring a reference range for every condition. Furthermore, different assays detect different TSH isoforms. In any situation, not all of the TSH that we are measuring is biologically active, and an increase in bioinactive TSH may be involved with aging.

**Q** What is your opinion regarding manufacturers' addition of albumin to their FT<sub>4</sub> reagent?

**A** Manufacturers add a variety of proprietary components to try to engineer a FT<sub>4</sub> immunoassay to overcome TBG

effects. I believe it is not unusual to add albumin. From my reading, it is apparent that current FT<sub>4</sub> immunoassays are all albumin dependant to varying extents. The tests work fairly well with uncomplicated hypo- or hyperthyroidism but are prone to artifacts with many drug therapies or in low albumin states. We need to remember FT<sub>4</sub> immunoassays are only estimate tests. Under most circumstances TSH is the more reliable FT<sub>4</sub> biosensor provided that thyroid status is stable and hypothalamic-pituitary function is intact.

**Q** Is the T<sub>3</sub> uptake coming back? How do we prevent its rebirth?

**A** Thyroid Hormone Binding Ratio (THBR) tests used to be called "T<sub>3</sub> uptakes"—they estimate TBG concentrations. THBR tests are available on many platforms. Free T<sub>4</sub> indexes (FT<sub>4</sub>I) calculated by dividing total T<sub>4</sub> by THBR is particularly useful for evaluating pregnant patients because the non-pregnant FT<sub>4</sub>I reference range applies to pregnancy whereas the FT<sub>4</sub> immunoassay values can fall below the nonpregnant lower limit by the third trimester causing unnecessary anxiety. FT<sub>4</sub>I is also useful for assessing thyroid status of hospitalized patients for the same reasons. Our hospital allows our endocrinologists and obstetricians to request FT<sub>4</sub>I as a write in test for these reasons.

**Q** Could you please share the most current recommendations for thyroid reflex testing along with the appropriate cut-off values for abnormal TSH? We would like to offer the option for physicians to order TSH with reflex to avoid delays in follow-up testing.

**A** Because of the log/linear TSH/FT<sub>4</sub> relationship, you would not expect FT<sub>4</sub> to be abnormal unless TSH was  $>10$  mIU/L or  $<0.05$  mIU/L. There isn't much point to reflex test unless TSH is grossly abnormal.

**Q** Did you see any correlations between thyroid and vitamin D?

**A** I have seen no correlations between thyroid and vitamin D.

**Q** What tests are essential for thyroid disorders?

**A** It depends on the disorder. The most sensitive test of thyroid dysfunction is TSH. Because of the log/linear relationship between TSH and FT<sub>4</sub> you don't expect FT<sub>4</sub> to be abnormal unless TSH is  $>10$  mIU/L or  $<0.05$  mIU/L. TPO antibodies (TPOAb) is the most sensitive marker for thyroid autoimmunity. T<sub>3</sub> is used in some

cases when it is necessary to determine the etiology of hyperthyroidism (the TT<sub>3</sub>/TT<sub>4</sub> ratio is high ( $>20:1$ ) in cases of Graves' hyperthyroidism). TSH +TPOAb is becoming important for preconception and pregnancy evaluations for thyroid dysfunction. Thyroglobulin is used as a tumor marker for thyroid cancer.

**Q** What would be the risks of a rapid home test for elevated TSH? If such a test were available, what would be a good cut off level?

**A** I do not believe that rapid home TSH tests have optimal sensitivity and precision. It is important not only to be able to detect high levels of TSH but also to reliably determine whether TSH is above 2.5 mIU/L for preconception and pregnancy evaluations and be able to reliably detect low TSH  $<0.1$  mIU/L (subclinical hyperthyroidism) in patients taking too much levothyroxine replacement therapy for hypothyroidism

**Q** What are the advantages of a third generation TSH method versus a second generation TSH method? Should a third generation method be reported to three decimal places? What makes a method a third generation TSH method?

**A** A third generation TSH method is a method that has a functional sensitivity  $\leq 0.01$  mIU/L and a second generation

TSH method has a functional sensitivity of 0.1 mIU/L calculated according to NACB guidelines (Thyroid 2003;13:34). Only 2 decimal places are relevant measuring in the 0.01–1.0 range. I suggest one decimal place above 1.0 and whole numbers above 20 mIU/L. In short the functional sensitivity limit is the TSH that can be measured in human sera with a between-run 20% CV over 6–8 weeks using at least two lots of reagents and two instrument calibrations. Most current instruments can achieve this. It is critical to have reliable low range measurement for detecting iatrogenic hyperthyroidism (a problem for 15–20% of LT<sub>4</sub> treated hypothyroid patients), thyroid cancer patients (in whom a suppressed TSH is often the goal) and hospitalized patients with nonthyroidal illness (in whom a TSH  $<0.01$  mIU/L likely indicates hyperthyroidism whereas a low but detectable TSH more likely indicates a transient state of illness). CLN

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# Pain Management

## What Role Can Pharmacogenetics Testing Play?

BY SAEED A. JORTANI, PHD, GARY E. LOYD, MD, AND ELAINE STAUBLE, MD

**P**ain management refers to a broad range of services designed to diagnose the source of acute or chronic pain and remove or control it without surgery. As a specialty, pain management has experienced tremendous growth in the past decade and has become an important aspect of patient care. In the course of treatment, physicians frequently prescribe analgesics to maintain patients' mobility and functionality and to limit impairment. However, administration of analgesics is plagued with toxic and often fatal side effects, such as respiratory depression for opioids and gastrointestinal and cardiovascular adverse effects for non-steroidal anti-inflammatory drugs (NSAIDs).

These well-recognized side effects have prompted caregivers and patients to look for more effective ways to manage pain. Using pharmacogenetic (PGx) tests to select the most appropriate medication and the optimal dose holds promise for facilitating personalized pain management. Although clinical labs have been slow to implement PGx tests in general, now several important developments are making the utilization of PGx testing in clinical practice timely. Here we briefly describe the genetic variants that are involved in metabolism of pain management drugs and discuss recent developments that may impact the field of PGx testing. Two case studies of PGx testing are provided to demonstrate the value of this emerging field.

### The Case for Integrating PGx in Pain Management

Pain medications, especially opioids, are notorious for their variable and frequently unpredictable toxicity and efficacy. Due to the unpleasant effects of analgesics, patients often forgo taking them for pain. In other

morphic, genetic differences in how an individual metabolizes or responds to a drug are rational targets for assessing variability in drug response.

*CYP2D6* is one of the major groups of enzymes taking part in the metabolism of many drugs including the opioids such as

single nucleotide polymorphism at position 118 (A to G) in the gene encoding for the  $\mu$ -opioid receptor (*OPRM1*) require larger morphine doses for analgesia (3). Interestingly, polymorphisms in this gene have also been associated with a tendency for addiction to opioids (4). Researchers are currently investigating *OPRM1* genotyping for assessing sensitivity to the analgesic effects of opioids.

### Analgesics and Pain Management

In current pain management practice, much focus is centered on the use of opioid analgesics that are narcotics. Either alone or in combination with milder analgesics such as acetaminophen or NSAIDs, these drugs are used to treat a wide spectrum of pain intensities. However, caution is needed because of the potential for abuse and addiction.

Table 1 (p. 9) lists analgesics and adjuvants often co-administered in pain management. Many of these drugs and their counterparts are metabolized by enzymes that are polymorphic in various patient populations. In Table 2 (p. 9), enzymes relevant to the metabolism of pain management analgesics are provided.

### Avoiding Toxicity

Physician demand for PGx testing for management of pain patients so far has been limited; however, highly publicized patient deaths have brought more attention to the discipline. For example, a report involving an infant who was breast fed by his mother and died after the mother had taken codeine for several days was widely reported (5). The mother had multiple copies of *CYP2D6* gene, a rapid metabolizer, and therefore converted codeine to morphine at a higher level than normal. As a result, her milk contained toxic amounts of morphine that caused her infant's death. This case prompted both Canadian and U.S. regulators to issue warning labels on codeine regarding its administration to breastfeeding mothers.

patients, however, analgesics lack efficacy and offer little to no pain relief. This variability is now better understood in relation to an individual's genetic makeup.

The body's handling of drugs is primarily carried out by proteins serving as metabolizing enzymes or transporters, and the effects caused by drugs involve protein receptors. Therefore, proteins play a central role in both the pharmacokinetics and pharmacodynamics of a given drug. Since the genes encoding these proteins are poly-

codeine, hydrocodone, and oxycodone. Other enzymes such as the *CYP3A4* and *CYP3A5* are responsible for the metabolism of the synthetic opiates, buprenorphine and fentanyl (1,2). It is also important to note that not only can the same enzymes metabolize other classes of drugs that may be co-administered with opioids, but a given opioid can also be metabolized by multiple polymorphic enzymes.

Drug receptors can be a source of variability as well. For example, patients with a



Table 1

## Selected Analgesics and Adjuvants Used in Pain Management

Type of Drug	Example	Site and Mechanism of Action
Analgesic (mild)	aspirin, acetaminophen	Peripheral action, blocking synthesis of prostaglandins in damaged tissue
Analgesic (narcotic)	morphine, fentanyl	Central action on opiate receptors in the CNS
Local anesthetic	lidocaine, bupivacaine	Prevents propagation of action potentials by blocking axonal sodium channels
Tranquilizer	benzodiazepines, phenothiazines	Alteration of CNS transmitter function
Antidepressant	tricyclines (desipramine), SSRIs (citalopram, sertraline)	Alteration of CNS transmitter function
Anticonvulsant	phenytoin, carbamazepine	Alteration of CNS transmitter function
NMDA antagonists	ketamine and some opioids (methadone)	Altering CNS sensitization

Abbreviations: central nervous system (CNS); selective serotonin reuptake inhibitors (SSRI)

There is also a growing body of information on the use of PGx assays in monitoring patients receiving hydrocodone, fentanyl, and oxycodone. Several articles and book chapters have described use of these tests for assessing toxicity, as well as interpreting postmortem opioid results (6).

Recent developments are now poised to contribute to the translation of PGx testing into clinical practice. First, the National Academy of Clinical Biochemistry (NACB) has developed the first set of laboratory medicine practice guidelines for PGx. Laboratorians can currently access a draft of the guidelines on the NACB website ([www.nacb.org](http://www.nacb.org)). Second, the College of American Pathologists and other proficiency testing organizations have made testing material available for several enzymes that are involved in the uptake and breakdown of pain medications, including: *CYP2D6*, *CYP2C9*, *CYP2C19*, and others.

Labs can also now purchase FDA-cleared tests for PGx testing from several manufacturers. These tests detect *CYP2C9*, *CYP2C19* and *CYP2D6*, some of which are available in a multiplexed format and use whole blood collected in an EDTA tube. The sample must be centrifuged to obtain the buffy coat layer that is used to isolate the DNA. Alternative samples such as buccal swabs or saliva have also been shown to be useful for DNA isolation. The typical turnaround time for PGx testing is 5 to 7 days, and a growing number of reference labs offer this service.

Not surprisingly, challenges must be overcome before PGx testing can become more widespread. Obtaining adequate reimbursement for PGx tests is often difficult. While some labs have had sporadic success in getting reimbursement from third-party payers, in other cases patients are willing to pay out of their own pockets. Furthermore, more outcome studies are needed to encourage physician adoption of this new

paradigm of pain management.

In spite of these challenges, labels for more than 20 different medications have statements about PGx testing for drug selection and dosing. Examples include warfarin dosing and *CYP2C9/VKORC1* genetic variants and irinotecan therapy and testing for *UGT1A1* polymorphisms.

### PGx in Post-operative Pain Management

PGx testing in management of post-operative acute pain is also emerging as a valuable tool to improve patient safety. At our institution we have investigated the use of PGx testing for expectant mothers about to deliver their infants. These women are good candidates for individualized pain management for several reasons. PGx tests that identify the mother-to-be's genetic variants of genes involved in drug metabolism can help clinicians look for alternative means of post-operative pain control if necessary. Not only can the clinician avoid putting the patient and her newborn at risk, but he or she can also make better informed decisions about effective post-surgical pain management.

Opioid analgesics are the most commonly used medications for post-operative pain relief, but their side effects can pose significant risks for women who undergo Cesarean section. These mothers need to recover quickly and be relatively pain-free so that they are competent to care for their newborns. Pain relief is of vital importance in allowing new mothers to move about, eat normally, and have normal bowel and bladder function.

The side effects of opioid analgesia include nausea and vomiting, constipation, sedation or drowsiness, pruritus, urinary retention, and respiratory depression. Immobility due to over-sedation can be especially problematic in pregnant mothers. Pregnancy doubles the risk of thromboembolic disease, which is compounded by

Table 2

## Analgesics and Polymorphic Enzymes

Drug	Enzyme	Comment
<b>Opioids</b>		
Codeine	<i>CYP2D6, CYP3A4</i>	10% converted to morphine by <i>CYP2D6</i>
Hydrocodone	<i>CYP2D6, CYP3A4</i>	Hydromorphone is active metabolite
Oxycodone	<i>CYP2D6, CYP3A4/5</i>	Oxymorphone is active metabolite
Morphine	<i>CYP3A4, UGT2B7</i>	
Buprenorphine	<i>CYP3A4</i>	Norbuprenorphine more toxic than parent
Fentanyl	<i>CYP3A4/5</i>	Norfentanyl generated by <i>CYP3A4</i>
Tramadol	<i>CYP2D6, CYP2B6, CYP3A4</i>	(-)-O-desmethyltramadol is active metabolite Tramadol inhibits <i>CYP2D6</i>
Meperidine	<i>CYP2B6, CYP3A4, CYP2C19</i>	Normeperidine is a potent CNS stimulant
Methadone	<i>CYP3A4, CYP2B6, CYP2C19</i>	Others (e.g., <i>CYP2D6</i> ) also have minor role
<b>Non-Opioids</b>		
Acetaminophen	<i>CYP2E1, CYP3A4/5</i>	Toxic metabolites generated by <i>CYP2E1</i>
Naproxen	<i>CYP2C9</i>	Several other NSAIDs (Diclofenac, Celecoxib and Ibuprofen) also metabolized by <i>CYP2C9</i>

Abbreviations: non-steroidal anti-inflammatory drugs (NSAID); central nervous system (CNS)

Cesarean section surgery and immobility due to pain medications. Thromboembolic phenomena are also increased in the postpartum time frame compared to the antenatal period. Other common factors such as obesity, diabetes, and preeclampsia increase the risk of deep venous thrombosis or pulmonary embolism. A newly delivered mother's inability to ambulate due to pain, anxiety, or over-sedation may significantly worsen the risk of post-operative morbidity.

Potential side effects with concomitant medicines that affect metabolism and efficacy of opioids may also greatly increase the risk of respiratory depression. An example is the anti-nausea medication promethazine. New mothers who have been taking excessive amounts of pain medication in the post-operative time period may also be less successful at breast feeding and have difficulty bonding with their infant in the first few days after surgery. These early interactions between mother and baby are crucial in establishing secure bonding; therefore, physicians must take extra precautions when prescribing analgesics.

All these factors make post-operative analgesia of newly delivered mothers a balancing act between pain relief and the ability to return to the activities of daily living and caring for the newborn. Within a few hours of Cesarean delivery, the patient can tolerate oral medications and clinicians frequently prescribe codeine, oxycodone, or

hydrocodone along with NSAIDs.

With all of these drugs, *CYP2D6* polymorphisms have been shown to result in variable toxicity and response among patients with normal activity (extensive metabolizers) versus those with reduced activity (poor or intermediate metabolizers) or enhanced activity (ultra-rapid metabolizers). Reduced activity in the case of codeine dosing can mean inadequate pain relief since the morphine generated by the body is less than optimal for analgesia. The ultra-rapid genotype can result in a situation similar to the case previously mentioned with too much morphine generated leading to toxicity. For hydrocodone, patients with more than two copies of *CYP2D6* gene (ultrarapid metabolizers) generate more hydromorphone than normal. Since hydromorphone is several-fold more potent than hydrocodone, serious toxicity and side effects are likely.

### PGx and Forensic Applications

Today, pain management drugs are frequently implicated in forensic settings, including urine drug screening and interpretation of postmortem drug concentrations. Compared to clinical applications, PGx is gaining considerable popularity in forensics because turnaround time and reimbursement do not hinder adoption of the technology.

It is now well understood that the ability of an individual to metabolize an

opioid can affect drug screening results. For example, extensive metabolizers (*CYP2D6*) clear more of the administered doses of hydrocodone as hydromorphone. One study reported the difference between extensive and poor metabolizers to be significant:  $28.1 \pm 10.3$  mL/hr/kg versus  $3.4 \pm 2.4$  mL/hr/kg hydromorphone, respectively (7), a result that could be predicted from an individual's genetic makeup.

In postmortem forensic applications, PGx has been very useful in describing unusual death situations that result from drug toxicity. In one published report, a set of monozygotic, 3-year-old male twins had been prescribed 10 mg of codeine to treat their cough following the diagnosis of upper respiratory infection (8, 9). After 6 days of therapy with this opioid, one of the twins was found dead in his bed. The second twin was discovered to be apneic and had vomited 5 hours after taking the last dose of codeine. The parents began resuscitation and took the child to the emergency room. He was treated in the intensive care unit and

eventually recovered. The serum concentrations of both codeine and morphine in this child, as well as in his dead brother's blood collected at autopsy, were in the toxic range.

Genotyping for *CYP2D6* was used to confirm that the children had adequate metabolic capacity since they both were extensive metabolizers; therefore, investigation focused on the dosing amount. Further insight into the case revealed a problem with parental understanding of the "drop" sizes prescribed for dosing the children, leading to greater amounts of codeine given to each child than prescribed.

#### Standing at the Threshold

Pain management covers almost all disciplines of medicine and is widely recognized as a growing segment of healthcare. While the analgesics used to provide pain relief have many beneficial effects, knowledge of each drug's pharmacokinetic and pharmacodynamic characteristics would help physicians assess toxicity and efficacy in a given patient.

Currently, utilization of PGx testing in the field of pain management is rather limited. Many complex clinical and technical issues must be tackled before individualized pain management takes off. Equally daunting, however, are the concerns related to administration of opioids for treatment of long-term pain.

Many case reports and studies on the utility of genotyping for enzymes with a role in metabolism of opioids, as well as the availability of commercial tests, have set the stage for adoption of PGx in pain management. Clinical laboratories now have access to several FDA-cleared genotyping tests and platforms for the three most common enzymes—*CYP2D6*, *CYP2C19*, and *CYP2C9*—that are involved in metabolism of the majority of drugs used in pain management.

Despite the fact that progress has been slow, the promise of optimal dosing and selection of the right medications on an individualized basis continues to fuel further interest in this area. Until research provides

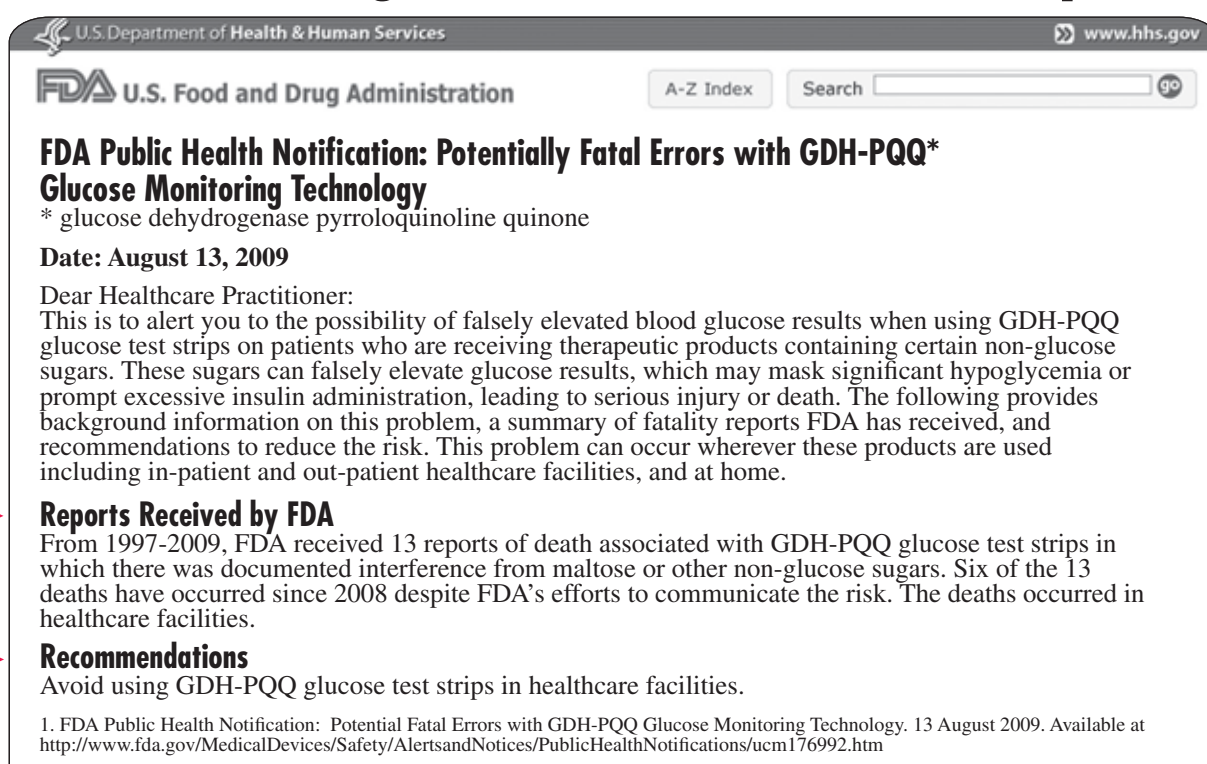
better answers, labs can play a role in optimal opioid selection and therapy for acute pain, especially in post-operative settings. **CLN**

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<http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm176992.htm>

## FDA Notifies Hospitals: Avoid Using GDH-PQQ Glucose Test Strips



**FDA Public Health Notification: Potentially Fatal Errors with GDH-PQQ\* Glucose Monitoring Technology**  
\* glucose dehydrogenase pyrroloquinoline quinone

**Date: August 13, 2009**

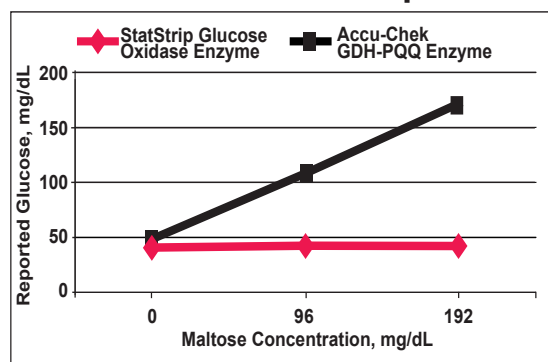
Dear Healthcare Practitioner:  
This is to alert you to the possibility of falsely elevated blood glucose results when using GDH-PQQ glucose test strips on patients who are receiving therapeutic products containing certain non-glucose sugars. These sugars can falsely elevate glucose results, which may mask significant hypoglycemia or prompt excessive insulin administration, leading to serious injury or death. The following provides background information on this problem, a summary of fatality reports FDA has received, and recommendations to reduce the risk. This problem can occur wherever these products are used including in-patient and out-patient healthcare facilities, and at home.

**Reports Received by FDA**  
From 1997–2009, FDA received 13 reports of death associated with GDH-PQQ glucose test strips in which there was documented interference from maltose or other non-glucose sugars. Six of the 13 deaths have occurred since 2008 despite FDA's efforts to communicate the risk. The deaths occurred in healthcare facilities.

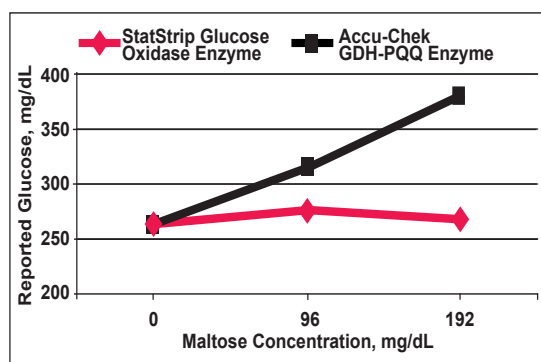
**Recommendations**  
Avoid using GDH-PQQ glucose test strips in healthcare facilities.

1. FDA Public Health Notification: Potential Fatal Errors with GDH-PQQ Glucose Monitoring Technology. 13 August 2009. Available at <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm176992.htm>

### Nova StatStrip® Glucose System Has No Maltose Interference



At a hypoglycemic level of **43 mg/dL**, StatStrip provides interference-free results in the presence of maltose. The Accu-Chek GDH PQQ method reports erroneously high glucose results in the presence of maltose. Erroneously high glucose readings by GDH-PQQ methods could lead to undetected hypoglycemia



At a hyperglycemic level of **261 mg/dL**, StatStrip provides interference-free results in the presence of maltose. The Accu-Chek GDH PQQ method reports erroneously high glucose results that could lead to insulin overdosing and iatrogenic hypoglycemia.

Maltose interference data above from Bewley B et al. Evaluation of the Analytical Specificity and Clinical Application of a New Generation Hospital-Based Glucose Meter in a Dialysis Setting. *Point of Care*, volume 8, Number 2, June 2009

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Foundation at the University of Louisville. Email: [estasc01@louisville.edu](mailto:estasc01@louisville.edu)

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## Hepcidin Testing Kit

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provides fast and accurate quantitation of hepcidin to help clinicians diagnose and treat iron deficiency diseases, including anemia, chronic kidney disease, inflammation, diabetes mellitus, and hemochromatosis.

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## Buprenorphine Assay

This new test provides qualitative and semi-quantitative screening of norbuprenorphine (buprenorphine metabolite) in human urine. The assay's cutoff value is 10 ng/mL



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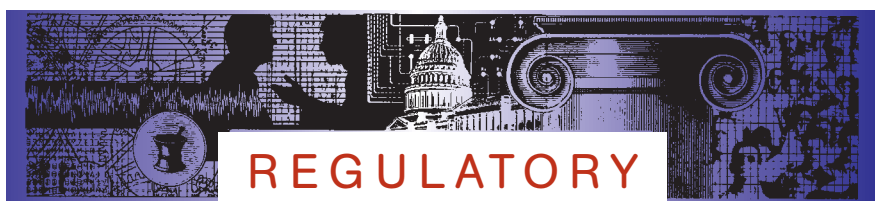
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## Senate Scraps Co-Pay But Cuts Payment

In the rapidly changing work on health-care reform legislation, labs have now survived two major skirmishes. The latest version of the reform legislation from the Senate Finance Committee, chaired by Sen. Baucus (D-Mont.), no longer includes a lab co-pay or levies a \$750 million "performance" tax on labs.

The American Clinical Laboratory Association (ACLA), the Advanced Medical Technology Association (AdvaMed), and other lab groups argued that the lab tax was unfair, due to the fact that Medicare spending for laboratory tests has not kept pace with inflation. Payment for lab services has been reduced by about 40% in real, inflation-adjusted terms between 1984 and 2004. In fact, since 2000, labs have received the smallest cumulative update of any

provider in Part B of Medicare, only 5.6% compared to 12% for physicians and 34% for hospitals.

Unfortunately, the current reform legislation is likely more bad news for payment policy. The current bill includes a measure that would mean a 5-year reduction of 1.75% from 2011 through 2015. The measure would also change the way that the Medicare lab fee schedule is updated to reflect inflation. The current formula subtracts 0.5% from the Consumer Price Index. The new formula would replace this 0.5% with a variable "productivity adjustment" that could mean a lower update, though it would not be allowed to reduce the update below zero.

Manufacturers also have reason to worry. The legislation still carries a \$40 billion tax applied to medical device manufacturers based on market share. ACLA and AdvaMed released a report that concluded

that the tax rate on the medical device industry would rise from 23% to nearly 50%. More information about lab groups' lobbying during debate of healthcare reform legislation is available from ACLA, [www.clinical-labs.org](http://www.clinical-labs.org).

## States Worry Over Medicaid After Stimulus Runs Out

According to a new report from the Government Accountability Office (GAO), states are anxious about what will happen when money from the stimulus package runs out and they're forced to face recession-driven increases in enrollment without the boost of federal funds. States have already received about \$48 billion of the \$90 billion set aside in the American Recovery and Reinvestment Act for Medicaid, called FMAP funding. States told GAO that they have been using the money to keep their Medicaid programs afloat and free up other funds during budget crises, according to the report. "The increased FMAP continues to help states finance their growing Medicaid programs, but state and District officials expressed concern about the longer term sustainability of their Medicaid programs after the increased FMAP funds are no longer available, beginning in January 2011," according to the report. The GAO report is available online, [www.gao.gov/new.items/d091016.pdf](http://www.gao.gov/new.items/d091016.pdf).

## CMS Examines Paying For HIV Screening

The Centers for Medicare and Medicaid Services (CMS) announced a new proposal that would cover HIV screening for Medicare and Medicaid beneficiaries who are at increased risk, including women who are pregnant and Medicare beneficiaries of any age who request the service.

The announcement noted that while younger age groups account for most cases of HIV infection in the U.S., the Centers for Disease Control and Prevention (CDC) estimates that in 2006, about 19% of all U.S. residents with AIDS were age 50 or older when the disease was diagnosed.

The proposal marks the first time that Medicare has proposed to expand its list of covered preventive services under a new authority established by Congress. The

Medicare Improvements for Patients and Providers Act of 2008 (MIPPA) gave CMS the ability to consider whether Medicare should cover "additional preventive services" if certain requirements are met.

Under MIPPA, CMS can consider whether Medicare should cover preventive services that Congress has not already deemed as covered or non-covered by law, as long as they have been "strongly recommended" or "recommended" by the U.S. Preventive Services Task Force.

CMS uses the national coverage determination process to make decisions on these types of preventive services. CMS is expected to issue a final coverage decision by December 8, 2009. The proposal is available online, [www.cms.hhs.gov/mcd/view-draftdecision-memo.asp?id=229](http://www.cms.hhs.gov/mcd/view-draftdecision-memo.asp?id=229).

## Not Enough Evidence to Recommend Screening Infants For Hyperbilirubinemia

According to a new evidence synthesis from the U.S. Preventive Services Task Force (USPSTF), the evidence is insufficient to recommend screening infants for hyperbilirubinemia to prevent chronic bilirubin encephalopathy. The USPSTF report found that, though screening can identify infants at risk of developing hyperbilirubinemia, not all children with chronic bilirubin encephalopathy have a history of hyperbilirubinemia. Furthermore, there is no known screening test that will reliably identify all infants who are at risk of developing chronic bilirubin encephalopathy.

The main barrier to establishing a recommendation was that evidence about the benefits of screening is lacking, especially because the condition is so rare that research is very difficult. On the other hand, the two treatments—phototherapy and exchange transfusion—both include a multitude of risks. Potential harms of phototherapy include weight loss, gastrointestinal problems, interruption of breastfeeding, disruption of the maternal-infant relationship, and possibly growth of melanocytic nevi. Exchange transfusions may result in apnea, bradycardia, cyanosis, vasospasm, thrombosis, necrotizing enterocolitis, and, rarely, death. The evidence summary and recommendation are available online, [www.ahrq.gov/clinic/uspstf/uspshyperb.htm](http://www.ahrq.gov/clinic/uspstf/uspshyperb.htm).

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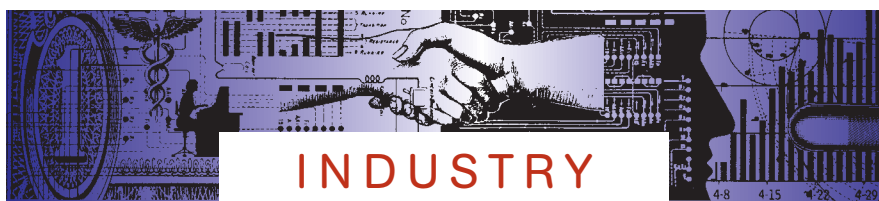
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## INDUSTRY

### Qiagen Acquires PCR Rights From Roche, Idaho Technology

Qiagen announced that it has acquired licenses from Roche and Idaho Technology for the use of instrumentation and reagents used in PCR-based molecular testing. The agreements cover thermal cycler rights and real-time PCR methods for diagnostics, as well as high-resolution melting curve analysis technology (HRM). Combined with Qiagen's Rotor-Gene Q detection platform, this technology is used in applications such as mutation discovery, pathogen detection, and methylation analysis.

With these agreements in place, Qiagen is the first Idaho Technology and Roche licensee to offer HRM-related instruments and reagents in all formats for research and diagnostics worldwide. "This additional intellectual property portfolio enables us to develop and market PCR solutions based on the most advanced technologies for molecular diagnostics," stated Achim Ribbe, executive director of business development for Qiagen. "It puts us in the position to offer our customers in molecular diagnostics, pharma, applied testing, and life science research the latest PCR technology running on the most versatile platform and covering all markets and fields, including human in vitro diagnostics." Financial terms of the agreement were not disclosed.

### Osmetech, Fisher Healthcare Terminate Distribution Deal

Osmetech announced that following discussions with Fisher Healthcare both companies have mutually agreed to terminate their U.S. distribution agreement, effective immediately. The two companies originally signed a 5-year distribution agreement in March 2009 for Fisher Healthcare to distribute Osmetech's eSensor XT-8 instrument platform and molecular diagnostic tests. Osmetech stated that it made the decision to build its own direct sales force with the objective of targeting key molecular diagnostic testing laboratories and clinics that monitor the administration of certain therapeutic drugs. The company's sales force will expand over the next 3 years as the molecular testing market grows and more tests are added to the eSensor XT-8 platform.

### Sequenom Completes Investigation, Fires Executives for Mishandling Prenatal Test Data

Sequenom announced that it has completed its independent investigation related to test data and results for the company's noninvasive prenatal test for Trisomy 21 (Down syndrome). The investigation concluded that Sequenom failed to use adequate protocols and controls when conducting studies in the Trisomy 21 pro-

gram and that certain employees also failed to provide adequate supervision, resulting in unsubstantiated claims, inconsistencies, and errors being reported to the public. Sequenom has terminated employment of its presidents and chief executive officer, Harry Stylli, PhD, and its senior vice president of research and development, Elizabeth Dragou, PhD, along with several other employees. A special committee has begun implementing measures to address these issues, including new procedures for the conduct of research and development and clinical studies and new procedures for the storage and management of samples for testing. At CLN press time Sequenom was unable to provide a schedule for the completion of research and possible development for its Trisomy 21 test, but indicated that it continues to believe the underlying science is sound and useful for the development of new diagnostic tests.

### Correlagen to Develop Gene Tests with Helicos

Correlagen Diagnostics purchased the Helicos Genetic Analysis System from Helicos Biosciences, and the two companies announced plans to collaborate on future genetic tests. The Helicos Genetic Analysis System is the first and only commercially available single molecule sequencing technology that enables genetic analysis without DNA ligation or amplification. Correlagen plans to use the system for genetic tests based on the targeted resequencing of genes involved in cardiology, endocrinology, neuropsychiatry, and immunology. Helicos and Correlagen will collaborate on optimizing methods of sample preparation, as well as on data analysis and visualization technologies for sequence variant detection, annotation, and clinical reporting. "We believe that the Helicos System will allow us to provide DNA-based clinical assays on unprecedented value for the diagnosis of genetic disorders," stated David Margulies, chairman and chief executive officer of Correlagen.

### Thermo Fisher Completes Purchase of BRAHMS

Thermo Fisher Scientific completed its acquisition of BRAHMS for €330 million, or approximately \$470 million. BRAHMS will be integrated into Thermo Fisher's Analytical Technologies Segment, and its headquarters in Hennigsdorf, Germany will serve as Thermo Fisher's European Center of Excellence for its clinical diagnostic business.

### Veridex's Tumor Cell Test Wins Best Medical Technology Award

The CellSearch Circulating Tumor Cell (CTC) Test developed by Veridex has been honored with the first-ever Prix

Galien USA 2009 Award for Best Medical Technology. The CellSearch system is the first diagnostic test used to automate the detection of CTCs—tumor cells that have detached from solid tumors and entered the patient's bloodstream. The test helps determine the prognosis and survival of patients with metastatic breast, colorectal, or prostate cancer during the course of treatment. Candidates for the Prix Galien USA Award are evaluated on innovation, applicability, and future uses to biomedical science. It is considered the industry's highest prize for research and development.

### Gen-Probe Buys Prodesse for \$60 Million

Gen-Probe signed a definitive agreement to acquire Prodesse for approximately \$60 million in cash, with the possibility of future milestone payments pushing the purchase price up to \$85 million if Prodesse achieves certain financial and regulatory objectives in 2010 and 2011. As part of the acquisition, Gen-Probe's sales representatives were expected to begin co-promoting Prodesse's products in mid-October across the U.S., Canada, and Europe. "Our acqui-

sition by Gen-Probe validates the significant progress we have made in developing and commercializing molecular assays that help doctors and laboratories diagnose respiratory and other infectious disease more accurately than traditional methods," said Tom Shannon, president and chief executive officer of Prodesse. "We believe we can prepare for and accelerate our stage growth by leveraging the resources and expertise of one of the most established and highly respected molecular diagnostics companies in the world." Both companies' boards of directors have unanimously approved the transaction and the deal was expected to close by early November.

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## DIAGNOSTIC

### Treatment for Mild Gestational Diabetes Beneficial

New research indicates that treatment of mild gestational diabetes reduces the risk of common birth and maternal complications (NEJM 2009;361:1339–1348). The study, which was conducted by 15 medical centers that are part of the Maternal Fetal Medicine Units Network of NIH, provided the first conclusive evidence that even mild gestational diabetes should be treated. While virtually all pregnant women are screened for the condition and treatment efficacy for severe cases has been demonstrated, there had been not been sufficient evidence to encourage treatment in milder cases.

The study involved 958 women who were between the 24th and 31st week of pregnancy and had abnormal oral glucose tolerance test results but fasting glucose levels <95 mg/dL. A total of 458 were assigned to treatment, which included a minimum of 4 blood glucose checks per day, counseling on diet and exercise, and insulin as necessary (only 7% of patients). There was no significant difference between treatment and control subjects in the primary composite outcome of stillbirth or perinatal death and neonatal complications, including hyperbilirubinemia and hypoglycemia. However, there were significant differences in several secondary outcomes, including mean birth weight (3,302 g in treatment subjects versus 3,408 g in controls) and neonatal fat mass (427 g in treatment subjects versus 464 g in controls). In addition, the rates of shoulder dystocia, cesarean delivery, preeclampsia, and gestational hypertension were significantly lower in the treatment arm.

### Study Suggests New Role for CRP

New research suggests that C-reactive protein may play a protective role in some patients with acute respiratory distress syndrome (ARDS) (Chest 2009;136:471–480). If confirmed in other patient populations and mechanistic studies, the findings could lead to a reappraisal of conventional views of the role of CRP in disease.

The prospective observational study sought to characterize plasma CRP levels in patients with early ARDS. CRP levels have been demonstrated to have prognostic and/or diagnostic value in many diseases such as sepsis, pneumonia, coronary artery disease, stroke, and rheumatic disease, among others. In most instances, higher CRP levels have correlated with adverse outcomes. However, the relationship between CRP levels and ARDS and acute lung injury has not been explored extensively.

The study involved 177 patients admitted to intensive care units at Massachusetts General Hospital in Boston who had risk factors for ARDS and no exclusion criteria. CRP measurements were taken within 48

hours of ARDS onset. Outcomes included 60-day mortality, 28-day daily organ dysfunction scores, and number of ventilator-free days. The researchers found that CRP levels were significantly higher in ARDS survivors versus non-survivors (median, 176.5 mg/L versus 133.5 mg/L), and that patients with higher CRP levels had less organ dysfunction over time and more ventilator-free days than those with lower levels. An increasing CRP level was associated with a significantly higher probability of survival at 60 days, a difference that persisted after adjustment in a multivariate analysis. The greatest difference in mortality occurred between patients in the two highest and two lowest deciles of CRP levels.

According to the investigators, the findings seem to contradict long-held views about the role of CRP as an inflammatory marker predictive of risk. Studies have demonstrated a link between elevated CRP levels and adverse outcomes in coronary artery disease, sepsis, and septic shock, but some, particularly those involving sepsis and septic shock, have not found CRP levels to be associated with altered outcomes, and others have suggested that failure of CRP to decrease over time is predictive of worse outcomes.

Neutrophils recruited to the lung through chemoattractant molecules accumulate in the lungs in patients with ARDS and are thought to be crucial in lung injury. The authors speculate that lower levels of CRP may stimulate neutrophil chemotaxis but higher levels inhibit it, along with other neutrophil functions.

### Intervention Timing Not Associated with Outcomes in ACS

New research indicates that among patients with non-ST elevation acute coronary syndrome (NSTEMI-ACS), an immediate intervention strategy compared with waiting until the next working day does not result in a difference in myocardial infarction as defined by peak troponin I (cTnI) level (JAMA 2009;302:947–954). Investigators in the Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention (ABOARD) sought to evaluate the optimal timing of coronary angiography and intervention in high-risk patients. Little information has been published in this regard, although invasive strategies have generally been accepted as the best treatment option. ABOARD involved 352 patients at 13 institutions, all of whom had NSTEMI-ACS and a thrombolysis in MI (TIMI) score of 3 or greater. Patients were randomized to undergo invasive treatments immediately or on the next working day, which was defined as 8 to 60 hours after enrollment. Patients also received antithrombotic and anticoagulant medications including abciximab, aspirin, and clopidogrel.  $\beta$ -blockers, statins and

angiotensin-converting enzyme inhibitors also were strongly recommended as concomitant therapies. The primary end point was the peak cTnI value during hospitalization. The secondary endpoint was a composite of death, MI, or urgent revascularization at 1-month follow-up.

Mean time from randomization to sheath insertion in percutaneous coronary intervention was 70 minutes in the immediate intervention group, versus 21 in the delayed intervention arm. The researchers found that peak cTnI values did not differ between the two strategies. The secondary end point occurred in 13.7% of patients in the immediate intervention arm, and in 10.2% in the delayed intervention arm ( $p = 0.31$ ), and the three components of the secondary end point evaluated individually did not differ significantly between the two groups. The study demonstrates that a strategy of immediate catheterization of NSTEMI-ACS patients is not superior to one of waiting until the next working day.

### Timing of Levothyroxine Administration Affects Serum TSH Levels

Georgetown University researchers have documented that when patients take levothyroxine ( $LT_4$ ) in a nonfasting regimen, their serum thyrotropin (TSH) concentration is higher and more variable (J Clin Endocrinol Metab 2009;94:3905–3912). This finding has particular implications for patients in whom specific TSH targets are of great importance, such as pregnant women, the elderly, and those diagnosed with thyroid cancer, cardiac disease, or osteoporosis. Although studies have shown that optimal intestinal absorption of  $LT_4$  occurs when patients fast, and  $LT_4$  is known to have a narrow therapeutic index, analyses of the impact of variable  $LT_4$  regimens on serum TSH concentrations have had inconsistent results.

In this study, 65 patients were randomized to one of six sequences, each consisting of three 8-week  $LT_4$  regimens in a three-period crossover design. The regimens were: overnight fasting before breakfast; within 20 minutes of having eaten breakfast; and at least 2 hours after the last meal of the day. Serum TSH, free  $T_4$ , and total  $T_3$  levels were measured at baseline and at the conclusion of each 8-week period—TSH using third-generation immunochemiluminometric assays with a sensitivity of 0.01 mIU/L,  $FT_4$  and  $T_3$  with chemiluminescent immunoassays.

The researchers found that when  $LT_4$  was taken in a fasting state, the mean TSH concentration was  $1.06 \pm 1.23$  mIU/L. In contrast, TSH levels were significantly higher when  $LT_4$  was taken with breakfast ( $2.93 \pm 3.29$  mIU/L) or at bedtime ( $2.19 \pm 2.66$  mIU/L). As the authors note, these findings suggest that patients who have difficulty complying with a fasting regimen of  $LT_4$  could simply have their doses increased to achieve lower TSH levels. However, the study also revealed that when patients took  $LT_4$  with breakfast or at bedtime, their TSH concentrations were much more variable, with TSH extremes of 0 to 19 mIU/L observed. The authors conclude that in cases

in which the goal of therapy is to maintain a specific serum TSH within a relatively narrow range and without significant oscillations, then patients should be advised to take  $LT_4$  in a fasting state. Alternatively, if a patient needs to take  $LT_4$  at bedtime, then serum TSH levels should be monitored closely for a while to determine whether that individual's TSH concentrations vary by more than 1 mIU/L from the desired range.

### Large Serum Sodium Level Fluctuations Associated with Functional Impairments in Premature Neonates

New research indicates that significant changes in serum sodium levels in preterm neonates are associated with increased risk of impaired functional outcomes after adjustment for gestational age and perinatal and neonatal hospitalization characteristics (Pediatrics 2009;124:e655–e661). The authors of the study cautioned that their findings simply may reflect the severity of illness and/or quality of care of these infants, although a causal relationship between serum sodium levels and development outcomes cannot be excluded. The results suggest that very premature infants should receive cautious fluid and electrolyte management.

Hyponatremia in infants has been associated with increased risk of cerebral palsy and hearing loss, while hypernatremia has been linked with cerebral edema and thrombosis, intracranial bleeding and severe hyperbilirubinemia. However, few studies have examined neurodevelopmental outcomes in very preterm babies who experience hypo- or hypernatremia in the first days of life.

The study involved 237 preterm infants born at <33 weeks who were hospitalized in the neonatal intensive care unit. A total of 3,927 sodium measurements were performed. The researchers assigned the babies to three tertiles based on changes in sodium levels, with small change defined as 0 to 7 mEq/L, large as 8 to 13 mEq/L, and very large defined as >13 mEq/L. The infants subsequently were given clinical and development assessments when they were at the corrected age of 2, and were classified into two groups, either with impaired functional outcomes or not.

The investigators found that after adjustment for gestational age and perinatal and neonatal hospitalization characteristics, the odds ratio for risk of impaired functional outcome was 3.5 in babies with large serum sodium changes and 5.1 in those with very large changes. The authors speculate that significant variations in serum sodium levels may cause cerebral lesions and consequently impair functional outcomes.

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# NEWS FROM THE FDA

## Diagnostic Hybrids Flu Kit Cleared

Diagnostic Hybrids received 510(k) clearance of its D3 FastPoint L-DFA Respiratory Virus Identification Kit, which allows for the detection of influenza A, influenza B, respiratory syncytial virus, human metapneumovirus, adenovirus, and parainfluenza viruses from a patient specimen in under 30 minutes. The kit uses the same fluorescent labeling technologies as the company's D3 Ultra and D3 Duet product lines in combination with newly developed L-DFA processing technology.

## HIV Donor Screening Assay Approved

Abbott announced that it has received approval from FDA for its Prism HIV O Plus test, the first fully automated blood screening test for HIV-1/HIV-2. The test can be used to screen donors of blood and plasma for antibodies to HIV type 1 Groups M and O (anti-HIV-1) and type 2 (anti-HIV-2), and as an aid in the diagnosis of HIV-1/HIV-2 infection. The assay provides labs with a fully automated test capable of processing 160 samples per hour on the Abbott Prism system. With this approval, Abbott now has a complete panel of hepatitis and retrovirus tests available on the Prism system.

## FDA Commissions IOM to Study Premarket Clearance Process

FDA announced that the Institute of Medicine (IOM) has been commissioned to study the premarket notification program used to review and clear certain medical devices marketed in the U.S. As part of the study, IOM will assemble a committee to investigate whether the current 510(k) process protects patients and promotes innovation that supports public health, and what changes are necessary to achieve these goals. The \$1.3 million review is scheduled to be completed in 2011.

## Cepheid's Thrombophilia Gene Test Cleared

A new test developed by Cepheid to detect genetic variations associated with thrombophilia received 510(k) clearance. The Xpert HemosIL FII & FV test detects Factor II and Factor V Leiden genetic variations that can lead to an increased risk for blood clots. The test produces results in just over 30 minutes using a single GeneXpert cartridge. Although developed and manufactured by Cepheid, the test will be available worldwide through a partnership with Instrumentation Laboratory, the exclusive distributor of the test.

## Meridian, Quidel Cleared To Update Flu Test Labels

Two rapid flu tests used to detect the 2009 H1N1 virus have been granted special 510(k) clearance for updated labeling claims. Meridian Bioscience will update its TRU FLU package insert to include analytical sensitivity claims for two strains of the 2009 H1N1 virus cultured from respi-

ratory specimens, and Quidel will update its QuickVue Influenza A+B test package insert to include reactivity with culture isolates of the 2009 H1N1 Influenza A virus. Although the performance characteristics of either test in regard to the 2009 H1N1 virus have not been established, the analytical sensitivity claims add an additional product benefit. Both tests have been used to distinguish between influenza A and B viruses.

## Nanosphere Cleared for New Respiratory Virus Test

FDA 510(k) clearance has been granted to Nanosphere for its Verigene Respiratory Virus Nucleic Acid Test and the Verigene SP System. The test detects influenza A and B and the respiratory syncytial virus, and the Verigene SP System provides automated molecular diagnostics capabilities in a multiplexed, random-access, modular system using the same imaging technology as the first generation Verigene system. The platform is intended for both molecular and microbiology labs.

## Ovarian Cancer Test Cleared

Vermillion's ovarian cancer test, OVA1, received FDA clearance as an aid in determining if a woman is at risk for a malignant pelvic mass prior to surgery. The new blood test is the first FDA-cleared test that can indicate the possibility of ovarian cancer with high sensitivity prior to biopsy or surgery, even if radiological tests fail to indicate a malignancy. An in vitro diagnostic multivariate index test, OVA1 combines the results from five immunoassays using an algorithm to produce a single score indicating the chance of a malignancy. Quest Diagnostics participated in development of the test and retains exclusive rights to offer it to the clinical reference lab market within the U.S. for 3 years.

## Anti-HIV Test Receives FDA Approval

Ortho Clinical Diagnostics received FDA approval for its VITROS Anti-HIV 1+2 Assay on the VITROS 5600 Integrated and VITROS 3600 Immunodiagnostic Systems. The assay is designed for the qualitative detection of HIV 1+2 in human serum and plasma and can be used by physicians as a quick HIV test or to screen pregnant women to identify neonates at high risk of acquiring HIV. This is the first HIV diagnostic assay approved for an integrated system in the U.S., allowing labs to run HIV and other tests on a single testing platform. Since 2008, OCD has released 112 assays for the VITROS systems.

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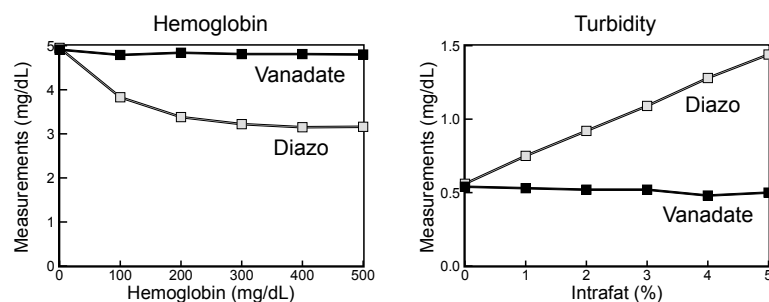
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