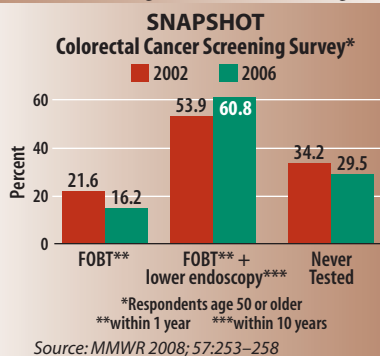


COLORECTAL CANCER SCREENING STILL INADEQUATE

Although colorectal cancer screening rates have doubled since the late 1980s, the various screening methods still are underused, according to a recent systematic review of evidence about the use and quality of colorectal cancer (CRC) screening. The report, commissioned by the Agency for Healthcare Research and Quality and prepared by the RTI International–University of North Carolina Evidence-based Practice Center, also concluded that the growth in screening can be attributed entirely to increased use of colonoscopy; screening with fecal occult blood testing (FOBT) and sigmoidoscopy declined over the same period. The investigators found no data on usage trends or the quality of fecal immunochemical testing, fecal DNA testing, or computed tomographic colonoscopy.

Factors consistently and significantly associated with reduced CRC screening include low income, lack of health insurance, and being Hispanic or Asian, among other reasons. Strategies



with the most evidence of increasing the appropriate use of CRC screening methods include patient reminders, one-on-one interactions, and patient navigators to help patients obtain timely CRC screening.

While CRC screening rates generally are lower than desired, the report also found evidence of both overuse and misuse of CRC screening methods. Overuse exists in the frequency of surveillance colonoscopy after polypectomy, and in continuing to screen people older than age 85, a group guidelines recommend no longer screening. Misuse was noted in continuing to rely on in-office FOBT when the literature “is clear that home FOBT is preferable.” This practice substitutes a less effective test for a more effective one, according to the report. There also is evidence of inadequate follow-up for positive FOBT results.

The researchers pointed to multiple studies exploring the characteristics of potential new CRC tests but cautioned that while “improving screening tests is a reasonable research agenda,” these evaluations need to be balanced with more research on how to successfully implement screening methods already known to be effective.

The full report is available online at www.ahrq.gov.

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The Perils of Fatty Liver Disease

Can Biomarkers Replace Biopsy?

BY GENNA ROLLINS

Over the past 2 decades, hepatologists have been observing with growing concern a less-publicized consequence of the developed world’s sedentary lifestyle and poor eating habits: fatty livers in people who do not drink alcohol excessively. The conditions associated with this phenomenon, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH), are the leading causes of chronic liver disease in the U.S. and pose a potential public health crisis. As clinicians grapple with the growing disease burden of NAFLD and NASH, labs may soon be on the frontline of diagnosing, staging, and managing the diseases. Experts predict that panels of serum markers, probably in combination with non-invasive radiologic tests and liver biopsy, eventually will be part of the standard work-up for these conditions. Emerging metabolomic, lipidomic, and genomic information also may one day enhance the diagnostic and disease management picture.

“There’s been a change in perception about biomarkers in the field. Until recently, they were regarded as just a flash in the pan, but they are here to stay,” said Neil Guha, MD, PhD, clinical associate professor of hepatology at the University of Nottingham. “It’s now a question of when, not if, they’ll be in routine use. What we have to do is define what severity of disease can be delineated by current biomarkers.”



See **NAFLD**, continued on page 2

The Path to Success for Early Career Laboratorians

How to Survive Publish or Perish

BY BILL MALONE

With the ever-expanding number of laboratory tests, the incoming generation of lab directors must go through a structured and demanding sequence of academic degrees, formal training, and certifications in order to be successful. This is why many young professionals are attracted to organizations like AACC’s Society for Young Clinical Laboratorians (SYCL), a professional network for AACC members under the age of 40 that helps them tackle challenges like passing board exams, finding a job, or securing travel grants.

One of the keys to professional achievement where SYCL and other leaders in the lab field are now focusing attention for early-career laboratorians is getting published in academic journals. Many young laboratorians remain long overdue for help in this area, where the roadmap to success seems to go cold and a lack of formal instruction or training leaves them feeling unprepared.

This is the first step in getting published usually amounts to overcoming fear and building confidence, emphasized Thomas Annesley, PhD, professor of clinical chemistry at the University of Michigan and deputy editor of *Clinical Chemistry*. “A lot of people think that because they’re younger, they can’t write good articles. And that just isn’t true. Younger individuals can sometimes write better papers than well-known individuals,” he said. “It’s about ignoring your fears and going for it. It’s deciding you’re going to break the ice and try

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Complexity Hinders Biomarker Development

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A Growing Problem

The disease burden of NAFLD and NASH is pressing, to put it mildly. An estimated one-third of American adults—about 90 million people—have NAFLD, and perhaps as many as one-quarter of those have NASH. Among patients with NASH, nearly one-third develop cirrhosis within 8 years of follow-up. New research also indicates that individuals with NAFLD have increased mortality in comparison to the general population, not only from liver disease but also from cardiovascular conditions and extrahepatic malignancies.

In keeping with these statistics, understanding of the conditions and their potentially serious outcomes has grown with time. “When I finished my fellowship in the early 1980s, we knew fatty liver disease was usually very bad in diabetics and could progress to cirrhosis, but it was a curiosity, something that was discussed at grand rounds,” observed Arthur McCullough, MD, chair of gastroenterology and hepatology at the Cleveland Clinic and professor of medicine at Case Western Reserve University. “In the subsequent 25 years, we’ve come to realize that this is a serious and common disease. And it’s important

to realize we’re talking about a spectrum of illness that varies from there not being much to worry about to being a lot to worry about.”

With the prevalence rising and the continuum of fatty liver disease becoming more apparent, clinicians have been crying out for noninvasive tools to effectively diagnose and stage NAFLD and NASH, and monitor patients. Research in this area—especially for serum markers—has been prolific during the past decade, but so far, no single analyte or panel stands out above the others or the admittedly less-than-perfect gold standard, liver biopsy. “The various proposed tests haven’t reached a point to where we have confidence in them as decision-making tools in clinical practice,” explained Jayant Talwalkar, MD, MPH, consultant in gastroenterology and hepatology and associate professor of medicine at the Mayo Clinic. “They haven’t provided an incremental advance in our decision-making in terms of whether or not a patient has fibrosis or needs biopsy. They’ve made some difference, but not enough to get people to change their practice.”

Opinion, however, is divided on this subject. “Nonexpert physicians and patients are waiting for an almost perfect test that is a

biomarker with less than 10% of false positive/negative results and more than 99% of applicability. This is not possible, even with liver biopsy,” contended Thierry Poynard, MD, professor of medicine at Group Hospitalier Pitie-Salpetriere in Paris. “It is an illusion to wait for an almost perfect biomarker with adjusted AUROC greater than 90% for the diagnosis of advanced fibrosis” (Adv Clin Chem, 2008;46:131–60). Still, Poynard, who holds the patent for several serum marker panels used in diagnosing liver fibrosis, agrees that further validation of proposed biomarkers specifically in NAFLD and NASH is needed.

A Complicated Disease

The flurry of research has advanced understanding of NAFLD and NASH considerably in recent years. In most patients, fatty liver—simple steatosis—is more or less a benign condition associated with diabetes, obesity, age, sex, ethnicity, dyslipidemia, and the metabolic syndrome. However, as the number of risk factors rise, so does a person’s likelihood of developing NASH, which involves steatosis with hepatocellular inflammation and damage. NASH, in turn, sets-up some patients for progressive fibrosis and cirrhosis and its complications, including liver failure and hepatocellular carcinoma.

NAFLD and NASH seem to develop as a result of a series of insults to the liver. Insulin resistance drives triglyceride production and macrovesicular fat in the liver, through a single factor or the combination of three factors, including decreased hepatic free fatty acid oxidation, raised hepatic de novo lipogenesis, or decreased lipid export from the liver. Once this dysregulated lipid metabolism is in place, it can worsen insulin resistance, creating a vicious cycle. Oxidative stress from agents such as cytochrome P-450 enzymes, endotoxin, cytokines, or environmental toxins promotes lipid peroxidation, which activates pro-inflammatory cytokines like tumor necrosis factor- α , leptin, adiponectin, and C-reactive protein, causing inflammation.

In addition, the white adipose tissue associated with abdominal obesity acts as an endocrine organ, secreting adipokines and cytokines, and furthering inflammation. The tissue injury associated with inflammation changes the metabolism of the extracellular matrix, leading to fibrosis. As the scarring associated with fibrosis progresses, cirrhosis eventually sets in.

More recently, hepatocyte apoptosis has emerged as a major culprit in the progression of NAFLD to NASH. “A number of papers over a short period of time identified

that the mitochondria are not functioning properly in people with NASH,” explained McCullough. “We think now that the common final pathway that causes injury in fatty liver disease is due to mitochondrial injury and death. Oxidative stress and inflammation cause mitochondrial injury, and there is some speculation that apoptosis associated with this can stimulate fibrosis itself.”

What’s Wrong with Liver Biopsy?

By all accounts, liver biopsy currently is the best diagnostic and staging tool for NAFLD and NASH, but it is far from perfect. Indeed, one author noted wryly that “clearly the liver biopsy standard is not gold but a burnished bronze” (Clin Chem 2004;50:1299–1300). This costly, invasive procedure, which requires patients to take off the better part of a day from work or school, also has risks of complications and death. In addition, liver biopsy is subject to both sampling and interpretation errors, particularly since fibrosis and cirrhosis do not affect the liver uniformly. Complicating matters further, NAFLD and NASH look similar histologically to alcoholic liver disease. With all these caveats, biopsy has an estimated negative predictive value of 74%. The prevalence of NAFLD and NASH also presents a practical challenge in terms of the healthcare system not being able to support the volume of biopsies that may be needed in the future.

So as imperfect as liver biopsy may be, for now it remains the gold standard. “It’s still an incredibly valuable tool. It tells us not only about the damage in terms of the amount of inflammation, fat and fibrosis, but also about etiology,” explains Guha. “However, using it as a first-line investigation in NAFLD has practical, ethical, and health economic considerations. So what we’re trying to find is the balance of when to use liver biopsy. It’s not an either-or modality. It depends on the question you’re trying to ask.”

The Search for Noninvasive Tools

A variety of non-invasive radiologic markers have been proposed, including ultrasound, computerized tomography, and magnetic resonance imaging, all of which can detect NAFLD but not distinguish NAFLD from NASH. More recently FibroScan, an elastographic device manufactured by Echosens that measures liver stiffness, has shown promise.

Serum markers long have figured into attempts to develop tools that distinguish NASH from NAFLD, accurately stage NASH, and identify which patients with

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NAFLD or NASH are in the minority who will progress to more advanced disease. Indeed, basic, routine lab tests like alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ -glutamyltransferase (GGT), and platelet count not uncommonly are the first tip-off that there is a problem, since for many people NAFLD and even NASH are asymptomatic. An AST/ALT ratio ≥ 0.8 has been substantiated as an independent marker of advanced fibrosis in NAFLD, but ALT, which is more specific to altered liver function than AST, has a reported sensitivity of 40%–53% for diagnosing NASH and a specificity of about 50%. Clearly, these tests alone are not good enough. “The problem is, many people who have completely normal AST or ALT levels have significant disease,” noted McCullough.

Use of AST and ALT also has been hampered by standardization issues. According to McCullough, different labs use different normal values and reference ranges for these analytes. At least one study suggested that lower ALT cutoffs of >30 U/L for men and >19 U/L for women may better distinguish NASH, but still with relatively poor sensitivity (Ann Intern Med 2002;137:1–9). The Institute for Reference Materials and Measurements and the International Federation for Clinical Chemistry and Laboratory Medicine (IFCC) issued reference material ERM-AD454/IFCC in 2005 for ALT and reference material ERM-AD457/IFCC in 2009 for AST, and the IFCC Committee on Reference Intervals and Decision Limits is in the process of drafting a publication on reference intervals for AST, ALT, and GGT.

Despite some limitations, these analytes still provide valuable information, and they have been incorporated in several composite prediction models for NAFLD and NASH. For instance, the HAIR score is based on the presence of hypertension, elevated ALT, and insulin resistance index; the BAAT score incorporates body mass index (BMI), ALT, age, and serum triglycerides; and the NAFLD fibrosis score includes age, platelet count, albumin, the AST/ALT ratio, presence of diabetes, and BMI. More recently, the BARD score, which uses BMI, AST/ALT ratio, and diabetes, has been proposed to predict advanced fibrosis in NAFLD patients.

Is a Panel of Biomarkers a Solution?

Without a clear winner among the various testing strategies, researchers have turned to panels of serum markers that reflect the complicated and incompletely understood pathophysiology of NAFLD and NASH. Between 1991 and 2007, researchers proposed at least 14 such panels using between two and seven analytes. Most combine indirect measures of altered hepatic structure and function, such as ALT, AST and platelet count, with direct indicators of oxidative stress, inflammation and fibrosis, the principal pathways of NAFLD-NASH pathophysiology (See Box). Some also include other variables such as age and sex.

Probably the most investigated of these combination markers is FibroTest, which uses a panel of five analytes— α 2-macroglobulin, haptoglobin, apolipoprotein A1, GGT, and bilirubin—and other variables in a proprietary algorithm to provide an estimate of fibrosis stage. FibroTest suffers from some of the same shortcomings as many of the other panels, in that

NAFLD/NASH Serum Panels

Various serum panels for liver fibrosis have been proposed, but none stand out above the others or in comparison to the gold standard, liver biopsy.

Test (Author/Year)	Components	Proprietary (Y/N) (Company)	AUROC for Advanced v. Mild Fibrosis*
FibroTest (Imbert-Bismut, 2001)	α 2M, haptoglobin, apo-A1, GGT, bilirubin	Y (BioPredictive; LabCorp)	0.84
European Liver Fibrosis Panel (Rosenberg, 2004)	HA, TIMP-1, PII-NP	Y (iQur)	0.78 (0.74–0.82)
FibroSpect II (Patel, 2004)	α 2M, HA, TIMP-1	Y (Prometheus)	0.82
Hepascore (Adams, 2005)	α 2M, HA, GGT, bilirubin	Y (Quest Diagnostics)	0.82 (0.74–0.90)
FibroMeter (Cales, 2005)	α 2M, HA, AST, platelets, prothrombin time, urea	Y (BioLiveScale)	0.85
FibroIndex (Koda, 2007)	AST, platelets, gamma globulin	N	0.86 (0.81–0.92)
APRI (Wai, 2003)	$\frac{\text{AST/ULN} \times 100}{\text{platelets}}$	N	0.76 (0.74–0.79)

Legend: apo-A1, apolipoprotein A1; α 2M, alpha2-macroglobulin; AST, aspartate aminotransferase; HA, hyaluronic acid; PII-NP, N-terminal propeptide of type III procollagen; GGT, γ -glutamyltransferase; TIMP-1, tissue inhibitors of metalloproteinases

*Fibrosis stage F 2–4 versus F 0–1

Courtesy Dr. Robert P. Myers, University of Calgary, Presentation from the American Association for the Study of Liver Diseases 2008 Liver Meeting

most of the performance data collected thus far has involved chronic hepatitis C rather than NAFLD or NASH, a point the test's developer, Poynard, acknowledges. “FibroTest is less controversial for hepatitis C, hepatitis B and alcoholic liver disease

than in metabolic liver disease, because it's difficult to perform a lot of biopsies in that population. The patients have diabetes, metabolic syndrome, and other problems and it's difficult to convince them to have liver biopsies. So of course there is less

validation in metabolic liver disease at this time,” he explained.

FibroTest and the other marker panels generally perform well with areas under the receiver operator characteristic curves

See **NAFLD**, continued on page 4



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Research Suggests Possible New Analytes

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(AUROC) ranging from 0.75 to 0.86 in differentiating severe fibrosis, but like biopsy they are less discriminating, and typically have low negative-predictive values, for the presence of mild to moderate fibrosis and for discriminating adjacent stages such as mild versus moderate fibrosis. In addition, most of the panels have not been validated longitudinally in sufficiently powered studies.

Some studies also have had methodological issues, according to Anna Mae Diehl, MD, chief of gastroenterology at Duke University School of Medicine. “The way most of these studies have been done is to take a cross-sectional population that differs by stage of fibrosis, perform a liver biopsy, take serum samples, test them, compare them to the biopsy, and then generate positive- and negative-predictive values,” she said. “The problem with this approach is that the serum isn’t always sampled at the same time as the liver biopsy, and the liver could have changed in the mean time.” The NIH-funded Nonalcoholic Steatohepatitis Clinical Research Network (NASH-CRN), a consortium of eight clinical centers now in its second funding cycle, has trials in the offing that will address this study design issue. In addition, results from NASH-CRN’s two major initial clinical trials, one in adults and one in children, along with various other studies emanating from the first round of funding, are expected to be published this year, she added.

At this point, insufficient data have limited the use of the various proposed NAFLD and NASH biomarker panels. Although two are non-proprietary and others are available as reference tests in the U.S., they have not gained traction in clinical practice. For instance, both Talwalkar and McCullough reported that they only employ the tests for research purposes.

Emerging Diagnostic Tools

Even as the body of evidence grows on the various biomarker panels, new research is leading to still other potential biomarker candidates. Reflecting the latest findings about the role of hepatocyte apoptosis in the pathophysiology of NAFLD, a research team lead by McCullough recently reported that plasma cytokeratin 18 fragment levels correlate with the magnitude of apoptosis and independently predict the presence of NASH, with AUROC estimated to be 0.83 (*Hepatology* 2009;50:1072–1078). Similarly, an analysis of the lipidomic signature of NASH indicated that although increased lipogenesis, desaturases, and lipoxygenase metabolites characterize both NAFLD and NASH, impaired peroxisomal polyunsaturated fatty acid metabolism and nonenzymatic oxidation are associated with progression to NASH (*Hepatology* 2009;50:1827–1838).

In the case of the latter findings, “these provide novel insights into the metabolic basis for activation of inflammation and the disease phenotype in NAFLD. Also the differential changes in these pathways with progression from fatty liver to NASH raises the possibility that these could be used to develop lipidomic signatures to diagnose the disease phenotype,” explained senior author Arun Sanyal, MD, professor of

medicine and chairman of gastroenterology at Virginia Commonwealth University Medical Center in Richmond. “It must be emphasized that while these are very encouraging, much additional work is necessary before this can be actualized.”

McCullough agrees that there probably will be a role for genomics and metabolomics in NAFLD and NASH, but with some caveats. “Those kinds of tools are going to be cost-effective if they can help meaningfully increase that approximately 80% AUROC in most of these panels,” he observed. “But an important thing that must be considered too, is the residuals from this work. It may allow us to tailor therapy for NAFLD and NASH so that there won’t be one therapy that fits all here. But we’re a few years away from that.”

The Role of Labs

As research in the field proceeds, labs not only will have a valuable role in the future, but they also provide vital information with the tools available today. “I would like to emphasize the importance of evaluating global cardiovascular risk in patients with NAFLD,” said Giovanni Targher, MD, researcher in endocrinology in the department of biomedical and surgical sciences at

the University of Verona, Italy. “Early and aggressive treatment of underlying cardiovascular risk factors needs to be initiated, as many subjects with NAFLD will have major cardiovascular events and die prior to the development of liver disease.”

Guha emphasized that labs should review the normal ranges for routine lab tests used in the work-up of NAFLD and NASH, as well as participate in validation tests of the various proposed biomarkers. McCullough looks forward to a time when lab and hepatology associations join in developing diagnostic and treatment guidelines for the conditions.

If the science is not settled around NAFLD and NASH, leading researchers remain optimistic that better tools are just around the corner. “We, in the field of NAFLD and NASH, are where the field of viral hepatology was 15 years ago, and look how much progress they’ve made,” observed Diehl. “At the beginning they also only had a surrogate marker—ALT—which didn’t actually measure the hepatitis C virus. So they demonstrated that even without having a great diagnostic test, the tests that are available can be instructive in moving the field forward. Having said that, development of a non-invasive serologic marker was instrumental in getting pharmaceutical companies into the field. Could that happen in NAFLD? I’d say, why not?” CLN

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Elite Journals Becoming More Selective

Publish, continued from page 1

writing something up. You have to go through the learning curve, so the younger you start the better.”

It turns out that there are, in fact, many common threads in how successful early-career professionals go about building their skills to become well-respected, published authors. While not usually a part of their formal education and training, there is a fairly predictable path that involves trial and error, mentorship, effective networking, and a strategic approach to holding together the many threads of a demanding profession.

Easier... But Harder

A counter-intuitive trend in scientific publishing is that even while the number of academic journals has exploded over the last two decades, with more than 8,500 unique titles in the ISI Web of Science indexing service, the high-impact journals that professionals aim for have become much more competitive and highly selective. As a result, it's much easier to get a manuscript published by any means, but much harder to break in to the more elite publications in a specialized field, like *Clinical Chemistry*, which only accepts about 15% of submitted original reports. This leaves early-career

laboratorians with more choices than ever when it comes to where to publish, but higher pressure to turn out excellent, well-written papers if they want to publish in the more prestigious publications.

The ease of electronic manuscript submissions and expanding resources in developing countries have led to a swell of manuscripts competing for the pages of each journal, Annesley explained. “With the explosion of research throughout the world, especially in China, India, and other developing countries, it's just the sheer numbers of people doing research and submitting papers that has increased,” he said. “But *Clinical Chemistry* still publishes about the same number of pages as it did

20 years ago, meaning that we have to be much more selective. So it has become more difficult to publish over time in the higher impact journals, and I think we'll become even more selective in the future.”

The issue is critical for those doctorate-level clinical lab professionals because getting published has a big impact on a person's career, and for those at academic institutions, publishing is a necessary element for promotion through the academic ranks, Annesley pointed out. Even for laboratorians not directly involved in teaching or research, a record of publication enhances their national and international recognition, which can be a contributing factor towards promotion in commercial jobs or community medical centers. Furthermore, laboratorians who publish are often chosen as peer reviewers, invited speakers,

and members of committees and panels, activities which also factor into career advancement. Yet scientific writing courses and workshops to help prepare young professionals for publishing are “infrequent or nonexistent” at many universities and training programs, Annesley noted.

Despite the high stakes and competitive nature of publishing, several factors remain in the laboratorian's favor, said Joshua Bornhorst, PhD, assistant professor of pathology at the University of Arkansas for Medical Sciences in Little Rock and the director of the clinical chemistry, immunology, neonatal, and point-of-care testing sections of the University of Arkansas Hospital System. In 2009, AACC honored Bornhorst with the Award for Outstanding Scientific Achievements by a Young Inves-

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Clinical Chemistry's Guide to Scientific Writing

A new, unique series of how-to articles is planned for *Clinical Chemistry* that aims to make the practical and sought-after advice of the journal's deputy editor, Thomas Annesley, PhD, available freely to subscribers and the public. On sabbatical to develop a biomedical writing course at the University of Michigan—a rare instance of formal education addressing the subject—Annesley has developed a series of educational articles for the journal instead of publishing the material in book form, thereby benefiting a wider audience. Published monthly, the articles will be compiled on the *Clinical Chemistry* website.

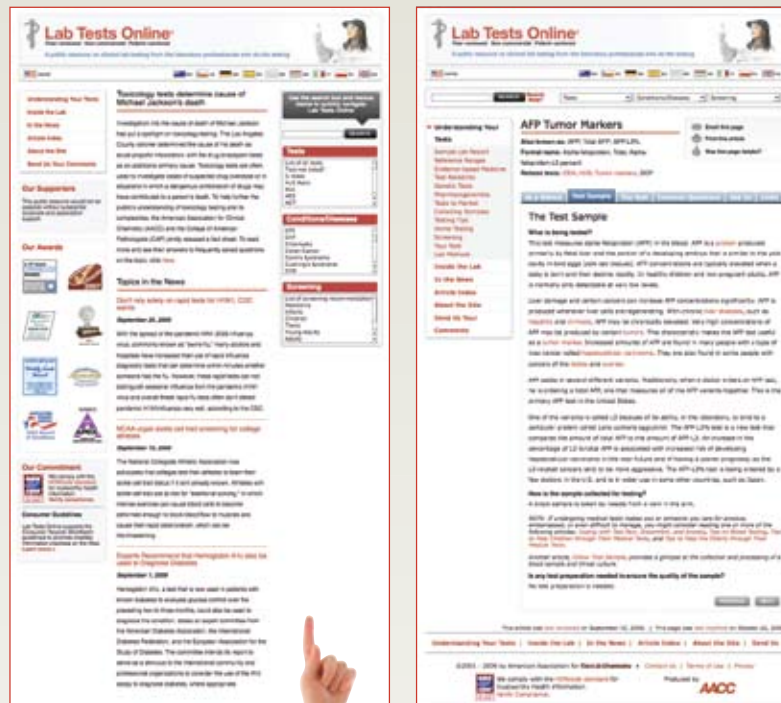
So far, these articles are planned as part of the series, covering the following topics:

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Overcoming the Publishing Hurdles

Publish, *continued from page 5*

tigator. "In some ways, I think it has gotten easier to get published: there are more journals, online resources are better, and there is more computer archiving of data that can be accessed," he said. "At the same time, I'm not convinced that all the journals out there are as rigorous as they should be in requiring solid scientific contribution and presentation. I'm worried about a dilution in the quality of some publications."

Annesley recommends that young laboratorians focus on preparing high quality manuscripts. "Those who publish fewer papers but in the high-impact journals, or perform studies that are highly cited and highly recognized—that does more for your reputation than publishing a large number of papers that just get lost in the ocean of all the other papers out there," he said. "The quality of what you do is what stands up in the long run. If you don't do high-quality work, people realize that you're not making a significant contribution over time."

Changing Roles

Though not quite a make-it-or-break-it mentality, the current trends in publishing do mean that tackling scientific writing without formal instruction leads to what some early-career laboratorians refer to as

"trial by fire," a lot of which has to do with the sometimes awkward and always challenging and abrupt shift from student or fellow to that first professional position.

"If you're in an academic medical center, it's absolutely essential to be prolific," said Alison Woodworth, PhD, director of esoteric chemistry, associate director of clinical chemistry, and assistant professor of pathology at the Vanderbilt University Medical Center in Nashville. "For most of us, publishing is actually a requirement, and there is a steep learning curve at the beginning of one's career. It's quite challenging because there is a significant transition from postdoctoral fellow to assistant professor."

As director of the postdoctoral training program at Vanderbilt, Woodworth has experience mentoring lab fellows, as well as medical students and residents. She noted that classically-trained PhD students usually lack familiarity with the clinical lingo and are intimidated by writing for publication. In contrast, her residents are more confident and don't have a problem just getting something out on paper, likely because they get a lot of practice writing interpretations for anatomical pathology. "Clinical chemistry fellows will come fresh from PhD training, and they're very timid

about the clinical language," she said. "In most cases, they learn exponentially when they start to do clinical studies, where they delve into the patient charts and read how clinicians write. Fear of the unknown is significant. Appropriate mentorship is critical in building a fellow's confidence."

Woodworth also emphasized how critical it is to be persistent at this early stage. "A lot of our publications as clinical chemists come from writing invited reviews at the beginning. And when your name is not as well known, it's challenging to get those invitations," she said. "You just have to keep being persistent and get yourself out there. Present data or give talks whenever you can, and then the invitations will start to come." Woodworth recommended presenting posters, abstracts, even brown bag sessions or symposia at the AACC Annual Meeting, and networking through SYCL to help gain name recognition among peers. "I've found that the more things I do, the more active I am with AACC, the more opportunities present themselves," she said. "Once you build yourself a bit of a reputation, people start to get to know you and you get invitations for bigger projects."

Chris McCudden, PhD, vice chair of the SYCL committee, highlighted how important it is to have realistic expectations. "It's difficult to publish a big, high-impact project right out of the gate at a new job," he said. "If you've shown up at a new place and you're just learning your way around, then it is helpful to start with a small project that you can get off the ground, then work your way towards larger projects. You're probably not going to start a multicenter trial in the first month of your new job. Early on, it's better to do something simple very well than do something big and not do a great job on it." McCudden is assistant professor of pathology and laboratory medicine and associate director of the core laboratory at the University of North Carolina, Chapel Hill.

He also reminded early-career laboratorians that following the common-sense advice to start small and have realistic expectations can sometimes pay off in a big way. "As a trainee you won't be the senior investigator on the first project you do, but that doesn't mean you can't publish in the top journals as part of a group, depending on whom you work with," he said. "But your role changes greatly from graduate school, to post doc, to faculty." Early on, with multiple authors and mentors, a person may not have the opportunity to write the entire manuscript, he explained. For example, the less experienced person might just write a draft and someone else will edit it extensively. But with more experience and seniority, he or she eventually will become the last person who looks at a manuscript before submission with the final say about what is included.

Annesley echoed McCudden's advice. "The normal path is to start small and develop a niche or expertise over time. Begin by writing a review article, case study, or special feature. These do not require that you be a funded researcher," he said. "Look for or solicit opportunities to collaborate with someone on a project, look for unsolved problems, and look for a mentor. Senior faculty will often have a smaller segment of a larger project that they are willing to let you participate in, which may lead to a publication or even a new area of investi-

Manuscript Writing 101

A Workshop at the 2010 AACC Annual Meeting

An interactive workshop on July 26 at the 2010 AACC Annual Meeting in Anaheim, Calif. titled "Preparation of Manuscripts for Publication: Improving Your Chances for Success" will be moderated by Christopher McCudden, PhD. Thomas Annesley, PhD, and James Boyd, MD, will give presentations. For more information or to register, visit www.aacc.org/events/2010am. Registration opens in late April.

gation. Also, co-peer review of a paper with someone can help you make connections."

Annesley, along with the other deputy editor of *Clinical Chemistry* James Boyd, MD, and the editor-in-chief Nader Rifai, PhD, recently authored a paper in the journal to help younger scientists better formulate manuscripts for publication (See Box, p. 7). Now Annesley is working on distilling his editorial experience in a series of articles in the journal called "The *Clinical Chemistry* Guide to Scientific Writing," the first of which was published in March (See Box, p. 5).

A common theme among laboratorians who have found success in publishing is to find and make full use of a mentor. In fact, working with a mentor is probably the most crucial step towards getting published. "Finding a good mentor and an area of research you are passionate about is key—someone to help you break into a field, get you started, and give you advice and opportunities to publish with them—someone who has already established a name for themselves," said Amy Saenger, PhD, assistant professor of laboratory medicine, director of the central clinical laboratory, and associate director of the postdoctoral training program at Mayo Clinic.

"I have been fortunate to have a few outstanding mentors, and in that respect I make sure to utilize their knowledge to the fullest: I ask questions as much as I need to, brainstorm about ideas for studies, and ask to collaborate if there is something I feel I can productively contribute to. If you can make it a two-way street and benefit both parties, that's ideal." Saenger is the 2010 winner of the AACC Award for Outstanding Scientific Achievements by a Young Investigator.

Often, the line blurs between collaborator and mentor, and this is when an early-career person has a unique opportunity to learn, emphasized McCudden. "Typically you learn the most through co-authors or lead authors on a project, and you'll write the first or second draft, then get their feedback on it, then go improve it, then send it back," he said. "So they're both mentors and collaborators at the same time, and they have a vested interest in the project, so you're very likely to get constructive feedback."

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More Resources

The laboratorians interviewed for this article suggested the following books and articles.

Journal articles

Annesley TM. The title says it all. *Clin Chem* 2010;56:357–360.

Boyd JC, Rifai N, Annesley TM. Preparation of manuscripts for publication: Improving your chances for success. *Clin Chem* 2009;55:1259–1264.

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Welch GH. Preparing manuscripts for submission to medical journals: The paper trail. *Eff Clin Pract* 1999;2:131–137. Available from www.vaoutcomes.org/downloads/papertrail.pdf.

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Zeiger M. *Essentials of writing biomedical research papers*. McGraw-Hill: New York; 2000.

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Once that first article is published, your networking with colleagues can take on momentum of its own, said Bornhorst. "Getting that first article out gives you a voice and it gives you recognition, which can lead to more opportunities for further research," he said. "So once you get the boulder rolling downhill, you pick up speed and can do well in publishing."

Keeping Your Eyes Open

After that first publishing success and with growing confidence in his or her writing and research skills, the next mountain young laboratorians face is finding relevant and engaging projects based on personal ideas and research, experts noted. The common theme for this step could be summed up in what Annesley simply referred to as "keeping your eyes open."

"If you get a question from somebody in the laboratory, or a clinician calls and says, 'I have this unusual case and don't understand why I'm getting this result with this disease,' keeping your eyes open means you tend to recognize opportunities for tackling unsolved problems," he said. "Look it up in the literature and see if anyone has really examined the problem yet, or go through patient records to see how often this anomaly or problem occurs. Be ready for those opportunities when they come. Think about the problems you encounter

in your laboratory and ask, 'why are they still problems?' Maybe there is a solution no one has looked at."

This strategy has been borne out in the experience of laboratorians who juggle clinical, research, and academic responsibilities. "In my position where I'm the director of several laboratories, of course there are clinical 'problems' that pop up all the time, some of which may be of unexpected academic interest," said Bornhorst. "In my experience, having laboratory sections in addition to teaching responsibilities actually gives you a wealth of opportunity for individual projects."

Saenger agreed, noting that the raw material and some of the best ideas for research projects and publications comes from seemingly humdrum clinical issues. "We try to take a recurring everyday problem, do as much research into it as we can, and investigate new methods or technologies to make the solution novel," she said. "And to make it a productive project academically, we often have a resident or fellow working on the project with us—they often bring fresh perspectives and ideas and provide us opportunities to educate along the way."

Another tactic to keep a steady stream of publication-worthy projects going is to have more than one project underway at a time, at least once you have some experience under your belt, suggested McCudden. "You

have to be careful with high-risk research. If you have just one of these projects going on and it doesn't work, you're going to have a hard time having anything to show for it," he said. "But if you have multiple things going on at a time, or some less-risky type of projects concurrent, you're more certain you'll have at least something to publish." Even still, be prepared for spells of even a year or more when nothing works, he said. "It takes a lot of multi-tasking. One useful trick is to spin together a research study with a clinical project you're already doing." He offered the example of bringing in new technology or developing a new method for a clinical service, where if done in a certain way, it could become the subject of a paper.

Balancing Act

Of all the stories and strategies common to laboratorians who research and publish, the most vexing trial that transcends place, training, and even experience is the attempt to balance on the so-called three-legged stool of service, teaching, and research. Annesley stressed that even the most senior and prolific leaders in the field struggle to fulfill all of these roles at the same time.

"The image of the perfectly proportional three-legged stool is a good one, but not realistic," he said. "Today most individuals are hired with an emphasis on expectations in one area. Therefore, it becomes difficult to be a true 'triple threat,' let alone split one's time equally among the three. The key is to strive towards the three-legged stool without worrying about a perfect balance."

Exactly in what proportion a person focuses his or her time depends on the person's individual job description as well as where his or her time and talent are focused, said Bornhorst. Some might concentrate on clinical service, whereas others might aim to be influential through professional associations, in publishing clinical observations, or in obtaining grant funding—but you need to be good in at least one of these, or even better, some combination of them, he said. Bornhorst's approach has been to tend toward short projects for which he can enlist residents to help him. This way he ties teaching with research, so that residents can complete their work within a few months.

"The typical workweek for an academic

clinical chemist is long," Woodworth commented. "I struggle with balance every day, so I'm constantly making lists of what's important and prioritizing. Of course my primary appointment is to cover clinical service, so if given a choice, patients always come first."

Annesley made a similar assessment. "For me, making it work has been that I decided long ago that I would devote some of what I would call my personal time to doing these sorts of things," he said. "I would come in evenings and weekends to do experiments or write papers, really doing a lot outside of the traditional work week. We are all busy during our regular eight-hour days with whatever our primary responsibilities are, and it's tough to carve out that time."

The Right Journal

After building confidence, finding a mentor, honing skills through experience, and giving up extra time to work on writing, laboratorians interviewed for this article also called attention to the fact that specializing and finding your niche also means picking the right place to publish.

Sometimes this translates into publishing in different types of journals over the course of a career, McCudden said. "I've switched fields a bit, from pharmacology and physiology to more clinical research, and so my goals have changed in terms of which journals I might target," he said. "When I was a grad student, the *American Journal of Physiology* was going to be the flagship journal for us, then as a basic science post doc, it had to be a one-word journal: *Science*, *Nature*, *Cell*, or it wasn't really considered worth doing." Now that he's working in the clinical world, McCudden realizes that those journals are not going to be interested in the kind of work he does anymore, even though he believes it has more impact on patient care.

The next step is to read and study the journals that the manuscripts are going to be submitted to, suggested Annesley. It's important to know how people write for these publications, what the standard is for a particular journal, and what is emphasized and how the papers are organized. "Then you go out and write your own papers and learn by experience how to improve them," he said. CLN



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Porphyrias

A Guide to Laboratory Assessment

BY M. LAURA PARNAS, PHD, AND ELIZABETH L. FRANK, PHD

A group of rare metabolic disorders, porphyrias are associated with defects in the enzymes involved in the heme or porphyrin biosynthetic pathway. Normally, the body makes the heme molecule needed for hemoglobin in a multi-step process. Porphyrins are produced during several steps of this process. However, individuals with porphyria lack certain enzymes in the pathway, causing abnormal amounts of porphyrins or related molecules to build up in the body and eventually be excreted. Each distinct porphyria has a characteristic accumulation pattern of heme precursors or reduced enzyme activities that can be detected readily in blood, urine, and feces. Individuals with even partial deficiencies of the enzymes in this pathway accumulate and excrete heme precursors and intermediates.

Clinically, patients with porphyria have either neurological complications or skin problems, although some individuals have both symptoms. These distinct disease manifestations have led clinicians to divide porphyrias into two subgroups: acute neurologic and non-acute cutaneous, according to the most dominant clinical manifestation. But porphyria symptoms mimic a variety of conditions, making correct diagnosis critical to successful management of the disease.

Here we describe how appropriately chosen and interpreted laboratory tests are sensitive and specific for the distinct porphyrias and play a crucial role in the diagnosis and management of these disorders.

Biochemistry: Heme Formation and Porphyrias

Biosynthesis of heme occurs in all nucleated cells, primarily in developing red cells of the bone marrow where hemoglobin is generated, and to a lesser extent in hepatocytes

form δ -aminolevulinic acid (ALA), which is catalyzed by δ -aminolevulinic synthase (ALAS). Porphobilinogen (PBG) synthase then catalyzes condensation of two molecules of ALA to generate the monopyrrole PBG. This step is followed by polymerization of four PBG molecules to form the linear tetrapyrrole hydroxymethylbilane. Hydroxymethylbilane synthase catalyzes this polymerization; however, spontaneous polymerization does occur if PBG concentrations are sufficiently increased.

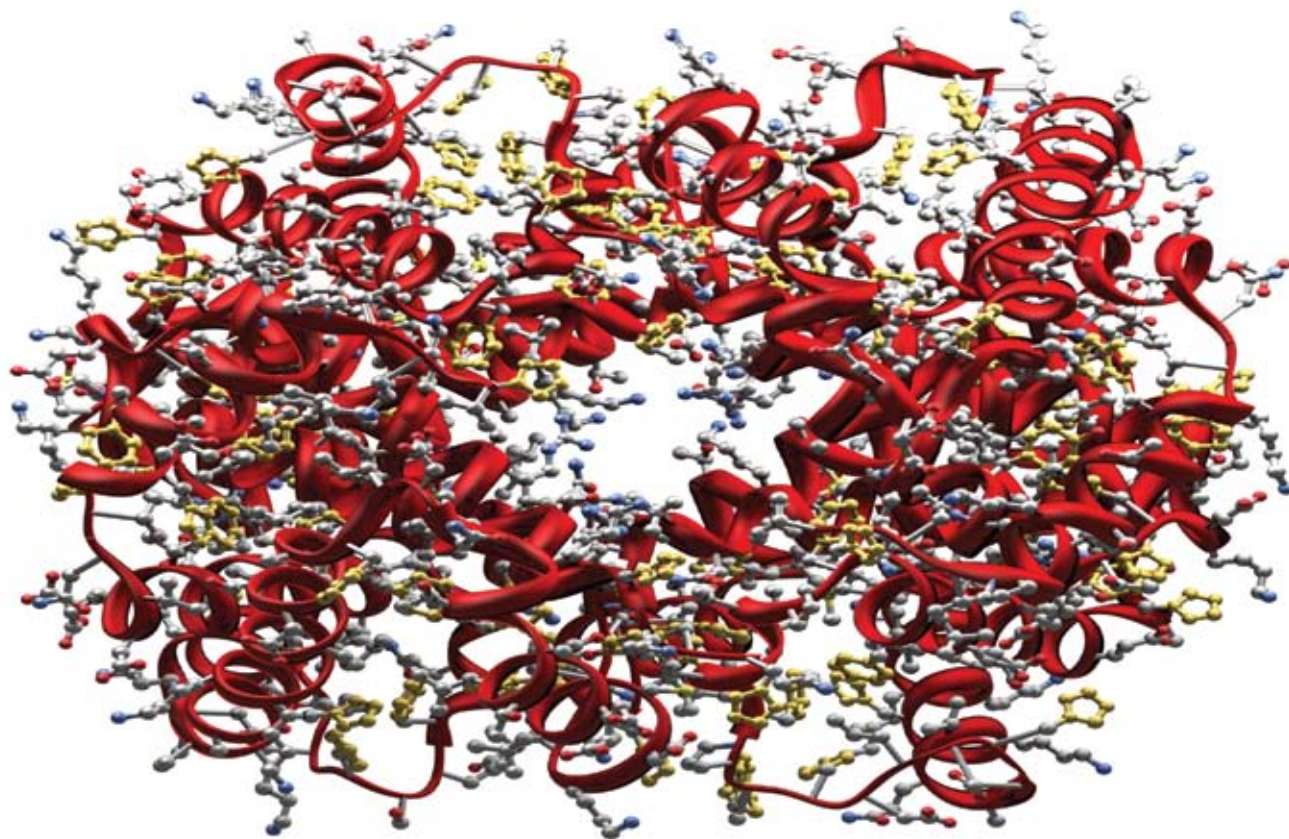
quent oxidation of this compound by protoporphyrinogen oxidase produces protoporphyrin IX, and finally ferrochelatase inserts the ferrous iron (Fe^{2+}) to generate heme.

Under normal conditions, this highly efficient biosynthetic pathway enables most of the ALA produced to be converted to heme. Only minimal amounts of precursors and intermediates are accumulated and excreted, with the route of elimination largely directed by the inherent aqueous solubility of each compound. For example, the porphyrin precursors ALA and PBG both are water-soluble and chiefly excreted in urine. The octa-carboxylate intermediate uroporphyrinogen is also water-soluble and excreted renally. On the other hand, dicarboxylate protoporphyrin IX, which is water-insoluble, is excreted in feces via the biliary tract. The remaining porphyrin intermediates, including the tetra-carboxylate coproporphyrinogens, are somewhat water-soluble and appear in both urine and feces.

In the body, it is important to note that the cyclic tetrapyrrole intermediates exist in a reduced chemical state and are called porphyrinogens. Upon exposure to air, these compounds are oxidized rapidly to the corresponding porphyrins, the analytes measured in the clinical laboratory.

Genetic Defects in Porphyrias

Genetic defects in seven of the eight heme biosynthetic enzymes give rise to the porphyrias. Individuals inherit most of these diseases in an autosomal dominant (AD) fashion, with one functional copy of the gene present. Therefore, the enzyme deficiency is partial, with sufficient enzyme activity to maintain heme homeostasis. Nevertheless, pathway precursors and intermediates that precede the enzymatic defect accumulate in body fluids, causing characteristic signs and symptoms of the different porphyrias. Although each type of porphyria originates from a different genetic defect, the clinical manifestations of these disorders are similar, falling into either the acute or non-acute subcategories.



where heme-containing enzymes are produced. Enzymes generate the tetrapyrrolic heme structure in a series of steps that take place in two distinct cellular compartments: the first and the last three steps occur in the mitochondrion, and the intermediate steps take place in the cytosol (Figure 1).

Eight enzymes catalyze the formation of protoporphyrin IX and the chelation of iron to produce heme. The initial and rate-limiting reaction in the pathway is the condensation of glycine and succinyl CoA to

Following polymerization, uroporphyrinogen III synthase catalyzes cyclization of the tetrapyrrole to form uroporphyrinogen III, although minor spontaneous cyclization occurs, generating the uroporphyrinogen I isomer. Then, uroporphyrinogen decarboxylase mediates the stepwise decarboxylation of uroporphyrinogen isomers to form coproporphyrinogen III and I. Only coproporphyrinogen III is oxidatively decarboxylated by coproporphyrinogen oxidase to protoporphyrinogen IX. Subse-

Acute Porphyrrias

The four disorders comprising this group are: acute intermittent porphyria (AIP); variegate porphyria (VP); hereditary coproporphyria (HCP); and aminolevulinic acid dehydratase deficient porphyria (ADP). Each disorder is associated with a different defective enzyme (Table 1).

AIP is the most common of the acute porphyrias, and it is inherited in an AD manner, as are VP and HCP. In contrast, the extremely rare ADP is inherited as an autosomal recessive (AR) trait. The predominant clinical phenotype of these disorders is acute neurovisceral attacks, characterized by diffuse abdominal pain, peripheral neuropathies, and mental disturbances. These acute attacks commence during early adulthood, more frequently in women than men, and may be accompanied by skin lesions in VP and HCP.

The genetic abnormalities present in the three AD acute porphyrias produce approximately 50% of the normal enzymatic activity. The body maintains sufficient heme concentration as a result of upregulation of ALA synthase. Consequently, acute porphyrias have low clinical penetrance, with most individuals remaining asymptomatic for life.

However, approximately 20% of affected individuals manifest symptoms in the presence or absence of precipitating endogenous and exogenous factors. These exacerbating agents, including drugs, hormones, stress, and infection, increase demand on the liver for heme, which in turn induces heme synthesis. The enzyme deficiency becomes rate-limiting, causing precursors and intermediates to accumulate. Individuals with acute porphyrias experience variable incidence and severity of attacks that become more frequent upon exposure to precipitating factors. All patients with acute symptoms and some asymptomatic individuals have increased urinary excretion of PBG and ALA.

Non-acute Porphyrrias

There are three non-acute porphyrias: porphyria cutanea tarda (PCT); erythropoietic protoporphyria (EPP); and congenital erythropoietic porphyria (CEP) (Table 1).

Among the non-acute porphyrias, PCT

is the most common. Both PCT and EPP are inherited as AD traits, while the very rare CEP is inherited in an AR fashion. Clinically, these disorders are characterized by photosensitization of the skin due to accumulation of porphyrin intermediates in body tissues. The symptoms develop as a result of the light-absorbing properties of the porphyrin ring.

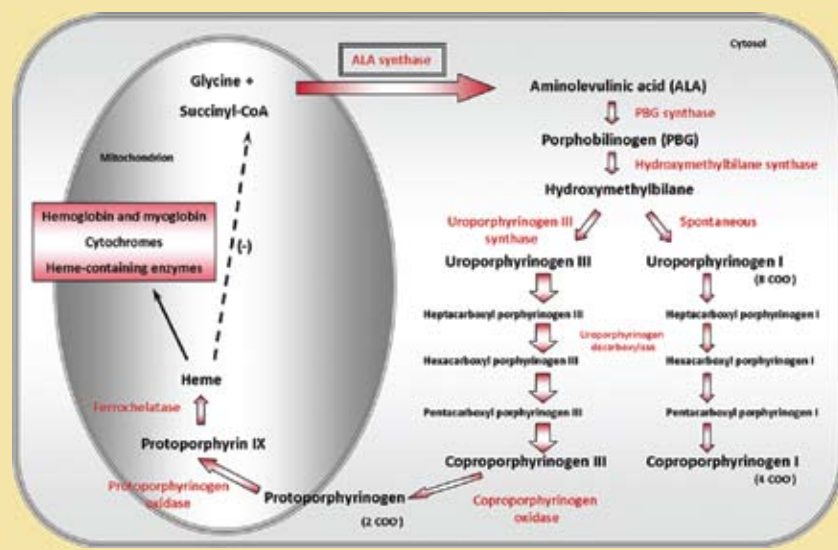
However, two distinct groups of manifestations occur with sun exposure, particularly on the hands, forearms, neck, and face. Burning, itching, and erythema that appear in childhood on sun-exposed areas are characteristic features of EPP. In this disease, a partial deficiency of ferrochelatase causes protoporphyrin to accumulate in red blood cells. In contrast, individuals with PCT and CEP typically experience increased fragility of the skin, with trauma leading to erosions, subepidermal bullae, hypertrichosis, and patchy pigmentation. Erosions and bullae heal slowly leaving scars and hyper- or hypo-pigmentation. Patients with CEP tend to have more severe symptoms that appear earlier. These individuals also may experience disfiguring mutilation of light-exposed body parts such as the nose, ears, and hands.

Laboratory Investigations

Because porphyrias are relatively rare, many clinicians may not be familiar with them. Furthermore, physicians may not suspect porphyria in their initial clinical workup because affected individuals present with ambiguous clinical phenotypes. In-depth understanding of the biochemical pathway of the disease, however, provides a logical guide for laboratory investigations.

Figure 2 (p. 10) outlines a diagnostic algorithm for porphyria that incorporates clinical presentation with high suspicion of the disease. Since porphyrin precursors and intermediates are produced in excess and excreted in body fluids, initial testing should demonstrate abnormal elevation of porphyrins. If this is the case, interpretation of the specific pattern of precursor and intermediate compounds will lead to diagnosis. Additional investigation can be performed to identify the specific enzymatic defect and guide treatment.

Figure 1
Heme Biosynthetic Pathway



Eight enzymes (red) catalyze synthesis of heme from glycine and succinyl-coenzyme A. Formation and polymerization of porphobilinogen (PBG) are followed by cyclization to uroporphyrinogen III, the octa-carboxylate (8 COO⁻) intermediate. Spontaneous cyclization to uroporphyrinogen I occurs to a lesser extent. Sequential decarboxylation to both tetra-carboxylate (4 COO⁻) coproporphyrinogen isomers occurs, although only the enzymatically-produced coproporphyrinogen III isomer can be metabolized by coproporphyrinogen oxidase to form the di-carboxylate (2 COO⁻) protoporphyrinogen. Oxidation to protoporphyrin IX and insertion of Fe²⁺ to form heme completes the biosynthetic cycle. Production of heme regulates the activity of ALA synthase, the rate-limiting enzyme in the pathway, by negative feedback inhibition (-).

Dx: Patients with Acute Symptoms

For patients who present with acute manifestations, including diffuse abdominal pain, peripheral neuropathy, and/or mental disturbances, and for whom there is high suspicion for a porphyria attack, quantification of urinary PBG is the test of choice (Figure 2). While normal urinary PBG concentrations indicate that the patient is not suffering an acute attack currently, it does not completely rule out acute porphyria. If clinical suspicion for the disease remains high, testing should be repeated on a specimen collected when symptoms are present. Increased urinary excretion of PBG indicates presence of an acute porphyria, and further testing is necessary to identify the specific disorder.

Labs also use quantitation of porphyrins

in feces to differentiate the acute porphyrias. No increase of fecal porphyrins indicates that AIP is the cause of the attack. Elevated fecal protoporphyrin and coproporphyrin suggest VP, while a significant increase of coproporphyrin is characteristic of HCP. VP can be confirmed by testing plasma or serum for porphyrin fluorescence; a characteristic peak at 626–628 nm confirms the diagnosis.

Dx: Patients with Non-acute Symptoms

For clinical manifestations of cutaneous photosensitivity that trigger suspicion of porphyria, the appropriate test is quantitative fractionation of urinary porphyrins (Figure 2). If urinary porphyrins are not increased, porphyria is unlikely. Excess urinary excretion of porphyrins, particularly uroporphyrin and heptacarboxylate porphyrin, along with the presence of the unique product, isocoproporphyrin, is diagnostic of PCT.

Slight or no increase in urinary porphyrin excretion when suspicion for non-acute porphyria is high, together with presentation during childhood, should also trigger evaluation of porphyrins in red blood cells (RBCs). Increased erythrocyte porphyrins are consistent with EPP.

Confirmation of the extremely rare CEP is also straightforward. These patients excrete massive amounts of uroporphyrin I and coproporphyrin I isomers, and they typically present with symptoms early in childhood. They also may have severe skin lesions.

Hepatoerythropoietic porphyria (HEP), a rare homozygous disorder of uroporphyrinogen decarboxylase, has also been described. Clinically, the disease resembles CEP, but can be distinguished by a predominance of protoporphyrin in blood and appearance of isocoproporphyrin in feces.

Enzyme and Molecular Testing

The ideal method to demonstrate the presence of a porphyria is testing for activity of

Table 1

Biochemical Profile of Porphyrrias

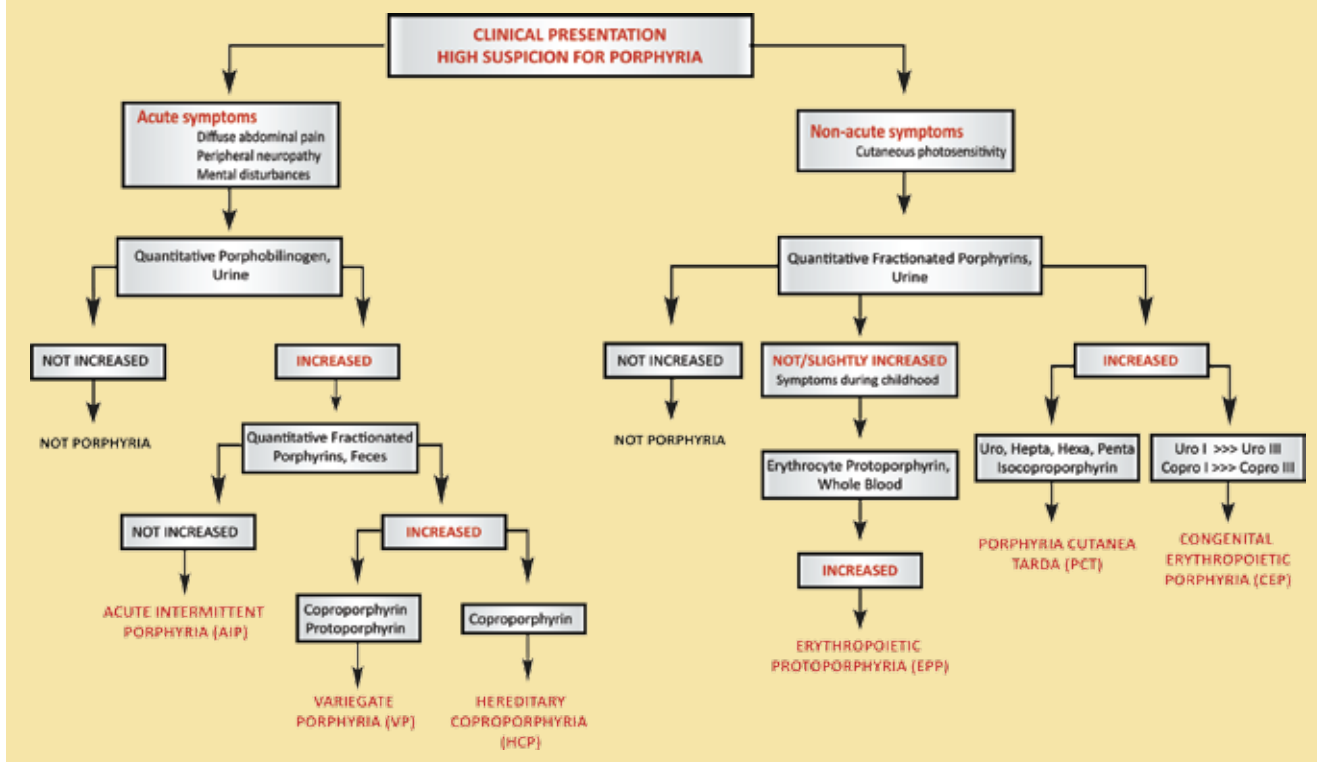
This table shows the accumulation and excretion patterns of heme precursors and intermediates in body fluids during symptomatic episodes of porphyria. Diseases are grouped into acute (blue) and non-acute porphyrias (green) and listed in order of decreasing prevalence.

Porphyria	Enzyme Deficiency	Urine Precursors	Urine Porphyrins	Fecal Porphyrins	Erythrocyte Porphyrins	Plasma fluorescence
Acute Intermittent Porphyria (AIP)	HMB synthase (PBG deaminase)	PBG > ALA	Uro from PBG	Not increased	Not increased	618–622 nm
Variete Porphyria (VP)	Protoporphyrinogen oxidase	PBG > ALA	Uro from PBG Copro III	Proto IX > Copro III	Not increased	626–628 nm
Hereditary Coproporphyria (HCP)	Coproporphyrinogen oxidase	PBG > ALA	Uro from PBG Copro III	Copro III	Not increased	618–622 nm
ALA Dehydratase Deficient Porphyria (ADP)	PBG synthase (ALA dehydratase)	ALA	Copro III	Not increased	Zn-proto	N/A
Porphyria Cutanea Tarda (PCT)	Uroporphyrinogen decarboxylase	Not increased	Uro, Hepta, Isocopro	Isocopro	Not increased	618–622 nm
Erythropoietic Protoporphyria (EPP)	Ferrochelatase	Not increased	Not increased	Proto IX	Proto IX	634–636 nm
Congenital Erythropoietic Porphyria (CEP)	Uroporphyrinogen III synthase	Not increased	Uro I, Copro I	Copro I	Uro I, Copro I, Proto IX, Zn-proto	618–622 nm

Abbreviations: PBG, porphobilinogen; ALA, δ-aminolevulinic acid; Uro, uroporphyrin; Hepta, heptacarboxylate porphyrin; Copro, coproporphyrin; Isocopro, isocoproporphyrin; Proto, protoporphyrin; Zn-proto, zinc protoporphyrin

Figure 2

Diagnostic Algorithm for the Porphyrrias



the suspected defective enzyme; however, this is rarely necessary for diagnosis. In family studies, measuring enzyme activity is useful and it complements molecular testing for defective heme biosynthetic enzymes.

Labs can measure the activity of the cytoplasmic enzymes involved in heme biosynthesis in red blood cells; however, the mitochondrial enzymes require nucleated cells, such as fibroblasts or leukocytes. The only enzyme assay currently available for routine use measures hydroxymethylbilane synthase (HMBS) activity, the enzyme associated with AIP. In most patients with AIP HMBS activity in erythrocytes is reduced to approximately 50%, although significant overlap in values at the lower end of the reference interval exists between unaffected and affected individuals. Furthermore, there is a subtype of AIP in which the enzymatic defect is expressed in liver, but not in peripheral blood cells. Additional limitations of enzymatic testing are related to erythrocyte age, since younger RBCs have higher enzymatic activity, or to inappropriate specimen handling. Despite these limitations, determining HMBS activity helps confirm AIP and identify carriers in asymptomatic family members of affected individuals.

After biochemical analysis identifies the type of porphyria present, molecular testing can reveal the specific mutations causing disease. Most importantly, genetic testing aids in identifying carriers in families of symptomatic patients. Molecular testing cannot predict disease course or severity, but individuals carrying a mutation can be advised on lifestyle changes and ways to avoid precipitating agents and prevent symptoms.

Secondary Causes of Elevated Porphyrins

Abnormalities in metabolism and excretion of heme precursors and intermediates can also occur in the absence of inherited porphyrias. Such abnormalities can be caused by a variety of conditions, which should be considered at the time of interpretation of results in the context of clinical presentation.

For example, lead poisoning is one rea-

son for elevated porphyrins in body fluids. It can cause attacks of acute abdominal pain and neurological disturbances that mimic acute porphyria attacks. Lead inhibits PBG synthase, the second enzyme in the pathway, and to a lesser extent coproporphyrinogen oxidase. As a result, lead toxicity is associated with significantly increased urine ALA concentration and increased urinary coproporphyrin, predominantly coproporphyrin III. Lead reduces intracellular iron availability, and zinc replaces iron as a substrate for ferrochelatase, forming zinc protoporphyrin (ZPP) in red blood cells. Tests for ALA, porphyrins, and ZPP provide indirect evidence for lead toxicity, but definitive diagnosis requires a finding of lead in blood and/or urine.

Labs sometimes encounter isolated increases in the concentration of urinary coproporphyrin during porphyria testing. These are typically associated with hepatobiliary malfunction that occurs in hepatitis, cirrhosis, and obstructive jaundice. In these conditions, coproporphyrin III is the predominant urinary isomer present. Inherited disorders of bilirubin metabolism—Dubin-Johnson syndrome, Rotor syndrome, and Gilbert disease—also increase urinary coproporphyrin concentrations; however, more coproporphyrin I than coproporphyrin III is excreted.

Treatment and Management

Clinicians treat acute attacks of porphyria by immediately withdrawing the suspected precipitating agents, treating co-existing illnesses and/or infections, and managing patients' pain with non-porphyrinogenic agents. In some cases, drugs that trigger porphyria attacks must be replaced with alternative medications.

Today, intravenous heme preparations (hematin) are the preferred therapy for patients with a diagnosed acute porphyria attack. Hematin specifically inhibits hepatic ALAS activity and effectively decreases urinary PBG and ALA excretion. Additionally, carbohydrate loading in the form of oral or intravenous glucose can help halt an attack by moderate inhibition of hepatic ALAS activity. To prevent acute attacks, patients

should: maintain adequate caloric intake, especially in the form of carbohydrates; avoid precipitating factors, including specific drugs, alcohol, and tobacco; and reduce stress.

Treatment of non-acute porphyrias is primarily preventive. In general, cutaneous symptoms can be minimized by avoiding ultraviolet light exposure and using topical sunscreens. For PCT, the treatment of choice is phlebotomy, which removes iron and stimulates erythropoiesis, resulting in decreased serum ferritin and urinary porphyrin excretion. An alternative treatment is administration of a low dose of chloroquine, which removes excess porphyrins from tissues. Patients should also avoid precipitants such as excess alcohol consumption, use of hormones, and smoking.

EPP patients also need to minimize sun exposure by wearing protective clothing and using topical sunscreens. Oral administration of β -carotene provides systemic photoprotection by quenching excited species formed by UV-activated porphyrins and preventing damage from oxidative radicals.

In the most severe form of porphyria, CEP, strictly avoiding sunlight and protecting skin from trauma are essential. Blood transfusions also help decrease hemolysis and suppress overproduction of porphyrins.

Improving Recognition and Diagnosis

Given the relatively uncommon occurrence of porphyrias, clinicians may initially suspect that patients presenting with neurological symptoms or skin problems have other, unrelated conditions. However, appropriate laboratory analysis can provide sensitive and specific diagnostic information. For example, urinary PBG should be the first test ordered for a patient with abdominal and neurological symptoms. Increased urinary excretion of PBG strongly suggests the presence of an acute porphyria. Additional biochemical testing can elucidate the specific type of acute porphyria.

In addition, adults experiencing cutaneous photosensitivity on sun exposure should be screened for urinary porphyrin excretion; a 24-hour specimen is preferred.

The most common non-acute porphyria, PCT, can be diagnosed by its characteristic pattern of urine porphyrin excretion. Children who complain of burning, itchy skin following exposure to sunlight should be tested for erythrocyte protoporphyrin concentration. Enzymatic and molecular analyses, available from specialized reference laboratories, are best used to confirm a particular disorder and to identify family members at risk for the disease. **CLN**

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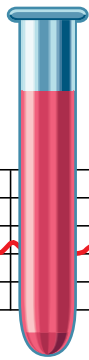
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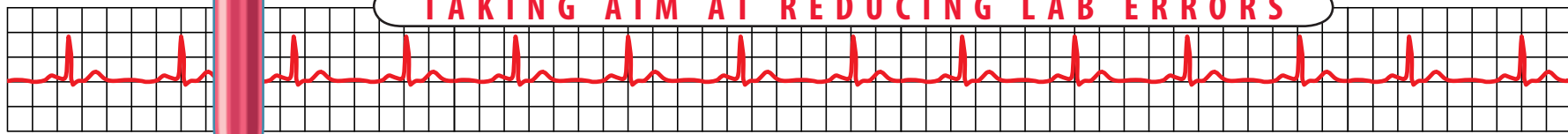
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PATIENT SAFETY FOCUS

TAKING AIM AT REDUCING LAB ERRORS



Patient- and Family-Centered Care

Putting the Patient in Patient Safety



Hollis Guill-Ryan, program coordinator, Patient and Family Centered Care Program, University of Washington Medical Center

In this interview, we discuss the core values of patient- and family-centered care and how they can be implemented in various areas of healthcare, including the lab.

NANCY SASAVAGE, PHD, CONDUCTED THIS INTERVIEW.

What is patient- and family-centered care?

It is an approach in which the healthcare organization partners with patients and their families to design policies, programs, and facilities that improve all aspects of the healthcare experience. We think it leads to better outcomes, better use of resources, and enhanced patient and family satisfaction. The core concepts of our Patient and Family Centered Care Program are communication, partnership, information sharing, choices, and respect. At the University of Washington Medical Center, these core concepts are embodied in the logo of our program.

What do you mean by partnership between healthcare organizations and patients?

Partnership means that we view all aspects of patient care as collaboration between patients and the healthcare staff. Obviously, it includes patient interaction with the direct-care team. But it goes beyond that, too. It also includes incorporating the patient's point-of-view into essential services—nutrition, radiology, and lab—as well as administrative functions like billing. Overall, we want to allow patients and

their families to contribute to the policies, programs, facilities, and quality improvement initiatives of the entire organization, and we want to be held accountable to patients.

How do you define “information sharing” as a core value?

Information sharing includes transmitting information in a way that is rapid, accurate, usable, and complete. This is directly relevant to laboratory testing, both in terms of instructions to patients undergoing testing, as well as in the formatting of lab test reports that patients and their care providers read. We want to give patients the information they need so they know what is happening.

When did this program start at your institution?

We started in 2002. The chief nursing officer at the time was one of the key forces driving the program. The university hired the Institute of Family Centered Care in Bethesda, Maryland to assess our readiness for such a program, and their analysis indicated we were ready. We were a relatively early adopter for adult medicine. The program started by recruiting patient and

family advisors to serve on a steering committee. Since that time the initiative has grown to include three staff members and 60 patient and family advisors.

What patients and families are eligible to participate in your program and how do they participate?

Patients who have received care at the medical center are eligible to participate as patient advisors, as are their family members. They sign privacy agreements and agree to volunteer, usually about 2 hours per month. Patient and family advisors can participate in one or more ways. They can serve on advisory councils for specific care areas, serve on committees, review and improve educational materials and forms that are regularly used by patients and their families, teach medical students and residents, and participate in special projects like facility design. Currently, we have about 60 patient and family advisors who are serving in these various capacities.

What is a council?

A council is a group consisting of about 50% patient or family advisors and 50% staff, which often includes doctors and nurses. The purpose of a council is to improve care in a specific area. Examples of councils include the neonatal intensive care unit council, the adult intensive care unit council, the inpatient oncology council, and the rehabilitation council. Typically, councils ask questions like: “What would be helpful for patients and their families to know about this area of care before they arrive?” or “What are some key items they need to know once they are located within this care unit?” Clearly, patient and family advisors who have been through an area of care are ideally suited for answering these questions.

What are some specific accomplishments of the councils?

I will use the inpatient oncology council as an example. They developed a guide to services that orients oncology patients to the medical center and to the oncology units, specifically. They helped edit a patient safety document on preventing falls, and they were important consultants regarding some improvements in inpatient identification policies and procedures for patients receiving blood products. They were instrumental in changing food service delivery to “on demand”. They also developed care team posters that allow patients and families to identify the various medical providers taking care of them.

What are some of the committees that include patient and family advisors?

Patient and family advisors participate in a number of standing committees such as the Patient Safety Committee, the Grievance Committee, the Ethics Committee, and the Customer Service and Satisfaction Committee.

Have you used patient advisors to help hire staff?

Yes. We have patient advisors on the selection committee for resident physicians in one of our departments. Patient advisors have also helped hire nurse managers and hospital administrators, including medical directors and the chief nursing officer. This is a particularly good use of family advisors as it helps select employees who reflect the core values of patient- and family-centered care.

What do you think of using patient advisors to help improve quality in clinical laboratory services?

It is a very good idea. Clearly, patient and family advisors could help clinical laboratories in a number of ways that are analogous to some of the examples we just discussed (see box). In fact, we are just starting to explore laboratory services. For example, over the last few months we collaborated with our Department of Laboratory Medicine to pilot a program in which patient advisors attend selected lab meetings.

Can you give examples of how patient advisors could help improve lab services?

Patients could help design systems that would encourage patients to contact care providers if lab results were overdue. Similarly, they could help design systems that would encourage patients to participate actively in patient identification and specimen collection.

Do you have any final thoughts about incorporating the values of patient- and family-centered care into quality improvement initiatives?

One way to incorporate these values is to ask the following question: “Would this quality improvement initiative benefit from the patient’s voice?” If the answer is yes, then there are a number of ways to hear that voice. One is to have patient or family advisors participate actively in the quality improvement initiative.

What could patient and family advisors do to help lab leaders improve quality and enhance patient safety?

- ▶ Help plan facilities that patients visit, such as phlebotomy centers.
- ▶ Help design systems for communicating lab results that enhance patient understanding and enhance patient interaction with their care providers.
- ▶ Help develop systems that encourage patients to participate in patient safety.
- ▶ Participate in quality improvement committees and staff meetings.
- ▶ Help develop policy and procedures related to how best to deliver an apology to patients and their families in cases of harmful lab errors.
- ▶ Participate in developing educational materials about lab testing for patients and their families.

The Benefits of Lab Visits

Dear Patient Safety Focus Editors,

My staff and I read the article “Disconnection from Patients and Care Providers” (CLN, April 2009, p. 14) with great interest and wanted to share our story regarding this topic.

Our lab seemed to have a dark cloud hanging over it. We didn’t know if we should attribute this gloom to the economy or just the daily stresses of getting the work out. Whatever the case, there was an increasing amount of talk and grumbling in the lab about mundane things like dress codes and on-call duty. In other words, conversations were often not focused on patients.

After reading the article, we were inspired to invite patients to the lab and have them share their experiences so that our employees could connect a specimen with a face. We worked with our Office of Care Transformation to identify patients or family members who would be willing to come in and talk about their experiences with their lab tests. We were open to all stories, both positive and negative.

We received many enthusiastic responses from patients and family members willing to participate and scheduled eight visits. We matched patients with lab sections based on the type of testing the patient had. For example, a heart transplant patient with many biopsies was matched with anatomic pathology; a liver transplant patient who had hepatitis testing was matched with immunology; a patient with septicemia was matched with microbiology; and a cancer patient was matched with the cancer center laboratory. Flyers announcing the visits were distributed throughout the lab and everyone was welcome to attend. The response was overwhelming. Not only did all of the technologists in the particular section attend, but staff from other sections came, as well as residents, faculty, pathologists, managers, support personnel, and administrators. After the initial visits, the word spread and attendance swelled.

While some patients spoke freely and others had written their thoughts, each patient shared their hospital encounters and included specifics about their lab tests. Without exception, each patient told their story and thanked the lab employees for

their work. The patients also very generously shared personal information while telling their stories. Some brought journals and photo albums that they passed around to the group. One of the patients said, “This is my life and you are a big deal to me. I have to honor everyone who helped me. I have to honor you for what you do for me.” Another patient, who had 105 lab tests ordered in one month, said, “My body has secrets that I don’t even know. But you know, and you unlock those secrets.”

All of the patients’ stories were very moving, and while listening, our lab employees rode a roller coaster of emotions with the patients. They laughed and cried together. Our employees even asked questions that the patients never hesitated to answer. One employee said, “We see names come through the lab on a regular basis, and you are our patients, too. But we never see the actual person, and we thank you for coming to see us.”

We ended each session with a group photo and everyone wanted to be in the picture with the patient. Staff members took their photos and posted them on their bulletin boards. The experience created a palpable sense of community in the lab. For weeks following these sessions, we got comments from employees saying how good the experience had been. Our employees’ focus returned to the patient.

In closing, we would like to share this advice with CLN readers. If you are still skeptical about bringing patients into the lab, trust us. Your skepticism will evaporate the moment you meet your first patient and hear their story.

Sincerely,



Cathy Groen, MT(ASCP)
Emory Medical Laboratory
Quality Coordinator



Corinne Fantz, PhD
Assistant Professor of
Pathology and Laboratory
Medicine
Quality Lead for Clinical
Pathology

Emory University School of Medicine
Atlanta, Ga.



Although her liver transplant was failing, this patient (seated) visited the Core Lab. She recently had a second transplant and is doing well. The lab staff surprised her with flowers.

Dear Patient Safety Focus Editors,

I was wondering if your publication would be interested in including a poem some time? Anyone who has worked in a clinical lab for very long has probably experienced the feelings that I wrote about in this poem.

Unlike smaller hospital labs, the techs here almost never interact with patients; the phlebotomy staff does. On extremely hectic days, not surprisingly, our relationship with the nursing staff can be strained.

The poem speaks to the human side of being in the healthcare profession and reminds us of the reason we, techs and nurses, are in our respective fields. And yes, sometimes it hurts.

Sincerely,



Thomas Cantolini
Medical Technologist
NorDx Laboratory
Maine Medical Center
Scarborough, Maine

I knew her just enough

By Thomas Contolini

late December — gray —
cold rainy windows:
lab computer data /
rows of numbers —
to measure a child’s life
this way / to watch her
fade
an increment at a time:
calling — critical — results —
nine; I think,
her age; I forget.
hard to hear the nurse’s voice
above the analyzer’s drone —
I recall the little girl’s name on
other tubes / other days / too
many days /
to be here now and know
how she spent
herself
fighting the unwinnable fight:
yet I never got to hold her /
never looked into her eyes;
but I knew her —
I knew her **just** enough to hurt
when the voice said she
(expired).



A grateful lung transplant patient (dark jacket) poses with the happy staff of the molecular lab.

The Scarcity of Peer-Reviewed Literature on QI in Laboratory Medicine



Can the Bias Against Publishing be Broken?

If specimen loss is such an important quality improvement issue, why is there such a scarcity of peer-reviewed medical literature on the topic?

BY FREDERICK STRATHMANN, PHD

As scientists, we have been taught to follow up on new experimental results and hypotheses by performing a thorough search of the published literature. Knowledge of the literature can reduce the repeating of experiments, help hone ideas, and provide a needed perspective on how a new finding fits into a field of study. Unfortunately, laboratorians interested in how to improve quality by reducing specimen loss find that there is not much to read on the subject in the peer-reviewed literature.

To illustrate this point, I conducted a literature search using the term “specimen loss” on Pubmed (www.ncbi.nlm.nih.gov/pubmed/), a common first stop for literature searches. On February 5, 2010, only four articles matched this exact search phrase. One article compared methods of the specimen loss rate during macular hole surgery (1), and two papers reported on the loss of specimens during biopsy procedures (2, 3). The last publication detailed problems with specimen loss in a longitudinal study of beef cattle (4). In contrast to the paucity of literature on specimen loss, 64,383 articles matched the search phrase “method validation”, 31,219 articles matched “cardiac marker”, while 512 articles turned up using “vitamin D mass spectrometry” as the search term. While it is clearly important to validate laboratory methods, investigate cardiac markers, and explore the pros and cons of various methods to measure vitamin D, why are there so few peer-reviewed journal articles on specimen loss?

I believe there are three major reasons why a variety of quality improvement (QI) topics like specimen loss are neglected in the medical literature. First, clinical laboratory directors, both in academic and nonacademic settings, prefer to conduct research on other topics, especially those involving analytic methods or clinical use of tests. Second, risk management officers may block or slow down the publication of the QI data because they fear the institution could suffer a financial loss or damage to its reputation. Finally, laboratory direc-

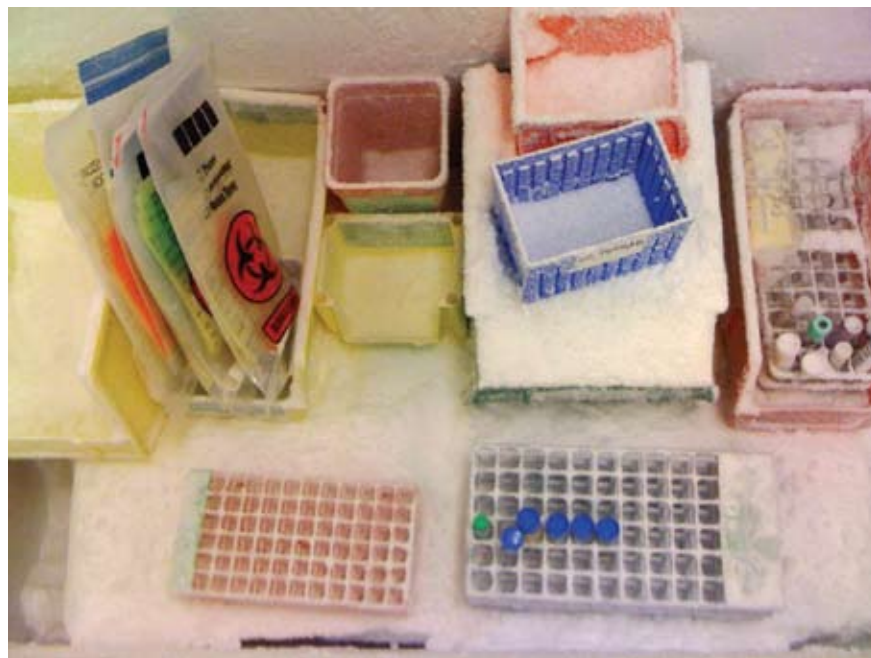
tors themselves may fear revealing QI data due to the prospect of losing their job or damaging their reputation.

The Law of Supply and Demand

It is fair to assume that to some degree the principle of supply and demand is a contributing factor to the limited amount of research on the subject of specimen loss. In this context, demand is determined by comparing the number of laboratorians engaged in QI projects or research versus those working on method development or validation. Supply would refer to the available number of QI projects versus those dealing with method development or validation. In general, on both the supply and demand side, laboratorians favor research on analytic methods and clinical use of tests over QI-related topics. In academic settings, longstanding trends in research funding perpetuate this situation by discouraging academic faculty from investigating how laboratories deliver healthcare.

The Other Factor: Fear

Interest, or lack thereof, is not the only reason for the scarcity of published data on specimen loss. Given the current focus on patient safety, it is not surprising that lab directors and their institutions are hesitant to reveal their specimen loss data. Within healthcare organizations, the primary goal of the risk management system is to reduce and control risk associated with the day-to-day activities of the institution. An unfortunate side effect of this goal is the reluctance to publish QI results. Typical risk management questions include: 1) What good can come from publishing how often we lose or destroy specimens? 2) Even if we de-identify our institution, won't readers be able to determine where the data is coming from based on the authors' institutional affiliations? 3) Will our competitors use the data to represent us in a negative light? 4) Will patients and their lawyers use the data to sue us? Similar questions haunt individual lab directors as they assess the possible damage to their careers if they publish QI



A common place to lose specimens in the clinical laboratory.

data. The end result is that very little such data are published.

Totally Accurate?

Another important factor concerning publication of specimen loss data is its accuracy. In order to publish such data, the laboratory actually must know its current specimen loss rate and, if such a measure is in place, staff also must be confident about its accuracy. The concept of accuracy can quickly become a gray area because definitions of specimen loss tend to be laboratory specific. Some laboratories narrowly define loss to mean simply the physical loss of a specimen, while others include situations where the lab compromised, and therefore failed to analyze, what was essentially a perfectly good specimen.

With an accepted definition in place, implementing a metric for specimen loss is conceptually quite simple; however, ensuring its accuracy remains a challenge. For example, in most institutions, tracking all the processes involved in the “specimen life cycle”—the point at which the specimen is taken from the patient to final result reporting—is a complex task spread across multiple areas of the organization.

Change Ahead?

It is unlikely that the topic of specimen loss will ever be as attractive to researchers as developing and validating the next great laboratory test. Nor will this QI subject suddenly result in a comparable number of studies as those on applying the latest technology to a clinical question. After all, a classic method validation project, especially one dealing with an automated laboratory instrument, is typically straightforward and well-suited for a transitory trainee in the lab. In contrast, projects related to specimen loss are often hard to define, difficult to accurately measure, and not easily executed into the time allotted for a typical laboratory research project.

Hopefully, as the application of disciplined problem solving methods like Lean/Six-Sigma spread to all areas of the lab, there will be an expansion of the peer-reviewed, scientific literature on specimen loss and other aspects of QI. Undoubtedly, this expansion will be a helpful resource to laboratory directors whose primary focus is QI and patient safety.

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Learning about Specimen Loss from Related Literature

Helpful literature on topics related to specimen loss does exist and can be found with some patience, a favorite Internet search engine, and a discerning mind. Such information can be valuable to anyone interested in measuring, improving, or understanding the concept of specimen loss in the clinical laboratory. For example, useful information can be gained by reading about the application of radio frequency identification (RFID) technology to the complex process of specimen and asset tracking both within and outside of clinical settings (5–7). Though RFID in-and-of-itself is not a final answer to the issue of specimen loss, reports of successful RFID applications in various health- and non-healthcare environments can be used to jumpstart the mental processes needed to address loss at the level of the individual, laboratory specimen.

How Can Labs Benefit From Implementing 'Forcing Functions'?

BY KAREN APPOLD

Forcing functions are an aspect of a design that prevents a target action from being performed or allows its performance only if another specific action is performed first. For example, automobiles are now designed so that the driver cannot shift into reverse without first putting her foot on the brake pedal.

But the concept doesn't necessarily have to involve device design. For instance, one of the first forcing functions identified in healthcare was the removal of concentrated potassium from general hospital wards. This action was taken to prevent inadvertent preparation of intravenous solutions with concentrated potassium, an error that has produced small but consistent numbers of deaths for many years (1).

Other examples of forcing functions

include lockins, lockouts, and interlocks. Lockins maintain a condition and prevent easy exit from a sequence of actions until the right conditions are met. Lockouts prevent easy entrance to a dangerous set of actions or a segment of software without the proper conditions and access authority. Interlocks enforce correct sequencing or isolate events in time; often they are used to prevent one action from being taken while another is already active (2).

John Gosbee, MD, human factors engineering and healthcare specialist at Red Forest Consulting LLC in Ann Arbor, Mich., says that implementing forcing functions in the lab can offer many safety benefits. Putting a hard stop interlock system in place that does not allow a centri-

fuge to open until it has stopped spinning or until it has finished heating up or cooling down is one example of a useful force function. Another example would be to design a forcing function that requires a tube to be filled to a certain level in order for the specimen to be analyzed.

Forcing functions can also be applied to computer systems, Gosbee notes. One example would be a computer system that doesn't allow the user to quit without first saving or transmitting data. Another would be an analytical device that can't be shut off until it reports data in some manner, such as printing it out or sending it to the laboratory information system.

However, for more creative and practical solutions that involve forcing functions, the best source is your lab's staff. They have

the knowledge and experience to make a difference.

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How Executive Walk Rounds Can Improve Your Lab's Safety Culture

BY KAREN APPOLD

The focus on patient safety across the country has hospitals looking at all facets of their operating procedures. One practice being used to shed light on problems is known as executive walk rounds. This rather simple concept, in which the institution's executive leaders visit patient care areas or ancillary services like the lab, allows executives to engage care providers and discuss safety concerns on the front lines of patient care. Although largely unproven as a method for improving safety culture, growing numbers of hospitals are instituting the practice.

One of the first reports of executive walk rounds was published in 2005. The study targeted more than 20 clinical units and looked at the impact of the practice on perceived safety climate. Results from an established survey tool suggested a positive effect on nurses' attitudes about the safety climate. The authors concluded that greater implementation of executive walk rounds might serve as an important tool to improve safety culture and, ultimately, patient safety (1).

But when it comes to patient safety improvement initiatives, more often than not, laboratorians must choose between taking an evidence-based approach versus a practical one. How should laboratory professionals choose various interventions and what should hospital leaders target for implementation? Some experts advocate for a "balanced diet" approach, combining momentum-generating projects like executive walk rounds and important practices with strong evidence, such as prevention of catheter-related blood stream infections or system-level interventions like computerized physician order entry (2).

Kaveh G. Shojania, MD, director of the University of Toronto Centre for Patient Safety, Canada Research Chair in Patient Safety and Quality Improvement, and associate professor of medicine at the Uni-

versity of Toronto, offered insight on how executive walk rounds can be applied to the clinical lab setting. "The goal of an executive walk round in a lab would be to identify problems that front-line technologists face and to engage management in solving them. In a lab setting, this would entail either having hospital executives tour the lab or, if the lab is large enough, having the lab director tour each section of the lab with the director of that area in addition to a senior technologist."

The keys to program success are the active role of an executive advocate and the willingness of staff to openly discuss safety issues on their unit. Regular meetings between the advocates and the units should provide a forum for enhancing executive awareness, increasing staff confidence and trust in executive involvement, and swiftly and effectively addressing areas of potential patient harm. "Topics could range from safety or quality issues to efficiency problems, particularly because gains in efficiency can often have safety or quality benefits," explained Shojania. "Resolving efficiency or issues faced by technologists will improve the morale and hopefully the lab's culture."

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A hospital executive takes notes before engaging lab staff on executive walk rounds.

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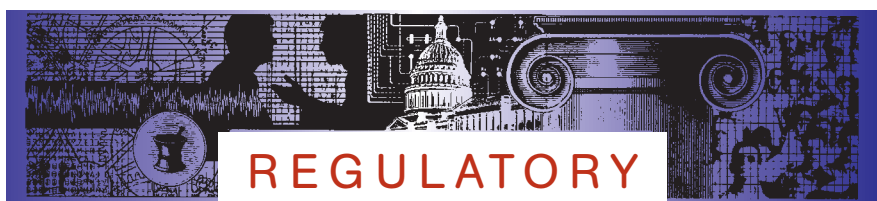
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NIH and FDA to Collaborate On Regulatory Science

FDA and NIH announced a first-of-its-kind collaboration designed to speed new drugs, tests, and devices through the regulatory process. The initiative aims to incorporate both translational science—the shaping of basic scientific discoveries into clinical use—and regulatory science, defined as the tools and standards to efficiently evaluate a product's safety, efficacy, and quality.

One subject FDA wants help on from NIH is personalized medicine, said FDA Commissioner Margaret Hamburg at a recent event hosted by the Personalized Medicine Coalition. "New approaches to the drug development paradigm are needed such that new drugs are developed along with the tests that inform their use," she said. "New designs for clinical trials are needed so that genetics or other markers can be used to assist in patient selection, and both clinicians and patients need to be educated so that we can actually see personalized medicine move from concept to practice. As a foundation to this all, we must ensure that FDA has the scientific knowledge, tools, and standards needed to regulate these novel products—often combination products. This is an important component of our new initiative in regulatory science."

As part of the effort, the two agencies will establish a Joint NIH-FDA Leadership Council to spearhead collaborative work on important public health issues. The Joint Leadership Council will work to help

ensure that regulatory considerations are integrated in biomedical research planning, and vice versa.

In addition, NIH and FDA will jointly issue a Request for Applications, making \$6.75 million dollars available over 3 years for work in regulatory science. The research supported through this initiative should add to the scientific knowledge base by providing new methods, models, or technologies that will inform the scientific and regulatory community about better approaches to evaluating safety and efficacy in medical product development.

A public meeting will be held in the spring to solicit input on how the agencies can work better together. More information about the new collaboration is available on FDA's website, www.fda.gov/ScienceResearch/SpecialTopics/RegulatoryScience.

Report: Electronic Personal Health Information Exchanges Working

After studying four health information exchanges (HIE), the Government Accountability Office (GAO) reported that these entities are generally following practices that protect patient privacy, including limiting disclosure of information, securing electronic information that they store and transmit, and helping ensure accountability for safeguarding electronic personal health information. GAO also found that sharing electronic personal health information about patients has had a positive effect on the quality of care delivered to patients.

HIEs are electronic networks that allow sharing of electronic health records among

providers in a geographic area, such as an entire state or a metropolitan area. The HIEs that GAO studied reported that they implement disclosure practices that reflect widely accepted standards for safeguarding personal information—called the Fair Information Practices—to help ensure the appropriate use and disclosure of electronic personal health information for treatment purposes. For example, some providers in the study require direct interaction with patients, such as informing patients of the use and disclosure of personal health information and providing patients access to their own records. Some providers also inform patients that their electronic personal health information may be shared through HIEs.

The HIEs reported that although they have not conducted formal studies or evaluations of the overall effect of electronically sharing personal health information, both the exchanges and providers provided examples of ways that quality of care was improved, such as more quickly reporting abnormal laboratory results and directly linking hospitals to their state's department of health for real-time reporting.

The report is available from GAO's website, www.gao.gov/new.items/d10361.pdf.

Large Recovery Act Awards Aim to Speed Health IT

Health and Human Services (HHS) Secretary Kathleen Sebelius and Labor Secretary Hilda Solis announced a total of nearly \$1 billion in awards from the American Recovery and Reinvestment Act of 2009 (ARRA), aimed at helping health-care providers adopt the so-called "meaningful use" of health IT and train workers for healthcare jobs.

According to HHS, the awards will help make health IT available to more than 100,000 hospitals and primary care phy-

sicians by 2014. The funds are targeted at growing the emerging health IT industry, which is expected to support tens of thousands of jobs ranging from nurses and pharmacy techs to IT technicians and trainers. Hospitals and physicians in the U.S. have until 2014 to deploy comprehensive electronic health records (EHR) to meet federal guidelines. If they get started sooner, extra reimbursement is available to those who are up and running in 2011.

Of the more than \$750 million investment, \$386 million will go to 40 states and qualified State Designated Entities to facilitate health information exchanges (HIE) at the state level, while \$375 million will go to an initial 32 non-profit organizations to support the development of regional extension centers (RECs) that will aid health professionals implement and use health IT. Additional HIE and REC awards are to be announced in the near future. RECs will provide outreach and support services to at least 100,000 primary care providers and hospitals within 2 years, according to HHS.

In addition, more than \$225 million in Department of Labor grant awards will be used to train 15,000 people in job skills needed to access careers in healthcare and IT through existing partnerships with local employers. The recipients of these grants have already identified roughly 10,000 job openings for skilled workers that likely will become available in the next 2 years. Employment services will be available via the Department of Labor's local One Stop Career Centers, and training will be offered at community colleges and other local education providers.

Additional information about the state HIE and RECs may be found at <http://HealthIT.HHS.gov/statehie> and <http://healthit.hhs.gov/extensionprogram>. Information about other health IT programs funded through ARRA can be found at <http://HealthIT.HHS.gov>

Information about Healthcare/High Growth Grants, and other DOL training programs is available at www.doleta.gov/.

AACC and AMP Present

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This course is being presented by:
The American Association for Clinical Chemistry (AACC)
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Experts in the field will give presentations on the role of molecular testing in:

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- Infectious diseases
- Pharmacogenetics
- Laboratory regulations
- The future of laboratory medicine

In addition to the presentations and lively question-and-answer sessions, there will be opportunities for interacting with laboratory colleagues and exchanging thoughts and suggestions.

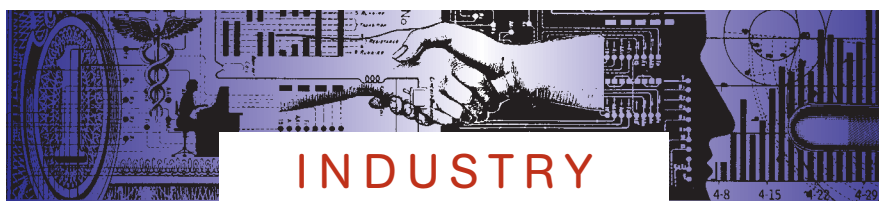
The Hyatt Regency Atlanta (just 12 miles from Hartsfield-Jackson International Airport), is close to several attractions, including Peachtree Center Mall, Georgia Aquarium, Georgia World Congress Center, CNN Center, Phillips Arena and the Georgia Dome.

Next Month in CLN

New Guidelines for Gestational Diabetes

Blood Glucose Meter Controversy

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INDUSTRY

Abbott, GlaxoSmithKline to Develop Test for Skin Cancer Drug

Abbott and GlaxoSmithKline announced that they will jointly develop and commercialize a molecular diagnostic test to aid in selecting patients who may benefit from a skin cancer treatment being developed by GlaxoSmithKline. The companies plan to develop a PCR test for use on Abbott's m2000 automated molecular instrument system that will detect MAGE-A3, a tumor-specific antigen expressed in skin and other cancers, but not normal cells.

GlaxoSmithKline's MAGE-A3 antigen-specific cancer immunotherapeutic is being evaluated as an adjuvant treatment for melanoma in a Phase III clinical study. Patients must have MAGE-A3 expressing melanoma tumors to be eligible for the treatment. Previously, the companies announced a similar arrangement involving the MAGE-A3 marker in non-small-cell lung cancer. "This is an exciting continuation of our important collaboration," said Stafford O'Kelly, head of Abbott's molecular diagnostics business. "The agreement is indicative of our commitment to personalized medicine and our focus on developing innovative companion diagnostic tests that can be used to identify patients most likely to benefit from specific cancer therapies."

US Oncology, Baylor Health To Launch Lab Joint Venture

US Oncology and Baylor Health Care System have formed a joint venture to operate a molecular diagnostics lab with a particular emphasis on validating the clinical utility of pharmacogenetic and companion diagnostic tests. The joint venture has leased a 172,000 square foot facility in Lewisville, Texas, and plans to employ more than 200 people by the end of this year, and more than 900 by 2014. Other investors in the \$25 million collaboration include Pathologists Biomedical Laboratories and Texas Oncology. For now the venture is being called NewCo, pending the outcome of a branding campaign to select the final name.

GenomicVision Receives Grant To Develop FSHD Test

Genomic Vision, a biotechnology company in Paris focused on nanotechnology-based DNA analysis, has signed an agreement with and received a €250,000 grant from the Association Française contre les Myopathies to optimize and validate a diagnostic test for facio-scapulo-humeral dystrophy (FSHD), the third most prevalent form of muscular dystrophy. The test uses Genomic Vision's molecular combing technology, which enables individual sections of single DNA molecules to be visualized directly. Genomic Vision has been

working to develop the test with the Université de la Méditerranée and the Timone Hospital in Marseille.

License Agreement Signed for Antibodies to Group 1 Influenza

Boston-based Dana-Farber Cancer Institute and Sanford-Burnham Medical Research Institute in LaJolla, Calif. have

signed a license agreement with Roche and its wholly owned subsidiary, Genentech, that grants the companies exclusive rights to manufacture, develop, and market human monoclonal antibodies to treat and protect against group 1 influenza viruses, which include the current seasonal and H1N1 strains. Researchers at Dana-Farber, Sanford-Burnham, and CDC first reported discovery of the antibodies in February 2009. The antibodies attach to the stem region of viral proteins rather than the head region—the target of current influenza vaccines—and appear to prevent changes in the protein that are necessary for viral entry into the host cell. Terms of the agreement were not disclosed, but Dana-Farber

and Sanford-Burnham will receive license fees and may receive milestone payments and royalties if treatments or diagnostics result from the antibodies.

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DIAGNOSTIC

Procalcitonin-Guided Strategy Reduces Antibiotic Use in ICUs

New research indicates that a procalcitonin-guided strategy to treat suspected bacterial infections in intensive care unit (ICU) patients reduced antibiotic exposure with no apparent adverse outcomes (Lancet, 2010; 375:463-74). This strategy could help curb the growing rate of antibiotic resistance, according to the authors.

The study involved 621 patients in eight ICUs who had suspected bacterial infection at admission or during their ICU stay. Patients were randomized into either control or treatment arms, with those in the treatment arm receiving antibiotics based on procalcitonin levels established in predefined algorithms, subject to physician discretion. At procalcitonin levels ≥ 1 $\mu\text{g/L}$ or between ≥ 0.5 and < 1 $\mu\text{g/L}$, antibiotic use was strongly encouraged or encouraged, respectively; at concentrations ≥ 0.25 and < 0.5 $\mu\text{g/L}$ and

< 0.25 $\mu\text{g/L}$, antibiotics were either discouraged or strongly discouraged, respectively. For patients in the control group, physicians received a reminder about the recommended length of antimicrobial treatment of the most frequent types of infections. However, in both groups, drug selection and final decision to start or stop antibiotics was left to the treating physician.

After treatment arm subjects began receiving antibiotics, investigators used serial serum procalcitonin measurements to guide antibiotic discontinuation. Physicians were encouraged to discontinue antibiotics when procalcitonin concentration was $< 80\%$ of the peak concentration or when the patients had an absolute concentration of < 0.5 $\mu\text{g/L}$.

The investigators found that patients in the treatment arm had significantly more days without antibiotics than those in the control group, reflecting an absolute mean difference of 2.7 days and an estimated 23%

relative reduction in antibiotic exposure. In addition, there was no significant mortality difference between the two groups.

Recommended Tests Not Performed for Antipsychotic Therapy

FDA warnings issued in 2003 about the need to monitor glucose levels in patients taking second-generation antipsychotic (SGA) drugs who have an established diagnosis of, risk factors for, or symptoms of diabetes "appear to have had no detectable effect" on glucose or lipid testing rates in a Medicaid population analyzed as part of a recent study (Arch Gen Psychiatry 2010;67:17-24). The findings underscore that "more effort is needed" to ensure that patients who receive this class of drugs are screened and monitored for potential adverse drug events, according to the authors.

In late 2003, FDA required a label change on SGAs describing an increased risk of hyperglycemia and diabetes, and compelled drug manufacturers to mail letters to healthcare providers informing them of the warning. Concurrently, the American Diabetes Association (ADA) and American Psychiatric Association (APA) issued a consensus statement that described the metabolic risks of SGA drugs and outlined a monitoring protocol for patients taking the medications.

In the newly published paper, researchers conducted a retrospective analysis of claims data for 109,451 Medicaid patients who had a new prescription claim for an SGA drug, either before or after the FDA warnings and ADA/APA consensus statement. The investigators compared testing rates in a control cohort of 203,527 patients who started on albuterol therapy but not SGA medications. The goal of the study was to determine whether glucose and lipid testing increased for this population of patients and whether prescribing patterns shifted to drugs with lower metabolic risk after the warnings.

The study indicated that before the warnings were issued, only 26.9% and 10% of patients initiating SGA therapy had baseline serum glucose and lipid testing performed. Patients who continued SGA medications did not have higher rates of testing than those who initiated therapy. Further, testing rates in SGA-treated patients were similar to those in the control group, despite the well-characterized increased risk of diabetes and cardiovascular disease in patients taking SGA medications.

Reference Values Established For CSF WBC Count in Infants

Researchers at Children's Hospital of Philadelphia have developed age-specific cerebrospinal fluid (CSF) white blood cell (WBC) count reference values for neonates and young infants that can be used to interpret accurately the results of lumbar puncture (Pediatrics, 2010;125:257-64). The analysis addressed important methodological limitations in the few studies aimed at determining reference ranges in this population, and by using PCR testing was able to detect and exclude from the study children with CSF positive for en-

terovirus, who had not been excluded from other studies.

Reference values for CSF WBC in infants have been based on mostly older children considered healthy after initial evaluation for central nervous system infection. A limited number of studies looked at patients ≤ 56 days but did not exclude those with traumatic lumbar puncture, seizures, sepsis, and other conditions that might affect the reference ranges. This retrospective analysis included 380 infants ≤ 56 days old who presented to the emergency department with an indication for lumbar puncture and who did not meet exclusion criteria from the study, such as having CSF positive results for enterovirus by PCR.

Infants who were 0-28 days had a median CSF WBC count of 3/ μL with a 95th percentile value of 19/ μL . In contrast, infants 29-56 days had a statistically lower median CSF WBC count of 2/ μL with a 9/ μL 95th percentile value.

Proteinuria Enhances eGFR Risk Prediction

A study by Canadian researchers indicates that higher levels of proteinuria independently increased the risks of death, myocardial infarction (MI), and progression to kidney failure at a given level of estimated glomerular filtration rate (eGFR) (JAMA 2010;303:423-429). The findings are significant because current guidelines for the classification and staging of chronic kidney disease (CKD) are based on eGFR without specifically considering the severity of coexisting proteinuria. The study also suggests that simple dipstick urinalysis adds "considerable prognostic information" to eGFR alone, according to the authors.

The study involved 920,985 adults in Alberta, Canada, who had at least one outpatient serum creatinine and proteinuria measurement, respectively, and who were not receiving kidney dialysis or had not had a kidney transplant at baseline. The researchers estimated index eGFR based on baseline serum creatinine measurements using the Modification of Diet in Renal Disease Study equation. Proteinuria was determined by either urine dipstick or albumin-creatinine ratio (ACR). Median follow-up time was 35 months.

The researchers found that age-adjusted rates of MI, death, doubling of serum creatinine, and renal replacement therapy all were increased at lower levels of eGFR but at heavier proteinuria. However, the difference in risk associated with moderate or heavy proteinuria versus no proteinuria was clinically relevant in every eGFR stratum and for all four outcomes. For instance, patients with heavy proteinuria but normal eGFR appeared to have worse clinical outcomes than those with moderately reduced eGFR but no proteinuria.

In addition, although ACR generally is favored over dipstick urinalysis for assessing CKD, the researchers found that the magnitude of excess risk associated with heavy proteinuria appeared similar whether assessed by dipstick or ACR. This suggests that dipstick urinalysis is a valid alternative to ACR for stratification, particularly in resource-limited settings.

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NEWS FROM THE FDA

Tensions Rise in Buildup to IOM Report on FDA 510(k) Process

Although not due out until 2011, the forthcoming report on FDA's 510(k) regulatory process from IOM is already raising the pressure on the agency from both sides in the debate, as test and device manufacturers worry about more demanding regulation while others within and without FDA push for more dramatic changes. Both FDA and IOM recently held public meetings to discuss the fate of 510(k)s, and FDA officials hinted at their meeting that they were not going to wait for the IOM report to start tweaking the 30-year-old program that reviews upwards of 90% of tests and devices on the market.

Representing manufacturers whose tests and devices fall under the purview of the 510(k) system, also known as premarket notification, the Advanced Medical Technology Association (AdvaMed) released a statement saying that it hopes the IOM analysis will "underscore the strengths of FDA's current regulatory approach." AdvaMed pointed out that while the 510(k) system has been characterized as a "fast track" for moderate- and low-risk tests and devices, FDA considers specifications and performance testing information, including, in many cases, clinical data, before the agency determines whether a device can be made available for patients, and that the length of review is determined by FDA and based on potential impact to public health and on technological complexity.

Among other issues, FDA officials spoke extensively at their public meeting about how predicate devices are used in the current regulatory scheme. These are the tests or devices to which a manufacturer must prove "substantial equivalence" as part of 510(k) review. FDA noted that companies sometimes reference a "lowest common denominator device" as the predicate. To improve the system, the agency said it will consider releasing data about cleared devices and try to eliminate the use of very outdated devices as predicates.

An archived video webcast of the FDA meeting is available from the FDA website, www.connectlive.com/events/fda021810/.

Calibration Verifiers Cleared

DiaSorin announced FDA clearance for its LIAISON N-TACT PHT calibration verifiers. The calibration verifier set is a four-level control set which can be used to meet CLIA requirements for calibration verification in labs. The set is intended for use in the quantitative verification of calibration of reportable range when performed on the LIAISON analyzer. The set is not intended for use as routine quality control materials or as calibration materials.

FDA Approves Anti-HBs Assay

Ortho Clinical Diagnostics announced approval of its VITROS Anti-HBs assay. The approval is for revision of the intended use to include use of the VITROS 5600 Integrated System and VITROS 3600 Immunodiagnostic System with the VITROS Immunodiagnostic Products Anti-

HBs Assay. The assay is indicated for the quantitative in vitro determination of total antibody to hepatitis B surface antigen (anti-HBs) in human serum using the VITROS ECI/ECiQ Immunodiagnostic Systems, the VITROS 3600 Immunodiagnostic System and the VITROS 5600 Integrated System. Assay results may be used as an aid in the determination of susceptibility to hepatitis B virus (HBV) infection for individuals prior to or following HBV vaccination, or where vaccination status is unknown. Assay results may be used with other HBV serological markers for the laboratory diagnosis of HBV disease associated with HBV infection.

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