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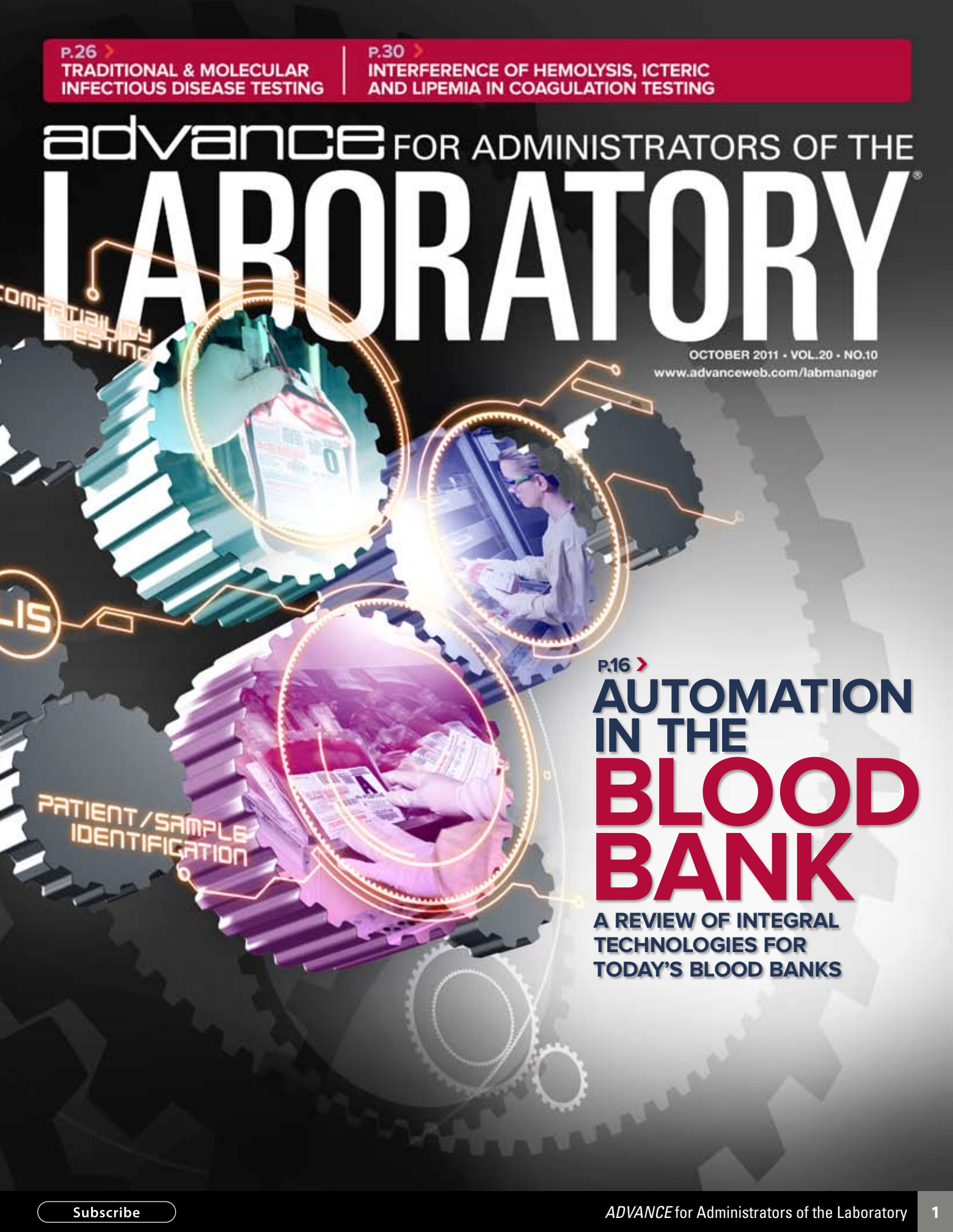

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AUTOMATION IN THE BLOOD BANK

A REVIEW OF INTEGRAL TECHNOLOGIES FOR TODAY'S BLOOD BANKS

ADVANCES IN TESTING FOR CRC

New laboratory tests for colorectal cancer diagnosis offer clinicians more choices when it comes to screening.

VAL COSTANZO

By Jill Hoffman

Within the medical institution, the decision to use laboratory testing for colorectal cancer (CRC) screening may come down to a clinician's philosophy about diagnosis. For Anil Rustgi, MD, T. Grier Miller professor of Medicine and chief of Gastroenterology at the University of Pennsylvania Perelman School of Medicine, the decision is firmly rooted in numbers. And the data does not give him the kind of feedback he needs for sensitivity and specificity to support broad-based use, so for now he and many of his colleagues opt for the more established colonoscopy. "It's not to say we're not interested or lack desire [in lab testing]," he says. But show him the data.

On the other hand, Charles F. Glassman, MD, FACP, founder of the NY Center for Longevity & Wellness, Pomona, NY, who has practiced general internal medicine for 20 years, began using blood-based testing as part of a CRC screening strategy as soon as the laboratory-developed testing (LDT) became available two years ago. "I'm always looking for cutting-edge testing that goes beyond the general 'What-do-we-see-with-our-eyes' kind of thing," he says.

Screening

Weighing in to clinician decisions are a series of CRC screening guidelines. The March 2009 U.S. Preventive Services Task Force guidelines[1] recommending fecal occult blood tests (FOBTs), sigmoidoscopy or colonoscopy in 50-75 year-old adults are fairly supportive of lab testing. As are the 2011 American Cancer Society (ACS) CRC guidelines[2] for tests that "primarily find cancer." The guidelines say that 50-year-old and older people should undergo yearly FOBTs, yearly fecal immunochemical tests (FITs) or stool DNA tests with uncertain intervals (with caveats recommending multiple stool take-home tests and colonoscopies to follow positive tests).

However, the ACS doesn't include lab testing under its category of tests to find polyps and cancer, opting for flexible sigmoidoscopy, double-contrast barium enema or CT colonography every five years (all with caveats) or colonoscopy every 10 years. A 2008 joint guideline from the U.S. Multi-Society Task Force on Colorectal Cancer, ACS and American College of Radiology[3] mimics the ACS guidelines.

FOBTs, FITs

Physicians opting for lab testing can utilize FOBTs to detect hemoglobin in the stool via a card-based assay as part of a strategy to screen for pre- or cancerous polyps or cancer. A color change in the assay indicates evidence of blood. Some products are established in the market; the Hemoccult family of FOBTs from Beckman Coulter has been manufactured/distributed for 30 years. Sensitivity of FOBTs is heightened by doing samples over several consecutive days, although specificity can be affected by dietary factors such Vitamin C and iron that can potentially cause false positives.

Quantitating hemoglobin is another lab test option. The FIT test is believed to

be more sensitive and specific than some FOBT methods, but tends to be more costly.

DNA Testing

Within human stool samples are millions of bacterial DNA. A lab can extract human DNA and perform molecular testing to look for mutations in genes that also appear in polyps and/or cancer, or changes in gene patterns due to methylation or "microsatellite instability."

"Using a panel of these molecular assays, one can come up with a good test performance," Dr. Rustgi says.

Blood-based Testing

In 2009, Quest Diagnostics released the first U.S. blood-based, molecular diagnostic LDT—ColoVantage—measuring levels of the circulating marker methylated dicptin 9 in plasma.

"The plasma-based approach overcomes a lot of barriers to screening," says Jay G. Wohlgemuth, MD, vice president of Science and Innovation, Quest Diagnostics. "In the case of colonoscopy it's a procedure people have a fear of. With the fecal occult methods, there's just a general aversion people have to doing that."

Dr. Glassman recommends his patients get the ColoVantage test if they are contraindicated for or refuse to get a colonoscopy, since he has found his patients are more likely to get a colonoscopy if the blood test indicates a possible problem. The biggest down side to the ColoVantage for Dr. Glassman is having to send out the frozen sample. "Certainly it's not perfected yet; there are things that we have to be careful about—whether it's false positives or false negatives, but overall I think it's a great adjunct to what we have now," he says.

Hereditary CRC

The May 2010 issue of *Gastroenterology* says individuals with hereditary nonpolyposis colorectal carcinoma fall into two categories—Lynch syndrome associated with hereditary defects in DNA mismatch repair (MMR) and familial colorectal cancer type X

with no detectable mutation in DNA MMR genes.[4]

A technology called DNA combing, in development by Quest Diagnostics and Genomic Vision, may detect mutations in genes missed by traditional DNA technologies, which would be particularly helpful for patients with hereditary cancers.

EGFR

Among patients with stage III colon cancer, some have epidermal growth factor receptor (EGFR) abnormalities driving cancer by complex pathways involving signaling molecules (such as *RAS* and *PI3K*), impacting how their late-stage cancer responds to certain therapies.

"So if someone's going to embark upon EGFR [therapy], the *RAS* mutation status should be checked in the tumor, and that can be done routinely," Dr. Rustgi says.

Dr. Wohlgemuth adds that *KRAS, BRAS, NRAS* and *PI3K* are "pretty well clinically validated."

Traditional vs. New

Noting that colonoscopy has superior sensitivity and specificity over lab methods, Dr. Rustgi says he would need to see more conclusive data before applying molecular, stool- or blood-based approaches to the average-risk population. "These things need to be evidence-based before launching into them because we're not talking about a discrete focus population here, we're talking about millions."

Alternatively, Dr. Glassman continues to implement new lab technologies to add to his knowledge about a patient's condition, with less concern for institutional or peer validation of the tests.

"It's very comfortable for us to fall back to what we're familiar with," he says. "If we see a problem or someone has a symptom or there's blood in the stool or we do a colonoscopy and see a polyp, that's when we think something must be wrong, but there are different processes that go on in our bodies all the time. If a cancer is large enough yet still small enough, there's certain molecular changes in that tumor, and blood-based tests/biomarkers may be able to pick that up much sooner than the actual polyp getting to a point where you can excise it. I think blood-based biomarkers are the wave of the future, and there are a lot available that doctors just don't know about because they're not up to date with the literature or are afraid to explore." ■

Jill Hoffman is managing editor.

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