G2 INTELLIGENCE

Diagnostic Testing & Emerging Technologies

New Trends, Applications, and IVD Industry Analysis

Issue 12-13/December 2013

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Inappropriate Test Ordering Practices Driving Health Care Costs

Unnecessary ordering of tests and inappropriate bundling of tests is contributing to an increase in health care costs, asserts a health care expert in a recent editorial published in a major medical journal.

"'What is the biggest driver of health care costs in the hospital?' Answer: the physician's pen," writes Cheryl Bettigole, M.D., chief medical officer at Complete Care Health Network in New Jersey, in a perspective piece published in the Oct. 17 issue of the *New England Journal of Medicine*. "A mouse or a keyboard, rather than a pen, now drives the spending, but we physicians and our staff are responsible for ordering these unnecessary tests and hence responsible for the huge bills our patients are receiving. Yet we are not doing this alone. Laboratories have learned that one easy way to increase revenue is to make it easy for clinicians to order more tests."

As an example Bettigole cites a single-vial women's health test being "heavily marketed" that takes a cheap, cost-effective Pap test previously priced at $20 to $30 and makes it "a four-figure budget item." Without alerts, checking the Pap box in an electronic record may lead to unnecessary testing for human papillomavirus as well as for tests for multiple infections that would rarely have been ordered.

Given the increasing cost-consciousness of health care consumers, providers are being called on not only to be good stewards of limited health care resources, but also to understand the financial effects that ordering tests has on patients. For more information on the increasingly cost-conscious consumer, please see *Inside the Diagnostics Industry* on page 5.

Electronic Laboratory Reporting Advancing, But Greater Adoption Needed

Two recently published studies indicate that electronic laboratory reporting (ELR) is substantially penetrating laboratory and physician workflow, although much more needs to be done to reach meaningful use stage 2 goals. ELR holds promise for both improving the quality of individual clinical care and speeding the nation's response to infectious disease outbreaks.

State and local public health departments have made substantial progress in ELR in recent years. The number of state and local health departments receiving electronic reports from laboratories has more than doubled since 2005, with 54 state and local public health departments now receiving

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▲ **Electronic Laboratory Reporting Advancing,** *from page 1*

laboratory reports electronically, compared with 26 in 2005, according to a Sept. 27 study in *Morbidity and Mortality Weekly Report (MMWR)*. Additionally, nearly two-thirds (62 percent) of the 20 million total lab reports received were reported electronically in 2013, an increase of 8 percent in just the past year.

"Electronic laboratory reporting can give health officials better, more timely and complete information on emerging infections and outbreaks than they have ever received before," said Robert Pinner, M.D., associate director for surveillance, programs, and informatics at the U.S. Centers for Disease Control and Prevention (CDC), in a statement. "Implementing these systems is a complex task that requires substantial investment, but ELR will provide health departments the tools they need to quickly identify and respond to disease threats and monitor disease trends now and in the future."

In addition to the Centers for Medicare and Medicaid Services' financial incentives, since 2010 the CDC has provided funding to 57 state, local, and territorial health departments through the Epidemiology and Laboratory Capacity for Infectious Diseases cooperative agreement to aid with ELR from clinical and public health laboratories to public health agencies. In this *MMWR* report monitoring ELR implementation, the CDC and state and large local health departments (Los Angeles County, Philadelphia, New York City, Chicago, Houston, and the District of Columbia) analyzed data from each jurisdiction. In total 10,400 laboratories that send reportable results to public health agencies nationwide were identified, with 52 percent of these laboratories considered priority targets.

Of all lab reports received electronically by state and large local health departments, 40 percent come from one of four large commercial laboratories, 14 percent from hospital laboratories, and 30 percent from public health laboratories.

—CDC

At the end of July 2013, 54 of the 57 jurisdictions (48 state and six large local health departments) were receiving at least some laboratory reports through ELR. However, only 28 percent of the targeted laboratories reported to at least one public health agency through ELR. Of all reports received electronically, 40 percent come from one of the four large commercial laboratories (LabCorp, Quest Diagnostics, ARUP Laboratories, and Mayo Clinic), 14 percent from the approximately 5,300 hospital laboratories, and 30 percent friom public health laboratories.

The proportion of laboratory reports received electronically varied significantly geographically. Fourteen jurisdictions received more than 75 percent of laboratory reports electronically, while nine received less than 25 percent of reports electronically. The proportion of reports received electronically also varied by disease category, with 76 percent of reportable laboratory results for general communicable diseases received through ELR, but only 54 percent of HIV and 63 percent of sexually transmitted disease reports sent electronically, even though overall reporting volumes for these conditions were higher.

"Substantial work remains, however, to achieve full and effective ELR implementation. Nearly three fourths of reporting laboratories, including half of those that are priority targets, still are not reporting electronically," writes lead author Kathryn Turner, Ph.D., from the Idaho Division of Public Health in the *MMWR* report. "Public health agencies, laboratories, and laboratory information management system vendors should work together to achieve consistent and accurate use of standardized vocabulary, to ensure that all reports are sent and that they are complete, and to reduce inessential state-to-state variability in electronic disease reporting requirements."

Office-Based Electronic Use of Laboratory Results

In a second study from the Department of Health and Human Services, researchers from the Office of the National Coordinator for Health Information Technology analyzed data from the 2011 National Ambulatory Medical Care Survey Electronic Medical Record Supplement, a nationally representative sample of more than 4,300 office-based physicians, in order to establish a better understanding of electronic use of laboratory data in private offices.

According to the study published online Oct. 23 in the *American Journal of Managed Care*, the researchers found that in 2011 roughly two-thirds (67 percent) of physicians had the ability to view lab results electronically, 42 percent were able to incorporate lab results into their electronic health records (EHR), 35 percent were able to send lab orders electronically, and only 31 percent exchanged patient clinical summaries with other providers.

Again, there was substantial variation in these numbers geographically. Electronic lab ordering ranged from 58 percent (Washington) to 19 percent (Delaware). The ability to receive lab results electronically ranged from 88 percent (Wisconsin) to 44 percent (Louisiana). Incorporating those results electronically into an EHR varied from 73 percent (Minnesota) to 21 percent (Louisiana).

As might be expected, larger practice size was significantly associated with the capability to conduct all facets of electronic lab exchange, particularly the capability to incorporate lab results into an EHR. The study noted that a substantial minority of physicians with no EHR also have electronic lab exchange capabilities, suggesting that proprietary portals continue to play in facilitating physician access lab result data. However, very few physicians without an EHR have the capability to electronically order lab tests.

Takeaway: While progress has been made in ELR both to public health agencies and in physician workflow, laboratories are far from meeting meaningful use goals.

FDA Releases Personalized Medicine Report

Next-generation sequencing (NGS)-based tests, complex laboratory-developed tests (LDTs), and companion diagnostics are all challenging the conventional regulatory process at the U.S. Food and Drug Administration (FDA).

In an October report, "Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development," the agency details how it is responding to and anticipating challenges related to review of personalized medicine (PM) products and the measures it plans to take to ensure the regulatory processes are properly suited to address these rapid innovations.

The FDA says the era of PM is definitely here and cites internal evidence that of the new drugs approved since 2011, approximately one-third included some form of genetic or other biomarker data in the submission to characterize the drug's efficacy, safety, or pharmacokinetics. Additionally, more than 100 approved drugs contain labeling information on genomic biomarkers.

"The FDA has worked to bridge developments in genomics and other relevant sciences to clinical practice by advancing the tools necessary for evaluating targeted therapeutics and bringing them to market more efficiently, collaborating in key research, defining and streamlining regulatory pathways and policies, and applying new knowledge in product reviews," the report says.

Core to the FDA's responsibilities is consideration of the benefits and risks during evaluation of medical products. The agency believes that PM should increase benefits and reduce risks for patients by improving both the safety and efficacy of therapeutics. It adds, though, that in this early stage of PM it has the additional responsibility to "provide clarity, predictability, and guidance to industry in order to help encourage development" and to identify "opportunities for streamlining regulatory processes and advancing the science and tools that will help drive innovation."

But in this time of transition, there are challenges in determining how to evaluate PM products, including appropriate evidentiary standards with an emphasis on examination of clinical trial design and statistical methods to analyze genomic data. Logistical and organizational considerations are also being reviewed to better coordinate the review of companion or combination products.

"Reviews of co-developed products pose a number of challenges to the Agency, since they require expertise from and careful coordination between the Centers to ensure consistent reviews and contemporaneous approval of the two products. Challenges stem from the co-developed products falling within the purview of multiple FDA centers each operating under different laws, regulations, systems for tracking submissions, and timelines," the report explains.

The Office of Combination Products (OCP) was created to enhance transparency, predictability, and consistency of combination product regulation and also to ensure timely approval of combination products.

What's more, the explosion of emerging evidence documenting genetic associations, and the volume of emerging diagnostics and their increasing complexity, are posing challenges to the review process. This can be seen particularly in the area of NGS-based tests and complex LDTs, where the FDA has taken a number of steps toward developing new methods for evaluating these tests.

"The Agency has since started to assess sequence-based tests using a strategy that focuses on validating the analytical performance of the sequencing platform—whether it measures what it is supposed to measure accurately and reliably and precisely," the report says. "While it will be impossible for the Agency to assess the platform's performance for every single variant, the Agency is looking at possibilities for identifying a representative set of markers that could be assessed in order to develop an understanding of the performance of the platform as a whole."

When it comes to LDTs the FDA has generally withheld enforcement, but with the "product interdependency" created by tailored treatments, the FDA has begun to reconsider its regulatory position on some LDTs, where the test results impact the ability of a specific therapeutic product to achieve its established safety and effectiveness, the agency says.

"FDA has been developing a risk-based framework for regulatory oversight of LDTs that would assure that tests, regardless of the manufacturer, have the proper levels of control to provide a reasonable assurance of safety and effectiveness, while also fostering innovation and progress in PM," says the report.

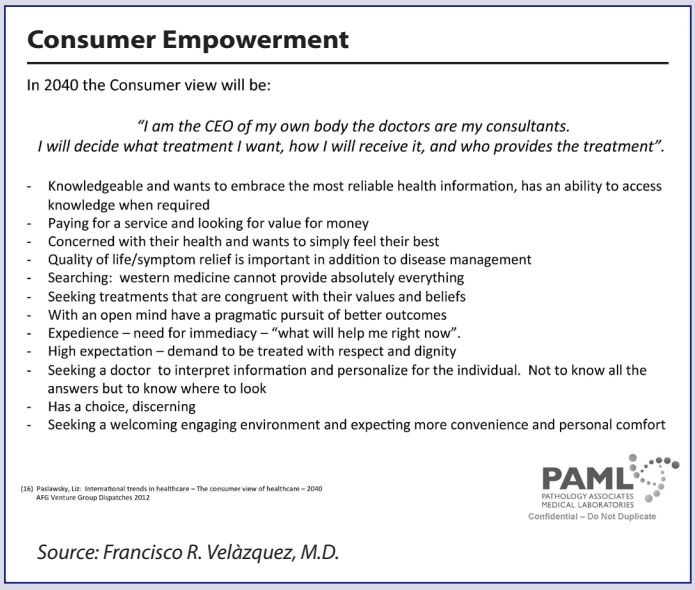
Takeaway: Advanced diagnostic testing, central to the application of personalized medicine strategies, poses a challenge to the traditional regulatory review process. But the FDA is evaluating modifications to the review processes to meet the challenges posed by these innovations.

G2 INTELLIGENCE
Inside the Diagnostics Industry

Labs Facing Increasingly Cost-Conscious Consumers

Among the emerging trends that were discussed both in speakers' presentations and among attendees at G2 Intelligence's 31st annual Lab Institute "It's Make or Break Time: A Path Forward for Labs" (Arlington, Va.; Oct. 16-18), none were so prominent as the trend of increasing consumerism in health care. The facet of this consumerization trend that is likely to most affect the laboratory and diagnostic industries is the rising cost-consciousness among both providers and patients.

"Consumerism is here, like it or not," explained Francisco R. Velàzquez, M.D., CEO of PAML (Spokane, Wash.) in a breakout session at the conference. "It is coming because we are shifting the cost to consumers. As they are being asked to pay more, they are more interested in what they are paying for. Cost will drive where they go and what we do."



Source: Francisco R. Velàzquez, M.D.

Aside from the health care system reforms driving consumerization, Velàzquez says that the push toward consumer health has been accelerated in recent years because of technology, the poor economy, and, even more broadly, a shift in the consumer base.

By the year 2040, Generation Xers will make up the majority of consumers, and their thought process in addressing health care is markedly different from the traditional mindset of older generations, who largely never questioned doctors. Velàzquez says Xers think of health care providers more as consultants, able to impart knowledge, but Xers believe providers are there to help them think about what to do, not make the ultimate decision.

"For those over 50 years old, the way we see value is perceived quality and if you are nice to me," Velàzquez says. "For those under 30 years—what do they value most? Knowledge and information, although cost matters. Health and wellness in 2013 is different than 10 to 15 years ago. It used to be that if I'm not falling apart, I must be OK. Now it is not the absence of disease. It is—am I at my peak physiological performance?"

More Skin in the Game

What underlies all of these shifts in the consumer population at large is that patients are starting to pay for an increasing share of their own health care bills. With a profound shift toward high-deductible health care plans, in part due to health care reform, Americans will no longer be shielded from the full cost of medical and laboratory bills, and they will soon face paying for a greater share of their own health care bills out of pocket than ever before with no increase in disposable income.

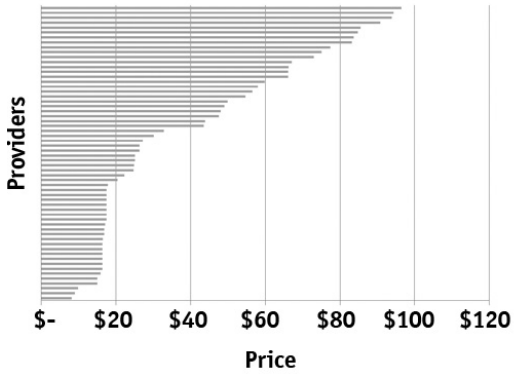
In a paper published in the Oct. 16 issue of the *New England Journal of Medicine (NEJM)*, J. Frank Wharam, from Harvard University in Boston, and colleagues

uncovered some staggering statistics quantifying the magnitude of health care-related expenses patients will soon be facing:

- In California, bronze and silver plans on the exchanges may have deductibles as high as $4,000 to $10,000 for family coverage.
- Cover Oregon estimates that cost sharing for Oregon families with incomes between 200 percent and 399 percent of the federal poverty level will include $5,000 deductibles, 30 percent coinsurance for many services even after reaching the deductible, and out-of-pocket spending maximums of $8,500 to $12,700.
- For a family of four with an annual income of just over $47,000 (200 percent of the poverty level) the highest allowable deductible plan could cause them to face out-of-pocket payments of 8 percent to 27 percent of its annual income.

With more skin in the game, experts predict consumers will rapidly become more discriminating consumers.

Price Variation: Comp Met Panel



Source: Healthcare Blue Book

"So are we seeing the dawn of a consumer-driven health care economy, in which patients undertake the same deliberations regarding medical purchases as they do when purchasing furniture or a new car?" ask Robert S. Huckman, Ph.D., and Mark A. Kelley, M.D., both from Harvard University, in a perspective piece also published in the Oct. 16 *NEJM* special issue. Many health care providers believe the answer is yes, the authors say, with consumers wanting clear, concise, understandable information regarding out-of-pocket costs.

"I have high cholesterol and I go yearly to have it checked," Jeffrey Rice, M.D., CEO of Healthcare Blue Book (Brentwood, Tenn.) tells *DTET*. "My physician switched networks, and what was normally a $20 to $30 test became a $300 test discounted to $200. If as a doctor and health care executive I was unapologetically taken advantage of, I decided I had to tell patients what I knew."

So are laboratories' worst fears of price-shopping patients going to become a reality? The answer may be yes.

Implications for Laboratories

In 2014, with the implementation of the bulk of health care reform, providers will likely see a big uptick in the number of patients inquiring about their expected out-of-pocket costs and the price of tests and other procedures. Decisions about which providers patients utilize will no doubt be motivated by cost.

"Since health care providers don't often discuss potential costs before ordering diagnostic tests or making treatment decisions, patients may unknowingly face daunting and potentially avoidable health care bills, writes lead author Peter Ubel, M.D., from Duke University (Durham, N.C.) in an *NEJM* perspective piece titled "Full Disclosure—Out-of-Pocket Costs as Side Effects." "Because treatments can be 'financially toxic,' imposing out-of-pocket costs that may impair patients' well-being [from financial strain], we contend that physicians need to disclose the financial

consequences of treatment alternatives just as they inform patients about treatments' side effects."

"There is no reason why you can't call a provider and find out how much something is going to cost," says Rice. "We have found that providers unwilling to disclose typically have bad pricing, and they are probably not the provider you want to go to."

This informational barrier is being addressed by insurance companies' and hospitals' development of online tools to better estimate patients' costs; legislation at the state level to improve price transparency; efforts by federal agencies, including the Centers for Medicare and Medicaid Services, aimed at disclosing cost variation; as well as private-sector efforts, like Healthcare Blue Book, all aimed at giving patients access to meaningful price information.

Rice advises that all providers, including laboratories, need to be prepared to answer patient price questions, and they must strategically position their services in part based on pricing.

"Unfortunately there are going to be winners and losers," Rice says. "For a patient, paying 10 times what another lab charges for the same test is not going to be a win for them. Patients will look for where they can save money. Providers must respond with thoughtful information or risk losing patient volume."

Takeaway: In 2014 the health care system will begin to feel more fully the effects of cost-conscious consumers. With the reality of a much larger share of medical bills becoming the patient's responsibility and an increasing number of measures to improve price transparency, laboratories and other providers must be prepared to respond to direct questions about the estimated costs consumer will face for testing.

Sampling of Initiatives to Improve Price Transparency

While early efforts to improve transparency in health care costs are targeting hospitals, expect the trend to continue to include laboratory test information as well.

Federal

- The Department of Health and Human Services released for the first time data sets with county-level Medicare spending and utilization information, including comparisons of the charges for the 100 most common inpatient services and 30 common outpatient services.
- The Health Care Price Transparency Promotion Act of 2013, introduced in the U.S. Congress, proposes that state Medicaid plans should require disclosure of information on hospital charges and provide individuals with information about estimated out-of-pocket costs for health care services.
- Possible expansion of Medicare's Hospital Compare Web site to include not only quality metrics, but also price data.
- Potentially requiring health plans participating in the health care marketplaces under the health care reform law to be more transparent.

State Action

According to Catalyst for Payment Reform, 34 states currently require reporting of hospital charges or reimbursement rates and more than 30 states are pursuing legislation to enhance price transparency in health care. Among these efforts:

- In August, North Carolina passed legislation requiring hospitals to provide public pricing information on 140 medical procedures and services.
- California, New Hampshire, Maine, Florida, Maryland, Oregon, and New Jersey have launched Web sites to view and/or compare data regarding hospital charges.

According to the APCD Council, nine states operate mandatory "all-payer claims databases" (APCDs), three states are currently implementing mandatory APCDs, and two states have voluntary APCDs. These statewide repositories of health insurance claims from all payers can provide invaluable price and quality information.

Private Action

- National health plans are developing transparency tools including cost calculators or estimators to allow members a better understanding of price information for various services.
- Health care transparency is a hot area within digital health and venture capitalists have invested $400 million into health care transparency startups since 2010, according to CB Insights. Among the later-stage startups benefiting from this investment are Castlight Health and GoHealth. But analysts say that startups are focusing on all facets of cost transparency including those aimed at patients, employers, providers, and even insurance companies.

Does the Marketplace Undervalue Cancer Biomarkers?

Given the known disparities in research and development and reimbursement dollars spent on diagnostics compared to therapeutics, the diagnostics industry can feel like an unloved stepchild, compared to the pharmaceutical industry. But what contributes to this undervaluation and how significant it is in the marketplace are the subjects of ongoing expert discussion.

Cancer biomarker tests are indeed undervalued, asserts Daniel Hayes, M.D., from the University of Michigan, Ann Arbor, and colleagues in a recent commentary piece published in *Science Translational Medicine* that critically looks at how to break the vicious cycle of undervaluation that perpetuates future undervaluation.

"Unfortunately, stakeholders have not fully recognized the potential value of tumor-biomarker tests; thus, the research, regulatory, clinical-use, and reimbursement standards are not as well defined or as rigorous as those applied to therapeutics," argues Hayes. "These conditions have generated little enthusiasm (or funding) for development of the high levels of evidence needed to support the clinical utility of tumor-biomarker tests, resulting in a vicious cycle of undervaluation of tumor-biomarker tests in both the professional and patient communities."

The vicious cycle perpetuates itself with too few tumor-biomarker tests establishing clinical utility or guideline recognition, thus leading to a lack of adoption and reimbursement that feeds, again, a lack of future funding to establish clinical utility or guideline recognition in other emerging diagnostic tests.

A Success Story?

Interestingly, an examination of Myriad Genetics (Salt Lake City), what has been perceived as a diagnostic success story, partially illustrates this view. On the one hand, BRACAnalysis has been embraced by national organizations for women meeting specific criteria. Critics, though, are quick to call the $3,000-plus cost "outrageous" and have blamed Myriad's previous monopoly on BRCA testing for its price tag. Yet, revenues for BRACAnalysis continue to rise, gaining 42 percent in part because of the Angelina Jolie effect, to a first quarter total of $149 million.

But now that the Supreme Court has struck down the legality of gene patents, naysayers have been predicting the worst for Myriad, which so far has been unfounded.

"While we acknowledge the stock is a 'show me' story and could be subject to further negative headlines (including the launch of a test by LabCorp and publication of variant data by competing labs), we continue to believe market share loss will be at a slower pace and not the magnitude implied in the shares," writes Amanda Murphy, an analyst at William Blair & Co., in an October research note. "Moreover, Myriad has

Will Added Comprehensiveness Increase Perceived Test Value?

The U.S. Supreme Court's decision that genes can't be patented has fostered a flurry of new breast cancer test development, including one that can examine all known breast cancer genes in a single assay. While it is too early to tell if the addition of more markers will increase the perceived value of the test, emerging evidence is demonstrating the success of such comprehensive panels at identifying variants.

Results from the BROCA test, developed by Tomas Walsh, Ph.D., and colleagues at the University of Washington, Seattle, were presented at the American Society of Human Genetics annual meeting (Boston; Oct. 22-26). The researchers utilized BROCA, a targeted capture sequencing approach, to detect all single base substitutions, insertions, and deletions, and copy number variants in all 26 genes known to be tied to breast cancer in breast cancer patients with a known "severe" familial history (at least three cases of breast and/or ovarian cancer), but who had normal BRCA clinical test results (BRACAnalysis; Myriad).

In 206 out of the 800 families (26 percent), mutations were resolved using BROCA, with the families found to be harboring 166 different damaging germline mutations in 21 different genes. Commercially undetected mutations in BRCA1 or BRCA2 were detected in 39 percent of the resolved families (80 of 206). An additional 27 percent of resolved families (77 of 206) carried other well-characterized mutations in other breast cancer genes (CHEK2, PALB2, and TP53), while 20 percent (41 of 206) had breast cancer gene mutations that have been published but have been less fully characterized (ATM, BARD1, BRIP1, CDH1, ABRAXAS, NBN, RAD51C, RAD51D, STK11, and XRCC2).

developed a competency in sequencing-based diagnostics and has a meaningful commercial infrastructure that should enable the company to remain a player in the space."

Analysts acknowledge though that Myriad does face an increasingly competitive market environment and the potential for price competition. Downward pricing pressures have been felt with announcements of new entrants to the BRCA testing market, including the reported $2,500 price tag for Quest's version of a comprehensive BRCA test and the $2,280 price for Ambry Genetics' test. Is this pricing pressure the result of an end of a monopoly, increasing price consciousness throughout the health care system, an undervaluing of biomarkers, or possibly some combination?

Despite Myriad's continued increases, albeit possibly slowing, in revenue and promising validation study results for the company's myPlan Lung Cancer test, Murphy says that the market does not fully appreciate the company. "Our view is that Myriad's pipeline, competency in sequencing-based diagnostics, commercial infrastructure, and private database are being undervalued by the market," she says.

Takeaway: Stakeholders will have to come together to create some systemwide reforms in order to break the cycle of undervaluation of cancer biomarkers.

New Low-Cost Molecular HPV Screening Tools Evaluated With Promising Results From New E6 Oncoprotein Test

Development and validation of novel, low-cost, and robust human papillomavirus (HPV) screening strategies are needed to address the disproportionate burden of cervical cancer in resource-limited areas of the world.

A clinical trial published in the September issue of *Cancer Prevention Research* provides some important advances in establishing evidence for population-based screening using emerging lower-cost tests. The study both confirmed the comparability of the lower-cost careHPV (Qiagen) DNA test to a U.S. Food and Drug Administration (FDA)-approved test and demonstrated that a new E6 oncoprotein low-cost test might be useful for screening in high-HPV-prevalence populations.

The increased sensitivity of molecular high-risk HPV (HR-HPV) testing provides an advantage over Pap testing, but it is too complex and costly for use in low-resource areas. Lower-cost tests are in development and validation, including careHPV, a signal amplification DNA test for a pool of 14 HR-HPV genotypes, as well as the lateral flow immunoassay OncoE6 (Arbor Vita Corp.) that targets HPV E6 oncoproteins, which are typically overexpressed in the precancerous phenotype.

The researchers conducted a large-scale clinical trial of both of these tests as well as evaluation of multiple screening strategies. More than 7,500 women (aged 25 to 65 years) living in rural China self-collected a cervicovaginal specimen, had two cervical specimens collected by a clinician, and underwent visual cervical inspection after acetic acid (VIA). The self- and one clinician-collected specimens underwent HR-HPV DNA testing using careHPV and Qiagen's FDA-approved Hybrid Capture 2 (HC2). The other clinician-collected specimen was tested for HPV16, 18, and 45 E6 using OncoE6.

The researchers found that 30.4 percent of women tested positive by at least one of the screening tests. The sensitivity for cervical intraepithelial neoplasia grade 3 or more severe (CIN3+; 99 cases) was 53.5 percent for OncoE6, 97 percent for both careHPV and

HC2 using the clinician-collected specimen, 83.8 percent and 90.9 percent, respectively using the self-collected specimen, and 50.5 percent for VIA. OncoE6 had the greatest positive predictive value (PPV), at 40.8 percent for CIN3+, compared with the other tests, all of which had a PPV of less than 10 percent.

"In those areas with insufficient resources to manage large numbers of screen-positive women that would result from using a more sensitive but less specific HR-HPV DNA test, the OncoE6 test might be used for primary screening, thereby achieving a sensitivity similar or superior to VIA, which is already being widely used," writes senior author Philip Castle, Ph.D., from the Global Cancer Initiative (Chestertown, Md.). "However, because of its much higher specificity compared with VIA, screening with HPV E6 might reduce either the number of referrals to colposcopy . . . or overtreatment."

Several authors report financial ties to the diagnostics industry, including Arbor Vita Corp.

Takeaway: HPV E6 oncoprotein detection appears useful for identifying women who have cervical precancer and cancer in low-resource areas.

Placental Growth Factor Predicts Preeclampsia Risk

For women presenting before 35 weeks' gestation with suspected preeclampsia, low levels of placental growth factor (PlGF) have high sensitivity and negative predictive value (NPV) for identifying women who will need to deliver within 14 days because of the disease, according to a study published online Nov. 4 in *Circulation*.

P1GF has better test characteristics than other currently used tests and can improve disease monitoring, preventing unnecessary care. The test, made by Alere (Waltham, Mass.), still needs U.S. regulatory approval for clinical use.

Current diagnosis relies on blood pressure and proteinuria, which experts say are of limited use because they are tertiary features of the disease reflecting end-organ disease and are poorly predictive of subsequent adverse outcomes. P1GF increases in concentration in maternal circulation (peaking at 26 weeks' to 30 weeks' gestation) but can serve as a secondary marker of associated placental dysfunction in preeclampsia, with low concentrations associated with the disease.

Researchers conducted a prospective, multicenter trial (from January 2011 to February 2012) in which the diagnostic accuracy of low plasma PlGF concentration (less than the fifth centile for gestation) was evaluated using the Alere Triage assay in 625 women presenting with suspected preeclampsia between 20 weeks' and 41 weeks' gestation. The study found that 55 percent of women developed confirmed preeclampsia. When limiting evaluation to the 287 women enrolled before 35 weeks' gestation, PlGF levels less than the fifth centile (or ≤100 pg/mL) had 96 percent sensitivity and a 98 percent NPV for preeclampsia within 14 days. Specificity was lower (0.55). Low PlGF was significantly better at predicting preeclampsia than all other commonly used tests, singly or in combination.

"We hypothesize that adding PlGF measurement to current clinical assessment of women with suspected preeclampsia before 37 (and particularly before 35) weeks' gestation could improve risk stratification, achieve an earlier diagnosis based on underlying pathophysiology, enable individualized management of women with the disease, with the potential to reduce associated maternal morbidity and unnecessary health service usage," write the authors, led by Lucy C. Chappell, Ph.D., King's College London (United Kingdom).

Paul Sheard, a spokesperson for Alere, tells *DTET* that the Triage PIGF assay, which launched in Europe in 2011, will likely not be released in the United States before 2015 as the company must complete the premarket approval process with the U.S. Food and Drug Administration (FDA). To date the company has completed the necessary clinical trials and has had preliminary discussions with the FDA. Several authors report financial ties to Alere, which partially funded the study.

Takeaway: PlGF has potential to improve the diagnosis of preeclampsia and impact both outcomes and usage of health care services.

Assay for TMAO Microbial Byproduct Predicts Cardiovascular Risk

As researchers and clinicians continue their search for new biomarkers capable of predicting cardiovascular event risk, there is optimism that the nontraditional marker trimethylamine N-oxide (TMAO), a microbial byproduct of intestinal bacteria, may serve as an accurate screening tool for predicting future risk of heart attack, stroke, and even death in persons not otherwise identified by traditional risk factors.

The TMAO assay, currently available from LipoScience (Raleigh, N.C.) for research only purposes, was recently named by the Cleveland Clinic as one of its top 10 innovations for 2014.

TMAO is produced when intestinal bacteria digest the nutrient phosphatidylcholine (choline) present in egg yolks, red meat, and dairy products. This metabolite is believed to directly contribute to the pathophysiology of atherosclerosis and resulting coronary artery disease.

A study led by Cleveland Clinic researchers (published in the April issue of the *New England Journal of Medicine*) established that intestinal microbiota, when suppressed with antibiotics, produce less TMAO, and when not suppressed TMAO was tied to dietary phosphatidylcholine through the use of stable-isotope-tracer feeding studies. Additionally, the study identified the potential clinical significance of the intestinal microbiota-dependent metabolite by showing that fasting plasma TMAO levels predict the risk of future cardiovascular events independently of traditional cardiovascular risk factors, even in low-risk subgroups. Increased plasma levels of TMAO were associated with more than a doubling of risk for a major adverse cardiovascular event.

Given these results, experts are optimistic that by testing the gut biome for cardiovascular risk, doctors soon will be able to personalize nutritional recommendations for their patients to prevent cardiovascular disease based on the production of TMAO, including diet recommendations, using bacteriotherapy (probiotics) to alter the gut microbiota, or potentially to suppress TMAO synthesis through targeted drugs.

LipoScience has developed the TMAO assay in conjunction with the Cleveland Clinic and is currently offering the assay for research use only. Future plans include offering TMAO as a laboratory-developed test on the Vantera Clinical Analyzer, the same nuclear magnetic resonance (NMR)-based diagnostic platform that runs the NMR LipoProfile test.

Takeaway: There is growing interest in utilizing markers generated from gut microbia to predict disease risk, including TMAO, which has been tied to significantly increased risk of a future cardiovascular event.

G2 Insider

Reducing Clinically Unnecessary CD4 Monitoring Yields Substantial Savings . . . Recent research has shown that CD4 monitoring may not be needed in clinically stable, virally suppressed HIV-infected patients, but new evidence goes further to show that there is potential for substantial savings by at least reducing this monitoring. According to a research letter published Oct. 14 in *JAMA Internal Medicine*, cutting CD4 monitoring from biannual to annual could result in up to $18 million of savings annually and up to $615 million over the lifetime of patient care.

In 2013, guidelines for HIV care from the Department of Health and Human Services recommend CD4 monitoring every six to 12 months in clinically stable patients with suppressed viral load (no detectable HIV RNA in blood) while on anti-retroviral treatment.

"I look at this 'every 6 to 12 months' frequency as a gentle way of trying to wean us off a monitoring strategy we have had now since the 1980s. Both patients and providers are so accustomed to regular CD4 monitoring that it seems too difficult to stop doing it cold turkey," writes Paul Sax, M.D., Brigham and Women's Hospital in Boston, in an editorial published in *Clinical Infectious Disease* in May.

Experts say that despite the recommendations, clinicians are still performing CD4 monitoring tests more frequently—even quarterly—and that these CD4 results rarely, if ever, influence HIV clinical management. To calculate the economic impact of unnecessary CD4 monitoring, the researchers used $38 to $67 per test as the range of CD4 test costs range, depending on whether CD4 percentage is included. Additionally, they based calculations on a life expectancy of 22 to 34 years after HIV diagnosis. By reducing the current strategy of biannual CD4 monitoring to annual testing, annual savings range from $10.2 million to $18.1 million, with a population savings of $225.7 million to $615.1 million over the lifetime of patient care. Savings could be even greater in clinical practices that monitor more frequently.

"Our results likely underestimate the potential savings," write the authors, led by Emily Hyle, M.D., from Massachusetts General Hospital in Boston. "The number of virologically suppressed patients with HIV is growing; as the population eligible for a reduced frequency of CD4 monitoring is increasing, so are the opportunities for savings."

The authors emphasize that evidence shows that reducing CD4 monitoring frequency does not adversely affect health outcomes as CD4 counts rarely decline to clinically significant levels without a rise in HIV RNA levels.

"Even greater savings would occur if CD4 monitoring in stable patients were eliminated entirely, which warrants consideration," concludes Hyle. "Given the still unmet medical needs of people living with HIV/AIDS, a recommendation for at most annual CD4 monitoring in stable, virologically suppressed patients offers a high value opportunity for a wise reinvestment of care."

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DTET 12/13

December 2013

 Diagnostic Testing & Emerging Technologies (ISSN 2330-5177) is published by G2 Intelligence, 24 Railroad Street, Keene, NH 03431-3744. Tel: 800-531-1026 or +1 603-357-8101. Fax: +1 603-357-8111. Web site: www.G2Intelligence.com.

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