**Microbiology, Advanced Tests Projected to Keep U.S. IVD Market Afloat**

Although cuts to lab reimbursement and other variables have dampened the growth of the U.S. in vitro diagnostics (IVD) market, its microbiology and advanced testing segments are still projected to experience above-average market development through 2018. Those were among the findings of “The United States Market for In Vitro Diagnostic Tests,” a report by Kalorama Information analyst Emil Salazar. Kalorama reached this conclusion by comparing each IVD market segment’s actual or projected monetary share of IVD market volume between 2013 and 2018 with the segment’s current share of the market.

**SNAPSHOT**

<table>
<thead>
<tr>
<th>IVD Market Segment Projected Growth, 2013–2018</th>
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<tbody>
<tr>
<td><strong>Above average growth</strong></td>
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<tr>
<td><strong>Below average growth</strong></td>
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<tr>
<td>Core Lab</td>
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<tr>
<td>0.63</td>
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Source: Kalorama 2014

Advanced tests in particular are expected to boom, with molecular assays for non-infectious diseases testing and histology projected to be the two fastest growing IVD market segments through 2018. This is because the use of histology to support cancer diagnosis and treatment is becoming increasingly reliant on immunohistochemical reagents and molecular hybridization techniques. Additionally, the U.S. is ground zero for an influx of advanced molecular assays for blood-based cancer testing, circulating tumor cell testing, pharmacodiagnosics, and other sequencing-based tests.

Several factors have also kept market growth robust for microbiology diagnostics. These include, among others, hospital investment in microbiology for healthcare-acquired infection testing and market penetration by higher-priced molecular infectious diseases tests.

On the downside, Kalorama projected below-average market development in the next 5 years in both the core lab and point of care IVD market segments. However, the report states that several factors such as continued product innovation will lend stability to IVD sales overall.


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**The Continuing Search for Alzheimer’s Biomarkers**

_Could a Blood Test Be Near?_

By Deborah Levenson

Despite extensive research on Alzheimer’s disease (AD), this devastating neurodegenerative condition is an enormous continuing social and public health problem. More than 5 million Americans live with AD, and the total national cost of caring for people with AD and other dementias is projected to reach $214 billion during 2014, according to the Alzheimer’s Association. The disease also takes a huge toll on the nation’s 15.5 million caregivers—usually family members—who, as the disease progresses, provide nearly constant unpaid care. Without medical advances leading to viable treatments, the already substantial burden of AD is expected to continue to weigh down society and the healthcare system. Imagine three times more AD patients, a figure the Alzheimer’s Association predicts could materialize by 2050 absent significant diagnostic and treatment strides. The Food and Drug Administration has approved five drugs that temporarily offset memory and other cognitive loss and three agents for use with positron emission tomography.

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**A New Era for Lab Reimbursement**

_Congress Overhauls Lab Fee Schedule_

By Bill Malone

In a bill originally focused on forestalling a steep drop in physician payment, Congress has laid out plans for a completely different approach to paying for laboratory testing that will lead to sweeping changes in laboratory medicine for decades. Signed into law by President Obama on April 1, the law will take the traditional means of pricing tests by the Centers for Medicare and Medicaid Services (CMS) and slowly turn it on its head. Beginning in 2017, Medicare will rely on an average of private payer rates to set Medicare’s fee schedule, and give special treatment to single-source proprietary tests. Among the law’s many changes are new procedures for coding new tests, a new expert advisory panel on lab reimbursement, and a ban on annual lab fee schedule updates, cuts, and adjustments.

While advocates for physicians, clinical laboratories, and in vitro diagnostics manufacturers all seem to have found aspects of the law to praise as well as to condemn, experts agree that it will set reimbursement on a new course that almost certainly will lead to payment cuts for some tests and increases for others.

“This is the first time that there has been anything substantial done to the clinical laboratory fee schedule since it was created nearly 30 years ago,” noted Charles Root, PhD, founder and president of the reimbursement and compliance consulting firm CodeMap.

“I think in the long term the new market-based structure will be more transparent and predictable, compared to the current payment system that can seem totally arbitrary. But there is no question that some tests will take a hit.”

**See Lab Reimbursement, continued on page 3**
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Medicare Will Follow Private Payer Market
Lab Reimbursement, continued from page 1

Two Paths for New Tests
Under the new physician payment law signed on April 1 by President Obama, market-based rates will become the norm for both existing and new tests. However, the law also introduced two key pathways for introducing new tests. These provisions could be good news for labs, according to experts. A unique provision in the law for the first time creates a special category for advanced diagnostic tests, defined as a test provided only by a single lab, not sold for use by other labs, and that meets one of three criteria: the test is an analysis of multiple biomarkers of DNA, RNA, or proteins combined with a unique algorithm to yield a single, patient-specific result; the test is cleared or approved by the Food and Drug Administration; or the test meets other similar criteria that the Secretary of Health and Human Services sees fit to create. These advanced tests for an initial period of 9 months will immediately receive the list price under Medicare. After that point, Medicare will review actual private payer data for the test and recoup any Medicare payments that ran more than 30% over the private payer median. At this point, the 3-year cycle of market-based reporting and rate-setting kicks in.

According to Paul Radensky, MD, JD, a partner with the law firm McDermott, Will & Emery in Washington, D.C., this provision for advanced tests will build upon the work labs already do to get contracts with private payers. “The idea is that if you convince a private payer to agree to a contract, they must feel it’s valuable to their beneficiaries, and the rate would demonstrate that sense of value,” Radensky said. “This will mean that Medicare will reflect at least the value that private payers see.”

One caveat to the excitement over immediate payment for these advanced tests is the quirks of the definition of “advanced” in the law. “The algorithmic requirement is one that the next-generation sequencing tests would not meet, and that’s where so much of the innovation is being done right now,” noted Rina Wolf, vice president of commercialization strategies, consulting, and industry affairs at XFIN, a revenue cycle solutions company. “This is a big unanswered question.” In addition, the law does not guarantee that Medicare will cover these tests—only set payment for them if and when they are covered.

For new tests that don’t fit the special advanced diagnostics criteria, the law promises to speed payment and force CMS to make more deliberate decisions on initial rates. The law spells out how CMS must assign codes and use the gapfill process for initial pricing of new tests. It also creates a new advisory board of laboratory medicine experts who must be consulted.

New assays almost certainly will benefit under this provision, emphasized Charles Root, PhD, founder and president of the reimbursement and compliance consulting firm CodeMap. “I think this could be a tremendous boon to new technology, especially for molecular diagnostics. It will avoid big disruptions like we had in 2013 where labs literally went out of business because Medicare had not priced the test,” he said.

Market-based pricing under the new law will reboot both CMS’s traditional rate-setting method as well as the yearly cycle of inflation updates. Instead, the system will seek to mathematically mirror the private market based on a continuous, 3-year cycle beginning in 2016. At the beginning of each cycle, labs will report the rate and volume paid by each private payer for each test—excluding capped payments such as the diagnosis related group system for inpatient care. CMS will then set a rate for each test using the weighted median of private payments. For the initial cycle, this means that CMS will set new, market-based rates on January 1, 2017 based on what private payers paid in 2015.

The looming question is, how low will these new market rates be? Currently, many labs offer significant discounts to private payers, with Medicare rates as only a starting point for negotiations. If going forward Medicare mirrors a highly discounted market—only to have the payers turn around and expect more discounts—the results appear bleak. “Right now the large national labs already have painfully low pricing with the big payers, and that pricing is going to skew what almost everyone else submits to CMS,” said Wolf. “The reasoning behind this law is to position CMS to be the lowest payer. However, if we see adjustments downward on the first cycle of market-based pricing in 2017 for CMS, then commercial payers which have already begun to set contracted rates at half or less of the Medicare rates, will likely attempt to reduce their rates, causing the next round of submissions to CMS in 2019 to be even lower, unless laboratories get much smarter about contracting before 2016. If not, where will it end?”

Market-based pricing also means a paradigm shift for Medicare that pits the agency’s healthcare mission against the profits of payers, commented Roland Valdes Jr., PhD, president of PGXL Laboratories and professor of pathology and laboratory medicine at the University of Louisville. “I think the concept of market-based pricing is somewhat misguided,” Valdes said. “The mission of CMS is..."
Small Labs Fear Big Cuts
Lab Reimbursement, continued from page 3

Big Questions on Law’s Effect on Coverage Policies

The “doc fix” law signed on April 1 by President Obama lays out a new reimbursement framework for clinical laboratory tests, but says little about coverage—which tests Medicare will deem “reasonable and necessary.” However, some language in the law does leave the door open to a long-standing question: could one Medicare administrative contractor’s (MAC) coverage and payment program be replaced by another? In particular, many in the diagnostics industry have wondered whether the Centers for Medicare and Medicaid Services (CMS) might not leverage a program created by the contractor Palmetto GBA into a national program. Palmetto’s Special Diagnostics Services Program (MoDiX) was the first in the nation to systematically evaluate, price, and determine coverage for molecular tests under Medicare. The program still determines the fate of molecular tests in California, Nevada, and Hawaii.

Under the new law, the Secretary of Health and Human Services (HHS) is given authority to designate 1 to 4 administrative contractors, a provision that could upend the current regime of 10 contractors across the country, noted Rina Wolf, vice president of commercialization strategies, consulting, and industry affairs at Xinfin, a revenue cycle solutions company. “A big concern is that this language in the law leaves the door open for the nationalization of the Medicare program that Palmetto has been lobbying for,” she said. “We welcomed the intent of this program to provide much needed clarity to the coverage process, but to date have seen inconsistencies in its application. It’s also unclear how CMS will decide if it is to be only one contractor or more, and what the criteria would be for the selected contractor. That’s a big unanswered question right now.”

A nationalized MoDiX program concerns Wolf and others in the industry for several reasons. “We’ve recently seen local coverage determinations for pharmacogenomics and drugs of abuse testing, in which they followed the process, allowed for a comment period, but then absolutely ignored all of the comments that they received,” Wolf said.

In response to such decisions, the law firm Hooper, Lundy & Bookman, which is lead attorney for the plaintiffs in a statement. “Our clients have been forced to bring this lawsuit to block, delay, and change, the current practice of denying coverage for critically important laboratory services. In addition, the same private insurers who make determinations for Medicare, also make determinations in the private market, so the entire population is affected.”

“Today, the MACs have a stranglehold on critical, cost-effective innovation,” said attorney Patrick Hooper of Hooper, Lundy & Bookman. “We feel that you are looking for every conceivable way for not paying for something, no matter how they view the evidence, and I suspect decisions are driven mainly by market share competition,” he said. “Especially a small lab like ours, what leverage do we have? I’m very concerned that this will bias lab medicine against small and even medium size laboratories.”

The predicted effects on different kinds of labs also played out in the response of the various societies and advocacy organizations that represent the laboratory medicine community, with some praising the law and others highly skeptical of it. The Advanced Medical Technology Association (AdvaMed) said it “supports provisions in the SGR legislation which will modernize the clinical lab fee schedule and recognize the value of important laboratory services. In response to such decisions, the law firm Hooper, Lundy & Bookman, which is lead attorney for the plaintiffs in a statement. “Our clients have been forced to bring this lawsuit to block, delay, and change, the current practice of denying coverage for critically important laboratory services. In addition, the same private insurers who make determinations for Medicare, also make determinations in the private market, so the entire population is affected.”

“The American Clinical Laboratory Association (ACLA) also voiced support for the law. In contrast, the National Independent Laboratory Association (NILA), which represents independent community labs, criticized the law, saying in a letter to the chairman of the Senate Finance Committee that the law "continues to build upon a flawed precedent" of cuts to labs that don't improve quality of care for patients or significantly reduce healthcare spending.  ACLA leaders also expressed concern.  "AACC is concerned about the impact of looming cuts in laboratory reimbursement," said James H. Nichols, PhD, medical director of clinical chemistry at Vanderbilt University Medical Center and chair of AACC's Government and Regulatory Affairs Committee. "We believe that Congress and CMS should assess the overall effect of some of these provisions on hospitals

Some Labs More Vulnerable Than Others

If market-based pricing does push Medicare rates down, the effect on labs could be uneven, depending on the size of the lab and even geography. For example, urban areas could face tougher competition for contracts compared to rural areas, given the higher number of players, Wolf noted.

With a drop in prices expected to hit routine tests hardest, Root believes that smaller labs will do better if they have a diverse menu. “These high-volume tests could easily migrate over to the big labs if the small labs can’t afford to do them anymore,” Root said. “That’s all the small lab is doing, they’re vulnerable. But if they have a fairly broad menu and they’re serving specialized clients that don’t just want basic metabolic panels and cholesterol tests, they might be okay.”

Market-based pricing could also favor independent labs over hospital outreach labs, if indeed CMS’s incentive outreach labs in the definition of an “applicable laboratory” under the law, according to Wolf. “This could really be a good thing for the independent lab industry because hospital laboratories until now have been very generously compensated to some of the independent labs, and this could even the playing field,” she said.

While large, national labs might feel empowered by the law to compete with the dynamics of their contracts, it’s hard to imagine small independent and hospital labs gaining any leverage with private payers, Valdes said. “I can tell you from experience, that when you go to a private payer, they are looking for every conceivable way for not paying for something, no matter how they view the evidence, and I suspect decisions are driven mainly by market share competition,” he said. “Especially a small lab like ours, what leverage do we have? I’m very concerned that this will bias lab medicine against small and even medium size laboratories.”
and small laboratories before implementing them. AACC is concerned these payment reductions may force some labs out of business and others to scale back their services, particularly in underserved areas."

Most concerning to NILA and the small labs it represents is the prospect of significant drops in prices to routine tests. Community and regional labs are especially sensitive to price pressures since they often serve vulnerable populations in niche markets that national labs do not, such as nursing homes or homebound patients who require phlebotomists to visit them. This leaves community labs little means to cope with declining reimbursement, noted Julie Allen, senior vice president at the District Policy Group, the lobbying division of Drinker Biddle and Reath and a Washington, D.C. representative for NILA.

“We take issue with this being called market-based reform, because it doesn’t fundamentally seek to address some real problems with the way laboratory services are priced, including how national contracts are derived,” Allen said. “There are arrangements where large labs have grossly underbid contacts and then turned around and charged Medicare more, which is the subject of significant lawsuits and accusations of fraud. But rather than take any time to consider those issues, Congress made a choice that those rates are going to be what CMS acts on.”

While the market-rate scheme will not bring capitated contracts into the equation, it is also a concern that the new law could be interpreted to not include hospital payments. This could significantly skew the data when labs report pricing information to CMS, Allen said, since hospitals are a significant part of the lab market and their rates can vary from independent labs.

Market-based pricing has the potential for uneven consequences for different testing methods as well. In particular, point-of-care testing (POCT) is at risk. If routine tests are sent into a downward spiral, POCT paid under the lab fee schedule looks nearly unsustainable, since POCT is more expensive than the central lab.

“We are very concerned that point-of-care testing could get thrown under the bus in the process because of the technology difference,” Root said. “Our strategy with CMS is to convince them to use different codes for point-of-care testing, or for certain essential tests. If they recognize those separately, eventually they get priced separately, and the market will come around.”

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**AACC Announces 2015 Board Election Candidates**

Robert Christenson, PhD, chair of AACC’s 2014 Nominating Committee, announced the slate of candidates for the 2015 Board elections. AACC members will receive instructions about voting online via email in September.

The candidates and positions are:

**President-Elect**

Elizabeth L. Frank, PhD, associate professor (clinical)/medical director, ARUP Laboratories, Salt Lake City

Patricia (Patti) M. Jones, PhD, professor of pathology, University of Texas Southwestern Medical Center, Children’s Medical Center, Dallas

**Board of Directors**

Paul Jannetto, PhD, director, Toxicology and Drug Monitoring Laboratory, Mayo Clinic, Rochester, Minnesota

Stanley F. Lo, PhD, associate professor of pathology, Medical College of Wisconsin, Children’s Hospital of Wisconsin, Milwaukee, Wisconsin

Stephen Master, MD, PhD, assistant professor of pathology and laboratory medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia

Carmen Wiley, PhD, scientific director, PAML, Spokane, Washington

**Nominating Committee**

Susan Evans, PhD, principal/owner, BioDecisions Consulting, Los Gatos, California

Deborah French, PhD, assistant director of chemistry and director of mass spectrometry, Department of Laboratory Medicine, San Francisco

Peter Kavalk, PhD, clinical biochemist, Juravinski Hospital and Cancer Centre, Ontario, Canada

Mark D. Kellogg, PhD, director of quality programs and associate director of chemistry, Department of Laboratory Medicine, Boston

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### Promising 10-Lipid Test Requires Crucial Validation

Alzheimer’s, continued from page 1

tomography (PET) of the brain. PET estimates amyloid (Aβ) plaque density in cognitively impaired patients who are being evaluated for AD and other causes of cognitive decline. But a more cost-effective test to spot early AD remains elusive.

Increasingly, research is focusing on prevention. “There’s been a paradigm shift from trying to find a cure to stopping the disease from happening in the first place,” noted Anne Fagan, PhD, professor of neurology at Washington University in St. Louis and a researcher in the Dominantly Inherited Alzheimer Network (DIAN). Reliable biomarkers are crucial to this strategy. Ideally, they not only would identify who will develop the condition and accurately measure its progression, but also enable researchers to test the efficacy of experimental treatments, she explained.

Studies have revealed several potential protein biomarkers in cerebrospinal fluid (CSF), with tau and Aβ among the most promising. Meanwhile, most research on proteins and other types of biomarkers in the blood, which are easier and cheaper to collect than CSF, has not been able to detect preclinical disease with high sensitivity and specificity.

However, a small proof-of-concept study from a team led by Howard Federoff, MD, PhD, dean at Georgetown University School of Medicine in Washington, D.C., showed that mass spectrometry analysis of 10 blood lipids distinguished, with 90% accuracy, who among an initial group of 525 cognitively healthy adults age 70 and older developed cognitive impairment over a 2–3 year period (Nature Medicine 2014; doi:10.1038/nm.3466). If these results are validated in larger and more involved studies, this line of research might someday lead to a relatively noninvasive test that could help clinicians determine who is at risk for the disease.

### Finding the Lipids

Federoff’s team enrolled mostly educated, middle-class Caucasians living in or near Rochester, N.Y. The researchers took blood samples and administered cognitive tests at baseline and at yearly follow-up visits. Over the course of the study, 28 participants developed either amnestic mild cognitive impairment (MCI) or AD.

The authors selected 18 of these patients and analyzed their plasma via mass spectrometry for lipid markers that differentiated them from 53 age, sex, and education-matched controls who did not have cognitive decline. Broad analysis of metabolites showed that levels of several plasma phospholipids important to the integrity and function of cell membranes differed between the groups. Follow-up analyses revealed eight lipids that had high discriminative power in the biosignature. Subjects who remained healthy had higher baseline levels of all 10, compared to those who developed MCI or AD. In contrast to extensive research that has shown the genetic variant ApoE4 as a strong risk factor for AD, this study found no relationship between this known risk factor and the lipids in the biosignature. That’s partially because it was designed to examine metabolites and not the gene variant as a primary outcome, said the paper’s first author, Mark Mapstone, PhD, associate professor of neurology at University of Rochester School of Medicine. Many researchers who work with lipids try using ApoE4 to make panels more predictive, so editors reviewing the paper “thought we should look at APOE because it’s a strong risk factor,” he explained. “But the classification of the subjects based on the biosignature was not related to ApoE4 presence.”

AD researcher Ling Li, PhD, a professor of experimental and clinical pharmacology at the University of Minnesota College of Pharmacy, said one reason ApoE4 did not prove to be predictive might be the study’s small sample size.

### The Crucial Validation Step

Validation of the Federoff team’s findings is crucial, said Mapstone, who offered a glimpse into their plans to do so. “The editors reviewing the paper thought we should look at APOE because it’s a strong risk factor,” he explained. “But the classification of the subjects based on the biosignature was not related to ApoE4 presence.”

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Validation studies should also pay careful attention to how samples are prepared and attention to how samples are prepared and mass spectrometry, which many labs lack. “But there’s big potential in the test if it uses blood,” she emphasized.

### Other Recent Biomarker Evidence

Most studies of lipid and other biomarkers have focused on CSF in symptomatic patients. The few that have examined blood lipids in preclinical disease have not yielded markers as accurate as those developed by the Georgetown-led team, said Mapstone. However, a study of several proteins in the blood came fairly close, but only in people with diagnosed AD. This study showed that 18 proteins tested by the Australian Imaging Biomarker and Lifestyle Research Group and validated in an ADNI cohort distinguished individuals with AD from cognitively healthy control subjects with a mean sensitivity of 85% and specificity of 93%. Of the 18
proteins, 11 were significantly increased in AD, while seven were significantly decreased (Arch Neurol 2012;69:1318–25).

Meanwhile, a more recent study suggested that limited metabolites could advance understanding of early disease mechanisms and identified some of the same metabolites as the Fagan study’s mass spectrometry. CSF and plasma samples from 45 people in the Mayo Clinic Study on Aging and Mayo Clinic Alzheimer’s Disease Center revealed that those with MCI and AD had significant changes in CSF and plasma, while changes in plasma accurately reflected changes in CSF. Overall, the researchers identified 342 and 351 significantly altered plasma and CSF metabolites, respectively (PLoS One 2013; doi:10.1371/journal.pone.0063644).

Tau, a well-established biomarker in Alzheimer’s studies, thus far has been reliably detectable only in CSF, but another recent study indicates headway in detecting the protein in circulating blood via an assay that employs arrays. A cross-sectional study of 54 patients with AD, 75 with MCI, and 25 cognitively normal controls found plasma tau concentrations to be significantly higher in AD patients compared with both controls and MCI patients. However, researchers found no correlation between tau levels in plasma and CSF (Alzheimer’s Res Ther 2013;5:9).

What’s the Change Over Time?

Meanwhile, biomarker data from patients with inherited disease in another study that included both cross-sectional and longitudinal data analysis emphasized the importance of looking at changes within individuals as part of the search for predictive biomarkers (Sci Transl Med 2014;6:226ra30).

Although autosomal dominant disease caused by mutations in three genes comprises <5% of all AD cases, DIAN and other research efforts focused on families with inherited mutations to help characterize biomarker changes across the disease process. That’s not only because dementia is a certainty in people with the mutations, but also “because they develop symptoms at an age similar to their parents so we have a better idea where they fall in the course of their disease,” explained Fagan. She was lead author of the Science Translational Medicine paper, which confirmed prior findings about biomarker changes in inherited AD and raised questions about how a few analytes behave over the course of the disease.

Specifically, Fagan’s study confirmed previous DIAN cross-sectional findings that indicate AD pathology exists 10–15 years before symptom onset. The initial findings came from studying 79 mutation carriers’ plasma Aβ1-42 and CSF Aβ1-42 and tau in relation to their individual estimated age of symptom onset (N Engl J Med 2012;367:795–804).

The cross-sectional part of Fagan’s study included evaluation of baseline data for five plasma and five CSF biomarkers from a larger DIAN cohort, including 96 non-carriers and 547 study participants with a variety of mutations in PSEN1, PSEN2, and APP. Mutation carriers had amyloid imaging and plasma analysis for four types of Aβ fragments, and visinin-like protein 1 (VILIP-1), a neuron-specific intracellular calcium sensor protein, a proposed marker of neuronal cell injury and death. The researchers also analyzed CSF markers including Aβ1-40, Aβ1-42, tau, phosphorylated tau (p-tau), and VILIP-1.

In this study, reduced concentrations of CSF Aβ1-42 were associated with the presence of amyloid plaque in the brain as evidenced by amyloid imaging, similar to what has been shown in late-onset, sporadic AD. The researchers saw higher-than-normal levels of CSF Aβ1-42 concentrations in carriers at 25 years before their expected age of symptom onset. However, while controls’ Aβ1-42 concentrations appeared to remain constant, carriers’ concentrations were significantly lower than controls’ values at least 10 years before their estimated age of symptom onset. Meanwhile, tau, p-tau, and VILIP-1 concentrations were elevated in carriers 15–20 years prior to symptoms, and remained higher than controls’ at subsequent ages, similar to what is observed in the more common late-onset form of AD.

In the within-individual longitudinal analysis involving 11 noncarriers and 26 carriers, CSF tau also rose over a period of 1–3 years in carriers prior to their expected age of symptom onset. But in carriers who were symptomatic and past their expected ages of onset, levels of tau, p-tau, and VILIP-1 all fell slightly, by about 10 pg/mL over time. Fagan speculated that drop in these analytes may reflect slowing release of these proteins from the brain into CSF as the rate of acute neuron cell injury and death diminishes and tissue shrinks.

Like the Fagan study’s study, these findings need to be further validated. If confirmed, they might warrant adjustment of the current thinking about AD’s biomarker trajectories and could affect evaluation of particular biomarkers’ behavior in clinical trials of disease modifying therapies, said Fagan. “These data also highlight that we should not make assumptions about biomarker changes over time from cross-sectional studies,” Fagan added. ADNI researchers observed a similar drop in tau over time among some ADNI participants with sporadic disease (Acta Neuropathol 2013;126:659–70).

Eventually, Fagan’s findings and other studies of inherited disease may inform understanding of sporadic disease because familial AD patients are younger, and therefore less likely to have signs of other brain pathologies like vascular disease, which is common in older patients with sporadic AD. The field “is getting closer and closer to viable biomarker tests,” Fargo noted. In addition to studies examining how biomarkers show disease progression, he pointed to progress on other fronts such as standardizing reagents and fluid handling techniques. Mapstone is confident that research will yield viable biomarkers, and urged laboratories to prepare themselves. “Clinical chemists will implement our findings and make them into CLIA-certified tests we can use to help patients,” he said. “You will be called upon to assist us.”

Deborah Levenson is a freelance writer in College Park, Md. She can be reached at dblevens@verizon.net.
immune response directed against “self” is referred to as autoimmunity. The 1908 Nobel Laureate, Paul Ehrlich, first envisioned the notion of autoimmunity, which he termed “horror autotoxicus” (1). Ehrlich’s pioneering theory considered that the immune system normally targets foreign substances and has an inbuilt tendency to avoid attacking self-tissues. However, when this process goes wrong, the immune system attacks self-tissues, resulting in autoimmune diseases (AID).

AID are a spectrum of diseases ranging from organ-specific, in which the immune system reacts against self-antigens in a particular tissue, to systemic, in which the immune response takes place against a specific antigen or antigens of multiple tissues. AID are a significant health concern throughout the world. Many of these diseases tend to be difficult or impossible to cure, for the obvious reason that the target of the immune response, which is self-antigens, cannot be eliminated. The chronic nature of AID has a significant impact on medical care utilization, direct and indirect economic costs, and quality of life. AID are among the leading causes of death among those younger than age 65 in the United States (2).

ANA Testing: From Microscopy to Multiplexing
BY KUN-YOUNG SOHN, MD, PhD, AND WALIUL I. KHAN, MBBS, PhD, FRCPATH

Immune response directed against “self” is referred to as autoimmunity. The 1908 Nobel Laureate, Paul Ehrlich, first envisioned the notion of autoimmunity, which he termed “horror autotoxicus” (1). Ehrlich’s pioneering theory considered that the immune system normally targets foreign substances and has an inbuilt tendency to avoid attacking self-tissues. However, when this process goes wrong, the immune system attacks self-tissues, resulting in autoimmune diseases (AID). AID are a spectrum of diseases ranging from organ-specific, in which the immune system reacts against self-antigens in a particular tissue, to systemic, in which the immune response takes place against a specific antigen or antigens of multiple tissues. AID are a significant health concern throughout the world. Many of these diseases tend to be difficult or impossible to cure, for the obvious reason that the target of the immune response, which is self-antigens, cannot be eliminated. The chronic nature of AID has a significant impact on medical care utilization, direct and indirect economic costs, and quality of life. AID are among the leading causes of death among those younger than age 65 in the United States (2).

Laboratory Investigation of Autoimmune Diseases

AID are very difficult to diagnose, and the right treatment must be carefully chosen for the right disease at the right time. Each diagnosis requires a detailed history, physical exam, and often multiple laboratory tests. Laboratory testing is of great value when evaluating a patient with a suspected AID. However, not a single laboratory test establishes such a diagnosis. Typically, the diagnostic work-up involves multiple tests, including complete blood count, inflammatory markers, flow cytometry, and autoantibodies. Circulating autoantibodies against a wide number of structural and functional molecules that present in ubiquitous or tissue-specific cells also are considered valuable markers of AID. Detection of autoantibodies is an important component of the diagnostic criteria for AID, helps anticipate the clinical phenotype of individual patients, and contributes to assessment of overall disease activity.

Anti-Nuclear Antibody Testing
Anti-nuclear antibodies (ANA) are hallmarks of many autoimmune connective tissue diseases. The term ANA is now obsolete and even puzzling, as this historical label has come to include antibodies directed at various cellular compartments including nuclear constituents, components of the nuclear envelope, mitotic spindle apparatus, cytosol, cytoplasmic organelles, and cell membranes. ANA testing is used extensively for diagnosing and monitoring various AID such as systemic lupus erythematosus (SLE), Sjogren’s syndrome, scleroderma, mixed...
connective tissue disease, polymyositis, and dermatomyositis. Development of the first method to identify ANA is considered one of the milestones in the history of clinical immunology over the last 60 years. However, the methodologies for measuring ANA have changed substantially over the years in recognition of a wider spectrum of potentially relevant autoantibodies and a sensible requirement to improve test performance and efficiency.

Both microscopy and immunoassay-based methods have significant importance in laboratory medicine. The traditional method for detecting ANA is indirect immunofluorescence (IIF) and enzyme immunoassay (ELISA) (Figure 1).

**Indirect Immunofluorescence Assay**

IIF assays to probe nuclear antigens were introduced more than 50 years ago, and this method still is the most widely used conventional technique for detecting ANA (3). The IIF method detects a large number of autoantibodies that bind to a variety of nuclear antigens mentioned earlier (Figure 2). Briefly, IIF involves placing patient serum on a slide containing tissue or HEp-2 cells (a human laryngeal epithelial cell line). ANAs bind to the specific antigen and after washing, the next step is to add fluorescein-labeled anti-human IgG. Laboratories view the slide under a fluorescence microscope and report results with staining pattern and titer. Common patterns reflecting the types of antigens include homogeneous, speckled, centromere, or nucleolar, all of which suggest associations with certain autoimmune diseases. IIF is highly sensitive and has broad screening potential but is not without limitations. Aside from a high false positive rate, IIF is time-consuming, laborious, and frequently yields discrepant inter-laboratory results. Moreover, IIF requires highly trained personnel and is hard to standardize because of the subjectivity of interpretation (4).

Since IIF still is recommended as the gold standard for ANA screening, in vitro diagnostics manufacturers have introduced automation to compensate for IIF’s drawbacks. These automated systems offer significant improvements in slide preparation, and feature software to read, analyze, and interpret slides of digital images. Several companies offer these systems, including Nova View (Instrumentation Laboratory, Spain), Akiles (Medipan, Germany), Euroscope-Europattern (Euroimmun, Germany), and Zenit G (Euroimmun, Germany), Euroscope-Europattern (Euroimmun, Germany), Euroscope-Europattern (Euroimmun, Germany), and Zenit G (Euroimmun, Germany). These systems introduced automation to compensate for IIF’s drawbacks. These automated systems offer significant improvements in slide preparation, and feature software to read, analyze, and interpret slides of digital images. Several companies offer these systems, including Nova View (Instrumentation Laboratory, Spain), Akiles (Medipan, Germany), Euroscope-Europattern (Euroimmun, Germany), Euroscope-Europattern (Euroimmun, Germany), Euroscope-Europattern (Euroimmun, Germany), and Zenit G (Euroimmun, Germany). These systems offer improved performance and efficiency.

**Multiplex Immunoassay**

Recent advances in protein identification methods have generated a reservoir of candidate biomolecules, thus creating an arcade for high-throughput multiplex immunoassays that allow simultaneous quantification of many analytes. Multiplex immunoassays yield abundant information on multiple proteins in diverse biological processes, thereby providing clinicians and scientists with insight into the identification and assessment of disease progression.

Two basic assay formats have been developed to facilitate simultaneous quantification of multiple antigens: planar array assays and micro bead assays. Planar array assays spot different capture ligands at defined positions on a two-dimensional array. Micro bead assays like those based on Luminex MAP technology involve multiple micro beads, each coated with different capture ligands. Flow cytometry then detects an assay-specific fluorescent signal, which allows simultaneous detection of multiple analytes in a single reaction. There is abundant evidence suggesting that automated Luminex-based systems can rapidly and efficiently determine a profile of multiple antibodies.

Recently, clinical diagnostic laboratories have introduced this technological advancement in multiplex immunoassay for simultaneous multiple analysis. Several studies suggest that this assay is a useful tool for detecting ANA in autoimmune diseases (5). Currently available commercial systems based on fluorescent micro beads technology include BioPlex 2200 (Bio-Rad Laboratories, Hercules, California), AtheNA Multi-Lite (Zeus Diagnostics, Raritan, New Jersey), QuartzPlex (Instrumentation Laboratory, Barcelona, Spain), and FIDIS (BioMedical Diagnostics, Marne la Vallée, France).

**Experiences With a Multiplex Platform**

Over the last 5 years our laboratory has been using one of these multiplex systems, BioPlex 2200, to test ANA. This is a fully-automated Luminex-based system developed for high-throughput simultaneous analysis of 13 autoimmune analytes in a single tube, reacting with SSA (52 and 60 kDa), SSB, Sm, Sm/RNP, RNP-A, RNP-68 kDa, Scl-70, centromere B, dsDNA, chromatin, Jo1, and ribosomal P proteins (Table 1). This system couples microspheres with different laser-reactive colors to antigens of interest and combines them in a single microtitre well. The specimen and a fluorochrome-coupled secondary antibody are then added. The analysis uses flow dual laser cytometry in which the first laser identifies the colour of the bead (addressing the identity of the coated antigen) and the second identifies the presence and quantity of autoantibody bound to the antigen (Figure 3). Among the 13 antibodies, anti-dsDNA antibody is calibrated against World Health Organization Wo/80 standard, and the results are quantitative and expressed in terms of IU/mL. Values ≥10 IU/mL are taken as positive. All other antibody results are semi-quantitative, expressed in terms of Antibody Index (AI), and values ≥1.0 AI are taken as positive. We report ANA screen as negative if the results for all 13 autoantibodies are negative. Conversely, if any of the 13 autoantibodies is positive, we report a positive ANA screen and show the AI of individual antibodies. The medical decision support software (MDSS) included in the system suggests a disease association based on how individuals with similar autoantibody values have been diagnosed. The MDSS uses a database of 1,200-plus real-world individuals and contains the specific ANA screen results (all 13 auto-antibodies) plus the autoimmune disease diagnosis as determined by a physician (if disease was present) for each individual included.

**Figure 1**

**Conventional methods of testing ANA**

<table>
<thead>
<tr>
<th>Tentative Diagnosis</th>
<th>ANA screening by IIF</th>
<th>Staining pattern, titer</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANA to specific antigens</td>
<td>ELISA for ANA</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2**

**Multiplex System (Bio-Plex 2200)**

Identification & Quantitation

- Magnetic beads
- Quantitation 1.0 AI
- Identification SS-A60

**Figure 3**

**Clinical Laboratory News**

JUNE 2014
Antibodies detected by Bioplex and their possible association with connective autoimmune diseases

<table>
<thead>
<tr>
<th>ANTIBODY</th>
<th>TARGETED CONNECTIVE TISSUE AUTOIMMUNE DISEASES</th>
</tr>
</thead>
<tbody>
<tr>
<td>dsDNA</td>
<td>Systemic Lupus Erythematosus, Mixed Connective Tissue Disease, Scleroderma</td>
</tr>
<tr>
<td>SSA-60 kD</td>
<td>Sjogren’s syndrome, Systemic Lupus Erythematosus, Polymyositis, Scleroderma, Mixed Connective Tissue Disease</td>
</tr>
<tr>
<td>SSA-52 kD</td>
<td>Sjogren’s syndrome, Systemic Lupus Erythematosus, Polymyositis, Scleroderma, Mixed Connective Tissue Disease</td>
</tr>
<tr>
<td>SSB</td>
<td>Systemic Lupus Erythematosus, Mixed Connective Tissue Disease</td>
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<tr>
<td>Sm</td>
<td>Systemic Lupus Erythematosus, Mixed Connective Tissue Disease</td>
</tr>
<tr>
<td>Sm/RNP</td>
<td>Mixed Connective Tissue Disease, Systemic Lupus Erythematosus</td>
</tr>
<tr>
<td>RNP-60 kD</td>
<td>Mixed Connective Tissue Disease, Systemic Lupus Erythematosus</td>
</tr>
<tr>
<td>Chromatin</td>
<td>Systemic Lupus Erythematosus, Mixed Connective Tissue Disease, Sjogren’s syndrome, Polymyositis, Scleroderma</td>
</tr>
<tr>
<td>ScI-70</td>
<td>Scleroderma, Mixed Connective Tissue Disease</td>
</tr>
<tr>
<td>Centromere B</td>
<td>Scleroderma, Systemic Lupus Erythematosus</td>
</tr>
<tr>
<td>Ribosomal P</td>
<td>Scleroderma, Systemic Lupus Erythematosus</td>
</tr>
<tr>
<td>Jo-1</td>
<td>Polymyositis</td>
</tr>
</tbody>
</table>

The Bioplex system has been successfully evaluated in several studies for detection of ANA. One study assessed the positivity rate of 510 samples collected from a cohort of apparently healthy blood bank donors and reported a positivity rate per individual ranging from 0.0% to 1.8%, which translated into an individual analytic specificity ranging from 98.2% to 100% (6). Another study of a retrospective hospital cohort of 1,104 patient samples demonstrated that this system was suitable as a sensitive screening test to confirm or exclude the presence of a large number of autoantibodies simultaneously and rapidly (7).

A third, retrospective study analyzed 385 highly characterized antibody-positive sera (77% positive sera and 196 negative sera (5)). Overall sensitivity was 94.5% and specificity was 99.2%. A recent study using this multiplex system showed a higher sensitivity and a parallel specificity of the ANA-IIF (at 1:80 dilution) compared to the ANA screen (5). In addition, another study conducted for comparison of three anti-dsDNA testing demonstrated that Bioplex-multiplex and Farrzyme assays had similar overall agreement with the Farr assay, with Bioplex best reflecting disease activity in SLE patients (8).

A multicenter, prospective clinical study demonstrated that agreement between multiplex and EIA testing ranged from 99% (95% CI 98–100%) for Jo-1 to 70% (95% CI 76–82%) for ANA. The MDSS algorithm suggested an appropriate disease association in 75–100% of patients with SLE (9). These findings suggest that patterns of autoantibodies detected by this system, when analyzed by an interpretative algorithm, are useful in the evaluation of patients with autoimmune disorders.

This system offers advantages of being automated, having a shorter turn-around time, detecting multiple antibodies simultaneously, and being less subjective. On the downside, by employing a limited number of antigens it can lead to false-negative results compared with IIF testing (13). This is associated particularly with incompetence in detecting antibodies related to some specific disease profiles such as autoimmune liver diseases. In addition, recombinant proteins used in the assay may be poorly recognized by human autoantibodies, leading to false-negative results.

When our laboratory introduced this multiplex system in assessing ANA, we faced challenges with both hospital physicians and external clients in accepting a new style of reporting as well as the analytical process. A particular concern was that the new testing system did not provide an IIF pattern and tier. That led us to compare the new method with IIF for detecting ANA in 239 consecutive serum samples from our immunology clinic and to investigate the clinical significance of discrepant results (10). The new method showed 82.8% positive agreement, 83.7% negative agreement, and 83.3% overall agreement. Among 13 new method negative/IIF positive patients, only three showed a significant titer (>1:80) in IIF. These three were clinically stable on treatment. Twenty-seven patients showed new method positive/IIF negative results, of which 22 had been diagnosed with various AID, two had not been diagnosed with an AID, and the medical records of the other three patients were not accessible. A number of patients showed positive anti-double stranded DNA IgG (5/22), anti-ss-A (9/22), and anti-ss-B (6/22) results in the new method while these were missed by IFA.

Thus ANA testing with 13 selected antigens shows substantial agreement with IIF and appears to be a rapid, reliable tool for detecting ANA and displays overall comparability to IIF. The study’s findings helped our laboratory and clinics to accept the results of the new method. In addition, with continued communication regarding the principle of the new method and interpretation of results, the physicians in our hospital and referral laboratories became familiar with this new system.

We averaged about 70–80 specimens a day, and all the procedures are completed and reported within 90 minutes compared to the 7–8 hours required for setting up the test manually, obtaining results, and reporting. In situations where there is a strong clinical suspicion of underlying systemic autoimmune disease, where the ANA screen by multiplex method produces negative results, we arrange additional IIF tests.

Conclusions

Multiplex technology represents a real improvement of the diagnostic power of autoimmune testing. ANA testing by multiplexing has good concordance with the comparative methods. This multiplex system represents a rapid, sensitive, and specific method for diagnosing AID, particularly when the specificities of individual antibodies and the combinations of antibodies are taken into consideration. In laboratories with a large daily volume of samples, the labor savings and absence of subjective error in interpretation of results associated with this approach could result in significant savings and quality improvement. The physician receives results faster and gets the results of additional antibodies compared to the conventional ELISA method. In the future, inclusion of additional antigens associated with the nuclear pattern and autoimmune liver disease would further enhance the capability of this system in detecting ANA.

Acknowledgements

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References:


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Announcing the New, Improved CLN

It's no secret that the world of laboratory medicine is changing rapidly. You've read about it in the pages of CLN and lived it in your lab. From advanced automation systems and discoveries in proteomics and genomics to huge shifts in the reimbursement landscape, today's clinical lab is not the same as even a year ago, nor will it be the same in just a year.

In keeping with all this change, CLN is changing, too. In a survey last fall, readers told us they loved the magazine's content, but wanted more—more stories on new technologies and cutting-edge tests, more of CLN's trademark analysis of trends in medicine and laboratory practice, more on challenging reimbursement and policy matters—all in a concise and practical package.

Readers also told us that they often pass along CLN to their colleagues, save issues for future reference, and keep copies around the lab for their staff.

We heard you, and we're really excited to announce a bold new design for CLN—both inside and out—with our readers in mind, beginning with the July 2014 issue.

The most obvious change will be the magazine's size, look, and feel. We're stepping away from the oversized tabloid paper that jams your mailbox and doesn't fit in your file drawer. On the inside, you'll discover new features designed for CLN's broad readership, with new departments that tackle the issues you face in the lab every day, and speak to our readers' need to stay ahead-of-the-curve with medicine, policy, and technology advancements.

We hope you like the changes you'll see in CLN, and we want to hear what you think. Please email me personally with your thoughts, suggestions, and especially your ideas for how CLN can help you achieve better health through laboratory medicine.

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12th Annual Point-of-Care (POC) Coordinators Forum
CAP and TJC Considerations for Risk-Based QC Practices and Preparation Tips for POC Testing Programs
7:30–10 a.m. McCormick Place Convention Center
Sponsored by the AACC Critical and Point-of-Care Testing Division.
This year’s POC Coordinators Forum will highlight current accreditation organization efforts and updates related to POC testing quality control practices based on risk management principles. A panel of experienced POC Coordinators will discuss emerging strategies in POC testing for utilizing risk assessment findings in the development of quality control and quality assessment plans.
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Stacy Olea, MBA, MT(ASCP), FACHE, Field Director, The Joint Commission
Panel of Experienced POC Coordinators
May Louie, CLS, POCT and PSC Operations Manager, Stanford University Medical Center
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Lou Ann Wyer, MS, MT(ASCP), CQA(ASQ), Laboratory Director, Sentara Healthcare
Norfolk, Virginia
Registration: AACC/ASCLS member/non-member, $20. The registration includes breakfast followed by scientific sessions.

Nutrition Division Networking Symposium
Non-Alcoholic Fatty Liver Disease—A Silent Foe
6–9:30 p.m. Hyatt Regency Chicago
Sponsored by the AACC Nutrition Division.
The pathophysiology and epidemiology of non-alcoholic fatty liver disease will be the subject of this session. In addition, Irina A Kirpich, PhD, of the University of Louisville, and Edgard Delvin, PhD, of McGill University in Quebec, Canada, will explore current and emerging NAFLD biomarkers, give an overview of recent findings addressing the role of nutrition in the development and progression of NAFLD, and discuss the role of gut microbiota in the pathogenesis of NAFLD.
Registration: AACC/ASCLS member/non-member, $20. Includes a reception followed by awards presentation and scientific session.
With more than 200 sessions to choose from, the AACC Annual Meeting lets you customize a program that meets your needs.
Hospitals, Physicians Face Problems With Meaningful Use Stage 2

According to the latest data from the Centers for Medicare and Medicaid Services (CMS) Office of Health Standards and Services, only four hospitals and 50 physicians nationwide had met the 2014 stage 2 meaningful use requirements for electronic healthcare records (EHR) through April.

For providers to move into this stage, at least 30% of lab orders must be entered into the EHR through computerized physician order entry, and 55% of orders must be received electronically in a structured data format among other requirements. Hospitals and physicians also must be measured by quality metrics that rely on lab data.

According to a letter from the American Medical Association (AMA), physicians will also fall behind and face penalties due to what it sees as burdensome requirements of stage 2. AMA is recommending that physicians only be required to meet 50% of the stage 2 requirements to avoid penalties in 2015.

For its part, the American Hospital Association is focusing on problems with the government certification program for EHRs. According to comments submitted on April 28 to the Office of the National Coordinator for Health Information Technology (ONC), certification criteria for EHRs are not clear, making it difficult for hospitals to implement certified EHRs in time to meet stage 2 meaningful use requirements. AHA also urged ONC to "adopt a regulatory pace that allows for evidence-based analysis of the maturity of standards to support regulatory requirements."

More information is available from the AHA website, www.aha.org/advocacy.

Report: Hospital Quality Gains Saved 15,000 Lives, $4 Billion

New preliminary data from the Department of Health and Human Services (HHS) show an overall 9% decrease in hospital-acquired conditions nationally during 2011 and 2012. National reductions in adverse drug events, falls, infections, and other forms of hospital-induced harm are estimated to have prevented nearly 15,000 deaths in hospitals, avoided 560,000 patient injuries, and approximately $4 billion in health spending over the same period.

Additionally, between January 2012 and December 2013, the Medicare all-cause 30-day readmission rate dropped 8%—falling from 19% to 18.5%. According to HHS, these improvements reflect policies and public-private collaboration made possible by the Affordable Care Act. Beginning October 1, 2012, the law began penalizing hospitals with excess readmissions for common, expensive conditions. CMS trims up to 1% of a hospital's total reimbursements if its readmissions for heart failure, myocardial infarction, and pneumonia rise above a target based on national averages for Medicare patients.


Stolen Laptops Lead to HIPAA Settlements

Two entities have paid the Department of Health and Human Services Office for Civil Rights (OCR) $1.975,220 collectively to resolve potential violations of the Health Insurance Portability and Accountability Act (HIPAA) Privacy and Security Rules. These penalties underscore the significant risk to the security of patient information posed by unencrypted laptop computers and other mobile devices, according to OCR.

OCR opened a compliance review of Concentra Health Services upon receiving a breach report that an unencrypted laptop was stolen from one of its facilities, the Springfield Missouri Physical Therapy Center. OCR’s investigation revealed that Concentra had previously recognized in multiple risk analyses that a lack of encryption on its laptops, desktop computers, medical equipment, tablets, and other devices containing electronic protected health information (ePHI) was a critical risk.

In the second incident, OCR received a breach notice from QCA Health Plan of Arkansas reporting that an unencrypted laptop computer containing the electronic protected health information of 148 individuals was stolen from a staff member’s car. While QCA encrypted its devices following discovery of the breach, OCR’s investigation revealed that QCA failed to comply with multiple requirements of the HIPAA Privacy and Security Rules.

Healthcare providers can access six OCR educational programs on compliance with the HIPAA Privacy and Security Rules. One module focuses specifically on mobile device security. The programs are online, www.hhs.gov/ocr.
Abbott, Idera Partner on B-Cell Lymphoma Co-Diagnostic

Abbott and Idera Pharmaceuticals have joined forces to develop a companion diagnostic test for use in Idera’s clinical development program for IMO-8400, a drug for the potential treatment of two forms of B-cell lymphoma characterized by the presence of the oncogenic mutation MYD88 L265P. This mutation can be identified in approximately 90% of patients with Waldenstrom’s macroglobulinemia and approximately 30% of patients with the ABC sub-type of diffuse large B-cell lymphoma, and plays a key role in activating the Toll-like receptor (TLR) pathways targeted by IMO-8400. Under the terms of the agreement, Abbott will develop a test using polymerase chain reaction technology to identify the presence of MYD88 L265P in tumor biopsy samples with high sensitivity and specificity.

“Research by Idera and by independent investigators has established TLR antagonism as a potentially promising and novel therapeutic approach for patients with B-cell malignancies harboring the MYD88 L265P mutation,” said Lou Brenner, MD, senior vice president and chief medical officer of Idera. “This companion diagnostic will be an important tool for the clinical community in evaluating whether their patients are potential candidates for IMO-8400 therapy for the treatment of these genetically defined forms of B-cell lymphoma.”

Quest Takes Over Steward Health Care System’s Outreach Laboratory Testing Services

Quest Diagnostics has acquired the outreach laboratory service operations of Steward Health Care System, New England’s largest community-based accountable care organization (ACO) and one of the nation’s largest Pioneer ACOs. This transaction is an extension of a previous partnership with Steward that began in 2010, when Steward acquired the Caritas Christi Health System, an affiliate of which (Caritas Medical Laboratories) was already owned by Quest. Under this new arrangement, affected physicians, patients, and other providers will have the ability to access Quest’s 200 patient service centers in New England as well as broader clinical testing and healthcare information technologies that connect with electronic health records used by the Steward network. Quest will also provide outreach laboratory testing services to physicians, nursing homes, and other providers previously served by Steward. The financial terms of this transaction have not been disclosed.

Next Month in CLN

• Point-of-Care Testing: Managing Risk

IBM, Coriell, CareKinesis Join Forces to Reduce Adverse Drug Reactions

In collaboration with IBM and CareKinesis, Coriell Life Sciences is launching an initiative with Program for All Inclusive Care of the Elderly’s more than 5,000 senior clients to help enhance medication safety by better understanding how high-risk individuals respond to specific medications and drug treatments. The partnership aims to accomplish this goal by using a scalable, cloud-based solution built by Coriell and IBM to safely and cost-effectively store genetic data from elderly patients in Coriell’s GeneVault. Under the strict privacy controls of the interconnected CareKinesis and Coriell Life Sciences systems, physicians, healthcare providers, and medical experts will then be able to access a patient’s genomic interpretation via any web-connected device. Using this information, they can determine whether a medication will cause any adverse reactions for a patient or be at odds with other drugs the patient is currently taking.

“This approach of treating conditions ‘one at a time’ even if the treatments might conflict with one another has been common in medicine, in part because little information exists to guide practitioners in how to consider this problem, weigh alternatives, and identify different options. Better understanding of an individual’s genome can lead to a more effective dosage regimen,” said Scott Megill, CEO of Coriell Life Sciences.

Berg, Medical University of South Carolina Team Up to Discover Lupus Biomarkers

Berg and the Medical University of South Carolina, a leading lupus research center, have entered a collaboration to identify new therapeutic pathways and potential biomarkers to treat lupus. Current lupus therapies are effective for approximately half of all patients, but these treatments only partially control the disease and often lead to harmful side effects such as infertility, infection, and cardiovascular disease. In this partnership, Berg’s Interrogative Biology platform will be applied to several serum, urine, and kidney data points from both lupus patients and controls followed in the Medical University of South Carolina’s rheumatology clinics. The two organizations will analyze the pathophysiology of lupus using the metabolomics, lipidomics, and proteomics data from tissue samples, expanding the search for a biomarker to predict the onset and progression of the disease. The partnership hopes that any discovered biomarkers can then be used to create safer personalized medicine for the disease. Previously, Berg’s Interrogative Biology platform has been used successfully for the discovery of targets, therapeutics, and biomarkers for diverse diseases including cancer, metabolic diseases, and neurodevelopment disorders.

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A pilot proof-of-concept study demonstrated that not routinely reporting urine culture results from non-catheterized inpatients can greatly reduce unnecessary antimicrobial therapy for asymptomatic bacteriuria (Clin Infect Dis 2014;58:980–3).

Researchers at the University of Toronto conducted the study after observing that urine cultures from non-catheterized patients were rarely associated with urinary tract infection (UTI). In addition, prior studies have shown that antimicrobial therapy for asymptomatic bacteriuria (ASB) does not confer benefits except in specific populations, yet is associated with adverse drug reactions and selection for infection with increasingly resistant bacteria.

Realizing that to change urine culture ordering practices would require modification of long-standing clinical protocols and beliefs, the authors tested what effect a change in lab reporting practices would have. During the study’s implementation period, they stopped routinely reporting positive results from non-catheterized patients, and instead posted a message in the electronic health record advising clinicians that most positive urine cultures from inpatients without catheters were likely due to ASB. The message then requested clinicians who strongly suspected their patients of having UTI to contact the laboratory.

The researchers found that 23% of urine specimens were positive, but UTI was present in only 2% of non-catheterized patients and 3% of those with catheters. The rate of antimicrobial therapy for ASB before the intervention was 48%; but during the intervention period it dropped to 12%, for a 36% absolute risk reduction. Based on these findings the researchers concluded that no longer reporting positive non-catheterized urine culture results unless physicians called the lab and requested them greatly reduced antimicrobial therapy for ASB.

**Biomarker-Based Sepsis Risk ModelValidated**

A multinational, multi-institutional research team reported deriving, testing, and validating a biomarker-based risk model that estimates mortality in adults with septic shock (Crit Care Med 2014;42:781–9). The researchers sought to determine how well QFT-GIT—a specific test for tuberculosis skin testing (TST) in a diverse population of students at the University of Pennsylvania (Clin Infect Dis 2014;58:1260–6). The findings support the use of TST for college students in the United States and risk-stratified result interpretation for students tested with QFT-GIT, according to the authors.

About 750,000 of the 20 million college students in the United States were not born in the U.S., and many come from countries with a high incidence of Mycobacterium tuberculosis infection and have been vaccinated at birth with Bacillus Calmette-Guerin (BCG). Guidelines of the Centers for Disease Control and Prevention suggest that while TST and interferon gamma release assay (IGRA) may be used interchangeably, IGRA is the preferred test in people who have received BCG vaccination because it does not cross-react with BCG. However, the authors suggested cautious interpretation of this proposed benefit of IGRA because BCG has a variable effect on TST and cross-reactivity wanes over time.

The researchers sought to determine how well QFT-GIT—an IGRA—and TST performed in detecting tuberculosis infection in students with varied risk profiles. During the study period, 9,483 students received 15,936 tuberculosis tests. Coming from a tuberculosis-endemic country was the only risk factor significantly associated with a positive test result. TST had higher specificity than QFT-GIT; 99.7% versus 91.4%. When the researchers assessed a high incidence of tuberculosis skin testing (TST) in a diverse population of students at the University of Pennsylvania (Clin Infect Dis 2014;58:1260–6).

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The researchers sought to determine how well QFT-GIT—an IGRA—and TST performed in detecting tuberculosis infection in students with varied risk profiles. During the study period, 9,483 students received 15,936 tuberculosis tests. Coming from a tuberculosis-endemic country was the only risk factor significantly associated with a positive test result. TST had higher specificity than QFT-GIT; 99.7% versus 91.4%. When the researchers assessed a high incidence of tuberculosis skin testing (TST) in a diverse population of students at the University of Pennsylvania (Clin Infect Dis 2014;58:1260–6).

The findings support the use of TST for college students in the United States and risk-stratified result interpretation for students tested with QFT-GIT, according to the authors.
Roche's HPV Test First Ever Approved for Primary Cervical Cancer Screening

FDA has expanded upon its 2011 approval of Roche's cobas human papillomavirus (HPV) test, making it the first HPV DNA test that can be used by itself to help healthcare professionals assess the need for a woman to undergo additional screening for cervical cancer. The test can also provide information about a patient's risk of developing cervical cancer in the future. Originally approved for use in conjunction with or as a follow-up to a Pap test, the cobas HPV test is for women age 25 and older. Using a sample of cervical cells, it detects DNA from 14 high-risk HPV types, specifically identifying HPV 16 and 18 while concurrently detecting 12 other types of high-risk HPV. Women who test positive for HPV 16 or 18 should then have a colposcopy. Women testing positive for one of more of the 12 other high-risk HPV types should have a Pap test to determine the need for a colposcopy. Healthcare professionals should use the cobas HPV test results together with other information, such as the patient's screening history and risk factors, and current professional guidelines.

FDA Warns Against Use of Unproven GenStrip Blood Glucose Test Strips

FDA advises both diabetics and healthcare providers to stop using Shasta Technologies’ GenStrip Blood Glucose Test Strips, which are advertised for use with the LifeScan OneTouch family of glucose meters, as FDA found extensive violations of federal regulations intended to assure the quality of products in the manufacturing of GenStrip Test Strips. Without assurance of an adequate quality system, FDA believes that the strips could report incorrect blood glucose levels, which is likely to lead to inappropriate or delayed treatment that could significantly harm patients. To date, Shasta Technologies has been unwilling to recall their test strips. As a result, FDA urges patients and healthcare providers to start using alternative glucose test strips that are designed for use with the LifeScan OneTouch family of glucose meters.

Draft Guidance Aims to Expedite LifeScan OneTouch family of glucose meters.

To be eligible for participation in the program, a medical device must be intended to treat or diagnose a life-threatening or irreversibly debilitating disease or condition for which either no approved alternative treatment or diagnostic exists, the new technology provides a clinically meaningful advantage over existing technology, or availability of the new technology is in the patient's best interest.

In addition to the EAP draft guidance, FDA published the document, “Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval.” This draft guidance outlines the agency’s current policy on when data can be collected after product approval and what actions are available to FDA if approval conditions, such as postmarket data collection, are not met. FDA is seeking public comments on both documents through June 22. Electronic comments may be submitted at www.regulations.gov.

New FDA-Cleared Vitamin D Assay Now Available on CLC720 Platform

Carolina Liquid Chemistries announced the availability of a new, FDA-cleared vitamin D assay on the company's CLC720 general chemistry analyzer. Known as the Vitamin D-direct assay, this test is a homogeneous immunoassay that measures true total 25-hydroxy vitamin D, which is the sum of D3 + D2. The test can produce a result without a technologist having to manually pre-treat the specimen or the reagent. The CLC720 can also run up to 400 vitamin D tests per hour, and can be run in random access mode with other chemistry tests, eliminating the need for batch testing. These two features combined reduce the time-to-result to less than 20 minutes from the 2 to 7 hours that microtiter plate vitamin D tests require. Additionally, the Vitamin D-direct assay offers a wide dynamic range with improved precision, and eliminates washing steps as well as inaccurate results caused by matrix effects.

Randox Receives Clearance for Four Clinical Controls

FDA has cleared four different Randox controls: the company’s Acusera HBAlc quality control, Acusera Aldolase and Ammonia Ethanol clinical chemistry controls, and immunology cerebrospinal fluid (CSF) control. Acusera HBAlc is used to ensure accuracy in the diagnosis and ongoing monitoring of diabetes. It is lyophilized to enhance stability and longevity, with assayed values provided for high-performance liquid chromatography as well as a wide range of clinical chemistry analyzers. Additionally, it is a 100% human whole blood control, which helps minimize matrix effects and reduces lot-to-lot variations between batches. Randox’s Acusera Aldolase calibrator and controls can be used when testing for liver damage as well as skeletal muscle diseases such as muscular dystrophy, while Randox Ammonia Ethanol control is liquid ready to use, with an open vial stability of 30 days at 2–8°C.

Lastly, Randox’s immunology CSF control is a multi-analyte CSF control that is suitable for use on most clinical analyzers, providing method-specific target values and ranges for 11 analytes.

510(k) Clearance for BioFire’s Gastrointestinal Panel

BioFire, a molecular biology affiliate of bioMérieux, has received 510(k) clearance for the FilmArray gastrointestinal (GI) panel. This panel contains 22 bacterial, viral, and parasite targets in one test—including several for which there were no FDA-cleared tests prior to this—thereby covering the breadth of pathogens that cause GI illness. Unlike open-platform testing that leaves labs vulnerable to cross-contamination, the FilmArray is also a closed system that integrates sample preparation, amplification, and detection. This panel is performed directly from stool in Cary Blair transport media, takes 2 minutes to set up, and produces results in about 1 hour.
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