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G2 INTELLIGENCE Upcoming Conferences

Lab Institute 2016
October 26-28, 2016
Hyatt Regency Washington on Capitol Hill, Washington, DC

Big Data, Informatics and Specimen Reliability Dominate Discussion at G2 Lab Revolution Event

Opportunities and challenges for laboratories was the key theme of G2 Intelligence's Lab Revolution and a one-day pre-conference workshop held at the Sheraton Wild Horse Pass Resort and Spa in Chandler, Ariz., April 6-8. The main conference explored innovative business models, market drivers, and practical solutions while the pre-conference workshop, focused on informatics, big data and the opportunities that data provides for laboratories.

Rise of Informatics

The Rise of Informatics and the Lab Workforce of the Future, co-hosted April 6 by G2 Intelligence and academic partner, Arizona State University's International School of Biomedical Diagnostics, addressed the need for standards concerning data, and how laboratories can profit from big data, establish informatics programs, and acquire the right talent to lead informatics initiatives.

Keynote speaker Dr. Anna Barker discussed data quality and integrity and noted the impact that a lack of reproducibility of research has on molecular diagnostics development.

Irreproducibility of published papers and quality of specimens were the centerpiece of a presentation by Dr. Carolyn Compton who asserted "for the biomedical business flipping a coin is … superior to reading *Science* or *Nature* in making business decisions." She explained the various pre-acquisition and post-acquisition factors that can affect specimen quality and the ability to identify biomarkers. Citing a dearth of standards concerning patient samples, she indicated, "the bar for specimen quality is going nowhere but up."

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California Bill Revamps Regulation of Clinical Laboratories

A bill is pending in the California Legislature that would take the licensing and inspection of clinical laboratories away from state regulators if signed into law.

Authored by Assemblywoman Susan Bonilla, a Democrat from the Northern California city of Concord, the bill would strip laboratory licensing from the California Department of Public Health (CDPH), the primary regulator in the state for both hospitals and laboratories. Licensure is required

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Big Data, Informatics and Specimen Reliability Dominate Discussion, *from page 1*

As Compton noted, the White House has agreed and issued in 2014 a Request for Information seeking public comment on how the federal government, a significant funding source for research, can help address this problem. Additionally, the National Institutes of Health held a workshop in June 2014 with the Nature Publishing Group and Science addressing principles to improve reproducibility and rigor of research. Compton noted those principles included a stipulation that "[s]ufficient information about sample collection must be provided to distinguish between independent biological data points and technical replicates."

An opening keynote address by laboratory industry veteran R. Keith Laughman emphasized that diagnostics are the "most actionable data in health care."

Compton and Barker both are working toward a solution to this problem through their efforts with the National Biomarker Development Alliance (NBDA). Dr. Barker is the President and Director, and Dr. Compton serves as Chief Medical Officer, for the NBDA, which is seeking an end-to-end, standards-based approach to biomarker development.

Revolutionary opportunities and challenges

The vast opportunities big data presents for laboratories continued to be discussed after the workshop throughout G2 Intelligence's Lab Revolution conference, April 7-8. An opening keynote address by laboratory industry veteran R. Keith Laughman emphasized that diagnostics are the "most actionable data in health care." Like Compton and Barker, he noted the need for reliable specimen integrity and advised that the industry needs to consider how diagnostic data generated from lab specimens can be used to improve health care delivery.

Among the challenges labs face, a panel highlighted the FDA's proposed oversight of laboratory developed tests. Michael Murphy, president of Conatus Consulting, and Richard S. Robinson MT (ASCP) from the American Red Cross Biomedical Headquarters Regulatory Affairs reviewed the current status of the FDA proposal and provided some practical advice to help labs prepare for anticipated new oversight. Murphy emphasized the importance of developing quality systems and noted that in the 20 cases the FDA mentioned in their recent reported concerning problematic LDTs, errors were due to "extremely deficient" quality control. In the short term, he recommended labs focus on quality systems, design controls and document controls. To establish a quality system he set forth three steps: 1) conduct a gap analysis, 2) get management buy in, 3) develop SOPs, and 4) train employees.

Panelists David W. Gee and Caitlin Forsyth, health care lawyers with Davis Wright Tremaine LLP in Seattle, invoked the Back to the Future theme to advocate that labs learn from the compliance problems of the past to prevent issues in the future. In particular, Gee and Forsyth recommend labs look closely at provisions of the corporate integrity agreements (CIA) involving labs, such as the recent CIA in the Millennium Health settlement. They also highlighted provisions of the OIG's original compliance guidance as well the recent Millennium CIA that address best practices with regard to requisition form design, medical necessity issues, and Anti-kickback Statute and Stark Law violations involving free items to ordering providers, relationships and agreements with ordering providers, and control of sales materials and operation of sale representatives. Returning to the topic of big data that permeated the conference, Gee and Forsyth highlighted how the government is using big data and real time analytics to spot fraud and compliance issues earlier. The five takeaways Gee and

Forsyth summed up with advised labs to 1) get medical necessity documentation right from the start, 2) do real time audits of test requisitions to confirm tests are properly ordered, performed and billed, 3) be cautious of custom profiles, 4) avoid third party marketing, and 5) train and monitor employed sales representatives.

Finally, the final presentations wrapping up the conference addressed future challenges for laboratories including not just management of data but changing technology, and a changing marketplace. George Poste, chief scientist, Complex Adaptive Systems Initiative and professor at Arizona State University and Chris Wasden, executive director and professor of innovation, Sorenson Center for Discovery and Innovation at the University of Utah and Dr. Robert Boorstein all highlighted the emergence of mobile and point of care diagnostic technology, including remote monitoring, wearables and even ingestable technology.

Drug Testing Gives Rise to Convictions and Costly Settlement in Recent Enforcement Cases

Pain management and drug abuse have received significant media attention and federal funding devoted to stopping an opioid epidemic. Health care fraud enforcement agencies are also focused on the providers who profit from unnecessary testing related to pain management and drug abuse treatment programs.

"Clinical labs play a critical role in providing care for people on Medicare."

— Nick DiGiulio, Office of Inspector General

Recent health care fraud enforcement cases involving diagnostic professionals performing drug testing for Medicare beneficiaries have resulted in a multi-million dollar settlement and the conviction of two lab professionals. "It's unconscionable that anyone would exploit this epidemic to enrich themselves on such a massive scale," said Virginia Attorney General Mark R. Herring in a press release announcing the convictions in one fraud case.

Two Tennessee lab professionals were convicted April 7, 2016, of federal conspiracy and health care fraud charges relating to urine drug screening tests. The government alleged that Beth Palin, 49, and Joseph D. Webb, 55, who owned Bristol Labs, billed Medicare, Medicaid, TennCare and other insurers for medically unnecessary drug tests which were not used by the treating physician to determine patient care.

According to the Department of Justice, the two lab professionals worked with a physician who set up a "purported" substance abuse treatment program next door to their lab in Virginia. The physician's program involved only medication assisted treatment, prescribing Suboxone, and required weekly drug testing for his patients, 100 percent of which the government said he referred to Bristol Labs. Insured patients were prescribed expensive drug screening tests (automated screens), which were billed to Medicare and Medicaid and other insurers, and paid nothing out of pocket, while uninsured, self-pay patients were prescribed a $25 dip-stick drug screen. The government also alleged that Palin and Webb set up their own addiction practice with a similar test ordering procedure. The government estimated the testing scheme led to more than $14 million in medically unnecessary drug tests.

"Clinical labs play a critical role in providing care for people on Medicare," said Special Agent in Charge Nick DiGiulio, of the Office of Inspector General. "Lab professionals who aim to get rich quick by cheating patients and taxpayers, as in this case, can expect to pay a high price for their crimes."

> *"This settlement is one of many that are sending a strong message to the lab industry that they need to clean up their act."*
>
> — Derrick L. Jackson, Office of Inspector General

In another case, PremierTox 2.0, Inc. settled for $2.5 million False Claims allegations relating to urine drug screenings in Tennessee and Kentucky. The government alleged three types of conduct gave rise to false claims: 1) PremierTox (doing business in Tennessee under the name Nexus) gave discounts on drug screen tests for uninsured patients in exchange for referrals of Medicare or TennCare covered patients; 2) PremierTox/Nexus submitted Medicare and TennCare claims for lab tests that were not medically reasonable and necessary; and 3) PremierTox provided Kentucky providers with free point of care testing cups for using its services. The settlement resolves two separate cases against PremierTox/Nexus brought by whistleblowers in Kentucky and Tennessee. Unlike the conviction in the Virginia case, a settlement means the allegations were not proven in court and no liability was determined.

"Medically unnecessary lab tests and financial incentives from labs to doctors in exchange for referrals are costing the taxpayers millions of dollars," said Derrick L. Jackson, Special Agent in Charge for the Office of Inspector General in Atlanta. "This settlement is one of many that are sending a strong message to the lab industry that they need to clean up their act."

Takeaway: Diagnostic professionals billing for drug screening tests relating to pain management and substance abuse treatment face government scrutiny.

Update: Federal Agencies Accelerate Preparations to Combat Zika Virus in the U.S.

As spring arrives and the threat of Zika virus grows in the U.S., the Centers for Disease Control and Prevention (CDC) and the U.S. Food and Drug Administration (FDA) are stepping up preparations to do battle against the virus. While mosquito-borne cases of Zika transmission haven't yet been detected in the continental United States, they are found in U.S. territories including Puerto Rico and the U.S. Virgin Islands. Also, as of April 13, 2016, the CDC reports 358 cases of travel associated Zika virus cases in the United States—with New York and Florida reporting the most cases at 54 and 82 respectively and seven cases nationwide determined to result from sexual transmission.

CDC's National Summit

April 1, 2016, the CDC hosted government representatives, health care professionals and private stakeholders at a national summit to discuss how to prepare for the Zika virus here in the U.S. "The mosquitoes that carry Zika virus are already active in U.S. territories, hundreds of travelers with Zika have already returned to the continental U.S., and we could well see clusters of Zika virus in the continental U.S. in the coming months. Urgent action is needed, especially to minimize the risk of exposure during pregnancy," said CDC Director Tom Frieden, M.D., M.P.H. in the CDC's release announcing the summit. In the same announcement, Amy Pope, J.D., White House Deputy Homeland Security Advisor and Deputy Assistant to the President highlighted the President's $1.9 million funding request to "prepare for, detect, and respond to any potential Zika outbreaks" in the U.S. (See *National Intelligence Report*, 2/11/16, p. 7 for further discussion of federal funding requests relevant to diagnostics for the Zika virus). "The Administration is coordinating a whole-of-government effort to ensure that we are taking all available steps to pre-

pare for Zika and work together with state, local, tribal, and territorial officials to protect Americans," said Pope.

In person participants of the summit included 178 state, local and tribal representatives, representatives from 24 non-governmental organizations and representatives from 20 government agencies and departments including the FDA, National Institutes of Health, Centers for Medicare & Medicaid Services, and the Department of Health and Human Services. Additionally, the CDC indicated approximately 2,000 people registered to attend the webcast of the summit. In opening remarks, Pope noted that "we don't have all the diagnostics we need" and thus part of the President's funding request includes support for preparedness efforts that include "accelerating vaccine development and diagnostics." Dr. Nicole Lurie, Assistant Secretary of Preparedness and Response, RADM, U.S. Public Health Service, similarly highlighted in her opening remarks the need for development of better diagnostics and increasing laboratory capacity. Lurie also explained that the government is active in regions with current outbreaks including Puerto Rico and the U.S. Virgin islands and using what is learned from outbreaks there to prepare the rest of the United States, including efforts to develop "better, faster, Zika diagnostic tests as quickly as possible."

Blood donation screening

Days before the summit, the FDA announced that a screening test to detect Zika virus in blood donations was available for use under an investigational new drug application. Noting the importance of protecting the nation's blood supply and screening blood in U.S. territories already affected by Zika transmissions, Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research, said in a statement: "In the future, should Zika virus transmission occur in other areas, blood collection establishments will be able to continue to collect blood and use the investigational screening test, minimizing disruption to the blood supply." Previously, in February 2016, the FDA issued recommendations on how to reduce risk of transmission via blood transfusion. Those recommendations advised blood establishments in areas with active Zika virus transmission obtain whole blood and blood components for transfusion from areas of the U.S. without active transmission. (See *National Intelligence Report*, 3/10/16, p. 1).

Roche, whose cobas® Zika test was authorized for use to screen blood donations, says the "first stage" will be to use the test in Puerto Rico to reduce the need to import blood and the "second stage of deployment" for the test will be use "in the southern United States, which will most likely be impacted by any spread in the virus." "All Testing Laboratories will need to be enrolled in and contracted into the clinical trial as specified and agreed with the FDA Center for Biologics Evaluation and Research."

Takeaway: Federal agencies increase efforts to raise awareness and prepare to combat the Zika virus in the U.S. while seeking Congressional action to fund preparedness efforts.

As Value-based Goals are Achieved, Medicare Spending Declines By Billions of Dollars

After announcing that the goal of linking 30 percent of Medicare payments to quality was reached months earlier than anticipated, the U.S. Department of Health and Human Services (HHS) recently reported that Medicare spending between 2009 and 2014 was $473.1 billion lower than it would have been if average growth in the eight years prior to that period had continued. HHS also estimated that Medicare spending could be $648.6 billion less between 2009 and 2015 than it would have been if 2000-2008 average growth rate had continued. "To put this in context, this reduction in spending is greater than all of Medicare's spending for personal health care expenditures in 2015," according to HHS' report. The prediction relies on per enrollee spending growth remaining as low as 1.1 percent.

Crediting the Affordable Care Act for the success, the HHS press release announcing the Medicare spending report said "[t]he health care law gives HHS new tools to pay providers for what works, better coordinate and integrate care, and make information more readily available to those who can use it to improve health. Initiatives to limit avoidable hospital readmissions and to promote new payment models that focus on value are contributing to the moderation in overall health spending, and particularly for Medicare." Despite the slowed growth in spending, the report does reveal that 2014 expenditures for national personal health care increased by 4.3 per cent per person. Still, even this increase is considered "modest" by HHS, compared to growth in prior years, and is attributed to the increase in health care insurance coverage under the ACA.

California Bill Revamps Regulation of Clinical Laboratories, *Continued from bottom of p.1*

from that agency if a lab is performing tests that are considered moderate or high complexity. The CDPH also collects fees for various inspections, which range from $25 for a clinical laboratory scientist's license renewal to $5,260 to relicense a lab that is performing more than one million tests annually. Bonilla's office was not immediately available for comment on the bill.If the bill becomes law, the duties for inspection and enforcement would likely be transferred to the Centers for Medicare & Medicaid Services (CMS), which was given the authority under the Clinical Laboratory Improvement Amendments (CLIA) passed in the 1980s.

The CDPH has come under scrutiny in recent years for personnel shortages, particularly in its hospital division. Fines and administrative penalties against acute care facilities have dropped in recent years, although the agency has recently made new hires of dozens of inspectors in Los Angeles County, the state's most populous county by a wide margin, CDPH officials said. CDPH also recently approved the use of private non-profit organizations to approve a lab's ongoing deemed status after their initial licensure. The state's primary lobbying group for laboratories has yet to take a position on the bill, which was introduced last month. Michael Arnold, executive director of the California Clinical Laboratory Association, said it is currently in a "watch position" on the measure, and that its position would evolve after an initial public hearing.

"We are working with the author. There are amendments being discussed," Arnold said. He added that "there is considerable opposition (to the bill) from employee organizations representing clinical lab scientists and others." The bill's first committee hearing is scheduled for April 19.

Takeaway: California could take actions to delegate laboratory licensure and inspections back to the federal government.

Sequenom to Petition U.S. Supreme Court to Regain MateriT21 Test Patent

With its sales and margins suffering unrelenting pressure, the beleaguered molecular testing firm Sequenom has decided to petition the United States Supreme Court in an attempt to regain a patent for a genetic test it lost three years ago.

The petition is centered around what has been referred to in laboratory circles as the "540 patent," in reference to the last three numbers of a patent Sequenom held until 2013 that it applied to its MateriT21 test. That assay is used to analyze cell-free fetal DNA (cffDNA) in a mother's blood to diagnose genetic conditions. Sequenom had claimed that Ariosa Diagnostics' Harmony Prenatal Test and Natera's Non-Invasive Paternity Test (licensed to DNA Diagnostics Center, Inc.) infringed the '540 patent. Last year in June, the Federal Circuit Court of Appeals affirmed a ruling that Sequenom's '540 patent relating to cffDNA failed to assert claims that were patent eligible. The appellate court said it was bound by a prior decision in the *Mayo Collaborative Services v. Prometheus Laboratories, Inc.* Judge Richard Linn, an appointee of President Bill Clinton, said he only went along with the majority because of the sweep of the Prometheus case, suggesting that some guidance as to how it should be applied in the future may be in order.

In the *Prometheus* case, the U.S. Supreme Court invalidated two patents held by Prometheus Laboratories. Those patents, which used metabolite levels in the blood-

stream to guide the dosage levels of certain drugs, merely described a law of nature. The rationale in that case was applied by the courts to invalidate patenting the use of cffDNA for genetic profiling the following year, as the phenomenon was considered to be naturally occurring. Sequenom's patent didn't claim patent eligibility for discovery of cffDNA but for the methods that used the cffDNA. The appellate court's June 2015 decision explained that Sequenom's patent claims addressed a natural phenomenon used "in combination with well-understood, routine and conventional activity" that wasn't patentable subject matter. The court explained that "groundbreaking, innovative or even brilliant discovery" wasn't necessarily patentable. In December, the appellate court denied Sequenom's request for a rehearing. However, one dissenting judge, Pauline Newman, an appointee of President Ronald Reagan, observed that "the new diagnostic method here is novel and unforeseen, and is of profound public benefit" and claimed that "[p]recedent does not require that all discoveries of natural phenomena or their application in new ways or for new uses are ineligible for patenting; the Court has cautioned against such generalizations."

"We continue to believe that the groundbreaking techniques embodied in the '540 patent are eligible for patent protection."

— Dirk van den Boom, CEO, Sequenom

As a result, Sequenom is essentially asking the High Court to narrow the scenarios in which the rationale from *Prometheus* may be applied, stating "overly-expansive patent eligibility criteria have not only negatively impacted Sequenom's patent, but have put into jeopardy the patentability of existing and future diagnostic method patent claims."

"We continue to believe that the groundbreaking techniques embodied in the '540 patent are eligible for patent protection," said Sequenom Chief Executive Officer Dirk van den Boom, in a statement. "More broadly, we believe our case provides a compelling opportunity for the Supreme Court to clarify patent eligibility criteria to protect the significant investments made by Sequenom and other life science organizations that have undoubtedly advanced the standard of patient care and treatment, as well as encouraging future such investments."

Whether or not the Supreme Court would take the case remains to be seen; it only grants hearings for a tiny minority of petitions that are presented. A 2013 case it decided, *Association for Molecular Pathology v. Myriad Genetics*, invalidated a patent Myriad tested for the BRCA gene, suggesting that it is likely to hew to a fairly narrow path as to what kind of testing is patentable.

Takeaway: Sequenom is taking a last-ditch approach with the U.S. Supreme Court in an attempt to gain more market control over its cell-free fetal DNA assays.

Government Scrutiny of Theranos Increases

Theranos continues to face challenges concerning its Newark, Calif., laboratory as its initial response to Centers for Medicare & Medicaid Services (CMS) failed to resolve inspection issues and the agency recommended the company's CLIA certification be revoked for that Calif. lab. CMS recommended that Theranos lose its CLIA certification unless the lab provides evidence why the recommended sanctions shouldn't be imposed. That was based on an inspection that took place late last year where the agency determined Theranos' Newark, Calif., laboratory had condition level deficiencies and posed an immediate danger to patients in the area of hematology. (See *National Intelligence Report*, 2/11/16, p. 3).

Theranos provided corrective action in response but CMS concluded that the lab's corrective actions were not credible, noting instances where Theranos plans were non-specific. Theranos can appeal the CLIA certificate revocation if it is imposed. CMS also recommended limitations on the lab's performance of hematology assays that would take place almost immediately. Theranos faces a $10,000 daily fine for non-compliance. CMS has also requested a list of all providers who have used the lab since January to notify them of the ongoing issues at the facility.

Theranos Chief Executive Officer Elizabeth Holmes also appeared on NBC's Today show in an interview with Maria Shriver and indicated she was "devastated" that her company didn't catch problems earlier and she vowed to fix the problems and continue her company's mission.

CMS' 147-page inspection report charted a number of omissions and failures in the operation of the laboratory (Theranos' facility in Arizona was not included in this report or the sanction recommendations). The issues enumerated relate to preanalytic systems and relevant documentation, chemistry quality control corrective actions, equipment calibration, laboratory director signoff on mandated procedures or changes to procedures, and failure to notify patient(s) of errors in test results in timely fashion.

There were some redactions to the report, including the annual test volume of the laboratory. Meanwhile, as our sister publication *Laboratory Industry Report* reported, a group of researchers from one of the most prestigious teaching hospitals in the nation questioned the validity of Theranos' testing platform in a study published in the *Journal of Clinical Investigation*. Researchers from the Icahn School of Medicine at Mt. Sinai Hospital New York had 60 patients undergo common testing via Theranos' retail sites in Arizona last year, and compared the results against more traditional venipuncture testing at LabCorp and Quest Diagnostics. The study included more than 18,000 data points and flagged tests outside its normal range of results 1.6 times more often than Quest and LabCorp. Of the 22 lab measurements evaluated, 15 (68 percent) showed significant interservice variability. And 2.2 percent of Theranos' data results were missing, compared to 0.2 percent for LabCorp and no missing results for Quest. Theranos criticized the test results and the integrity of the study and its researchers, who it claimed didn't disclose participation in a company Theranos labeled a competitor.

Finally, as we went to press, *Bloomberg* and *The Wall Street Journal* reported that in a memo to Theranos partners the company revealed it is the subject of investigation by the U.S. Securities and Exchange Commission and the U.S. Attorney's Office. Theranos Chief Executive Officer Elizabeth Holmes also appeared on NBC's *Today* show in an interview with Maria Shriver and indicated she was "devastated" that her company didn't catch problems earlier and she vowed to fix the problems and continue her company's mission.

Takeaway: The number of federal agencies scrutinizing Theranos operations in California increases.

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