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Public Ahead of Providers in Support for Personalized Medicine

Levels of public support for personalized medicine (PM) are seemingly outpacing organizational plans to implement PM-based clinical strategies, based on the results of two recently released surveys.

Public support for personalized medicine research is high and the majority would be willing to participate in federal research, if asked, according to a study published Aug. 17 in *PLoS ONE*. The survey was conducted as part of an early effort to understand the preferences of potential participants of the White House's Precision Medicine Initiative (PMI). The survey results were incorporated into recommendations for the design of the study.

The PMI Cohort Program aims to enroll 1 million U.S. participants willing to share long-term, prospective data about their health and lifestyle, including genetic information, to build a national resource for researchers. To be useful, data must be collected from a broad base of participants. The National Institutes of Health (NIH) anticipates launching initial phases of the cohort later this year. The survey was conducted to gauge support for PMI, to measure acceptability of design features, and to identify public concerns. Incorporating these findings into the study's design, and other participant engagement efforts, are intended to help build an inclusive and trusting cohort.

Survey participants answered a 44-question online survey (May to June 2015) to assess how different consent models affect participants' willingness to participate and share data. More than 2,600 participants, representative of

Continued on page 2

FDA Recommends Against Ovarian Cancer Screening and Industry Emphasizes Risk-Based Testing

The U.S. Food and Drug Administration (FDA) recommends against using currently available tests to screen for ovarian cancer, according to a safety communication the agency issued at the beginning of September. The FDA says there are risks associated with currently marketed, but not approved, ovarian cancer screening tests and the agency is especially concerned about inaccurate results that may delay effective, preventive treatments for asymptomatic women at increased risk for developing ovarian cancer.

Continued on page 9

Public Ahead of Providers in Support for Personalized Medicine, *Continued from top of p.1*

the U.S. population, were randomized to one of eight different consent scenarios. The scenarios varied by the structure of consent (broad, study by study, menu, or dynamic consent) and the presence or absence of access to a website where participants would be able to see what studies are going on, which studies are using their information, and what each study has learned.

> *"Maximizing information shared with research participants will be a key challenge of the PMI."*
>
> — David Kaufman, National Human Genome Research Institute.

Overall, 79 percent of the respondents expressed support for PMI, and 54 percent said they would definitely or probably participate if asked versus 46 percent that stated they would definitely or probably not participate, if asked. These findings were fairly constant across racial and ethnic groups. Only those with less than a high school education showed lower support for PMI (less than 70 percent).

Broad consent received less support when modeled alone, but showed similar support if broad consent was coupled with availability of a website that displays how samples and data are being used. People were most likely to report willingness to share personal data with researchers at the NIH (79 percent) and U.S. academic researchers (71 percent). Respondents were more reluctant to share data with pharmaceutical company researchers (52 percent) or university researchers in other countries (39 percent).

Respondents expressed high willingness to share multiple types of personal data, including: blood samples (73 percent); genetic information (76 percent); family medical history (77 percent); soil and water samples from their home (83 percent); and data on their lifestyle, diet, and exercise (84 percent). By contrast, only 43 percent of those with social media accounts said they would share social media information. People who said they supported the study, but would not participate were more likely to be concerned about privacy and the amount of time the study would take.

The greatest incentive for participation was information about their health (90 percent). Specifically, they wanted lab results, such as cholesterol and blood sugar levels (75 percent), genetic information (75 percent), and a copy of their medical records (68 percent).

"Maximizing information shared with research participants will be a key challenge of the PMI," write the researchers, led by David Kaufman, from the National Human Genome Research Institute. "The return of information may also benefit research, encouraging participants to stay engaged and enrolled, and to take part in other research studies based on their results."

Despite public opinion supporting PM research, the majority of health care organizations say they are not ready to invest in PM, yet, and current adoption is "limited," according to a new survey from HIMSS Analytics, released Aug. 30.

Representatives from137 hospitals were surveyed online. Respondents represented multi-hospital systems (36 percent), stand-alone hospitals (29 percent), academic medical centers (13 percent), and integrated delivery networks (10 percent). More than 60 percent of respondents were from hospitals with 250 or more beds and approximately 30 percent represented hospitals with more than 500 beds.

Less than one-third of respondents (29 percent) indicated their organizations conduct PM. PM programs are in place at larger, research-based organizations such as academic medical centers (35 percent), multi-hospital health systems (25 percent), and organization's with over 500 beds (41 percent). Of those using PM, 80 percent do so for cancer, followed by 38 percent for neurology, 31 percent prenatal screening, and 28 percent cardiology. HIMSS Analytics noted that the federal Precision Medicine Initiative and its associated funding is among the reasons that the focus has been on cancer.

More than 60 percent of respondents indicate the largest challenge to precision medicine is the integration of clinical data systems and clinical and genomic data. They are being held back by limitations in funding, technology, and expertise. As an alternative, 26 percent of respondents said they performed precision medicine through the use of third party laboratories, while a third used a combination of in-house and third-party services.

Finally, many organizations have uncertain plans regarding the future of their precision medicine initiatives. Nearly 43 percent said they had yet to develop a concrete strategy regarding their patients and the use of precision medicine. Another 21.4 percent were unsure about the strategy they would develop. Only 14.3 percent said they planned to develop a comprehensive marketing campaign to tout their precision medicine initiatives.

Takeaway: Public support for PM may be outpacing actual implementation in the clinical setting, although public willingness to participate in PM research may accelerate future adoption.

Genetic Variants May Personalize Diabetes Care

Two genetic variants predict the cardiovascular effects of intensive glycemic control, according to a study published online Aug. 15 in *Diabetes Care*. If validated with further studies, these genetic variants may function as a screening tool to help determine in which diabetic patients intensive glycemic control may be effective and in which patients the strategy may be harmful.

People with type 2 diabetes have substantially higher risk of cardiovascular disease than people without diabetes. Intensive glycemic control—an HbA1c less than 6.0 percent, rather than between 7.0 and 7.9 percent —was hoped to bring cardiovascular benefit. However, in the ACCORD trial's intensive treatment arm, benefits of intensive glycemic control were "surprisingly inconsistent." Intensive glycemic control reduced the risk of heart attack and major cardiovascular events, but actually increased cardiovascular mortality. This study, also by the ACCORD researchers, sought to determine if there was a way to genetically screen patients to identify those likely to be safely treated with intensive glycemic control.

The multi-institutional group of researchers analyzed more than 8 million common variants for genome-wide association with cardiovascular mortality among 2,667 white participants in the ACCORD intensive treatment arm. Significant loci were additionally examined in the entire ACCORD white genetic dataset (n = 5,360) and in a Joslin Clinic cohort (Boston; n= 422).

"After the report of increased mortality in response to intensive glycemic control in ACCORD, this intervention was dismissed as a viable strategy to decrease cardiovascular risk in high-risk patients with type 2 diabetes."

— Hetal Shah

The researchers identified two loci—at 10q26 and 5q13—that achieved genome-wide significance as determinants of cardiovascular mortality in the ACCORD intensive arm. Participants with a genetic risk score (GRS) of zero (a low score) showed a four-fold reduction in cardiovascular mortality in response to intensive treatment, while those with GRS of one (an intermediate score) experienced no difference and those with a GRS of two (high score) experienced a three-fold increase in cardiovascular mortality without the reduction in nonfatal events.

The effect of these genetic markers was independent of other previously identified predictors of higher mortality. The modulating effect of these variants on cardiovascular mortality response to treatment held for the entire ACCORD white genetic dataset and in the real-world Joslin cohort (P =0.029).

"After the report of increased mortality in response to intensive glycemic control in ACCORD, this intervention was dismissed as a viable strategy to decrease cardiovascular risk in high-risk patients with type 2 diabetes," writes lead author Hetal Shah, on behalf of the ACCORD trial researchers. "The results of our study suggest that it may be possible to revive this therapeutic approach by developing a precision medicine strategy, through which intensive treatment is prescribed for those patients who will benefit from it and who are at lower risk of being harmed. The fact that testing for two genetic markers is inexpensive and can be conducted at any point in time makes this possibility especially attractive, although the cost-effectiveness of this approach will have to be evaluated."

The applicability of these findings to non-white patients not at high risk for cardiovascular disease still needs to be evaluated.

Takeaway: While still requiring further validation, identification of two variants could mark an important discovery towards personalizing diabetes care.

Test Developed to Identify Alzheimer's Risk

An Irish company has announced a test that can detect an elevated risk of Alzheimer's disease in patients before symptoms develop.

The test, developed by Randox Laboratories, uses a microchip in blood testing. The chip can help detect a mutation of the ApoE4 gene, a variant in protein processing that can lead to an elevated risk of developing Alzheimer's. If a patient inherits the gene from one parent, they have a three times greater risk than average of developing the disease. If they inherit from both parents, their risk is elevated to as much as 12 times greater than average for developing Alzheimer's.

About 5 million Americans have been diagnosed with or are believed to have Alzheimer's. The disease, which leads to deposits of protein on neurons and robs patients of memory and other brain functions, eventually kills. The incidence of the disease has been rising in recent decades as the United States population continues to age and live longer. Treatment for dementia-causing diseases is extremely expensive, estimated to cost the U.S. $236 billion a year. Most sufferers of Alzheimer's are not diagnosed until they are symptomatic.

Results of a trial of the test, which is not yet available in the U.S., were compared in 384 patients against a standard molecular test that confirms the presence of Alzheimer's. Those patients that tested for an elevated risk were in complete concordance with the results from the molecular test.

"Pairing this test with medical and family history for risk of Alzheimer's disease has the real potential to advance personalized medicine," said Emma Harte, a research scientist with Randox. "This fast, accurate testing will allow doctors and patients to make more informed choices earlier to potentially slow the possible progress of Alzheimer's. This type of testing is important in our quest to understand and diagnose Alzheimer's and empower patients to understand risks, consider medication, and even make early lifestyle changes."

The findings of the study were presented at the American Association of Clinical Chemistry's annual conference in Philadelphia.

Takeaway: A new laboratory test that can indicate an elevated risk for contracting Alzheimer's disease may eventually enter the U.S. market.

Inside The Diagnostics Industry

Top 25 Lab Tests for 2015 by Medicare Payment

Medicare Part B paid $7 billion for lab tests in 2015, the same amount it shelled out in 2014. But 2015 Medicare payments for the top 25 lab tests dipped slightly to $4.1 billion, as compared to $4.2 billion in 2014. These are among the key conclusions of a new report issued by the Office of Inspector General (OIG) as part of its Protecting Access to Medicare Act of 2014 (PAMA) mandate to monitor Medicare payments for lab tests in advance of the new payment system taking effect on Jan. 1, 2018.

Medicare Lab Payments by the Numbers

The $7.0 billion paid for lab tests under the Clinical Laboratory Fee Schedule (CLFS) accounted for roughly 3% of all Part B payments made in 2015, according to the report. Where did that money go?

What Medicare's $7 Billion in 2015 Lab Spending Went Toward

Tests	Beneficiaries	Labs	Providers
■ **474 million:** number of tests billed ■ **3.7:** average number of tests received by beneficiaries in a day ■ **24:** average number of tests per day for top 1% of beneficiaries	■ **27 million:** Medicare beneficiaries that received at least one test ■ **17:** average number of tests per beneficiary ■ **109:** average number of tests per beneficiary among top 1% of beneficiaries	■ **61,040:** labs that received Medicare payments ■ **$113,981:** average payments per lab ■ **$1.0 billion:** payments made to the top three labs	■ **612,812:** providers that ordered lab tests ■ **570:** average number of tests ordered per provider ■ **7,250:** average number of tests ordered by top 1% of providers

Source: OIG "Medicare Payments for Clinical Diagnostic Laboratory Tests in 2015"

Fees Paid for Top 25 Lab Tests

As required by PAMA, the OIG report includes detailed analysis of the 25 most frequently ordered tests. Key findings:

- 23 of the top 25 tests of 2015 were also in the top 25 in 2014 (the two newcomers were drug confirmation (G6058), and amphetamine or methamphetamine (G6042));
- The $4.1 billion paid on the top 25 constituted 59% of Medicare payments made under the CLFS;
- Four of the top 25 tests posted increases in year-to-year payments of at least $10 million, including:
  - Opiates (drug) measurement (G6056)—up $35 million;
  - Drug screen, qualitative; multiple drug classes by high-complexity test method (e.g., immunoassay, enzyme assay), per patient encounter (G0431)—up $15 million;
  - Vitamin D-3 level (82306)—up $13 million; and
  - Benzodiazepines level (G6031)—up $10 million;

Inside The Diagnostics Industry

- Three of the top 25 tests posted decreases in year-to-year payments of at least $10 million, including:
  - Gene analysis (cytochrome P450, family 2, subfamily D, polypeptide 6) common variants (81226)—down $105 million;
  - Chemical analysis using chromatography technique (82542)—down $24 million; and
  - Blood test, clotting time (85610)—down $11 million;
- 54% of all Part B payments for the top 25 tests went to 1% of labs, i.e., 292 of 29,101;
- The next 4% of labs accounted for 25% of the payments for top 25 tests;
- The top eight tests *each* accounted for over $200 million in payments and, combined, $2.7 billion or roughly 66% of payments for the entire top 25 (see the table below for a breakdown of the individual tests).

Top 8 Lab Tests Based on Medicare Part B Payments in 2015

Rank	Test Description and Procedure Code	National Limitation Amount	Number of Tests (millions)	2015 Medicare Payments (millions)	Changes from 2014 Payments (millions)
1	Blood test, thyroid-stimulating hormone (TSH) (84443)	$22.87	21.2	$475	-$3
2	Blood test, comprehensive group of blood chemicals (80053)	$14.37	40.6	$458	+$5
3	Complete blood cell count (red blood cells, white blood cells, platelets) and automated differential white blood cell count (85025)	$10.58	41.5	$428	-$3
4	Blood test, lipids (cholesterol and triglycerides) (80061)	$18.22	27.2	$379	-$8
5	Vitamin D-3 level (82306)	$40.29	8.7	$337	+$13
6	Hemoglobin A1C level (83036)	$13.21	18.6	$241	+$5
7	Opiates (drug) measurement (G6056)	$26.48	8.1	$208	+$35
8	Drug screen, qualitative; multiple drug classes by high-complexity test method (e.g., immunoassay, enzyme assay), per patient encounter (G0431)	$98.96	2.3	$208	+$15

Source: OIG "Medicare Payments for Clinical Diagnostic Laboratory Tests in 2015"

Payment Trends

Although the $7.1 billion Medicare paid for all lab tests in 2015 was roughly the same as 2014's total, the report cites a couple of significant variances.

Drug tests up 19%: Medicare payments for drug tests were up 19% in 2015, from $910 million to $1.1 billion with 18 different drug tests generating increases of at least $1 million. Six of the year's top 25 were drug tests, as compared to four in 2014. According to the report, the spike "coincides with efforts to monitor drug abuse," according to the report. But, the report adds ominously, it could also be an indication of medically unnecessary testing. In fact, billing of medically unnecessary drug tests has been a focus of recent enforcement activity:

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- On August 31, a Florida pain clinic called Coastal Spine and Pain paid $7.4 million to settle claims of routinely billing Medicare for Quantitative drug tests performed on elderly patients regardless of medical necessity;
- On Aug. 18, two former lab professionals convicted of false billing of medically unnecessary drug tests were sentenced to 36 months in prison and ordered to pay $1.437 million in restitution; and
- Similar charges were among the allegations of a pair of whistleblowers in a case settled by PremierTox 2.0, Inc. for $2.5 million in April.

The report includes new insights into the new Medicare payment rates for lab tests.

Molecular pathology tests down 44%: On the flip side, Medicare payments for molecular pathology tests analyzing genetic material to determine how patients will respond to treatment decreased 44% from $466 million to $259 million year-over-year. The report says the decline was concentrated in payments for three different tests but does not specify the tests' names. The decline coincides with efforts to prevent medically unnecessary genetic testing, the report adds.

Looking Ahead

The report includes new insights into the new Medicare payment rates for lab tests. The private payer data that CMS will use under PAMA to set new payment rates is expected to come from 5% of labs, including 1,398 independent labs and 11,149 physician office labs (see box below for key PAMA implementation dates). These 12,547 labs accounted for 69% of Medicare payments for lab tests in 2015. The report also confirms that 0 of 6,994 hospital labs will report private payer data.

Although payment rates will be generally lower under the new payment system, the report states that rates for 22 of the 25 top tests will go up in some parts of the country, with 38 states seeing at least one of the top 25 tests increasing with increases ranging from $0.02 to $30.27 per test.

Takeaway: The OIG's report on the top 25 lab tests doesn't show a major shift in the top tests and mirrors a national focus on drug testing.

Key PAMA Implementation Dates

Here are key dates along the way to final implementation of PAMA

- **October or November 2016:** CMS to complete independent validation of data collection system; labs begin registering;
- **By December 31, 2016:** CMS finish educating labs on the new reporting requirements and publish guidance describing the new ADLT application procedure;
- **January 1, 2017:** Labs begin reporting private payer data;
- **April to August 2017 (roughly):** CMS tests to verify accuracy and completeness of reported data; and uses the data to set preliminary pricing rates;
- **September 2017:** CMS to publish preliminary pricing rates and seek public input;
- **November 2017:** CMS to finalize pricing rates;
- **January 1, 2018:** New pricing rates take effect.

Inside The Diagnostics Industry

OIG Assesses PAMA Implementation

In addition to reporting on the top 25 lab tests relative to Medicare payments, the OIG's other mandate in connection with the Protecting Access to Medicare Act of 2014 (PAMA) is monitoring implementation of the new payment system which takes effect on Jan. 1, 2018. Less than 15 months from the deadline, the OIG issued a report documenting the progress the Centers for Medicare and Medicaid Services (CMS) is making in implementing the new payment system.

The OIG report explains six tasks that CMS must do to implement PAMA's new lab fee schedule and describes the progress CMS has made with regard to each one so far, as summarized by the chart below.

PAMA Briefing: Current Status of Part B Payment Changes Implementation

Task	Status	What CMS Has Done	What CMS Still Must Do
1. Issue final rule and lab industry guidance	Almost complete	■ June 17, 2016: Final rule issued ■ Issued guidance on data reporting procedures and requirements	■ By January 2017: issue guidance on process for labs to apply to have a test designated as an ADLT ■ Determine if additional regulations or guidance is needed
2. Establish and consult with advisory panel	Complete	■ April 2015: Panel created ■ 2015-2016: Panel met four times ■ Panel has formed 2 subcommittees: i. One advises CMS on payments for automated "profile" tests ii. Other advises on ADLT application process	■ Through April 2017: Continue to receive and consider recommendations of panel and subcommittees
3. Collect private payer data reported by labs	Significant progress	■ December 2015: Completed building of data collection system used by labs to report private payer data ■ Testing of data collection system user experience, security and capacity partially completed—stress testing of user capacity hindered due to limitations of CMS's Presentation Zone	■ Finish testing of data collection system user experience ■ October 2016: Independent validation of system ■ October 2016: Data collection system to be made available for labs to begin registering ■ By January 2017: Finish educating labs about reporting requirements ■ January 2017: Reporting begins ■ January to March 2017: Collect first set of labs' private payer data
4. Ensure accuracy and completeness of reported data	In progress	■ Creation of preliminary plans to conduct checks in mid- to late 2017 after labs submit first round of data ■ Automated data verification and certification features incorporated into CLFS module	■ April to August 2017: Conduct checks on first round of data labs submit ■ September 2017: Publish pricing and volume data ■ Starting September 2017: Seek public input on accuracy of preliminary Medicare payment rates ■ CMS does not plan to independently verify whether all applicable labs submit their private payer data as required or the accuracy and completeness of the data of the labs that do report their data—Result: Risk of inaccurate payment rates
5. Determine and publish new Medicare payment rates	In progress	■ Capacity to calculate new rates from data labs report incorporated into data collection system	■ Early 2017: Collect data reported by labs ■ Calculate Medicare payment rates from data ■ November 2017: Publish the new payment rates ■ January 2018: New payment rates take effect
6. Identify ADLTs	In progress	■ June 2016: Publication of criteria for test to qualify as ADLT (as part of final rule) ■ July 2016: Advisory panel subcommittee recommends ADLT application procedure	■ By January 2017: Decide and issue guidance describing ADLT application procedure ■ Thereafter: Review applications and decide whether tests qualify as ADLTs

FDA Recommends Against Ovarian Cancer Screening, *Continued from bottom of p.1*

Despite the fact that ovarian cancer is the fifth-leading cause of cancer-related deaths among women, there is no approved or recommended screening test for the disease. Yet, cancer antigen (CA) 125 tests are extensively used.

"From what we know anecdotally, in spite of the fact that CA 125 isn't really meant to be used that way, many women who are concerned about the risk of ovarian cancer are getting the test every year," Sarah DeFeo, vice president of scientific affairs for the Ovarian Cancer Research Fund Alliance, told *STAT News*. "In practice, lots of people are doing it."

"We believe this clarity around the use of non-FDA approved test for ovarian cancer screening, demonstrates the need to manage high-risk, pelvic mass patients at the onset with our FDA-cleared technology."

— Valerie Palmieri, CEO, Vermillion/ASPiRA Labs

Current recommendations against screening for ovarian cancer are based on the large U.S. Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, which found that annual CA 125 measurement (using a fixed cutoff value for a positive test result) and vaginal ultrasound were not associated with a reduction in ovarian cancer mortality. Additionally, screening was tied to significant harms from surgeries resulting from false-positive results.

However, the United Kingdom Collaborative Trial of Ovarian Cancer Screening, published in *The Lancet* in December 2015, similarly used multimodal screening—CA 125 and ultrasound—but relied on a risk of ovarian cancer algorithm (ROCA) instead of a fixed cutoff. Use of the algorithm did increase sensitivity and led to fewer unnecessary surgeries and a positive trend towards earlier diagnosis, but led to questionable improvements in mortality—only seen after seven to 10 years of screening. While the authors concluded by saying further follow-up was necessary "before firm conclusions can be reached on the efficacy and cost-effectiveness of ovarian cancer screening," the algorithm at the center of the protocol began to be commercially marketed, in the United Kingdom and in the United States (for $295).

Abcodia (United Kingdom), the company marketing the ROCA test, announced in mid-September that it was temporarily suspending its test in the United States while the company continues to engage with the FDA and the clinical community for further evaluation of the ROCA test.

With women concerned about ovarian cancer still left without a viable screening option, the industry is emphasizing availability of risk-based testing—either to assess for hereditary cancer risk using BRCA testing, or likelihood of an ovarian cancer malignancy in women presenting with a pelvic mass.

"We believe this clarity around the use of non-FDA approved test for ovarian cancer screening, demonstrates the need to manage high-risk, pelvic mass patients at the onset with our FDA-cleared technology," said Valerie Palmieri, CEO of Vermillion/ASPiRA Labs (Austin, Texas), which markets OVA1 and OVERA tests, in a statement. "No technology exists today to support screening, but we believe that our technology is the best available to assess risk, optimally manage patients, and lower overall healthcare costs."

Takeaway: Research continues to develop a sensitive screening test to evaluate the general population for ovarian cancer. In the absence of such a test, industry does have available tests to evaluate risk of hereditary ovarian cancer and the likelihood an ovarian mass is cancerous.

CDC and the Diagnostics Industry Continue to Battle Zika

While summer has ended, the battle against the mosquito-borne virus Zika continues. The Centers for Disease Control and Prevention (CDC) updated prior travel and testing guidance on Zika transmission to cover all of Miami-Dade County in Florida, as mosquito transmission of the virus continues to be reported in that region. The number of locally acquired cases of the virus is low in the United States at 137 according to the CDC's Oct. 19 update, but there are a total of 4,016 cases in the U.S. with 3,878 related to travel. One reported case was laboratory-acquired.

While locally mosquito-transmitted cases in the United States have only occurred to date in Florida, travel related cases have been reported in all 50 states with the most occurring in California, Florida and New York. Just as virus transmission has not abated, efforts to develop better diagnostics continue in earnest. The FDA has issued a total of 12 Emergency Use Authorizations for diagnostics. Here's an update on some recent developments concerning available testing.

Hologic EUA Expanded to Urine Samples

Earlier this year, an Emergency Use Authorization (EUA) was granted to Hologic for its Aptima® Zika Virus Assay for use with serum and plasma. In September, the FDA expanded that EUA to allow use of the assay with urine samples collected with the patient-matched serum or plasma. Hologic's new authorization "expands the window in which an individual can be tested and we can get results from a 7-day window to a 14-day window," explains Tom West, Hologic's Division President of Diagnostic Solutions. That affords "better ability to identify if an individual is impacted by Zika and take appropriate measures and to see if Zika is expanding in the population," he added.

As discussed in *DTET*'s June 2016 issue, according to the CDC, Zika virus RNA is unlikely to be detected in serum after the first week of illness, but Zika virus RNA can be detected in urine for at least two weeks after onset of symptoms. See "Urine Becoming Preferred Zika Sample as Testing Industry Prepares for Summer Mosquito Season," *DTET*, June 2016 p. 1. The CDC says urine "should always be collected with a patient matched serum specimen."

Hologic's assay is run on its Panther system—which West indicates is a laboratory-based system that is "very successful … in the clinical environment and the blood screening environment because of the speed with which it can process a sample"—processing can occur within hours. West adds that what distinguishes the Panther system is its "high level of specificity and sensitivity." "The CDC identified this specificity and sensitivity as one reason to move this forward as quickly as it did," West notes.

Roche's LightMix

In August, EUA was also granted to Roche's LightMix® Zika rRT-PCR test to detect Zika in EDTA plasma or serum samples. The test utilizes Roche's LightCycler 480 Instrument II or cobas z 480 Analyzer. "The LightMix Zika test is an easy-to-use molecular diagnostic test that enables healthcare professionals to quickly detect the virus," Head of Roche Molecular Diagnostics Uwe Oberlaender said in a statement. Roche distributes the test manufactured by TIB MOLBIOL GmbH. "The end-to-end automated process from sample preparation to results for up to

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96 samples can be performed in just 2.5 hours," according to the Roche statement. Roche previously announced availability of the cobas® Zika Test for use with cobas® 6800/8800 Systems to screen blood samples under an Investigational New Drug Application protocol.

Vela Diagnostics' Sentosa

Another assay granted an EUA was the Sentosa® SA ZIKV RT-PCR test from Sinapore-based Vela Diagnostics, for use with serum, EDTA plasma and urine (with patient-matched serum or plasma). The FDA granted the EUA in September. Vela indicates the test can process 22 samples in three hours, its detection limit "enables detection of samples with low viral load," and it is "authorized to run on the automated Sentosa® SX101 real-time PCR workflow, along with the Sentosa® SX Virus Total Nucleic Acid Kit v2.0."

ARUP Laboratories' Zika Virus Detection by RT-PCR

Also receiving EUA from the FDA in September was the ARUP Laboratories Zika Virus Detection by RT-PCR test. That test is used for "in vitro qualitative detection of Zika virus with specified instruments" to detect Zika virus RNA "in human serum, EDTA plasma, and urine (collected alongside a patient-matched serum or plasma specimen)," according to the company's website. The test is authorized for use on the QuantStudio 12K Flex real-time PCR instrument (Thermo Fisher)--or other authorized instruments.

FDA EUA Authorizations

The following in vitro diagnostics have received emergency use authorization for detection of the Zika virus or diagnosis of virus infection:

- Zika Virus Detection by RT-PCR Test (ARUP Laboratories)
- Sentosa® SA ZIKV RT-PCR Test (Vela Diagnostics USA, Inc.)
- LightMix® Zika rRT-PCR Test (Roche Molecular Systems, Inc.)
- ZIKV Detect™ IgM Capture ELISA (inBios International, Inc.)
- xMAP® MultiFLEX™ Zika RNA Assay (Luminex Corporation)
- VERSANT® Zika RNA 1.0 Assay (kPCR) Kit (Siemens Healthcare Diagnostics Inc.)
- Viracor-IBT Laboratories, Inc.'s Zika Virus Real-time RT-PCR Test
- Aptima® Zika Virus Assay (Hologic, Inc.)
- RealStar® Zika Virus RT-PCR Kit U.S. (altona Diagnostics)
- Zika Virus RNA Qualitative Real-Time RT-PCR (Focus Diagnostics)
- Zika MAC-ELISA (CDC)
- Trioplex Real-time RT-PCR Assay (CDC)

Quest's MAC-ELISA

In September, Quest Diagnostics introduced an antibody test service to help detect Zika infection based on the CDC-developed Zika Immunoglobulin M (IgM) Antibody Capture Enzyme-Linked Immunosorbent Assay (Zika MAC-ELISA). Quest is operating under a CDC license to offer the service with EUA approval from the FDA. Earlier this year in April, Quest became the first commercial lab with FDA EUA approval for a Zika test—which provided qualitative detection of RNA from Zika in serum. Then in September, Quest announced availability of an RT-PCR-Zika test to detect the virus in serum and paired urine specimen. Quest explained in a statement that molecular testing "is most useful up to 14 days after" symptoms appear and "IgM antibody testing is most useful two to 12 weeks following the onset of symptoms."

"Not every lab provider has our level of expertise or scale. We believe our leadership positions us to aid clinical and public health response to emerging infectious diseases such as Zika," says Quest spokesperson Wendy Bost. "This is why Quest fast tracked development and FDA emergency use authorization for its first molecular Zika test earlier this year and has now introduced an antibody Zika test service. By providing these services, we significantly broaden physician and patient access to quality Zika virus test services in the United States and internationally."

Takeaway: While locally transmitted cases of Zika virus are limited so far to Florida, travel related cases continue to rise and the diagnostics sector continues to seek ways to improve virus detection.

G2 INSIDER

Theranos Shifts Focus from Labs to Technology

Theranos announced that it will shut down its laboratory operations in wake of the Centers for Medicare and Medicaid's Services (CMS) sanctions resulting from the 2015 inspection of its Newark, Calif., laboratory, even though it is appealing the sanctions.

> *"Our ultimate goal is to commercialize miniaturized, automated laboratories capable of small-volume sample testing, with an emphasis on vulnerable patient populations, including oncology, pediatrics, and intensive care."*
>
> —Theranos

On Oct. 5, the company released a statement indicating that "[a]fter many months spent assessing our strengths and addressing our weaknesses, we have moved to structure our company around the model best aligned with our core values and mission." That structure includes closing clinical labs and wellness centers affecting more than 300 employees in Arizona, California and Pennsylvania.

The company will now focus on developing technology—namely the miniLab, which Holmes detailed at the AACC annual meeting in August. The miniLab is a compact device (2.5 cubic feet) containing a mini-robot that processes single-use cartridges with a Theranos Virtual Analyzer remotely dictating protocols for processing. "Our ultimate goal is to commercialize miniaturized, automated laboratories capable of small-volume sample testing, with an emphasis on vulnerable patient populations, including oncology, pediatrics, and intensive care," according to the company's Oct. 5 statement.

In late July, the company brought in some heavy hitters with experience at major technology companies in-house, including attorney David Guggenheim as chief compliance officer and David Wurtz as vice president of regulatory and quality. Guggenheim previously served as an assistant general counsel at McKesson Corp., while Wurtz was senior director of regulatory, quality and compliance at ThermoFisher Scientific. Theranos's board also created a compliance and quality committee to "oversee and advise the board and the company's executive leadership on regulatory compliance and quality systems obligations," the company said.

In July, CMS had rejected the company's proposed corrective action as failing to "constitute a credible allegation of compliance and acceptable evidence of correction" of the deficiencies cited in the inspection. CMS's proposed sanctions include:

- Revocation of the lab's CLIA certificate;
- Cancellation of its approval to receive Medicare/Medicaid payment for lab services;
- Penalties of $10,000 per day until deficiencies are resolved; and
- Banning Theranos founder Elizabeth Holmes from owning, operating or directing a lab for two years.

CMS also asked the lab for a list of the names and addresses of all physicians and clients who used its services since January 2014. Theranos had taken steps to appeal those sanctions before this latest announcement that it would shift from lab testing to developing test technology.

Takeaway: Theranos is an excellent example of how CMS sanctions and the negative publicity they bring can cause a lab to shift strategic direction.

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