G2 INTELLIGENCE
A DIVISION OF PLAIN LANGUAGE MEDIA

DIAGNOSTIC TESTING & Emerging Technologies

New Trends, Applications, and IVD Industry Analysis

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INSIDE THIS ISSUE

Top of the News: Early Results Show Blood Test's Effectiveness in Early Alzheimer's Detection

Developing a cost-effective blood test capable of accurately detecting early Alzheimer's disease that can be furnished at a doctor's office has been a goal for decades. And now comes word that achieving the goal may be closer than we realized—perhaps only years away.

The Challenge

Alzheimer's damages brain cells well before it impairs cognitive ability. And by the time patients manifest symptoms of impaired thinking, it's too late to treat them. That's why it's so critical to be able to identify Alzheimer's as early as possible before patients suffer cognitive impairment.

Continued on page 2

Top of the News: Nonculture Molecular Tests Speed Diagnosis of Bloodstream Infections

The T2Bacteria Panel (T2Biosystems; Lexington, Mass.) can rapidly and accurately diagnose bloodstream infections (BSIs) caused by five common bacteria, according to a study published May 14 in the Annals of Internal Medicine.

Blood cultures, which are the gold standard for diagnosing BSIs, are known to be insensitive and are limited by a long wait for results. Development of nonculture-based diagnostic tests for BSIs are a top priority for patient care and antibiotic stewardship.

The U.S. Food and Drug Administration (FDA) recently cleared the T2Bacteria panel that can directly detect bacteria in whole blood samples. The nonculture test that uses both polymerase chain reaction amplification and T2 magnetic resonance in a closed system to identify the most common ESKAPE bacteria (Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa, and Escherichia coli), that together account for about

Continued on page 10

Early Results Show Blood Test's Effectiveness in Early Alzheimer's Detection, *from page 1*

The key to detection is the amyloid protein associated with the disease. Alzheimer's patients generate abnormally large amounts of the protein that clump together to form plaques in the brain, strangling nerves and severing nerve connections. Unfortunately, current amyloid identification techniques, including PET scans, are relatively expensive and only about 70% accurate. What's needed is a more accurate, easier and less costly amyloid detection test—like a blood test.

The New Blood Test

Industry has been working on developing such a test. And the Aug. 1 issue of the journal Neurology reports that researchers at Washington University School of Medicine in St. Louis that they've developed a blood-based test that may just fill the bill.

The researchers used mass spectrometry as part of a study to measure blood levels of amyloid beta, a protein biomarker for Alzheimer's. By combining blood amyloid levels with a patient's age and the presence of the genetic variant APOE4, the researchers were able to identify pre-symptomatic people with early Alzheimer's brain changes at an accuracy level of 94%.

Study Details

Using amyloid PET scans as the primary reference standard for amyloidosis ("because it is a well-established biomarker that is widely used in clinical trials"), the researchers used a mass spectrometry assay to measure the amounts of two forms of amyloid beta in blood—amyloid beta 42 and amyloid beta 40. They found that the ratio of the two forms decreases as the amount of amyloid beta deposits in the brain increases.

Of the 158 participants of age 50+, the researchers found all but 10 cognitively normal. They measured amyloid beta in 210 plasma samples and conducted a PET brain scan for each participant and then classified each blood sample and PET scan as amyloid positive or negative. The finding: The participant's blood test matched his/her PET scan 88% of the time—impressive but not accurate enough for a useable test.

So, the researchers set out to boost accuracy by incorporating the other two major Alzheimer's risk factors into the test—age and presence of the APOE4 genetic variant. They also considered gender to the extent that two of three Alzheimer's patients are women.

Although gender didn't have much of an impact, the researchers found that including age and APOE4 status raised the blood test's accuracy to 94%.

What's Next?

According to the researchers, a blood test may become available at doctors' offices within a few years. "A blood-based biomarker would enable more

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rapid and inexpensive screening of potential participants, particularly for prevention trials, where rates of negative amyloid PET scans are about 70%," the researchers wrote.

One of the remaining challenges for blood-based Alzheimer's testing is setting the threshold for "normal" and "high" levels of amyloid in the blood. Complicating that determination is the fact that while the diagnosis of Alzheimer's requires the presence of amyloid, some people who harbor amyloid plaques don't develop the disease.

Takeaway: If and when a blood test for early Alzheimer's does make it to market, it's likely to improve not only detection but treatment and prevention of the disease by giving a boost to new drug development. Explanation: One of the biggest problems of conducting clinical trials for new Alzheimer's drugs is identifying participants who have Alzheimer's-related brain changes but not cognitive problems. But an accurate Alzheimer's blood-based test would go a long way in overcoming that problem.

Genetics Update: 23andMe Seeks to Upend the Medical Industry via Genetic Testing Information Sharing

Can one company disrupt the entire lab industry? 23andMe seems determined to find out. The Mountain View, California-based personal genomics and biotechnology company, which first marketed its consumer services for tracing ancestry before moving into analysis of health traits, is now planning to take another conceptual leap. According to CNBC reports, 23andMe is looking at a pilot program that would incorporate customers' lab results, prescription information and medical history with genetic test findings using third-party medical data sharing platform Human API.

Implications of Information Sharing

The implications are significant. The new information sharing program would put genetics data front and center, allowing it to become a primary tool for evaluating and treating patients. It would also further medical research.

Of course, 23andMe isn't the only consumer company seeking to leverage medical information. Other notable examples include Apple which has developed the Health app enabling patients to aggregate their health records, including lab tests and prescription information, alongside data they generate on their own. Increasingly, Apple Health is used in conjunction with healthcare providers' patient portals.

Continued on page 4

23andMe Seeks to Upend the Medical Industry via Genetic Testing Information Sharing, *from page 3*

Diagnostic Challenges

The difference between 23andMe and Apple, CNBC points out, is genetics data. And no question, DNA provides the missing link, in more ways than one. This potentially makes it a much more attractive and far-reaching option.

But there are also big concerns. One of these is that providing genetic testing information directly to consumers without a medical professional's intervention will lead to misinterpretation of test results and promote false reassurance or unwarranted panic. Of course, the same concern applies to information aggregated and shared via Apple's Health app, but to a lesser extent.

While acknowledging the potential risks, proponents contend that knowledge is power and cite how patients have increasingly become more involved in their own healthcare decisions, which include researching treatment options and becoming their own patient advocates. This is a positive approach, one shared by many family caregivers.

Privacy Concerns

The other big concern is privacy. The customer data that 23andMe proposes to share is considered personal health information (PHI) under HIPAA and the companies would need consent to use it for the project. And that may prove to be a big stumbling block at least with some customers. After all, there's a big difference between using PHI for tracing a customer's ancestry and using it for providing healthcare services. In addition to these privacy issues, the proposed pilot raises concerns to the extent it redefines what constitutes a medical record.

Of course, providing consumers with health information is nothing new; the internet has been a source of information for decades. The difference is that personal data, including genetic testing and other lab results, has now become available to individuals who may or may not be qualified to interpret it.

Going Forward

For labs and other providers, this new genetic information sharing frontier will likely continue to raise questions, including legal ones. For example, if a patient has access to healthcare information such as lab test results via technology, is the healthcare service provider responsible for further outreach? And where does responsibility for interpretation of test results now begin and end?

The line between patient and provider continues to blur at the same time technology allows for new ways to share information and breakthroughs in medicine allow for new insight. It's a prescription for disruption, to be sure, with missteps likely to forge the path forward.

Yet, make no mistake ;there will be a path forward. Although 23andMe has indicated that its pilot program is still in the planning stages and is subject to change, the company has more than 10 million customers. That's a lot of data.

(Note: The number of individuals using Apple Health is not available. However, Apple has compiled a list of hospitals and clinics that share health records via the app. The list, updated on July 1 of this year and available at the company's website, is extensive.)

Genetics Update: Internet Use Can Help Patients Self-Diagnose Rare Genetic Disorders

The notion of empowering patients to take control over their own healthcare is particularly powerful within the realm of genomic diagnostics to the extent that patients can theoretically seek their own tests without a physician's order for an undiagnosed genetic disease or disorder they suspect they might have. Leaving aside the question of whether this is a positive or negative development, the theory rests on an essential but as yet unproven premise, namely, that patients will be able to find the information they need to determine which genetic diseases they may be at risk of having and where to go to get proper testing. One critical source of that information is the internet. But do or will patients actually use the internet to get information for genetic testing self-referrals? A new study published online in Genetics in Medicine on July 24, 2019, provides evidence that they actually do.

The Study

The study authors, including **Anthony J. Bleyer**, M.D., from the Wake Forest School of Medicine, set out to evaluate self-referral from the internet for patients seeking genetic diagnosis of several rare inherited kidney diseases in the period from 1996 to 2017 based on an analysis of data obtained from an academic referral center specializing in autosomal dominant tubulointerstitial kidney disease (ADTKD). Individuals were referred by academic healthcare providers (HCPs) nonacademic HCPs, or directly by patients and/or families.

The findings: Of the 665 referrals identified over the 21-year study period:

- 176 (27%) came directly from families;
- 269 (40%) came from academic HCPs; and
- 220 (33%) came from nonacademic HCPs.

Continued on page 6

Internet Use Can Help Patients Self-Diagnose Rare Genetic Disorders, *from page 5*

The authors then looked at the results of each group and found that 42 (24%) of the direct family referrals had positive genetic testing versus 73 (27%) for families referred by academic HCPs, and 55 (25%) for families from nonacademic HCPs referrals (P = 0.72). Of the direct family contacts, 99% were white and resided in zip code locations with a mean median income of $77,316 ± 34,014 versus U.S. median income $49,445.

The authors looked at whether the families in each group had internet access and concluded that undiagnosed families with internet access bypassed their physicians and established direct contact with the academic center specializing in inherited kidney disease to obtain a diagnosis. Twenty-five percent of all families diagnosed with ADTKD were the result of direct family referral and would otherwise have been undiagnosed.

Takeaway: The study suggests that if patients suspect that they or a family member has a rare disorder that is undiagnosed by their physicians, actively pursuing self-diagnosis using the internet can be successful. "While online searches can frequently fail to provide relevant or correct health information, the Internet does offer those with rare disorders a way to find the rare specialists interested in a particular condition and obtain accurate information about it," noted Bleyer in a statement. Last but not least, the study also suggests that laboratories and testing centers that perform tests for rare disorders should consider improving direct access to families.

FDA Watch: FDA Greenlights Assays Using New Test Model for Lyme Disease Diagnosis

Lyme disease is on the increase. And so is the number of products cleared for detecting it. In fact, products for detecting tickborne diseases have been reaching the U.S. market at a dramatically stepped up pace in the past two years. In 2018, the Food and Drug Administration (FDA) approved two different donor screening tests to detect Babesia, a tickborne parasite responsible for the babesiosis infection. Meanwhile, researchers at Columbia University developed the first multiplex array for diagnosis of Lyme disease and other tickborne diseases. The most recent development is the FDA's expansion of clearance for four previously cleared tests to cover new indications to aid in the diagnosis of Lyme disease. Here's why these approvals are significant and different from anything the agency has cleared before.

The Lyme Disease Challenge

Lyme disease is caused by the bacteria Borrelia burgdorferi which is transmitted to humans through the bite of infected ticks. Typical symptoms include fever, headache, fatigue, and skin rash called erythema migrans. If left untreated, infection can spread to the joints, heart, and nervous system.

In 2017, the last year for which the Centers for Disease Control and Prevention (CDC) has published data, a total of 42,743 confirmed and probable cases of Lyme disease were reported to the agency, an increase of 17% from 2016.

The Newly Cleared Tests

Laboratory diagnosis of Lyme disease has traditionally used a two-tier process for detecting the presence of antibodies against Borrelia burgdorferi in a patient's blood. Antibodies are proteins present in the blood when the body is responding to a specific infection. Testing follows a two-tier approach in which a pair of enzyme immunoassays (EIA) are performed followed by a separate protein test called a Western blot to confirm a clinical diagnosis of Lyme disease.

While the FDA has cleared laboratory tests for detecting Lyme disease before, the four clearances announced on July 29, 2019, break new ground because they are the first the agency has approved that follow a different model relying only on EIA technology-based tests which can be run concurrently or sequentially. The products which were approved via the FDA 510(k) pathway were all developed by Branchburg, NJ-based Zeus Scientific, including:

- The ZEUS ELISA Borrelia VlsE1/pepC10 IgG/IgM Test System;
- The ZEUS ELISA Borrelia burgdorferi IgG/IgM Test System;
- The ZEUS ELISA Borrelia burgdorferi IgM Test System; and
- The ZEUS ELISA Borrelia burgdorferi IgG Test System

In granting 510(k) clearance, the FDA relied on data from clinical studies demonstrating that the alternative modified two-tier test approach is just as accurate as current methods for detecting antibodies for assessing exposure to Borrelia burgdorferi. The FDA also reiterated in announcing the clearance that CDC recommendations should be followed for the diagnosis of Lyme disease and for determining when laboratory tests are appropriate.

Takeaway: "Clinicians have a new option to test for Lyme disease that is easier to interpret by a clinical laboratory due to the streamlined method of conducting the test," noted Tim Stenzel, M.D., Ph.D., director of the Office of In Vitro Diagnostics and Radiological Health in the FDA's Center for Devices and Radiological Health. "These tests may improve confidence in diagnosing a patient for a condition that requires the earliest possible treatment to ensure the best outcome for patients," he added.

FDA Watch: Agency Issues New Guidance on Biotin Interference Testing

On June 13, the FDA issued a draft guidance explaining how makers of in vitro diagnostic devices (IVDs) should perform biotin interference testing and communicate testing results to labs, clinicians and other device end-users.

How Biotin Skews Testing Results

Biotin, aka vitamin B7, is a common ingredient in multi-vitamins, prenatal vitamins and dietary supplements. Patients who consume high levels of biotin from such products have been linked with abnormally high rates of falsely high and falsely low test results. Of course, these results can lead to inappropriate patient management or misdiagnosis.

As the draft guidance points out, devices using biotin/avidin technology have historically been assessed for biotin interference at the normal recommended daily doses of biotin of 30 µg per day, which results in plasma/serum biotin levels of < 1 ng/mL. Nevertheless, it continues, "unanticipated biotin interference with the performance of some IVDs due to consumer use of "dietary supplements" have in some instances revealed much higher levels; extremely high biotin doses also have been observed of up to 300 mg per day, which results in plasma/serum biotin levels of > 1000 ng/mL."

The 6 Recommendations

The FDA recommended that IVD makers take six measures to prevent or minimize the impact of biotin interference:

1. Sponsors should contact the appropriate Center for Biologics Evaluation and Research (CBER) or Center for Devices and Radiological Health (CDRH) review division when biotin interference at clinically relevant analyte and biotin concentrations is demonstrated;

2. Studies testing for biotin interference should be designed in accordance with Clinical Laboratory Standards Institute (CLSI) EP07, Interference Testing in Clinical Chemistry; Approved Guideline;

3. Concentrations of biotin should be evaluated up to 3500 ng/mL to reflect current trends in biotin consumption;

4. Test samples should include analyte levels near the medical decision point(s) of the device;

5. The concentration of biotin at which no interference is detected should be determined for assays that are susceptible to biotin interference at concentrations less than 3500 ng/mL; and

6. Information on biotin interference testing should be listed in the labeling of the device, including the percent difference or bias at each concentration tested for both qualitative and quantitative assays and the consequence of biotin interference, e.g., any falsely elevated or falsely depressed observed.

Testing Trends: Guidelines at a Glance

Early-Pregnancy Screening for Preeclampsia

All pregnant women should be screened for preterm preeclampsia during the first-trimester with risk calculator assessing maternal risk factors and biomarkers, according to the International Federation of Gynecology and Obstetrics' guidelines published May 20 in the International Journal of Obstetrics & Gynecology.

The test includes maternal risk factors, measurements of mean arterial pressure, serum placental growth factor, and uterine artery pulsatility index. If maternal serum pregnancy-associated plasma protein A is measured for routine first-trimester screening for fetal aneuploidies, the test result can be included for preeclampsia risk assessment. This screening can be adapted for screening in twin pregnancies.

FIGO considers early screening to be a measure that would most likely increase savings to the health system, but calls for more cost-effective analyses to be conducted to demonstrate the financial benefit of the screening strategy. These recommendations support earlier guidance published by the Fetal Medicine Foundation.

Nonculture Molecular Tests Speed Diagnosis of Bloodstream Infections, *from page 1*

half of organisms responsible for positive blood cultures.

"We hope the promising performance and FDA clearance of these tests will encourage continued investment, research, and development in this area of pressing medical need," write the authors led by **M. Hong Nguyen**, M.D., from University of Pittsburgh in Pennsylvania. "Now that performance characteristics ... have been established in multicenter clinical trials, a top priority is to define their precise roles in clinical practice and their effect on patient outcomes."

The multisite study assessed the diagnostic performance of the T2Bacteria Panel, compared to paired blood cultures, in 1,427 adults (median patient age, 56 years) treated at 11 hospitals. T2 Biosystems provided financial support for the study.

Both aerobic and anaerobic blood cultures (one bottle each, the "companion blood cultures") and three whole blood samples for T2Bacteria testing were collected in that sequence from the same anatomical site. T2Bacteria results were not available to healthcare teams caring for study patients and were not incorporated into clinical decision making. Arbitration of incongruent case results was based on whether the same organism was recovered from clinical blood culture specimens unrelated to study samples or from cultures at nonblood sites (e.g., urine or respiratory tract).

The researchers found that blood culture results were positive for the five targeted bacteria in 3 percent of patients (39 of 1,427) and T2Bacteria in 13 percent of patients (181 of 1,427). Companion blood cultures detected a total of 85 organisms, including 39 of 82 with organisms included in the T2Bacteria panel plus additional species (Coagulase-negative staphylococci, diphtheroids, and Corynebacterium species) in 23 of 82 positive blood cultures.

Blood culture and T2Bacteria results were concordant in 90 percent of samples. Per patient sensitivity and specificity for T2Bacteria for proven BSIs (concordant results) were both 90 percent. The negative predictive value was 99.7 percent.

The rate of negative blood cultures with a positive T2Bacteria result was 10 percent (n = 146), of which 62 results were probable (defined as a negative blood culture but a positive T2Bacteria result which yielded isolation of a T2Bacteria-detected organism within 21 days from a clinical blood culture or specimen) and 26 were possible (defined as a negative blood culture but a positive T2Bacteria result in the absence of supporting culture data) BSIs. If probable BSIs were assumed to be true positives (missed by blood culture), specificity of the panel increased to 94 percent. The specificity increased to 96 percent if both probable and possible BSIs were assumed to be true positives. Specificities for specific T2Bacteria-targeted organisms ranged from 96 percent for E. coli to 98 percent or higher for other species.

Time to identification of pathogens was shorter for T2Bacteria (4 to 8 hours depending on how many samples were loaded for testing) versus 39 to 72 hours for blood cultures.

"The initial commercial experience appears to be aligned with the strong results demonstrated in the pivotal study, as several customers have shared case studies of the T2Bacteria Panel providing actionable test results that improved patient care and several have developed and implemented patient selection criteria for the intensive care unit, oncology units, and the emergency department," said Sandy Estrada, vice president of medical affairs at T2 Biosystems, in a statement. "We continue to engage with clinicians, stewardship teams, and laboratory personnel at hospitals as they expand utilization of the T2Bacteria Panel and develop independent data examining its clinical and cost-savings benefits, similar to what we have already seen with the T2Candida Panel."

However, in an accompanying editorial, published in the Annals of Internal Medicine, **David A. Weinrib**, M.D., from Atrium Health–Carolinas Medical Center (Charlotte, N.C.) advises caution saying that the published study is not clear how the panels add "value" to the clinical management of patients with suspected BSI or sepsis.

"In this era of increasing cost consciousness and 'lean operations,' clinicians and laboratories need to be good stewards of healthcare resources and make careful determinations of cost, utility, and benefit to the patient before adopting a new assay," writes Weinrib. "As with many other culture-independent diagnostic tests, incorporation of the T2Bacteria Panel would be additive. … Personnel, space, and efficiency are important issues that must be addressed, especially when adding testing that does not have proven clinical benefit is being considered."

Continued on page 12

Nonculture Molecular Tests Speed Diagnosis of Bloodstream Infections, *from page 11*

Data Emerging for T2 Panels' Cost Effectiveness

T2 Biosystems also recently published two papers, one in PLOS ONE and one in Diagnostic Microbiology and Infectious Disease, highlighting the potential of the T2Bacteria and T2Candida panels to improve outcomes and be cost-effective for several clinical scenarios, including adults presenting in the emergency department or the medical intensive care unit with severe sepsis or septic shock.

Models evaluated the cost-effectiveness of using two blood culture sets in conjunction with the T2Bacteria and T2Candida rapid molecular diagnostic assays (the bundle approach) versus blood culture alone. In both studies the bundle approach was cost effective when considering cost savings for deaths and in cases that the length of hospital stay differs by four days between patients receiving appropriate and inappropriate antimicrobial therapy.

"This is aligned with the real-world results reported by our customers, which includes actionable results in as little as 3 [to] 5 hours, allowing for appropriate adjustment of antibiotic therapy, or de-escalation of therapy in patients with a negative result," said T2 Biosystem's CEO, **John McDonough**, in a statement. "This rapid result uniquely provided by our products and benefits patient care can lead to cost-savings and supports improved antimicrobial stewardship."

Takeaway: T2 Biosystem's recently cleared panel may be a promising way to cost-effectively speed time to results for identification of pathogens responsible for BSIs.