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New Trends, Applications, and IVD Industry Analysis

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Emerging Tests: Progress & Key Developments in the Scramble to Develop a Rapid Coronavirus Detection Test

As coronavirus continues to spread and claim more lives, the development of a quick, safe and effective diagnostic test for detecting the 2019-nCoV virus has become an urgent global priority. Not surprisingly, the most progress has been made in China, Hong Kong and Southeast Asia where the outbreak began and continues to pose the greatest threat. Here is a quick overview of some of the more promising initiatives that have emerged from the region.

The Central Role of RT-PCR Test Technology

Although much remains to be learned about 2019-nCoV, researchers have noted its similarity to coronaviruses found in bats, including the severe acute respiratory syndrome (SARS) virus.

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FDA Watch: Agency Grants Emergency Clearance for CDC Novel Coronavirus Detection Test

Because the 2019 novel coronavirus outbreak was so unanticipated, there were no FDA-approved commercial products for it available in the US during its early days. On Jan. 28, the FDA unveiled its strategy for promoting the rapid development and availability of safe and effective investigational medical products "to address this urgent public health situation." As with previous infectious disease outbreaks like Zika, the centerpiece of the FDA strategy is expedited clearance of new coronavirus tests and treatment products via the Emergency Use Authorization (EUA) pathway. The FDA called on diagnostic test sponsors interested in potential EUA for detection tests to contact the Center for Devices and Radiological Health (CDRH) (CDRH-EUA-Templates@fda.hhs.gov) for information and templates.

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Progress & Key Developments in the Scramble to Develop a Rapid Coronavirus Detection Test, *from page 1*

Accordingly, test developers have based tests to detect and confirm the virus on rapid real-time reverse transcription polymerase chain reaction (RT-PCR) technology.

The BGI Group Assay

No diagnostic company has played a more direct and active role in 2019-nCoV response than Chinese genome sequencing company, the BGI Group. On Jan. 28, BGI and its MGI Tech subsidiary received emergency clearance from China's National Medical Products Administration (NMPA) for its real-time fluorescent RT-PCR kit for 2019-nCoV testing. In addition to scaling up production of the assay, BGI donated 230,000 kits and opened a medical test laboratory to support 2019-nCoV response efforts in Wuhan and Hubei Province. It also announced a collaboration with Ares Genetics, a Curetis Group company, to make 2019-nCoV tests available in Europe. Ares will launch a next-generation sequencing testing service for the virus using BGI reagents.

The Hong Kong Assays

On Jan. 31, the journal *Clinical Chemistry* published the results of a study by investigators from China and Hong Kong claiming to have developed a pair of assays for rapid identification and confirmation of 2019-nCoV. Using publicly available sequencing information about the virus, the researchers focused on viruses in the sarbecovirus subgroup of betacoronaviruses and developed one-step RT-PCR tests targeting two regions of the viral genome—ORF1b and N. They then evaluated the tests in a panel of negative and positive control samples, including respiratory specimens from patients suspected of having 2019-nCoV during different stages after the onset of the illness. Each RT-PCR took about an hour and 15 minutes to run.

The researchers found that the assays were sensitive only to sarbecoviruses, with both suspected patients testing positive. They also determined that the N gene assay was 10 times more sensitive than the ORF1b assay in detecting positive samples. Based on these findings, the researchers recommended:

- Using the N gene assay for initial testing;
- Using the ORF1b assay if the patient tests positive to confirm the result; and
- Follow up testing by a World Health Organization (WHO) reference laboratory if the first test is positive and the second test is negative.

The PolyU Multiplex Respiratory Screening Panel

Less than a week after publication of the *Clinical Chemistry* RT-PCR tests study, scientists from The Hong Kong Polytechnic University (PolyU) announced that they have developed a comprehensive panel

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capable of detecting 30 to 40 respiratory infectious disease pathogens, including 2019-nCoV, in less than an hour via a single test. Incorporating polymerase chain reaction technology into the diagnostic system allows the device to be fully automated from sample nucleic acid extraction and amplification to signal detection and analysis to achieve point-of-care capability. The system does not require manual interaction across the testing process.

Chips and Apps

Response has also extended to mobile point-of-care test lab-on-chip solutions that can diagnose pathogens via an end user's cell phone. One of the first applications of this technology to 2019-nCoV came on January 24 when Singapore biotech firm Veredus Laboratories announced plans for a February 1 commercial launch of a kit capable of detecting the coronavirus with "high specificity and sensitivity." The VereCoV kit is based on lab-on-chip technology which integrates two molecular biological applications, polymerase chain reaction and microarray. This is the same application that Veredus, which is currently owned by Japanese plastics giant Sekisui Chemicals, has used to create kits for detecting the Mers, Zika, Dengue and H1N1 viruses. The company claims the new kit can detect, differentiate and identify all three coronaviruses in a single test in about two hours.

Takeaway

*Although East and Southeast Asia have been the center of activity, scientists, public health laboratories and commercial test makers in the US, Europe and other regions affected by the outbreak are also working furiously to develop and secure expedited emergency regulatory approval for new experimental 2019-nCoV detection tests. (See "**FDA Watch**" on **page 1** for an overview of the response in the US.)*

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Testing Trends: Standard Pathology Tests Outperform Molecular Subtyping in Bladder Cancer Tumor Classification

The deadliness of muscle invasive bladder cancer has made the development of new diagnostic and treatment methods imperative. One strategy involves the use of molecular genetic testing to subtype tumors for aggressiveness. But now a new study published in the *Journal of Urology*, has found that molecular subtyping of bladder tumors was consistently outperformed by standard tests that pathologists have long used to

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characterize cancer as low- or high-grade and determine the extent of its invasion into the bladder wall and beyond.

Molecular Subtyping

Molecular subtyping involves the use of RNA sequencing (RNA-Seq) to compile databanks on gene expression and mutations present in a cancer type to find patterns of gene expression. The data are then used to subtype tumors that "pathologically look similar" but are molecularly different. The theory is that molecular subtypes are better equipped to indicate which cancer is more or less aggressive and to help steer treatment options, e.g., whether to use chemotherapy before surgery to remove a cancerous bladder. Originally, there were two subtypes for muscle invasive bladder cancer (there are now six):

- Luminal, which betokens better survival; and
- Basal, which predicts poor prognosis.

An Accidental Discovery

Information obtained from molecular profiling is no doubt helpful in guiding treatment. But the process is also complex and expensive. So, researchers from the Medical College of Georgia at Augusta University set out to find a simpler, cheaper and widely available test that could provide similar insight. They reviewed several sets of data on cancer specimens from patients with muscle invasive bladder cancer, including the one used to determine emerging molecular subtypes. They also had information about the patients' outcomes.

The researchers planned to base their new subtyping panel test, which they dubbed MCG-1, on the 11 genes they identified as being common in all subtype classification methods. But instead of doing RNA-Seq, which costs several thousand dollars, they used the readily available reverse transcription quantitative PCR method which also looks at gene expression and is actually used to verify RNA-Seq data, but costs less than $10.

First, they looked at their own cohort of 52 bladder cancer patients, of whom 39 had muscle invasive disease. They found that MCG-1 was only 31% to 36% accurate in predicting key diagnostic and prognosis indicators, including:

- Likelihood of metastasis;
- Disease specific survival, i.e., surviving bladder cancer; and
- Overall survival, i.e., survival from all causes of death from the time of cancer diagnosis or start of treatment until the end of the study.

To make up for the relative smallness of their dataset and lack of RNA-Seq use for analysis, the researchers then used three patient datasets from

the cancer database ONCOMINE which had more patients, including 151 with muscle invasive bladder cancer, and used RNA-Seq to assess gene expression.

They found that their own MCG-1 test was incapable of predicting disease-specific mortality. On some patients in this dataset, information on response to chemotherapy was available but subtypes could not predict chemotherapy response either, the researchers found.

> *"We were intrigued why MCG-1 could not predict anything in our cohort or ONCOMINE dataset but predicted overall survival in the TCGA dataset."*
>
> — Vinata B. Lokeshwar, chair of the College's Department of Biochemistry and Molecular Biology

So, the researchers looked at the dataset that has been used to identify the subtypes, The Cancer Genome Atlas (TCGA), a National Cancer Institute and National Human Genome Research Institute project that includes genetic material for 33 different cancers and routine pathology information on 402 specimens from patients with muscle invasive bladder cancer, including the patients' overall survival and recurrence-free survival.

"Up until this point, we had been looking at patients that other groups had not looked at," explains study author **Vinata B. Lokeshwar**, chair of the College's Department of Biochemistry and Molecular Biology. In this dataset, MCG-1 predicted overall survival similar to findings reported from subtypes in several high profile publications. "We were intrigued why MCG-1 could not predict anything in our cohort or ONCOMINE dataset but predicted overall survival in the TCGA dataset," Lokeshwar notes.

So, once more they looked at the 402 patients whose specimens were in the dataset and found that 21 of the patients' tumors were actually low-grade. When they removed the low-grade cases from the TCGA dataset, MCG-1 accurately predicted essentially nothing, not even overall survival. But after including some patients with low-grade tumors into their own dataset, they found that MCG-1 was now able to predict metastasis and disease specific survival.

All the existing subtypes are categorized as bad or better based on the cancer prognosis, the researchers say. The presence of the low-grade tumors in the classification of subtypes skewed the data to make it look like subtypes were predicting overall survival when really it was the grade of the cancer itself that was predictive.

More Evidence of Problems with Molecular Subtyping

Of course, one study is one study. But the Medical College of Georgia at Augusta University study is consistent with another recent study by investigators at Sweden's Lund University published in the journal Urologic Oncology finding that subtypes were not associated with cancer-

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Standard Pathology Tests Outperform Molecular Subtyping in Bladder Cancer Tumor Classification, *from page 5*

specific survival based on study of 519 patients who had their bladders removed because of bladder cancer.

Takeaway

Use of molecular subtyping to classify tumors is tricky business. One potential problem with subtyping, according to ***Daley S. Morera****, co-author of the Georgia study, is that the inherent heterogeneity in the gene expression of tumors, within both the same tumor type, e.g., bladder cancer, and different parts of the same tumor, makes it difficult to categorize any tumor into a single subtype. Adding to the problem is that the pattern of heterogeneity can change during both tumor growth and treatment. "Just because it's bladder cancer does not mean it's the same in all patients," adds Lokeshwar.*

Test Utilization: Payment Policies More Effective than Practice Recommendations in Curbing Orders of Low-Value Tests

When it comes to getting physicians not to order low-value laboratory tests, money talks. At least, that is the punchline of a new study finding that changes in payment policies are more effective than clinical practice recommendations in curbing utilization of low-value tests.

The Diagnostic Challenge

Overtreatment or low-value care accounts for roughly $75.7 billion to $101.2 billion worth of waste in the US. And those estimates are probably well below actual costs to the extent that "tests beget tests" and lead to unnecessary medical procedures. But while overutilization of low-value tests has been well documented, the question of how and why these patterns continue and how they can be changed has received far less attention.

Of course, there have been initiatives to reduce such overutilization, particularly via programs to educate physicians about the problem and recommend best practice guidelines discouraging them from ordering low-value tests. One notable example is "Choosing Wisely," a set of recommendations from the American Board of Internal Medicine.

The JAMA Study

Published online on Feb. 10 in *JAMA Internal Medicine*, the study is based on cross-sectional analysis of claims data to compare the effects of the Choosing Wisely recommendations versus payment policies for two laboratory tests that have long been associated with overutilization and low value: screening for vitamin D and thyroid hormone triiodothyronine

(T3) levels. The researchers looked at records from three different health systems covering roughly 54 million people:

- The US Veterans Health Administration (VHA);
- The US employer-sponsored insurance market; and
- Ontario, Canada (one of the places where the Choosing Wisely recommendations have been adopted).

Vitamin D and T3 are both on the list of low-value tests that Choosing Wisely recommends physicians not use for broad, population-based screening. And Canada is one of the more than 20 countries that have adapted the Choosing Wisely recommendations. But Ontario differs from the other two systems in one regard: In 2010, it instituted a payment policy to eliminate coverage for broad vitamin D testing.

The Findings

The researchers found that vitamin D testing in Ontario declined 92.7%(!) after the new payment policy took effect. By contrast, the declines in testing after publication of the Choosing Wisely recommendations against broad vitamin D screening were far more modest, including:

- 4.5% in Ontario;
- 13.8% for the VHA; and
- 14% for US employer-sponsored insurance.

But that was not all. The study also found that low-value T3 testing actually increased—albeit only by small levels—after the release of the Choosing Wisely recommendations, including:

- 0.3% in Ontario (where the 2010 payment policy affected only vitamin D and not T3 screening);
- 0.7% for the VHA; and
- 3% for US employer-sponsored insurance.

Takeaway: The Need for a Diverse, Balanced Approach

The findings suggest that recommendations alone may be insufficient to significantly reduce utilization of low-value services and that pairing recommendations with policy changes may be more effective, concluded the study authors led by James Henderson, PhD, from Consulting for Statistics, Computing & Analytics Research (CSCAR) at the University of Michigan. At the same time, the authors acknowledged that payment policy changes may go too far and may need to be accompanied in additional interventions, including payment incentives, to avoid the potential for underutilization of needed services.

In the News: CMS Issues New Guidance for Laboratories Performing Coronavirus Testing

On Feb. 4, the Food and Drug Administration (FDA) granted emergency use authorization (EUA) clearance for the first test approved in the US for detecting the novel coronavirus. Developed by the US Centers for Disease Control and Prevention (CDC) using sequencing information made public by Chinese authorities, the 2019-nCoV Real-Time RT-PCR Diagnostic Panel (Panel) is a real-time reverse transcription polymerase chain reaction panel capable of detecting coronavirus from respiratory and blood serum samples, including nasal or oral swabs.

The CDC has created and distributed kits containing the Panel to public health agencies in all 50 states. On Feb. 6, two days after the FDA granted the Panel emergency clearance, the Centers for Medicare and Medicaid Services (CMS) issued guidelines laying out the standards laboratories must follow in performing the assay. Here are the four things testing laboratories need to know about the guidelines.

The CMS Guidelines

Technically, the CMS guidelines are addressed not directly to the testing laboratories but to the state regulators in charge of enforcing the Clinical Laboratory Improvement Amendment (CLIA) who are charged with policing the performance of Panel testing within their jurisdiction. The guidelines also instruct regulators to notify their CMS Location if they discover that a laboratory is using an assay without an EUA that is testing for the same agent for which the emergency has been declared, or a modified EUA assay. The CMS Location will then relay the notification to CMS headquarters in Baltimore which will determine what action to take against the offending laboratory.

The guidelines make four key points with regard to actual testing standards.

1. Eligibility Criteria for Testing Laboratories

Panel tests may be performed only by laboratories that are CDC qualified, and, CLIA certified for high complexity tests.

2. Testing Must Meet CLIA Standards

As with other assays that have received EUA from the FDA, use of the CDC Panel and corresponding protocols remains subject to CLIA regulations. In other words, being CDC qualified, which a laboratory must be to perform the Panel, does not exempt the laboratory from the need to comply with CLIA requirements.

3. Laboratories Must Follow Manufacturer's Instructions

CDC qualified laboratories must also follow any and all applicable Manufacturer's Instructions (MI) in performing the Panel assays.

4. Laboratories Must Verify Performance Specifications

Upon receipt of the Panel assay, CDC qualified laboratories must verify assay performance specifications in their own laboratory as per the MI. Test laboratories are required to use the CDC kits and reagents but are permitted to use their own RT-PCR equipment and extraction kits.

Takeaway

If your laboratory is qualified to perform the new CDC Panel, be sure that you are aware of and strictly adhere to CLIA and the other requirements specified in the CMS guidelines. Also keep in mind that while similar eligibility and performance standards are likely to apply to other coronavirus detection tests if and when they receive EUA from the FDA, each test will come with its own MI.

Point of Care: Is the Blood-Drawing Robot the Phlebotomist of the Future?

Question: Is the human phlebotomist an endangered species? Answer: Not exactly. But a new study suggests that at least one robot may be able to collect blood samples just as well, if not better, than its human counterparts.

The Study

The focus of the story is the blood-sampling robot invented by researchers at Rutgers University in New Jersey. More precisely, the robot is a device that combines miniaturized robotics and ultrasound imaging to identify suitable vessels for cannulation and robotically guide an attached needle toward the lumen center. In addition to drawing blood, the device includes a module for handling samples as well as a centrifuge-based blood analyzer.

It all sounds quite ingenious, but does it actually work? Published in the journal Technology, the first clinical trial results suggest that it does. The device drew blood from 31 participants with an overall success rate of 87%, well within acceptable clinical standards. And the success rate increased to

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Point of Care: Is the Blood-Drawing Robot the Phlebotomist of the Future?, *from page 9*

97% for the 25 participants with veins that were easy to access.

To put these numbers into perspective, the researchers cited studies documenting the venipuncture failure rate of clinicians fail, including:

- 27% in patients without visible veins;
- 40% in patients without palpable veins; and
- 60% in patients who are emaciated.

In addition to endangering both patients and clinicians, venipuncture breakdowns can increase the time, cost and effectiveness of treatment.

"A device like ours could help clinicians get blood samples quickly, safely and reliably, preventing unnecessary complications and pain in patients from multiple needle insertion attempts," according to lead author Josh Leipheimer, a biomedical engineering doctoral student in the School of Engineering at Rutgers University-New Brunswick.

Takeaway

The Rutgers blood-drawing robot remains very much a work in progress. Among the bugs that need to be worked out is improving the success rates in patients with veins that are difficult to access. To accomplish that objective, researchers hope to use data from the study to enhance the robot's artificial intelligence. And while actual clinical deployment is likely to take years, if it happens at all, the odds are good that at least some day the robot or a device like it will become a useful fixture in ambulances, emergency rooms, hospitals, clinics and doctors' offices.

FDA Watch: Agency Grants Emergency Clearance for CDC Novel Coronavirus Detection Test, *from page 1*

The CDC Test

On Feb. 4, the agency took the first step by issuing an EUA for a reverse transcriptase real-time PCR (rRT-PCR) assay (aka, the 2019 Real Time RT-PCR Diagnostic Test Panel) developed by the US Centers for Disease Control and Prevention (CDC) for use in detecting coronavirus from respiratory and blood serum samples, including nasal or oral swabs. The test can be used in the US only by CDC-designated laboratories that are certified to perform high-complexity testing in accordance with agency protocol. The CDC published the test formula and created kits using the assay for distribution to state health departments and public health laboratories around the country.

Nancy Messonnier, director of the CDC National Center for Immunization and Respiratory Diseases, says that the agency deems the rapid development and distribution of the test a success. But while the agency has shipped the kits to all 50 US states (and 30 international sites), the kits may not be used unless and until they undergo quality assessment and validation by the public health laboratories of the particular state. "When a state gets the test kit, they have to verify that it works the same in their laboratory as it worked at CDC," Messonnier explained during a press conference. And, of course, some states will complete that process faster than others.

Already, the limitations of the CDC assay have become evident. Thus, while a positive result is a fairly reliable indicator of coronavirus infection, the early feedback suggests that a negative result cannot be counted on to rule it out. Accordingly, the FDA has warned against relying on negative tests as the lone basis for treatment and patient management decisions. Negative results must also be evaluated along with clinical observations, patient history and epidemiological information, the agency stresses. Meanwhile, the CDC acknowledged that it will probably need to remanufacture one of the kit reagents to address the test quality results issues.

Takeaway

While it has obvious flaws that need to be worked out, the CDC (rRT-PCR) assay is the only approved test for coronavirus currently available in the US, one designed as a stopgap measure to hold down the fort until the private sector develops better alternatives.

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FDA Watch: Agency Grants Emergency Clearance for CDC Novel Coronavirus Detection Test, *from page 11*

New FDA Approvals

Key new product approvals announced from late-January through mid-February 2020:

NEW FDA APPROVALS

Manufacturer(s)	Product(s)
US Centers for Disease Control and Prevention	Emergency Use Authorization for 2019-nCoV Real-Time RT-PCR Diagnostic Panel to detect coronavirus
Lucid Diagnostics	Breakthrough device designation for EsoGuard Esophageal DNA Test to detect esophageal dysplasia and potential cancer risk run on EsoCheck Cell Collection Device
Siemens Healthineers	510(k) clearance for Advia Centaur Total IgE assay to detect total IgE in serum + plasma run on Advia Centaur, Advia Centaur XP + Advia Centaur XPT systems
DiaSorin	Clearance for Liaison Lyme Total Antibody Plus assay and Liaison Lyme Total Antibody Plus Control Set to detect IgG and IgM antibodies to Borrelia burgdorferi in serum and plasma samples
Thermo Fisher Scientific	Clearance for Sensititre 20- to 24-hour Haemophilus influenzae/Streptococcus pneumoniae minimum inhibitory concentration or breakpoint susceptibility system with lefamulin (Nabriva's Xenleta), in 0.008 to 16 µg/mL dilution range
Shenzhen Bioeasy Biotechnology	Clearance for Bioeasy Multi-Drug Test Cup assays to detect drugs in human urine at specified cutoff concentrations
Beckman Coulter	510(k) clearance for Access PCT assay
DNA Genotek (subsidiary of OraSure Technologies)	510(k) clearance for Oragene Dx sample collection kits

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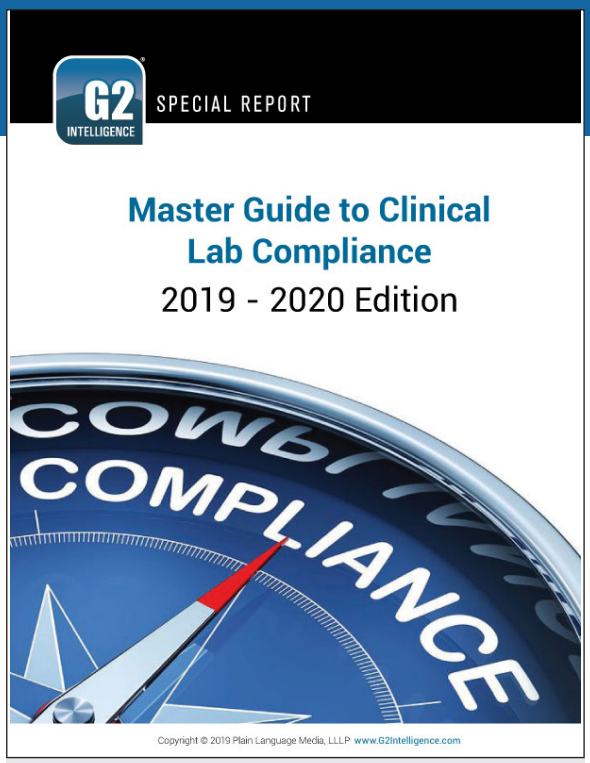

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