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A DIVISION OF PLAIN LANGUAGE MEDIA

DIAGNOSTIC TESTING & Emerging Technologies

New Trends, Applications, and IVD Industry Analysis

FEBRUARY 2021

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Emerging Tests: Pairing of VOC Breathalyzer Testing and AI Cloud-Based Analysis Could Be Coronavirus Game Changer

A handheld, easy-to-use breathalyzer device capable of accurately detecting COVID-19 at the point of care would represent a major breakthrough in the effort to contain the spread of the virus. That vision may now be closer to reality thanks to a new international collaboration established to perform a massive clinical trial to test the idea. Here is a briefing on the deal and its potential significance:

The Diagnostic Challenge

All agree that rapid and accurate point-of-care testing performed on a mass basis, including both the symptomatic and asymptomatic, is crucial to containing the spread of coronavirus. However, only a few of the COVID-19 diagnostic tests that have hit the market since

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Testing Trends: Report Analyzes Federal Health Programs' COVID-19 Testing Efforts in First Months of Pandemic

The COVID-19 outbreak caught the country and the world totally off guard. And even as the pandemic intensifies, the lessons from those first crucial months hold the key to managing not only coronavirus but also future public health crises, particularly with regard to diagnostic testing. A new government report offers sheds new light on one big part of the early efforts to meet the historically unprecedented demand for COVID-19 testing, namely, the role of federal agencies directly involved in administering or paying for tests. Here is a breakdown of the report's findings and the insights it offers for mass scale testing efforts in both the near- and long-term future.

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Emerging Tests: Pairing of VOC Breathalyzer Testing and AI Cloud-Based Analysis Could Be Coronavirus Game Changer, *from page 1*

the pandemic began have received regulatory approval for testing people who are asymptomatic.

Focusing on the symptomatic is completely understandable. After all, people displaying symptoms of illness should be the priority when testing resources are in scarce supply. By the same token, as the U.S. Centers for Disease Control and Prevention (CDC) reports, the coronavirus is mostly spread by persons who do not have symptoms. Accordingly, what is need is a method of providing mass testing to asymptomatic people without diverting resources that are desperately needed for testing the symptomatic?

A New COVID-19 Testing Modality

Current COVID-19 diagnostics, including laboratory developed tests (LDTs), are based molecular, antibodies or antigen detection. So, a potential solution would be to develop a new modality using a different biomarker to detect the virus. One biomarker candidate is exhaled volatile organic compounds (VOCs) that could be detected via a rapid breath test. And that is the idea behind the new research collaboration between Canary Health Technologies and Divoc Laboratories.

Instead of measuring the viral load the way current tests do, breath tests detect COVID-19 by evaluating metabolic response nearly immediately after infection. The modality is based on the fact that like influenza, rhinovirus, SARS, MERS and other viral infections, coronavirus increases oxidative stress releasing highly reactive free radicals that serve as powerful biomarkers contained in an infected person's exhaled breath. Moreover, each virus has its own unique VOC signature.

The Collaboration

Announced on Nov. 30, the objective of the collaboration between Canary and Divoc is to develop and validate a hand-held digital breath test for coronavirus. Canary is a U.S.-based medical technology company that uses proven biomarkers, proprietary nanosensors and AI-powered software to map and uncover data in human breath to detect cancers, inflammatory and infectious diseases on a rapid basis. Divoc is a Dehli-based laboratory focused on providing a digitally empowered integrated approach to diagnostics.

The new Canary test, called ASU Detect CV19, uses next-generation, highly sensitive nanosensors to collect breath samples which are then analyzed through the use of cloud-based artificial intelligence capable of detecting the SARS-CoV-2 virus in less than three minutes. In addition to being disposable, which mitigates the risk of infection, the Canary test is

DTET

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Diagnostic Testing and Emerging Technologies (ISSN 2330-5177) is published by G2 Intelligence, Plain Language Media, LLLP, 15 Shaw Street, New London, CT, 06320.
Phone: 888-729-2315
Fax: 855-649-1623
Web site: www.G2Intelligence.com.

scalable, low cost and viable for use at the point of care for mass screening of both the symptomatic and asymptomatic.

The Next Steps

The idea is exciting. The key question, of course, is whether it will actually work. In 2019, a clinical trial in Canada demonstrated that the Canary breath analysis platform is capable of detecting lung cancer with high sensitivity and specificity. To validate the concept for use with coronavirus, the partners will perform what they describe as the first and largest clinical trial using a real-time breath test using cloud-based artificial intelligence for pattern recognition to detect an infectious disease.

To be performed in Dehli, the trial researchers will collect breath samples from 750 people, including both COVID-19-positive patients and patients who do not have the virus. They will be asked to breathe for three minutes into the device. The ASU device will then translate their breath biomarkers into electronic signals which will be transmitted to a centralized "lab in the cloud" for analysis. Preliminary results could come as early as January. The partners also plan to start parallel trials in the U.S. and Europe.

If the trial is successful, Canary plans to seek fast-track regulatory approval in India, the U.S. and other markets while continuing to trial the test in real-world settings such as airports, resorts and other high-density areas.

Takeaway

The combination of VOC technology and cloud-based AI analysis could be the answer to the country's and the world's need for rapid, point-of-care COVID-19 screening of the asymptomatic. In addition to its detection capabilities, the platform carries the potential for use in real-time surveillance for disease monitoring, as well as track and trace initiatives. It would also empower public health authorities to identify COVID-19 hotspots as they form and take immediate responsive actions. "This is next-generation technology and has the ability to completely revolutionize testing for COVID-19 and play a critical role in stopping the spread of the virus," notes Dr. Kanav Kahol, CEO of Divoc and a renowned healthcare innovator. Fingers crossed that trials validate the concept.

SPECIAL FOCUS

CBC Scoring of COVID-19 Inpatients May Help Hospitals Save Lives and Preserve Precious Treatment Resources

Early detection and early intervention have the potential to improve the prospects of recovery and positive outcomes for a broad range of diseases, including coronavirus. And now researchers in Europe believe they have found a method that uses a COVID-19 patient's blood count to guide treatment and improve case outcomes. Here is an overview:

The Diagnostic Challenge

COVID-19 spans a wide clinical spectrum ranging from asymptomatic to severe pneumonia with multiple organ failure, and death. Early identification of critical patients requiring more aggressive intervention could go a long way in reducing COVID-19 deaths. But from almost the moment the pandemic began, the paramount objective of COVID-19 diagnostics has been to determine whether a person does or does not *have* the virus. Collecting information to guide medical treatment and improve clinical outcomes of patients who do have COVID-19 has received far less attention.

The initial emphasis on detection is understandable given how contagious the virus is and the fact that treatments for it remain largely unproven. However, as the crisis drags on and deepens, an increasing number of researchers have been delving into the treatment aspects of COVID-19 diagnostics.

The CBC Prognosis Test: Concept

One notable example of fruitful outcomes-based COVID-19 research is the recent study published by the journal *eLife Sciences* in December. The principal objective of the team of Dutch researchers sponsored by the Hamburg, Germany, subsidiary of the Japanese-based firm Sysmex, was to develop and validate a prognostic score using only hemocytometric data to predict a COVID-19 hospital patient's risk of deterioration and need for transfer to intensive care unit (ICU). The risk score would be generated within the first three days of admission and assess the patient's prognosis case over a period of 14 days to provide the opportunity for early intervention, if necessary, and objective risk stratification.

As the study authors note, COVID-19 has specific alterations in circulating blood cells that can be detected by a routine hematology analyzer, particularly in hematology analyzers that are capable of recognizing activated immune cells and early circulating blood cells. Accordingly, the team decided to base the test on a complete blood count (CBC) measuring the size, number and maturity of the different blood cells in a specific volume of blood, including:

- **Red blood cells**, which are important for carrying oxygen and fighting anemia and fatigue. The hemoglobin portion of the CBC measures the

SPECIAL FOCUS

oxygen carrying capacity of the red blood cells, while the hematocrit measures the percentage of red blood cells in the blood.

- **White blood cells**, which fight infection. Increased numbers of white blood cells, therefore, may indicate the presence of an infection. Decreased levels may indicate certain rheumatic diseases or reaction to medication.
- **Platelets**, which prevent the body from bleeding and bruising easily.

The scoring system incorporates a total of 10 parameters, including parameters for neutrophils, monocytes, red blood cells and immature granulocytes, and when available, reticulocyte and iron bioavailability measures.

The CBC Prognosis Test: Development

The research team developed the test using data from 982 adult patients presenting to a hospital from Feb. 21 to April 6, 2020, with outcomes followed until June 9. Among this cohort, only 7 percent were not admitted to a hospital; another 74 percent were admitted to a general ward and the remaining 19 percent were transferred directly to the ICU. The median age was 71 and approximately two-thirds of the cohort patients were male. The researchers used a Sysmex Europe GmbH XN-1000 hemocytometric analyzer to create an algorithm based on 1,587 CBC assays from 923 adults. They validated the scoring system in a second cohort of 217 CBC measurements in 202 people.

The Findings: The CBC score accurately predicted the need for critical care within 14 days in 70.5 percent of the development cohort and 72 percent of the validation group. The scoring system was superior to any of the 10 parameters alone. Over 14 days, the majority of those whom were classified as noncritical (NC) within the first three days of admission remained clinically stable, whereas the "clinical illness" (CI) group progressed, with clinical severity peaking on day 6.

Takeaway

A CBC-based scoring system that provides a reliable assessment of a COVID-19 inpatient's prognosis over a 14-day period within the first three days of admission would surely be a huge help to hospitals right about now. In the context of the COVID-19 crisis, information about whether early intervention is necessary is crucial to not only medical treatment and outcomes but also preservation of ventilators and other tightly stretched hospital resources. Stated simply, hospitals need to be able to assess the risks faced by each COVID-19 inpatient and make timely and scientifically sound determinations about which patients are likely to recover without ventilators and which patients are likely to deteriorate resulting in the need for intensive care and risk of fatality.

FDA WATCH

Molecular Tests May Miss New SARS-CoV-2 Strains, Agency Warns

Like many viruses, the SARS-CoV-2 is a shape-shifter. And that may make it harder to detect. With this in mind, the U.S. Food and Drug Administration (FDA) is warning clinical laboratories and health care providers of the risk that genetic mutations to the virus may lead to false negative test results.

The Diagnostic Challenge

The first and vast majority of tests with FDA emergency use authorization (EUA) for SARS-CoV-2 are molecular assay designed to detect specific RNA sequences found in the viral genome. However, the SARS-CoV-2 virus mutates regularly, resulting in several genetically unique variants, each with different RNA sequences. The presence of SARS-CoV-2 genetic variants in a patient sample can potentially change the performance of the SARS-CoV-2 test. If a molecular test is not engineered to detect the particular sequences associated with these variants, it may miss the variant leading to the false conclusion that the test subject does not have the virus. The resulting false negative may prevent the subject from receiving necessary treatment and enhance the risk of infection by keeping him/her out of self-isolation.

Molecular tests designed to detect multiple SARS-CoV-2 genetic targets are less susceptible to the effects of genetic variation than tests designed to detect a single genetic target. The clinical impact of genetic variants on test sensitivity is influenced by the sequence of the variant, the design of test and the prevalence of the variant in the patient population. Tests that rely on the detection of multiple regions of the genome may be less impacted by genetic variation in the SARS-CoV2 genome than tests that rely on detection of only a single region.

The FDA Response

The FDA has been monitoring the potential effects of genetic variation in molecular tests that have received EUA on an ongoing basis throughout the pandemic. On Jan. 8, it sounded the alarm in a letter. "The FDA reminds clinical laboratory staff and health care providers about the risk of false negative results with all laboratory tests," FDA wrote, including molecular tests. The FDA letter also identifies specific molecular tests that have received EUAs whose performance could be impacted by SARS-CoV-2 genetic variants. "No test is perfect," according to the letter. "Laboratories should expect some false results to occur even when very accurate SARS-CoV-2 tests are used." The letter lists three tests with EUA that could be impacted by mutations:

- The Mesa Biotech Accula SARS-Cov-2 Test, which received EUA on March 24;
- The Thermo Fisher Scientific TaqPath COVID-19 Combo Kit, which received initial EUA on March 15 and received subsequent expansions allowing for home collection and use with additional instruments and reagents; and
- The Applied DNA Sciences' Linea COVID-19 Assay Kit, first cleared on May 13 and subsequently cleared for use with robotic RNA extraction.

FDA Recommendations

The FDA recommends that clinical laboratory staff and providers who use molecular tests for the detection of the SARS-CoV-2 virus:

- Recognize that genetic variants of SARS-CoV-2 arise regularly and may result in false negative test results;
- Be aware that tests that use multiple genetic targets to determine a final result are less likely to be impacted by increased prevalence of genetic variants;
- Analyze negative results in combination with clinical observations, patient history and epidemiological information; and
- Consider ordering repeat testing with a different test with different genetic targets for patients who test negative after molecular testing if COVID-19 is still suspected.

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FDA Watch, *from page 7*

Meanwhile, here are the key new FDA EUAs and clearances announced in January:

New FDA Emergency Use Authorizations (EUAs) & Approvals

Manufacturer(s)	Product
Bio-Rad Laboratories	EUA for Bio-Rad Reliance SARS-CoV-2 RT-PCR Assay
United Biomedical	EUA for UBI SARS-CoV-2 ELISA antibodies test
SML Genetree	EUA for Ezplex SARS-CoV-2 G Kit
Ortho Clinical Diagnostics	Vitros SARS-CoV-2 Antigen test, first high-volume COVID-19 antigen test to get EUA
Phadia (Thermo Fisher Scientific subsidiary)	EUA for EliA SARS-CoV-2-Sp1 IgG Test fluoro-enzyme immunoassay
Abbott	510(k) clearance for rapid handheld blood test for traumatic brain injury
Helix	de novo clearance for Helix Laboratory Platform, first whole-exome sequencing platform to get FDA clearance
Helix	510(k) clearance for Helix Genetic Health Risk App (HRA) DTC genetic test for late-onset Alzheimer's
Siemens Healthineers	EUA for Dimension Vista SARS CoV 2 IgG (COV2G) antibodies immunoassay
Siemens Healthineers	EUA for lab-based IL-6 assay to measure presence of interleukin-6 in human serum or plasma
Advaite	EUA for RapCov Rapid COVID-19 Test point of care serology test
Quanterix	EUA for Simoa SARS-CoV-2 N Protein Antigen Test
Nirmidas Biotech	EUA for MidaSpot COVID-19 Antibody Combo Detection Kit point of care test
Roche	EUA for Elecsys Anti-SARS-CoV-2 S electrochemiluminescence immunoassay run on firm's Cobas E analyzers
Lucira Health	EUA for Lucira COVID-19 All-in-One Test Kit, first fully at-home test authorized for COVID-19
GenScript Biotech	EUA for cPass SARS-CoV-2 Neutralization Antibody Detection Kit, first SARS-CoV-2 neutralizing antibody test to receive EUA

Testing Trends: Report Analyzes Federal Health Programs' COVID-19 Testing Efforts in First Months of Pandemic, *from page 1*

The PRAC Report

Published on Jan. 14, 2021, the Federal COVID-19 Testing Report: Data Insights from Six Federal Health Care Programs report is the work of the Pandemic Response Accountability Committee (PRAC). In case you have

not heard the name, PRAC is a new federal agency established by the CARES Act to promote transparency and perform independent oversight over spending of CARES Act and other related federal emergency bill funds. Its responsibilities include supporting efforts to "prevent and detect fraud, waste, abuse, and mismanagement [and] mitigate major risks that cut across program and agency boundaries."

The report is an attempt to carry out that mission by evaluating federal government involvement in COVID-19 testing efforts from February through August 2020, the first seven months after declaration of the public health emergency. Although it is not a comprehensive in scope in the sense that it does not cover all agencies involved in testing, it offers a meaningful cross-section based on data supplied compiled from the Offices of Inspector General of six federal agencies that were directly involved in administration and/or reimbursement of COVID-19 testing, including the OIGs from the U.S.:

- Office of Personnel Management (OPM);
- Department of Defense (DOD);
- Department of Health and Human Services (HHS);
- Department of Justice (DOJ);
- Department of Labor (DOL); and
- Department of Veterans Affairs (DOVA).

The 6 Questions PRAC Asked the OIGs

To assess the agency's COVID-19 testing performance, the PRAC Subgroup that wrote the new report asked the OIGs six key questions:

1. How many COVID-19 tests were administered, and when?
2. Who was tested?
3. What types of tests were administered?
4. How much did the particular health care program pay for tests?
5. In what health care settings did people access testing?
6. How long did it take to return test results?

The Five Key Findings

The PRAC report's greatest value comes from its five key findings.

1. Demographics of COVID-19 Test Subjects

PRAC determined that, collectively, the six agencies that provided data for the report paid for or administered 10.7 million COVID-19 tests,

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representing 12.7 percent of all coronavirus tests performed in the U.S. during the study period. So, who exactly were these people? The report found that the gender, age, race or ethnicity and other demographic characteristics of those who got tested under the participating federal programs largely mirrored the demographics of the entire population those programs serve. The most significant data came from HHS because of the 6.5 million people that got tested under these federal programs, 5.1 million were Medicare Part B beneficiaries. Thus, for example, the 9 percent of Medicare Part B beneficiaries that identified themselves as Black/African American in the study data closely aligns with the nearly 10 percent of Black/African American Medicare Part B beneficiaries that received a COVID-19 test from all providers, i.e., other agencies, private labs, hospitals, etc.

The DOJ was the only other federal agency that furnished useable data for this analysis. But that data followed the same basic pattern, with the 33 percent of Bureau of Prisons subjects who self-identified as Hispanic/Latino in the study sample being just slightly above the 28 percent of all inmates who received a COVID-19 test that self-identified as Hispanic/Latino.

2. Types of Tests Performed

COVID-19 test types performed or administered by the federal agencies in the study also mirrored national testing patterns. The vast majority of tests were molecular viral assays but all of the other federal programs in the study (other than the Bureau of Prisons) also covered a limited amount of antibodies testing. The breakdown:

Types of COVID-19 Tests Paid for or Administered by Studied Federal Agency

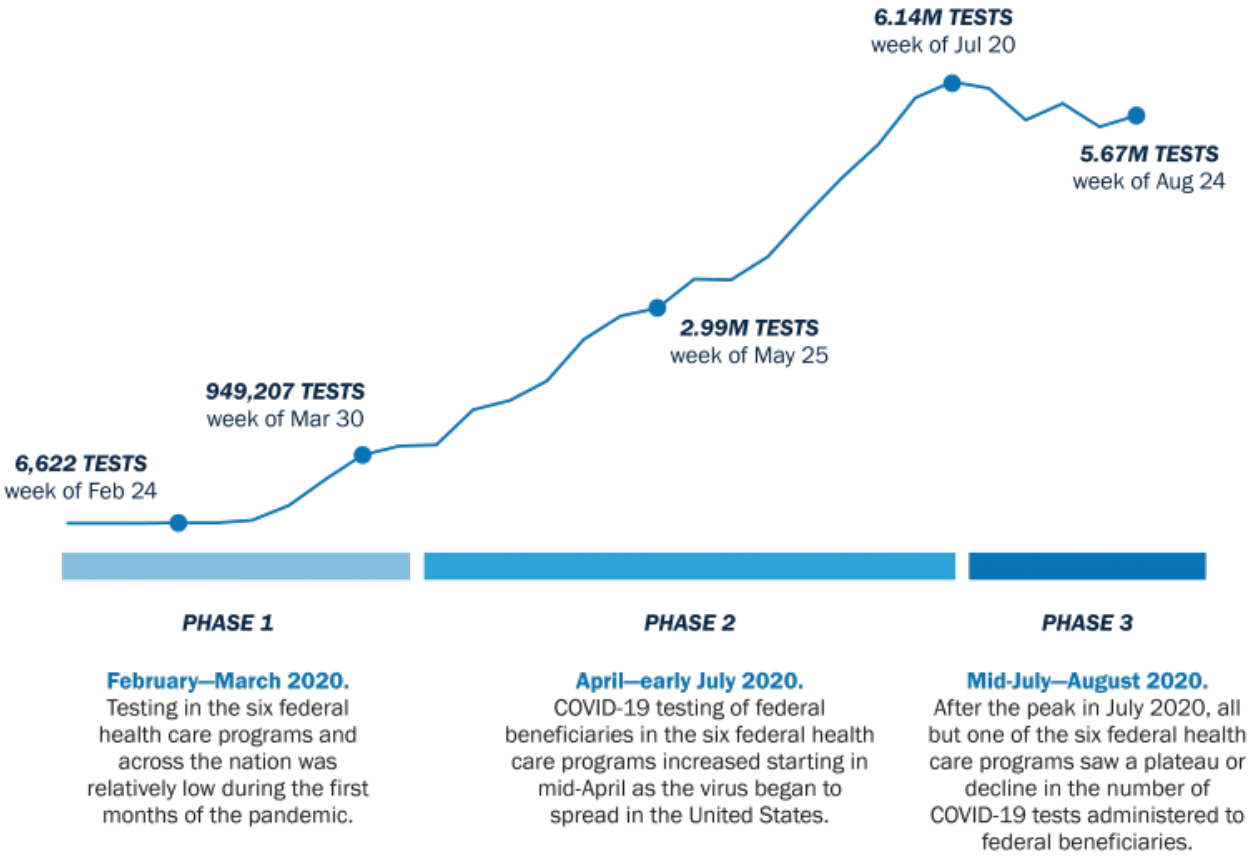
Agency	Molecular Viral	Antibodies
OPM	81 percent	19 percent
HHS (Medicare Part B)	86 percent	14 percent
DOL (Workers' Comp)	95 percent	5 percent
VA (VHA)	95 percent	5 percent
DOD (Medical Treatment Facilities)	96 percent	4 percent
DOJ (Bureau of Prisons)	100 percent	0 percent

Source: PRAC

3. Testing Volume

Testing by the federal agencies in the study was consistent with overall U.S. testing patterns, with little done in the first months of the pandemic, followed by significant increases in volume through the spring and summer.

COVID-19 Testing Volume Patterns



Source: PRAC

4. Test Reimbursement

During the study period, the six federal health care programs spent at least $659.5 million on COVID-19 tests for their beneficiaries. (This amount does not include testing at the VHA for which no spending data was available.) Average costs for COVID-19 viral tests, which accounted for the vast majority of those the federal agencies in the study administered or paid for, varied by program. Four of the six programs—Medicare Part B, the FEHBP, Workers' Compensation and the Bureau of Prisons—reported paying an average $69 to $130 per viral test processed at a commercial laboratory, with variances attributable to differences in product used, supplies involved and program reimbursement rules.

Of the programs that ordered and performed testing at facilities that they manage or operate, only two had data on average cost of viral tests. The DOD Medical Treatment Facilities' average per-test cost for viral tests ordered and performed at its facilities was $57. The Bureau of Prisons' average per test costs were $0 because tests were performed on site using testing machines and supplies from the Strategic National Stockpile provided by HHS free of charge.

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5. Test Turnaround Time

Only three of the agencies—Bureau of Prisons, VHA and DOD Medical Treatment Facilities— furnished data on COVID-19 test turnaround time. However, those data were also consistent with national testing trends. Thus, the VA and DOD reported turnaround times of more than four days and three days, respectively, in March 2020. But by the end of July, turnaround time had dropped to around one day. The Bureau of Prisons reported that at some sites, test turnaround took as long as two weeks in July and August as demand began to spike. The Bureau of Prisons also used rapid molecular testing, which returned results in as little as 15 minutes.

Takeaway

While it is not a comprehensive review of the entire federal government testing response, the report does provide valuable insight enabling Congress, federal and state agencies, health care entities and other stakeholders understand and plan for current and future response efforts. "Testing for COVID-19 is a critical component of the federal government's pandemic response," noted PRAC Chair Michael Horowitz in a statement on the day the report came out. "Today's report examines the testing processes in multiple federal programs, providing a detailed look at testing trends, demographics, and spending."

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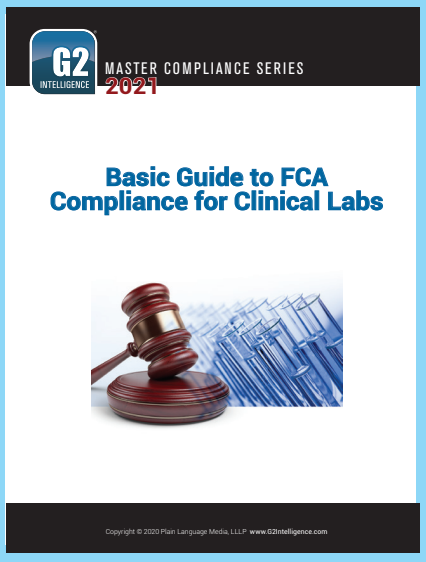

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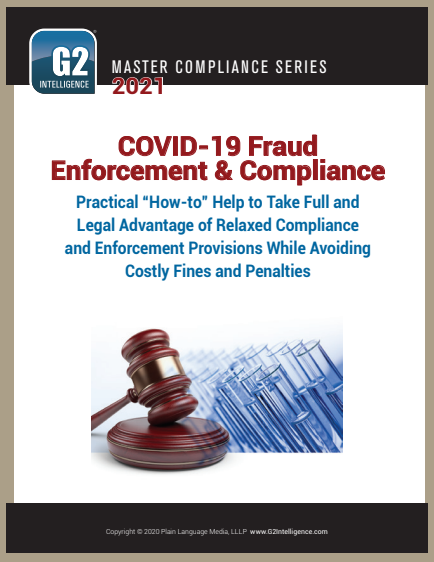

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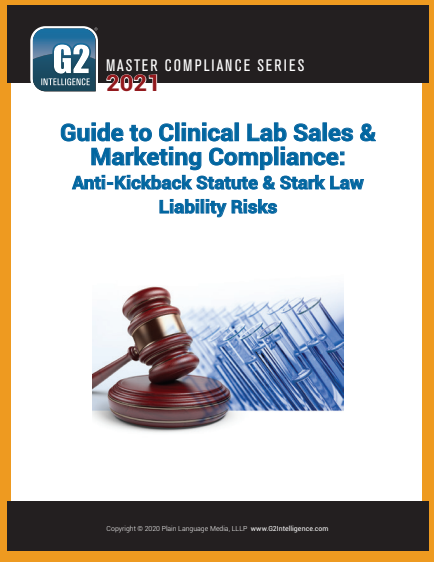

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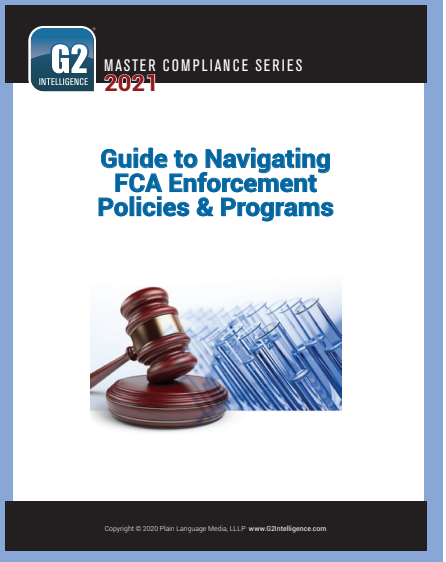

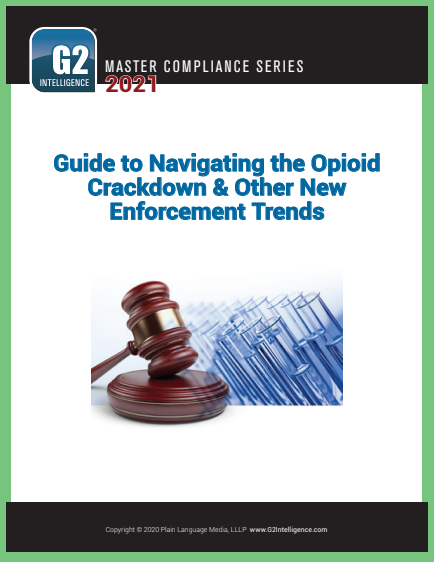

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