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Emerging Tests: COVID-19 Antigen Tests Are Ready for Mass Utilization but Antigen Test Reporting Is Not

It will take something on the order of 200 million COVID-19 screening tests per month, as opposed to the 25 million being performed currently, to safely reopen the U.S., estimates a new report from Duke University. Because of their low costs, scalability and speed, antigen tests may play a crucial role in meeting this unprecedented level of demand, particularly in nursing home, educational and workplace settings. However, if antigen testing is to be the answer, there is one significant problem that will need to be addressed: lack of reliable and consistent test data reporting.

The Promise of Antigen Testing

What the country and world need right now are point-of-care tests that can deliver accurate results at cost-effective prices that can be

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Testing Strategy: New Study Shows Saliva-Based SARS-CoV-2 Test to Be at Least as Accurate as Swab Tests

Saliva-based tests could go a long way in relieving the supplies shortages that have hampered COVID-19 testing efforts. The question, though, is whether saliva samples yield results as accurate as those produced by respiratory samples obtained by nasal and nasopharyngeal (NP) swabs. The good news is that a new study suggests that at least one of these saliva-based tests is every bit as reliable as the tests based on samples obtained by swabs.

The Diagnostic Challenge

Real-time reverse transcription polymerase chain reaction (RT PCR) testing for qualitative detection of SARS-CoV-2 nucleic

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COVID-19 Antigen Tests Are Ready for Mass Utilization but Antigen Test Reporting Is Not, *from page 1*

utilized to screen asymptomatic populations. Molecular tests using reverse transcription-polymerase chain reaction (RT PCR) to detect RNA material from the SARS-CoV-2 virus performed at an offsite laboratory are accurate but too slow and expensive to satisfy the need for screening services. Blood-based serology tests that detect SARS-CoV-2 antibodies are better suited for widespread and rapid screening, but lack the specificity and sensitivity of RT PCR assays.

Antigen tests that detect viruses indirectly by identifying the presence of antigens or toxins a virus produces that cause the body to produce antibodies are relatively inexpensive to produce and generate results rapidly at the point of care. And while its relative lack of sensitivity creates the risk of false negatives and need for confirmatory testing, antigen testing may still be appropriate for applications like screening health care workers and other high-risk groups and triaging patients during peak outbreak periods.

Moreover, developers and manufacturers of rapid antigen tests have declared that they are ready and able to meet demand for increased testing in the coming months. On Aug. 26, the U.S. Food and Drug Administration (FDA) announced that it had granted Emergency Use Authorization to Abbott Laboratories' BinaxNow COVID-19 Ag Card, a SARS-CoV-2 antigen test that does not require an analyzer to read the results. The $5 test provides results in 15 minutes from a nasal swab that is twirled on a test card with a testing reagent added. The results can be read directly from the card, like a pregnancy test, with one line indicating a negative result and two lines indicating a positive result. Other heavyweights like Roche, Quidel and LumiraDx have or soon plan to launch rapid and scalable SARS-CoV antigen tests that can be delivered on a bulk basis.

The Potential Stumbling Block

The cloud to the antigen testing silver lining is the lack of an adequate data reporting infrastructure to support it. The same features that make antigen testing so scalable also complicate reporting of test data to public health authorities. By contrast, testing laboratories have the equipment, skills and experience to report data electronically. Accordingly, more than 20 states either do not release or have incomplete data on rapid antigen testing, according to a new report from *Kaiser Health News* (KHN). After surveying the states on how they collect and report antigen test results, KHN found that:

- 21 states and the District of Columbia do not report all antigen test results;
- 15 states and D.C. do not count positive results from antigen tests as COVID cases;

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- Two states do not require antigen test providers to report results;
- Five states require only positive results to be reported; and
- Nearly half of states believe their antigen test results are underreported.

This resulting lack of data bedevils the efforts of public health officials and policy makers charged with monitoring the scope of the pandemic and making crucial decisions about reopening schools and other forms of public activity. It also artificially deflates the number of COVID-19 cases, potentially creating the dangerously false impression that the infection rate is declining when the virus is actually spreading on a continued or even accelerated rate. And as utilization of antigen testing continues to expand, this blind spot will only continue to grow.

States that Don't Report Antigen Test Results or Don't Count Antigen Positives as COVID-19 Cases

California, Colorado, District of Columbia, Georgia, Illinois, Maryland, Minnesota, Missouri, Montana, New Hampshire, New Jersey, North Carolina, North Dakota, Ohio, Pennsylvania, South Dakota, Tennessee, Texas, Vermont, Virginia, Washington, Wisconsin, Wyoming

Source: Kaiser Health News

What Counts as a COVID-19 Case

Part of the problems with antigen test reporting is that under U.S. Centers for Disease Control and Prevention (CDC) guidance, a case must be determined from a RT PCR test to be considered a "confirmed" case of COVID-19. Positive antigen tests are considered "probable" COVID-19 cases because the tests are less accurate. In early August, the CDC revised its guidelines to allow a positive antigen test to count as a probable case without assessing whether the person has COVID-19 symptoms or close contact with a person confirmed as having the virus.

This asterisk placed by the CDC on antigen positives has led to a disconnect among state reporting rules, with some states requiring reporting of only "confirmed" COVID-19 cases while others require reporting of both "confirmed" and "probable" cases.

Takeaway

Reporting of test data will be crucial to contain the spread of COVID-19 and make scientifically sound decisions about the pace and scope of reopening. In recognition of this, the U.S. Centers for Medicare Services recently imposed draconian new testing requirements on skilled nursing facilities and stepped up the penalties for violations of existing reporting rules for hospital and other laboratories. As the use of rapid antigen testing proliferates, policy makers at both the federal and state levels will have to confront and resolve the problems that are currently preventing full, consistent, and accurate reporting of antigen test results.

Emerging Tests: New Initiative Seeks to Standardize SARS-CoV-2 Antibody Tests

When the pandemic began, antibody testing was looked to as the kind of ace in the hole that would not only resolve the COVID-19 testing shortage fast and for good but also pave the way for society to reopen. Regrettably, those aspirations have not come to fruition. Although the lack of sensitivity has been the main stumbling block, the effectiveness of SARS-CoV-2 antibodies tests has also been hampered by lack of standardization. But a new collaboration teaming the U.S. Centers for Disease Control and Prevention (CDC), the European Commission Joint Research Centre and testing giant Siemens Healthineers has set out to fix that problem.

The Diagnostic Challenge

To deliver more effective treatment and achieve better outcomes, clinicians must be able to track patients' antibody level concentrations and make comparisons regardless of test methods and manufacturers. But while they all take the approach of diagnosing COVID-19 by detecting the antibodies the body produces to combat the virus that causes it, different tests target different SARS-CoV-2 proteins. This disparity among targets, which include the spike protein, S1/S2, S1 RBD and N protein found in different regions of the virus, makes comparison between and among different tests an exercise in apples to oranges.

All of this makes it difficult to determine whether a patient has achieved immunity. "Different SARS-CoV-2 antibody targets produce different levels of neutralization," noted **Deepak Nath**, president of laboratory diagnostics at Siemens Healthineers, in a statement.

The Standardization Initiative

The objective of the CDC, JRC and Siemens Healthineers research project is to come up with a new process for standardizing SARS-CoV-2 assays. The approach is to anchor each type of SARS-CoV-2 protein to a neutral antibody titer, i.e., a level of antibody to block the virus from entering cells in laboratory experiments. According to Siemens Healthineers, the thresholds displayed in the standardized unit of measure for IgG, arising either from natural infection or vaccination, may likely contribute to a standardized interpretation of immunity through test results.

The payoff: Defining a level at which neutralization is conferred for different targets could pave the way to creating a common ground to standardize assays on not only antibody production but also the ability to provide immunity.

Takeaway

Currently, each manufacturer of SARS-CoV-2 antibody tests standardizes its assays independently by using internal standards that are not

linked to a common reference. Creation and adoption of a standardized process defining which concentration confers neutralization for which SARS-CoV-2 protein would enable standardization by ensuring that all manufacturers targeting a particular antigen refer to common values during test development. "Our collaboration with the CDC and JRC will develop the framework that all antibody test manufacturers would be expected to adopt moving forward for greater benefit to patient care as the pandemic evolves," Nath said. G2

FDA WATCH

Agency to Provide Emergency Clearance for Multi-Analyte Respiratory Panels

We are now seven months into the COVID-19 public health emergency and flu season is rapidly approaching. Several diagnostics test producers have responded to this convergence by creating new multi-analyte tests that are capable of detecting (and differentiating) not only SARS-CoV-2 but also influenza and other respiratory viral infections. And while the U.S. Food and Drug Administration (FDA) has issued emergency use authorization (EUA) for SARS-CoV-2 assays, it had previously been unclear whether it would do the same for the multi-analyte tests. But now the FDA has confirmed that, yes, it will provide EUA for these tests.

As it customarily does, the FDA initiated this new policy not via regulation but informal guidance by posting a new Q&A to its website Questions & Answers for COVID-19 testing laboratories and test manufacturers. The new QA, which was posted on Sept. 9, notes "the overlap in signs and symptoms between SARS-CoV-2 and other respiratory viral infections, including influenza." Multi-analyte panels capable of detecting and sorting out different viruses "are useful when multiple respiratory pathogens are circulated at the same time, as is expected with the upcoming flu season." Tests that can kill two birds with one stone (our phrase, not the FDA's) are also an efficient use of resources during the pandemic.

The FDA also listed the factors it would consider in deciding whether to issue an EUA for such tests, including:

- The extent to which the test aids differential diagnosis;
- Whether the proposed use meets the requirements for the public health emergency declaration;
- The panel's suitability current patient testing recommendations by public health authorities; and
- The approval or clearance status of the individual tests in the panel.

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FDA Watch: Agency to Provide Emergency Clearance for Multi-Analyte Respiratory Panels, *from page 5*

Multi-Analyte Respiratory Panel Laboratory Tests with EUA Clearance

As of Sept. 16, the FDA has awarded EUA to the following multi-analyte respiratory panel tests (in chronological order of issuance):

- QiaStat-Dx Respiratory SARS-CoV-2 Panel (Qiagen)
- BioFire COVID-19 Test (BioFire Defense)
- BioFire Respiratory Panel 2.1 (RP2.1) (BioFire Diagnostics)
- Influenza SARS-CoV-2 (Flu SC2) Multiplex Assay (U.S. Centers for Disease Control and Prevention)
- Cobas SARS-CoV-2 & Influenza A/B Nucleic Acid Test for use on Cobas Liat System (Roche)

Here are other key new FDA EUAs and clearances announced in late August through mid-September:

New FDA Emergency Use Authorizations (EUAs) & Approvals

Manufacturer(s)	Product
Hologic	EUA for Aptima SARS-CoV-2 assay
Abbott Laboratories	EUA for BinaxNow COVID-19 Ag Card, a SARS-CoV-2 antigen test that doesn't require an analyzer to read results
Color Genomics	EUA for Color COVID-19 Self-Swab Collection Kit
Thermo Fisher Scientific	Premarket approval for Oncomine Dx Target Test as companion diagnostic for pralsetinib (Gavreto) drug developed by Blueprint Medicines to identify RET fusions in metastatic non-small cell lung cancer patients
Roche	510(k) clearance for Cobas test for BK virus to run on Cobas 6800 and 8800 Systems
Roche	Clearance for Cobas HIV-1/HIV-2 Qualitative Test on Cobas 6800 and 8800 Systems
BioCheck	EUA for BioCheck serological SARS-CoV-2 IgM and IgG test kits
Verily Life Science	EUA for Verily COVID-19 RT-PCR Test
DiaSorin	Clearance for Simplexa Flu A/B and RSV Direct Gen II kit
BillionToOne	EUA for qSanger-COVID-19 sequencing-based SARS-CoV-2 test
Sugentech	EUA for SGTi-flex COVID-19 IgG serological test
Bioeksen R&D Technologies	EUA for Bio-Speedy Direct RT-qPCR SARS-CoV-2 test
Detectachem	EUA for MobileDetect Bio BCC19 Test Kit
Optolane Technologies	EUA for Kaira 2019-nCoV Detection Kit

Manufacturer(s)	Product
Color Genomics	EUA for COVID-19 Test Unmonitored Collection Kit
Mammoth Biosciences	EUA for SARS-CoV-2 DETECTR Reagent Kit, a CRISPR-based RT-LAMP test
TBG Biotechnology	EUA for TBG SARS-CoV-2 IgG/IgM Rapid Test Kit
T2 Biosystems	EUA for T2SARS-CoV-2 panel
HelixBind	Breakthrough Device Designation for RaPID/BSI test for bloodstream infections associated with sepsis
Foundation Medicine	Clearance for s FoundationOne Liquid CDx, a multi-cancer comprehensive liquid-biopsy test, for multiple companion diagnostic indications including one for prostate cancer and three for lung cancer

Top of the News: CDC Withdraws Recommendation of Testing for Asymptomatic Individuals After Close Exposure to COVID-19

The U.S. Centers for Disease Control and Prevention (CDC) raised eyebrows on Aug. 28 when it revised its COVID-19 testing guidance to suggest that testing is not necessarily a must for asymptomatic individuals who have been in close recent contact with a person confirmed as having a COVID-19 infection. The new guidance departs from not only medical consensus but the agency's previous recommendations.

The CDC's New Testing Recommendation

According to the new guidance, if you have been in close contact (within 6 feet) of a person with a COVID-19 infection for at least 15 minutes but do not have symptoms, you do not necessarily need a test unless:

- You are a vulnerable individual; or
- Your health care provider or State or local public health officials recommend that you get tested.

Testing negative does not rule out the possibility of developing an infection from the close contact later, the CDC explains. But the does recommend that those with close contact self-monitor for symptoms and follow guidelines for testing of symptomatic individuals if they develop.

What Is Going On?

Previously, the CDC recommended that anybody with a "recent known or suspected exposure" to the virus get tested regardless of whether they have symptoms citing "the potential for asymptomatic and pre-symptomatic transmission." In fact, that recommendation is consistent with numerous

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CDC Withdraws Recommendation of Testing for Asymptomatic Individuals After Close Exposure to COVID-19
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studies showing that persons without symptoms may still carry and transmit the virus—in the pre-symptomatic stage or even if they never develop symptoms at all.

The new recommendation has drawn heavy criticism from medical professionals and the public health community, including the College of American Pathologists (CAP) which was among the many to request that the agency point to the scientific evidence and rationale for the change in guidance. "Laboratory supply shortages are a serious issue," the CAP acknowledged, but added that "the solution is not to halt testing of asymptomatic patients."

Takeaway

Withdrawing the recommendation for testing of asymptomatic individuals after recent exposure is a head scratcher and out of whack with findings showing that 30 percent of those who test positive for COVID-19 do not have symptoms. In the current political environment, it was inevitable that the CDC would be accused of bowing to White House pressure to reduce COVID-19 testing numbers ahead of the presidential election. Whether the accusations are true or not, the sad truth is that the CDC has gotten caught up in politics at a time when the country most desperately needs an objective source of scientifically sound guidance to keep the public safe from the most severe public health threat in a century.

Genetic Tests: New Guidelines Advise Against Using Polygenetic Risk Scores for Routine Patient Management

New guidelines from the National Comprehensive Cancer Network (NCCN) advise against using polygenetic risk scores for routine patient management and update previous recommendations for assessing hereditary cancer risk of the breast, ovaries, and pancreas as well as the use of cascade testing.

Polygenic Risk Scores

Polygenic risk scores reflect a mathematical aggregate of risk conferred by many DNA variants to estimate the likelihood of a specific outcome, such as disease onset in an individual. The scores are the output of statistical models developed using data from large genome-wide association studies (GWAS).

Such scores "should not be used for clinical management at this time," advises the NCCN in the latest version of its clinical practice guidelines,

entitled "Genetic/Familial Hight-Risk Assessment: Breast, Ovarian, and Pancreatic" published on Sept. 8. "There are significant limitations in the interpretation of polygenic risk scores," according to the guidelines, which suggests instead using such scores for clinical trials.

Genetic Assessments Associated with Prostate Cancer Risks

The NCCN also provides update guidance on when language on when personal and family history of prostate cancer indicates the need for genetic testing for high-penetrance breast and ovarian cancer risk genes, such as BRCA1, BRCA2, CDH1, PALB2, PTEN, and TP53. According to the guidelines:

- Any patients diagnosed with prostate cancer regardless of age should be tested if they have metastatic, intraductal/cribriform histology, or are in a high- or very high-risk group;
- Any patients diagnosed with prostate cancer regardless of age or risk group, should be tested if they have: (i) Ashkenazi Jewish ancestry; (ii) at least one close relative with breast cancer diagnosed at age 50 or younger; (iii) at least one close relative with ovarian, pancreatic or metastatic or intraductal/cribriform prostate cancer regardless of age; or
- At least two close relatives with breast or prostate cancer regardless of grade or age of diagnosis.

Cascade Testing

Cascade testing is a systematic process for the identification of individuals at risk for a hereditary condition which uses genetic testing to identify a pathogenic variant associated with the condition in the individual and thence to his/her at-risk biologic relatives. The process is repeated as more affected individuals or pathogenic variant carriers are identified.

The new guidelines revise NCCN's criteria for cascade testing who have a family history but no personal history of cancer. If the unaffected individual's affected relative has pancreatic cancer or metastatic, intraductal/cribriform, or high-/very high-risk prostate cancer, only first-degree relatives of the affected individual should be offered cascade testing, the NCCN. More distant relatives may be offered testing if there is additional history of cancers in the family indicating the need.

Testing Strategy: COVID-19 Retesting Should Be Pushed Back to 4 Weeks to Give Virus Ample Time to Shed

How long does it take a person infected with SARS-CoV-2 to finish shedding the virus? Coming up with the answer to this question to make scientifically sound decisions about not only the clinical treatment of the infected but also containment of asymptomatic or minimally symptomatic. Recently published research from Italy shines new light on the duration of virus shedding and need for retesting.

Bottom Line on Top

National regional testing protocols in Italy recommend COVID-19 retesting after 14 days of diagnosis. The study found that testing this early is more likely to result in false negatives and concluded that postponing COVID-19 retesting for 30 days from the date of diagnosis and 36 days from the date of symptom onset increases the efficiency of testing protocols.

The Study

The study was conducted in the Reggio Emilia province of Italy, one of the country's hottest COVID-19 hotspots. Scientists from the Istituto di Ricovero e Cura a Carattere Scientifico tracked 4,538 patients from the province who were diagnosed with COVID-19 between Feb. 26 and April 22. The study found a higher rate of false negatives for nasal swab tests when they were performed too early in a patient's recovery.

Of the 4,480 patients included in the researchers' preliminary analysis, 1,259 achieved viral clearance as indicated by at least one negative swab test following the initial positive test result, with a median time to viral clearance of 31 days. Sadly, 428 patients among this group died. The investigators then performed follow-up testing on 1,162 people who had been diagnosed at least 30 days prior and for whom the date of symptom onset was available. Patients were tested an average of three additional times, with the mean times of retesting about 15 days after the first positive test, 14 days after a second positive test, and nine days after a third positive test.

Viral clearance was detected in 704—nearly 61 percent—of the 1,162 patients and confirmed in roughly 79 percent of those who underwent a second test, suggesting that there was about one false negative for every five negative test results. Median time to viral clearance was 30 days from the first positive swab and 36 days from symptom onset, with the time increasing based on age and disease severity.

However, the rate of false negatives declined when the first negative test was performed more than 34 days after the first positive test.

Retesting Recommendations

The study suggests that it takes four weeks to finish shedding the SARS-CoV-2 and concludes that performing testing 14 days from diagnosis is too early and should be pushed back to more than four weeks.

The investigators also recommend that COVID-19 patients self-isolate for more than 30 days after their symptoms begin or until at least one follow-up test is performed to confirm viral clearance to avoid generating secondary cases.

Takeaway

The study suggests that COVID-19 retesting of infected patients after two weeks is too early and dangerous to the extent it results in releasing false negatives into society before they have shed the virus. Waiting four weeks will not only improve test accuracy but also prevent people who are not fully recovered from infecting others.

New Study Shows Saliva-Based SARS-CoV-2 Test to Be at Least as Accurate as Swab Tests,

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acid is the current gold standard for accuracy. The downside of RT PCR testing is its cost and lack of scalability, due in part to its reliance on upper and lower respiratory specimens that must be collected via NP swabs or bronchoalveolar lavage. In addition to being uncomfortable for patients, the sample collection process must be performed by qualified health care professionals using long cotton swabs, both of which happen to be in short supply right now. The process also sucks up scarce respiratory masks and other personal protective equipment (PPE) to the that it directly exposes the health professional to risk of infection.

The Advent of Saliva-Based Tests

Saliva-based testing overcomes all these bottlenecks. At least half a dozen saliva-based SARS-CoV-2 tests have received Emergency Use Authorization (EUA) the U.S. Food and Drug Administration (FDA). The first EUA for a saliva test was granted on April 13 to the Rutgers Clinical Genomics Laboratory TaqPath SARS-CoV-2 Assay test is based on the Thermo Fisher Scientific Applied Biosystems TaqPath COVID-19 Combo Kit which had been previously approved for detection in NP swab, nasopharyngeal aspirate and bronchoalveolar lavage specimens.

The Study

The simplification of saliva sample collection and elimination of the health professional "middleman" naturally raises questions about test results reliability. The new study, which was published in the *New England Journal of Medicine* on Aug. 28, evaluates the accuracy of one of the new

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New Study Shows Saliva-Based SARS-CoV-2 Test to Be at Least as Accurate as Swab Tests, *from page 11*

saliva-based test products, the Yale School of Public Health's SalivaDirect test for qualitative detection of nucleic acid from SARS-CoV-2 in saliva collected without preservatives in a sterile container.

The researchers studied a total of 70 inpatients with confirmed cases of COVID-19. After COVID-19 was confirmed with a positive NP swab at hospital admission, saliva specimens were collected by the patients themselves. Another NP test was done at the same time and health care workers collected and tested both the swabs and the saliva specimens.

Using primer sequences from the U.S. Centers for Disease Control and Prevention (CDC), the researchers found more SARS-CoV-2 RNA copies in the saliva specimens than in the NP swab specimens. At one to five days after diagnosis 81 percent of the saliva samples tested positive, compared to 71 percent for the NP swab samples. Additionally, a higher percentage of saliva specimens tested positive than the NP swab specimens tested positive 10 days after diagnosis. However, after 11 days only 41 percent of the saliva collected samples tested positive versus 50 percent of the NP swab collected samples. Based on these findings, the study authors concluded that saliva specimens and nasopharyngeal swab specimens have at least similar sensitivity in the detection of SARS-CoV-2, the authors of the study concluded.

Takeaway

The study supporting the reliability of the Yale saliva test bodes well but will, of course, need to be bolstered by further studies and evaluations of other products. Currently, at least half a dozen saliva-based SARS-CoV-2 tests have received EUA from the FDA, including products from Fluidigm, DxTerity Diagnostics, Clinical Reference Laboratory, P23 Labs and the Yale School of Public Health. With many more test makers having saliva-based products in the pipeline, that number is likely to at least double by the end of the year.

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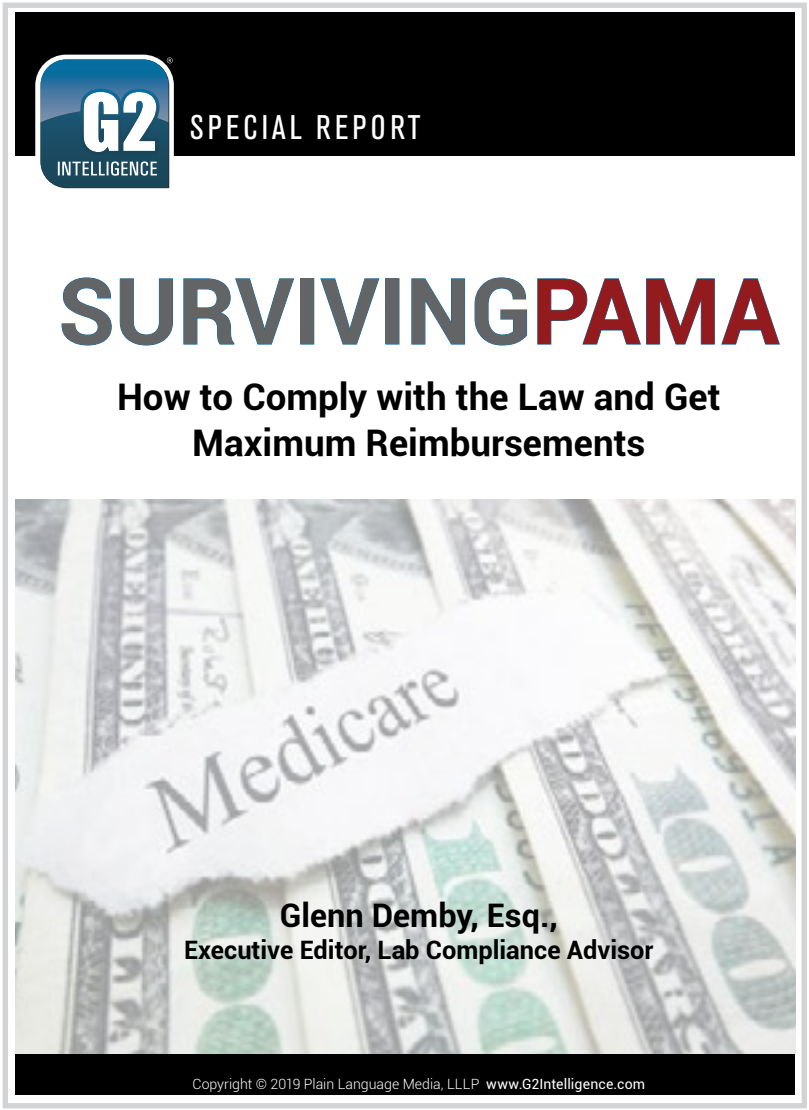

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