G2 INTELLIGENCE
A DIVISION OF PLAIN LANGUAGE MEDIA

DIAGNOSTIC TESTING & Emerging Technologies

New Trends, Applications, and IVD Industry Analysis

AUGUST 2020

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G2Intelligence.com

Test Utilization: Supplies Shortages Continue to Bedevil COVID-19 Testing Efforts

What was true at the beginning of the public health emergency remains true today: laboratories simply cannot obtain the supplies they need to deliver desperately needed COVID-19 molecular testing in a timely manner. And a new survey from the College of American Pathologists (CAP) points to a new problem: staff burnout. Here are the grim details.

High Test Numbers Belie Gaps in Supply vs. Demand

This is not about politics but the June 30 press briefing by assistant secretary of health Admiral Dr. **Brett Giroir** showing that 550,000 to 600,000 tests are being conducted each day, as compared to only a few thousand per day in March, do not do justice to the true

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Reimbursement: Payors Gradually Increasing Coverage of Liquid Biopsies but Obstacles Remain

Gaining the acceptance of insurers and payors for new tests and testing technology is a perennial challenge for laboratories and test developers. This has been especially true with liquid biopsy cancer testing, for which positive coverage determinations have been few and typically restricted to particular types of cancer. However, a new study suggests that payor attitudes have changed significantly in recent years. Here is a look at the progress that has been made and the obstacles that laboratories and test makers must still be overcome to maximize coverage of liquid biopsy cancer testing.

The Diagnostic Challenge

Blood-based circulating tumor DNA (ctDNA) sequencing tests, often referred to as "liquid biopsy tests," are used to select targeted cancer therapy and monitor nonresponding or progressive tumors.

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Test Utilization: Supplies Shortages Continue to Bedevil COVID-19 Testing Efforts, *from page 1*

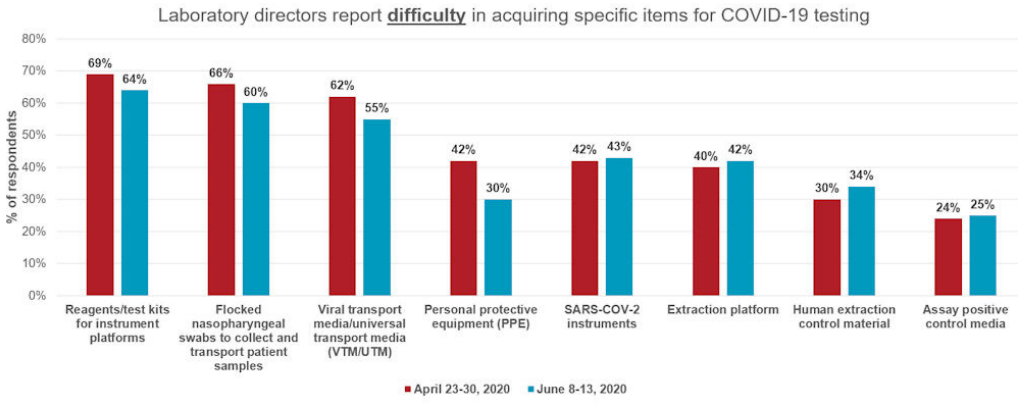
situation. The fact is that if laboratories were capable of delivering all the COVID-19 tests that were needed when they were needed, those numbers would be much higher.

Exhibit A: During his July 22 press briefing to go over the company's second quarter earnings, Quest Diagnostics' chairman, CEO and president **Steve Rusckowski** noted that Quest labs were currently capable of running 130,000 molecular SARS-CoV-2 tests per day and expect to increase that total to 150,000 over the next several weeks. Those numbers sound very impressive. But there is more to the story. Rusckowski continued by noting that this step-up in testing is still not enough to keep up with rising demand. The current average turnaround time for SARS-CoV-2 testing of high-priority patients is around two days and no less than seven days for non-priority patients. As anybody who has been through the experience can attest, seven days is an eternity when awaiting COVID-19 testing results.

The CAP Survey

The June CAP online survey of CAP surveyed 3,723 laboratory directors sheds light on what is causing the shortfall in COVID-19 testing. The chief culprit remains lack of testing supplies. Thus, of the 306 respondents, 70% of whom are based in hospital departments:

- 64% said they are having trouble acquiring reagents for platforms and test kits, only a slight improvement over the 69% who reported difficulties in April;
- 60% cited problems acquiring nasopharyngeal swabs for collection and transport of patient samples, and transport media, as compared to 66% in April; and
- 43% reported difficulties obtaining SARS-CoV-2 testing instruments, which is actually above the April total of 42%.



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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.

Significantly, 70% of respondents said they could be doing more testing if they had the needed supplies, as opposed to 79% who reported this in April. In other words, the capacity is there, but the supplies are not.

The Burnout Factor

While the shortage of laboratory testing supplies has been well documented, the impact of the pandemic on laboratory staff has gotten less attention. In addition to facing COVID-19 exposure on a daily basis, pathologists and staffers are undergoing furloughs and pay cuts, as the virus decimates demand for anatomical pathology services. Key findings from the CAP survey:

- 63% reported cuts in pathologists' pay;
- 43% reported reductions in hours; and
- 36% reported increased burnout among pathologists.

Takeaway

Yes, COVID-19 testing numbers are higher but they are nowhere near where they need to be. The source of the problem appears to be not so much lack of capacity as lack of supplies. The CAP survey suggests that laboratories have the COVID-19 testing platforms and personnel they need but cannot ramp up that capacity to provide testing because they do not have enough reagents, swabs or transport media. And until the supplies bottleneck problems are resolved, testing will continue to fall behind demand.

Letter to Pence: Strapped with COVID-19 Testing Supplies Shortages, Laboratories Ask White House for Help

On July 8, a group of eight organizations representing U.S. laboratories sent a letter to Vice President **Mike Pence** urging the government to find remedies for supply chain obstacles to performing COVID-19 tests. "Our members are on the front lines responding to the public health crisis," the letter begins. Since COVID-19 testing began, "they have experienced significant difficulty acquiring the supplies— test kits, nasopharyngeal and mid-turbinate swabs, transport media, and personal protective equipment (PPE)—needed to perform COVID-19 testing." The letter notes that labs have even been getting faulty or unusable equipment, including swabs from the Strategic National Stockpile.

Without proper testing supplies and PPE, laboratories will continue to struggle to meet the demand for COVID-19 testing and assistance in tracking its spread, according to the letter. The assistance requested:

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Letter to Pence: Strapped with COVID-19 Testing Supplies Shortages, Laboratories Ask White House for Help, *from page 7*

1. Supply Chain Contacts Information

First, the letter asks for a list of the names and contact information for individuals in each state who are overseeing the supply chain for testing supplies and PPE for the federal government. "Many of our members report that they are unable to identify or initiate contact with these individuals," the letter explains.

2. Transparency of the Supply Allocation Process

The other request is "visibility into the process of supply allocation, demonstrating that the supplies being distributed at the state level are being allocated in a way that reflects the greatest need to effectively address COVID-19 in the U.S." According to the letter, labs need to understand in real-time, resource availability and reagent and supply quantities for planning purposes. The federal government should take a leading role in increasing transparency about the availability of these materials from both government and commercial manufacturers.

The letter signatories include the:

- American Association of Bioanalysts;
- American Association for Clinical Chemistry;
- American Medical Technologists;
- American Society for Microbiology;
- Association of Public Health Laboratories;
- Association for Molecular Pathology;
- College of American Pathologists; and
- National Independent Laboratory Association.

Top of the News: Quest Test Gets First FDA Green Light for Sample Pooling to Detect SARS-CoV-2

Things sure happen fast during a pandemic. While the U.S. Food and Drug Administration (FDA) has historically "encourage all test developers to reach out to [us] to discuss appropriate validation approaches," the agency has remained largely silent on the practice of sample pooling allowing for the testing of multiple individuals with a single test. But that all changed on June 16 when the agency issued new guidance outlining its "validation expectations" for use of specimen pooling either to develop a new test for Emergency Use Authorization (EUA) or expand the use of a current EUA product. And barely one month later, the FDA pushed the button on the

latter by extending the EUA of an existing test to allow for pool sampling to detect the coronavirus.

The Quest SARS-CoV-2 Test

On July 18, the announcement came that Quest Diagnostics' SARS-CoV-2 RNA test had become the first coronavirus test cleared by the FDA for pooled sampling. Technically, the approval is a reissued version of the existing EUA issued back in March expanded to allow for use of the test with pooled upper respiratory specimens in sample pools comprised of four individuals.

Pooling and the COVID-19 Diagnostic Challenge

Pooling involves mixing sub-samples extracted from individual samples into a pool or "batch" that can be tested with a single test. If the entire pool tests negative, all of the constituent samples are also deemed negative; but if the pool tests positive, the individual samples must be retested to identify the source(s) of the positive.

Use of pooling enables testing laboratories to get the most out of testing resources and overcome supply shortages. But there is also an accuracy tradeoff: Because pooling dilutes the nucleic acids produced by the SARS-CoV-2 virus, it creates the risk of false negatives. Pooled sampling is "most efficient in areas with low prevalence, meaning most results are expected to be negative," the FDA noted in its statement.

To secure the EUA expansion for the SARS-CoV-2 RNA test, Quest provided the FDA clinical data showing that none of a total 3,091 specimens from a population with a prevalence rate of 1 to 10 percent would have come back falsely negative had the specimens been pooled. Quest began immediately to perform pooled sampling testing with the assay starting with its laboratories in Marlborough, MA, and Chantilly, VA.

Takeaway

It is no secret that laboratories lack the supplies and capacity necessary to meet the unprecedented demand for COVID-19 testing. Used effectively, sample pooling can go a long way in making testing available to mass populations while preserving testing supplies. As noted by FDA Commissioner ***Stephen Hahn*** *"sample pooling becomes especially important as infection rates decline and we begin testing larger portions of the population."*

Test Utilization: Rapid Testing the Linchpin of COVID-19 Contact Tracing Effectiveness

Without rapid testing and results, COVID-19 contact tracing will not work. That is the conclusion of a new study published in *The Lancet*. Even the most efficient contact tracing strategy will not reduce transmission advancement if testing is delayed by three days after a person develops symptoms, according to the July study.

The Diagnostic Challenge

Currently, it is believed that about 40% of COVID-19 transmissions are from people who are asymptomatic. Contact tracing, in combination with quarantining and testing, is considered critical to preventing transmission now that stay-at-home orders are being lifted.

Explanation: To contain COVID-19 and other diseases transmitted via human contact, people need to be monitored and their contacts recorded so that once an individual is confirmed to have the illness, public health officials can immediately notify those who have recently had contact with the infected person and advise them to get tested. Then, if they test positive, word can go out to their contacts, etc. That is what contact tracing is all about. And technology like mobile apps that automatically alert people who have been in the proximity of an infected person make it eminently workable.

The Study

To be successful, contact tracing must keep the rate of transmission, known as the reproduction or R number, below 1, i.e., on average, the number of people who will be infected by a single infected person must be less than one. However, conventional contact tracing for COVID-19 will keep the R number below 1 only if people with COVID-19 receive a positive test result on the same day they develop symptoms, the authors of the study conducted by researchers at Utrecht University (Netherlands) Universidade de Lisboa (Portugal) and the University of Liverpool (UK). Its purpose was to evaluate various strategies for identifying people who have been infected and containing the spread of the coronavirus to help inform policy as countries reopen their economies.

Researchers considered:

- The time of onset of infection;
- Tracing of close and casual contacts;
- Testing, isolation for cases that were positive; and
- Reproduction numbers for contact tracing strategies.

The authors used mathematical modeling to examine scenarios around transmission, contact tracing, timing of testing, and isolation of people who have been infected. The model showed that shortening the time between

symptom onset and a positive test result, assuming immediate isolation, is the most important factor for improving contact tracing effectiveness. The researchers also noted that apps for contact tracing are more effective than conventional tracing due to speed.

The mathematical model reflected the various steps and delays in the contact tracing process and enabled quantifying how such delays affect the R number and the fraction of onward transmission cases that can be prevented for each diagnosed person.

The Findings

The researchers assumed that approximately 40 percent of virus transmission occurs before a person develops symptoms. They found that, in the absence of any strategies to mitigate transmission, each infected person will transmit the virus to an average of 2.5 people. Introducing physical distancing alone, and assuming that close contacts are reduced by 40 percent and casual contacts by 70 percent, will reduce the reproduction number to 1.2.

In the best-case scenario, the model predicted that contact tracing could reduce the number of people catching the virus from an infected person from 1.2 to 0.8. However, for that to work:

- At least 80 percent of eligible people must be tested;
- There can be no delays in testing after the onset of symptoms; and
- At least 80 percent of contacts must be identified on the day the test results are received.

Takeaway

Testing, testing, testing. What location is to real estate, testing is to contact tracing. "As many infectious people as possible must be tested, and policymakers might consider lowering the eligibility threshold for access to testing," noted ***Marc Bonten****, one of the study's lead authors and a professor at the University of Utrecht. Testing that volume of potentially infectious people will lead to a large proportion of negative test results, and "future studies should focus on identifying the optimal balance between the proportion of negative tests and the effectiveness of contact tracing," Bonten added.*

The researchers also advised that methods of contact tracing should be reviewed and streamlined. Mobile apps can speed up the process of tracking down people who are potentially infected, they noted, but they depend on the willingness of the population to participate and set aside their personal privacy concerns.

FDA WATCH

Agency Sounds the Warning on False-Positives from Becton Dickinson SARS-CoV-2 Reagents

On July 6, the U.S. Food and Drug Administration (FDA) issued a warning letter alerting clinical laboratory staff and providers of the increased risk of false-positive results from Becton Dickinson (BD) BD SARS-CoV-2 reagents for its BD Max System test.

The Warning Letter

If you are currently using the reagents for the BD Max System and get a positive result, the FDA recommends that you treat the result as presumptive and consider confirming it with another authorized test. The warning letter also calls on laboratory staff and providers to report any issues with using COVID-19 tests.

The FDA granted Emergency Use Authorization (EUA) for the BD PCR-based SARS-CoV-2 kit on April 8. The test, which detects viral nucleic acid from SARS-CoV-2 in upper respiratory specimens, was cleared for moderate- and high-complexity testing laboratories on the BD Max System using BD reagents. However, the company began receiving reports of the potential for false positives when the test was used with the reagents, including one study in which a manufacturer found that approximately 3 percent of results were false positives.

Even though the users citing accuracy concerns represented a small subset of overall true-positive results, the firm approached the FDA to discuss the problems and go over the options to improve test performance, according to a BD spokesperson. The FDA is currently working with the firm to resolve the issue and promises to provide new or additional information as the situation develops.

Takeaway

Accuracy and the risk of false positives generated by EUA COVID-19 serology tests has been an ongoing concern. However, the BD test is a molecular PCR-based assay which are generally considered more accurate and reliable than serology-based antibody tests. Even so, the BD situation seems to be a bit of an outlier limited to a particular PCR product using a particular reagent on a particular platform.

Here are some of the key new FDA EUAs and clearances announced in July:

New FDA Emergency Use Authorizations (EUAs) & Approvals

Manufacturer(s)	Product
DiaCarta	EUA for QuantiVirus SARS-CoV-2 Multiplex Test Kit
Becton Dickinson (BD)	Premarket approval supplement for expanded BD Onclarity HPV Assay
BD	EUA for SARS-CoV-2 antigen test
Paige	510(k) clearance for use of FullFocus digital pathology image viewer with Philips Ultra Fast scanner for primary diagnosis
Access Genetics	EUA for OraRisk COVID-19 RT-PCR test
Megna Health	EUA for Rapid COVID-19 IgM/IgG Combo Test Kit (serology)
Luminex	EUA for xMap SARS-CoV-2 Multi-Antigen IgG Assay
Boston Heart Diagnostics	EUA for Boston Heart COVID-19 RT-PCR Test
Quest Diagnostics	Expanded EUA for SARS-CoV-2 RNA test for sample pooling use
Quest Diagnostics	EUA for 3 coronavirus assays: *PF SARS-CoV-2 Assay performed with Hologic's Panther Fusion SARS-CoV-2 RT-PCR-based test *RC SARS-CoV-2 Assay performed with Roche automated Cobas SARS-CoV-2 RT-PCR test *HA SARS-CoV-2 Assay
KogeneBiotech	EUA for PowerChek 2019-nCoV Real-time PCR Kit
Trax Management	EUA for PhoenixDx SARS-CoV-2 Multiplex
Beijing Wantai Biological Pharmacy	EUA for SARS-CoV-2 Ab Rapid Test lateral flow serology assay
Diazyme Laboratories	EUA for Diazyme DZ-Lite SARS-CoV-2 IgG antibody test
BioSewoom	EUA for Real-Q 2019-nCoV Detection Kit
Enzo Life Sciences	EUA for Ampiprobe SARS-CoV-2 Test System
Access Bio	EUA for CareStart COVID-19 MDx RT-PCR test
Gene By Gene	EUA for RT PCR-based SARS-CoV-2 Detection Test
Saladax Biomedical	*De novo* clearance for MyCare Psychiatry Clozapine Assay rapid blood test for clozapine levels in psychiatric patients
Assure Tech	EUA for Assure COVID-19 IgG/IgM Rapid Test Device
US Centers for Disease Control and Prevention	EUA for Influenza SARS-CoV-2 (Flu SC2) Multiplex Assay real-time RT-PCR test for simultaneous detection and differentiation of SARS-CoV-2, influenza A and influenza B
Centogene	EUA for PCR-based SARS-CoV-2 test
InBios International	EUA for SCoV-2 Detect IgM ELISA kit (serological)
3B Blackbio	EUA for Biotech India COVID-19 test
Bioperfectus Technologies	EUA for COVID-19 Coronavirus Real Time PCR Kit to detect SARS-CoV-2 ORF1ab and N genes
Omnipathology Solutions	EUA for Omni COVID-19 ASSAY by RT-PCR

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FDA Watch, *from page 9*

Manufacturer(s)	Product
Biohit Healthcare	EUA for SARS-CoV-2 IgM/IgG Antibody Test Kit
ADS Biotec	EUA for SARS-CoV-2 Antibody Detection Kit
Ohio State University	EUA for OSUWMC COVID-19 RT-PCR test
Thermo Fisher Scientific	Breakthrough Device Designation for Oncomine Precision Assay to identify low-grade glioma patients with isocitrate dehydrogenase 1 and 2 mutations eligible for treatment with vorasidenib

Battle of the SARS-CoV-2 Antibody Immunoassays: Only One Test Meets Both UK Sensitivity and Specificity Targets

Several of the world's biggest testing companies have created and secured emergency regulatory clearance for immunoassays that detect antibodies to the SARS-CoV-2 virus. But how reliable are these tests? And how do they stack up against each other? A July report from Public Health England (PHE) offers just a wee bit of insight into these questions.

The Head-to-Head Study

The two-month study was commissioned by the UK Department of Health and Social Care to compare four of the commercial immunoassays available in the UK for detection of SARS-CoV-2 antibodies:

- Abbott Laboratories' SARS-CoV-2 Immunoassay;
- DiaSorin's Liaison SARS-CoV-2 S1/S2 IgG assay;
- Roche's Elecsys Anti-SARS-CoV-2 test; and
- Siemens' SARS-CoV-2 Total (COV2T) test.

The assays were performed in accordance with the manufacturers' instructions and at the prespecified thresholds for determining positive vs. negative test results. The investigators calculated sensitivity and specificity for each test for comparison against Target Product Profile (TPP)-sensitivity criteria for "enzyme immunoassays" developed by the UK Medicines and Healthcare Products Regulatory Agency (MHRA).

The sensitivity of a test refers to its capacity to identify known positives, i.e., infected individuals; specificity is the test's capacity to identify

known negatives, i.e., uninfected individuals. The investigators evaluated sensitivity using 536 positive samples from adults with a lab-confirmed SARS-CoV-2 infection, taken at equal to or greater than 20 days post-symptom onset. They evaluated specificity on 994 specimens from healthy adults collected before the pandemic.

The Findings

As the report notes, the TPP for enzyme immunoassays requires a clinical sensitivity of greater than or equal to 98 percent in SARS-CoV-2-positive cases confirmed equal to or greater than 20 days after the appearance of first symptoms. It requires a clinical specificity of equal to or greater than 98 percent on samples collected greater than 6 months before the first identified cases of SARS-CoV-2 infection.

While all four tests met the specificity criteria, only the Siemens test met both the sensitivity and specificity criteria. The table below illustrates the primary results.

Assay	Sensitivity [95% CI]	Specificity [95% CI]	Appraisal against MHRA Target Product Profile (TPP)
Abbott	92.7 (90.2, 94.8)	99.9 (99.4, 100)	Meets specificity criterion
DiaSorin	95.0 (92.8, 96.7)	98.6 (97.6, 99.2)	Meets specificity criterion
Roche	97.2 (95.4, 98.4)	99.8 (99.3, 100)	Meets specificity criterion
Siemens	98.1 (96.6, 99.1)	99.9 (99.4, 100)	Meets sensitivity and specificity criteria

Takeaway

Even though the Siemens' test was the only immunoassay to meet both targets, the other products did not walk away empty-handed. In addition to meeting the specificity criteria, the

Abbott, DiaSorin and Roche assays did meet the sensitivity target after PHE tweaked the parameters. Thus, the Roche test exceeded the TTP sensitivity mark when the assay thresholds were changed to lower test specificity to 98%. The Abbott and DiaSorin tests fell just a tad short of the 98% sensitivity target. In addition, all four tests met the sensitivity and specificity criteria when the revised assay thresholds were applied to samples taken more than 30 days after the onset of symptoms.

Reimbursement: Payors Gradually Increasing Coverage of Liquid Biopsies but Obstacles Remain , *from page 1*

Although somatic (tumor) testing is usually performed on resected biopsy specimens, ctDNA tests can be used at the time of a cancer diagnosis to identify genomic alterations that may be effectively treated using targeted therapies. ctDNA tests are frequently used after a patient experiences disease progression on targeted therapy to determine the mechanism of therapeutic resistance, as well as after definitive therapy to detect recurrence.

Utilization of ctDNA tests has increased rapidly since 2014 when Guardant Health launched the first commercially available product for cancer. However, as with any new test, payor coverage plays a crucial role in determining patients' access to and utilization of ctDNA testing. Even so, nobody had ever done a study to analyze historical and current coverage of private and Medicare policies for ctDNA-based panel tests.

The ctDNA Cancer Coverage Study

The void in historical analysis of payor coverage of ctDNA cancer testing has now been filled, thanks to a new study in *Journal of the National Comprehensive Cancer Network*. Researchers from the University of California, San Francisco and City of Hope, reviewed data on both private and public payor coverage policies for ctDNA-based testing panels in cancer over a four-year period, from 2015 to 2019.

The researchers used the Canary Insights Database, a public library of more than 40,000 medical policies from commercial and public payers, to track private payor policies, Medicare National Coverage Determinations (NCDs) and Medicare Administrative Contractor (MAC) Local Coverage Determinations (LCDs). The authors note that the Canary Insights Database includes data from more than 200 payors, which makes it possible to analyze payment policies covering approximately 75 percent of the US population.

The Study Findings

The researchers found steady growth in both public and private payor coverage. Thus, at the start of 2016, not a single payor in the database provided coverage for liquid biopsies. However, by mid-2019, 65 private payors and 4 MACs had published policies about ctDNA testing, an increase in the coverage rate of 38%. Medicare policies specifically expanded from no LCDs for the use of ctDNA-based cancer panel tests in 2017 to eight final LCDs, two draft LCDs, and two future effective final LCDs in 2019.

Additionally, although there have not yet been any NCD policies issued explicitly providing coverage for ctDNA-based panel tests, CMS's NCD on sequencing for advanced cancer includes ctDNA-based panel test coverage

if the test is FDA-approved. There are currently no FDA-approved ctDNA-based panel tests, but several companies, including Guardant Health, Foundation Medicine, Personal Genome Diagnostics and Resolution Biosciences, have said they are bringing their products through FDA review.

The study authors also reported that individual coverage policies appear to have become more expansive from 2017-2019. In terms of tumor types covered, for example, there was a shift from just a single type (non-small cell lung cancer) to 12 solid and hematologic cancers by the end of the study period. Early coverage decisions, which were limited to a single gene, EGFR, have also transitioned to current coverage of multi-gene tests like Guardant's 73-gene panel.

The study also found that policies for liquid biopsy have trended in recent years from mainly cancer-specific indications to more agnostic use, mirroring the increasing emphasis on pan-cancer genotyping that has occurred for more traditional, tissue-based genomic tests.

Conclusions

The first and only study on the subject finds that both public and private coverage of liquid biopsy tests has grown significantly in recent years but that notable limitations remain, including policies that restrict testing to specific genes or endorse only certain branded test technologies.

The stakes are incredibly high. Growth and adoption of ctDNA-based testing for cancer is expected to increase, as is the number of genes included in the test. In addition, utilization of such testing is increasing beyond the targeting of cancer treatments to include the early detection of cancer in healthy populations. Payor coverage policies will go a long way in determining patient access to these new products and applications.

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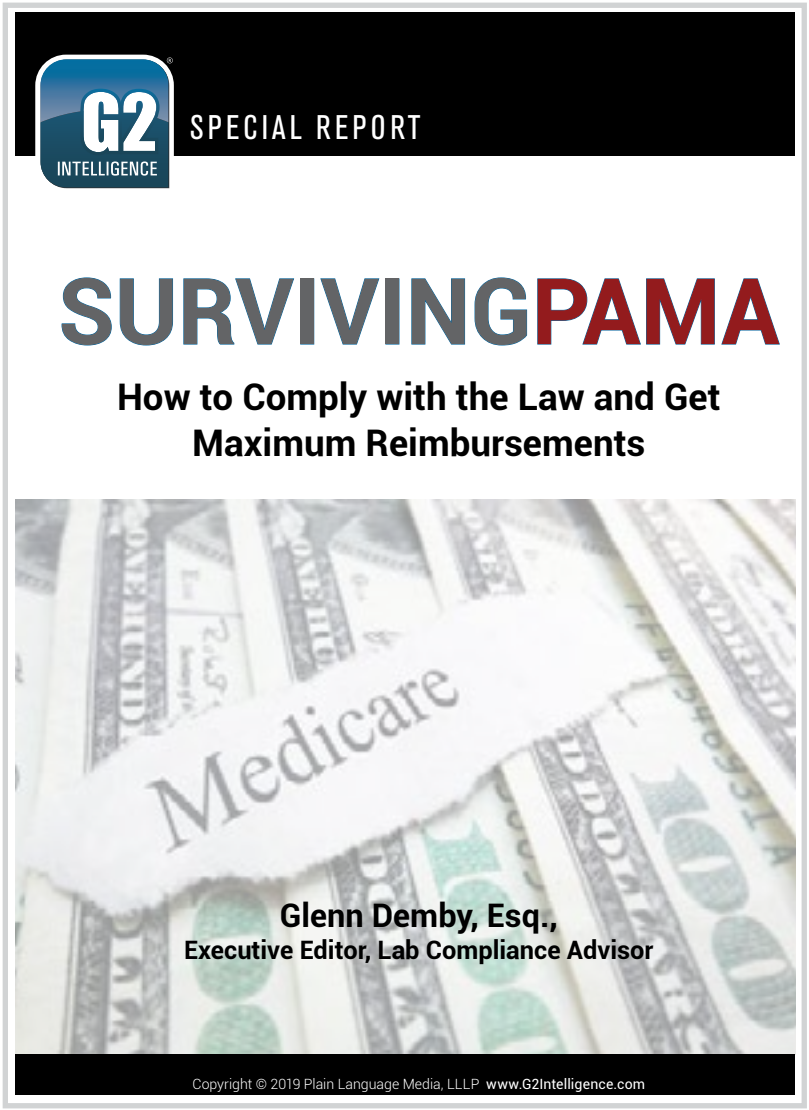

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