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New Trends, Applications, and IVD Industry Analysis

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Industry Trends: Investors Sink Nearly $15 Billion into Digital Health Companies in First 6 Months of 2021

The pandemic has enabled developers of Electronic Health Record (EHR), Laboratory Information Systems, ePrescription software and other digital health technologies to attract investment capital at record rates. In 2020, digital health companies set a new funding record of $14.8 billion. Halfway into 2021, that record has already been eclipsed with $14.9 billion in funding raised, a 138 percent increase over the $6.3 billion raised during the first six months of last year. Those are the findings of a new report from market research firm Mercom Capital Group.

Record 1H for Digital Health Funding

Total corporate funding for digital health, including venture capital, public market and debt in 1H 2021 was $19 billion, Mercom

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Testing Trends: New Evidence Supports Suitability of Antigen Testing for COVID-19 Screening

Not perfect, but good enough. That is the basic theory for using rapid antigen tests for COVID-19 surveillance even though they are less accurate than molecular assays in detecting the SARS-CoV-2 virus. A new research study published in the *Journal of Infectious Diseases* offers important evidence supporting that theory. Specifically, it suggests that performing antigen tests more frequently can raise their sensitivity commensurate with the sensitivity levels of PCR tests performed at longer intervals.

The Diagnostic Challenge

Molecular tests using reverse transcription-polymerase chain reaction (RT PCR) to detect RNA material from the SARS-CoV-2

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Industry Trends: Investors Sink Nearly $15 Billion into Digital Health Companies in First 6 Months of 2021, *from page 1*

reports. Digital health companies raised $7.7 billion in 195 deals in Q2 2021 compared to $7.2 billion from 179 deals in Q1 2021, a 7 percent increase. The $7.7 billion raised in Q2 was also 175 percent above the $2.8 billion in 161 deals in Q2 of 2020. The top digital health venture capital deals in 1H:

- $540 million raised by Noom;
- $500 million raised by Roman;
- $300 million raised by Capsule;
- $300 million raised by Hinge Health; and
- $300 million raised by KRY.

Telemedicine Commands the Lion's Share of Capital

Not surprisingly, Telemedicine attracted more capital than any other venture capital-funded category in 1H 2021 with $4.2 billion, more than tripling the $1.7 billion raised by the second-place category, Wellness. The massive fund-raising success of Telemedicine belies the actual decline in telehealth utilization since the apex of the COVID-19 crisis. The third most money was raised by mHealthApps with $1.6 billion, Analytics with $1.5 billion and Clinical Decision Support with $1.1 billion.

Consumer-Focused Companies Prove More Attractive than Practice-Based Ones

Of the $7.7 billion invested in digital health companies during Q2, $5.3 billion (69 percent in 129 deals) went to companies that focus on providing services to consumers. Practice-focused companies received $2.4 billion in 66 deals, accounting for the remaining 31 percent of Q2 venture capital investments.

Mergers and Acquisitions Continue to Dominate

Mergers and acquisitions (M&A) remain the most popular exit strategy, with no fewer than 136 companies acquired during the first six months of the year, the most 1H transactions that Mercom has ever recorded since it began tracking digital health capital flows in 2010 and almost double the 83 companies acquired in 1H 2020. Of the 73 M&A deals that went down in Q2 of 2021, 43 involved consumer-focused companies and 30 involved consumer companies.

Top 5 Digital Health M&A Deals in First Half of 2021

Acquiring Company	Target	Price
Microsoft	Nuance Communications	$19.7 billion
Optum	Change Healthcare	$13.0 billion

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Acquiring Company	Target	Price
Datavant	Ciox	$7.0 billion
KKR	Therapy Brands	$1.5 billion
Boston Scientific	Preventice Solutions	$925 million

Source: Mercom Capital Group

More Digital Health Companies Going Public

Not a single digital health company went public in all of 2020. Six months into 2021, 12 already have, the biggest 1H total for any year since 2010. Among these, 10 companies, including Bright Health, Doximity and Priva Health, initiated IPOs; the other two—23andMe and Hims & Hers merged with special purpose acquisition companies

Takeaway

Emboldened by the massive utilization of telemedicine during the pandemic, investors are pouring capital into digital health companies at record rates with producers of consumer-facing telemedicine technologies leading the way. It is a trend that is likely to continue despite the short-term curtailment in telemedicine that has accompanied the receding of the coronavirus threat and restoration of something approaching pre-pandemic market conditions.

FDA WATCH

Congress Retables VALID and VITAL Legislation to Regulate LDTs

The U.S. Food and Drug Administration's response to the COVID-19 public health emergency has infused the longstanding efforts to overhaul the agency's system of regulating Laboratory Developed Tests (LDTs) with new energy. This Spring, Congress exhumed a pair of bills, the VALID and VITAL Acts, that address the LDTs regulation conundrum in different ways.

The FDA's Current Regulatory "System"

Since the original *Food Drug & Cosmetics Act* legislation doesn't provide for regulation of laboratory tests, the FDA justifies its regulatory authority over LDTs, aka, *in vitro* clinical tests (IVCTs), as an extension of its power to regulate medical devices. Accordingly, it clears LDTs via the 510(k) premarket review pathway. Rather than following the notice of rulemaking

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FDA Watch: Congress Retables VALID and VITAL Legislation to Regulate LDTs, *from page 3*

process designed to ensure transparency and public input into new federal regulation, the agency regulates LDTs via informal guidance that it posts on its website. Adding to the arbitrariness is the "enforcement discretion" the agency exercises by deferring regulation of most LDTs to the Centers for Medicare and Medicaid Services (CMS) under the *Clinical Laboratory Improvement Amendments* (CLIA) law.

Fixing this mess has been an almost decade-long endeavor. On the legislative front, a bill called the *Diagnostic Accuracy and Innovation Act* (DAIA) would have removed diagnostic tests from the definition of a medical device and thus placed it outside the scope of the 510(k) pathway. Rather than totally stripping the FDA of regulatory authority over IVCTs, a 2018 bill called the *Verifying Accurate, Leading-edge IVCT Development* (VALID) proposed to limit it by establishing IVCTs as a new product category consisting of LDTs and test kits. The bill did not get far; nor did an updated version of it proposed in March 2020.

The VALID Act of 2021

The VALID Act of 2021 would create a risk-based framework for IVCT regulation:

High-Risk Tests: High-risk tests, like novel assays, would be required to go through premarket review to verify analytical and clinical validity.

Lower-Risk Tests: VALID would establish a separate technological certification program for lower-risk tests, as well as a new system allowing hospitals and laboratories to submit their tests electronically.

Emergency Use Tests: To eliminate the emergency use authorization (EUA) bottlenecks and delays that became apparent during the pandemic, validated tests would be authorized to use for emergency purposes pending review of their EUA clearance, analogous to the notification process FDA used for certain COVID-19 tests during the early days of the public health emergency.

Grandfathered Tests: Qualifying LDTs offered for clinical use before enactment of the legislation would receive "grandfathered" status and not require premarket review, provided that they carry a disclaimer on the label and are neither modified nor flagged by the FDA as posing a special concern.

Transitional Tests: IVCTs first offered between the date VALID is enacted and 90 days after it takes effect would be allowed to remain on the market as "transitional" IVCTs, provided that the test maker submits a timely marketing application to the FDA.

Other key features of the 2021 version of VALID:

- Establishment of test design and quality requirements for IVCTs, equivalent to the current Quality Systems requirements for medical devices;
- Creation of a new process that the FDA can use to request information from an otherwise exempt IVCT, such as a transitional or grandfathered test, in certain situations;
- Authority of FDA to participate in collaborative communities for purposes of "facilitating community solutions and decision-making" for IVCTs;
- A requirement that FDA create and maintain an IVCTs database that is more extensive than the current device registration and listing database; and
- New IVCT adulteration, misbranding and postmarket surveillance requirements mirroring current rules that apply to medical devices.

The VITAL Act

VALID isn't the only LDTs regulation bill on the table. First introduced by Senator Rand Paul (R-KY) in March 2020, the newly reintroduced *Verified Innovative Testing in American Laboratories Act* (VITAL) would transfer the FDA's regulatory powers over LDTs to the U.S. Department of Health and Human Services (HHS). Supporters of the bill believe that the FDA's slow response in expanding access to SARS-CoV-2 virus tests during the pandemic reaffirms the need for stripping the agency of power to regulate LDTs. "When we face a health emergency, government should trust academic, community and public health labs to do what they are already trained and certified to do," noted Senator Paul in a press release at the time. "With all of the debates about how government should respond, here's one thing it can stop doing: piling counter-productive bureaucratic hurdles in the way of our medical professionals."

Subsequent FDA management of the EUA process seemed to vindicate and strengthen the drive to get the agency out of the business of regulating LDTs. In August 2020, HHS issued a determination stating that the FDA cannot require premarket review of LDTs without notice and comment rulemaking. While not eliminating FDA regulatory authority over LDTs, the HHS determination barred the agency from its traditional—and to most in the industry—infuriating practice of exercising that authority via website guidelines and other informal pronouncements serving as shortcuts around the burdensome notice and comment rulemaking protocols.

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

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FDA Watch, *from page 5*

New FDA Emergency Use Authorizations (EUAs) & Approvals

Manufacturer(s)	Product
AnchorDx,	Breakthrough device designation for UriFind urine DNA methylation early bladder cancer detection test
First Light Diagnostics	Marketing clearance for SensiTox C. difficile Toxin Test
First Light Diagnostics	Marketing clearance for MultiPath Analyzer
GenBody	EUA for COVID-19 Ag point-of-care antigen test
Ortho-Clinical Diagnostics	EUA for Vitros Anti-SARS-CoV-2 IgG Quantitative test
Thermo Fisher Scientific	EUA for TaqPath COVID-19 RNase P Combo Kit 2.0
Ellume	EUA for COVID Antigen Test by CLIA labs
Exact Sciences	EUA for COVID-Flu Multiplex Assay
BioGx	EUA for Xfree COVID-19 Direct RT-PCR assay
Bio-Rad	EUA for BioPlex 2200 SARS-CoV-2 IgG assay
Foundation Medicine	Clearance for tissue-based FoundationOne Liquid CDx as companion diagnostic to identify patients eligible for treatment with capmatinib (Novartis' Tabrecta)
Foundation Medicine	Clearance for FoundationOne CDx test as companion diagnostic for Takeda's FDA-approved non-small cell lung cancer treatment brigatinib (Alunbrig)
Access Bio	EUA for CareStart EZ COVID-19 IgM/IgG, point-of-care version of firm's SARS-CoV-2 antibody assay
Inova Diagnostics	510(k) clearance for Aptiva System
Inova Diagnostics	510(k) clearance for Aptiva Celiac Disease IgA Assay
Diabetomics	EUA for CovAb SARS-CoV-2 Ab Test, first non-blood COVID-19 antibodies test approved with samples instead coming from painless mouth swabs
Wren Laboratories	EUA for COVID-19 PCR Test DTC, nonprescription version of previously approved test for over-the-counter sale
Siemens Healthineers	EUA for Advia Centaur SARS-CoV-2 IgG, or sCOVG, test
Roche	EUA for RT-PCR-based Cobas SARS-CoV-2 nucleic acid test for use on the Cobas Liat system

STI Update: CDC Updates Guidelines on Laboratory Testing for Sexually Transmitted Infections

On July 22, the US Centers for Disease Control and Prevention (CDC) revised its guidelines for the diagnosis and treatment of sexually transmitted infections (STI), including with regard to how to test for

certain kinds of infections. Here is an overview of what you need to know if STI testing is part of your laboratory's portfolio.

The Diagnostic Challenge

The term "sexually transmitted infection" refers to a pathogen that causes infection through sexual contact (not to be confused with the term "sexually transmitted disease" (STD), which refers to a recognizable disease state that develops from an infection). In addition to increasing the risk of HIV transmission, STIs can have serious health effects, including human papillomavirus (HPV) which causes genital warts and is implicated in cancer of the cervix. Many STIs are asymptomatic or sub-clinical and thus go undiagnosed. But screening, especially of high-risk individuals, is effective in preventing STIs.

In 2015, the CDC made waves by issuing revised guidelines (Sexually Transmitted Diseases and Treatment Guidelines, 2015) recommending the use of nucleic acid amplification tests (NAATs) for use in screening high-risk populations for *Trichomonas vaginalis* and routine trichomonas. The updated guidelines build on those recommendations.

NAAT-Based Diagnosis of *Mycoplasma Genitalium*

Back in 2015, there was no US Food and Drug Administration-cleared molecular test for *M. genitalium*, which can take up to six months to grow in culture. Accordingly, the CDC said the bacterial infection could be suspected only in cases of persistent or recurrent urethritis, cervicitis, and pelvic inflammatory disease (PID). But in 2019, the FDA cleared Hologic's Aptima assay for *M. genitalium* STI in men and women, a fact that the new guidance expressly mentions.

According to the new guidelines, men with recurrent Non-Gonococcal Urethritis (NGU) should be tested for *M. genitalium* using an FDA-cleared NAAT. Resistance testing should be performed if is available. Women with recurrent cervicitis should be tested for *M. genitalium*, and testing should be considered among women with PID. Testing should be accompanied with resistance testing, if it is available. However, the guidelines stop short of recommending screening of asymptomatic *M. genitalium* infection or extragenital testing for the infection.

The guidelines also highlight molecular assays available for diagnosis of *T. vaginalis*, including not only the Hologic Aptima test, but also Becton Dickinson's (BD) ProbeTec and BD Max TV tests, Cepheid's GeneXpert TV and Quidel's Solana and AmpliVue TV tests. They also mention non-molecular tests, including Sekisui Diagnostics' Osom trichomonas rapid test and BD's Affirm VPIII assay.

Diagnosis of Gonorrhea Infections

As before, CDC recommends routine annual screening for *N. gonorrhoeae* and chlamydia for all sexually active

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STI Update: CDC Updates Guidelines on Laboratory Testing for Sexually Transmitted Infections, *from page 7*

females ages 25 or older. Extragenital gonorrhea screening (pharyngeal or rectal) can be considered for females on the basis of reported sexual behaviors and exposure, via shared clinical-decision between the patient and the provider, the guidelines add. However, CDC says there is insufficient evidence of efficacy or cost-effectiveness to recommend routine screening for *N. gonorrhoeae* among asymptomatic sexually active young males who have sex with females only. Screening for gonorrhea, including pharyngeal or rectal testing, should be offered to young men who have sex with males (YMSM) at least once a year. Annual chlamydia rectal, but not pharyngeal testing is also recommended for this population.

Gonorrhea detection using molecular tests is more sensitive than culture-based methods, the guidelines note, but sensitivity may vary by anatomical site. Patient-collected samples are "reasonable alternatives to provider-collected swabs for gonorrhea screening by NAAT." The CDC also reiterates recent guidance that ceftriaxone alone be used to treat gonorrhea, rather than dual therapy with ceftriaxone and azithromycin, due to the emergence of azithromycin resistance.

Other Recommendations

Other notable CDC recommendations in the new STI guidelines:

- Clinical diagnosis for herpes simplex virus (HSV) testing should be confirmed by type-specific virologic testing using NAAT or culture for cases in which genital lesions are present;
- Type-specific serologic tests can be used to aid diagnosis of HSV infection in the absence of genital lesions. The CDC recommends two-step serologic testing for HSV;
- Universal hepatitis C (HCV) testing should be done at least once in a person's lifetime via an initial antibody test, with positive results confirmed using an FDA-cleared HCV NAAT; and
- Sekisui Diagnostics' Osom BV Blue point-of-care test may have utility for bacterial vaginosis (BV) but CooperSurgical's FemExam Test Card is not a preferred method of diagnosis.

The new guidelines also mention commercially available quantitative multiplex PCR assays for BV by name, including:

- BD's Max Vaginal Panel;
- Hologic's Aptima BV;
- LabCorp's NuSwab VG;
- Quest Diagnostics' SureSwab BV; and
- Medical Diagnostic Laboratories' OneSwab BV Panel PCR with Lactobacillus Profiling by qPCR.

The guidelines note that the BD and Hologic BV assays are FDA-cleared, while the other three are laboratory-developed tests.

Reproductive Testing: Don't Rely on Biomarker Tests to Predict Risk of Premature Births, Warns AACC

After steadily declining, the rate of spontaneous preterm births in the U.S. rose to 10 percent in 2018. Preventing premature births would save the nation over $26 billion per year. However, diagnostic tests that claim they can predict premature births are unreliable and should not be used as part of routine evaluation of women with symptoms of preterm delivery. That, at least, is the conclusion of new guidance issued by the American Association of Clinical Chemistry (AACC).

The Diagnostic Challenge

"Identifying women who will deliver preterm is critical to allow selective initiation of appropriate therapy, while preventing unnecessary treatment of women who will deliver at term," the AACC notes. But this task is "inherently challenging" because the best way to predict premature birth is by determining if the patient has a history of giving birth before term. Obviously, that solution is not available for first time pregnancies.

Another problem is that the signs that labor is beginning, things like backache and pelvic pressure, are "ubiquitous." Heck, you do not have to be pregnant to experience a backache. (Our words, not the AACC's.)

The New AACC Guidance

Currently available diagnostic tests using more specific biomarkers usually identify risk of premature birth by measuring the patient's fetal fibronectin (fFN), interleukin 6 (IL-6) and placental alpha macroglobulin-1 (PAMG-1). However, the AACC says that tests for these biomarkers have low positive predictive values and there have been no studies demonstrating their "definitive clinical value."

Thus, for example, "randomized controlled trials that assess patient outcomes and healthcare utilization by implementing fFN testing are lacking and existing studies have found conflicting results," according to the guidance document. The AACC also cites the lack of consensus among professional societies about the utility of fFN in predicting preterm birth.

What the AACC Recommends

"At this time, AACC does not recommend measurement of fFN, PAMG-1 or IL-6 in the routine evaluation of all women with symptoms consistent with preterm delivery," the guidance concludes. One potential solution is to "limit biomarker testing to high-risk women, thereby increasing the pre-test probability of the population being tested and improving the [positive predictive value] of currently available test methods." In the meantime, laboratory professionals and obstetricians should discuss all available recommendations on preterm birth testing together and take a

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Reproductive Testing: Don't Rely on Biomarker Tests to Predict Risk of Premature Births, Warns AACC, *from page 9*

collaborative approach to developing institutional testing strategies for preterm birth.

The Silver Lining: PAMG-1 May Signal Preterm Delivery Within a Week

The AACC makes one limited exception to its non-recommendation of measuring fFN, PAMG-1 or IL-6 as part of routine evaluation of all women with symptoms consistent with preterm delivery. A positive PAMG-1 test result in patients who present with symptoms of premature labor and who are at high risk of preterm delivery due to cervical length, a positive PAMG-1 result may be helpful for identifying women who are likely to deliver within a week. In patient populations with a higher prevalence of spontaneous preterm delivery within one week, PAMG-1 would likely "provide clinical value as the majority of women with a positive test result would go on to deliver prematurely," the report notes.

Takeaway

The AACC also addresses its recommendations to test makers. Among the limitations of current tests is that they measure only a single protein. Perhaps multi-marker panels may improve performance. However, the association quickly adds, the multi-marker panels that have been evaluated so far "do not demonstrate improved diagnostic performance relative to single biomarkers." Another solution would be to come up with "novel diagnostic tools with improved PPV to predict the minority of symptomatic women who will deliver prematurely."

Testing Trends: New Evidence Supports Suitability of Antigen Testing for COVID-19 Screening, *from page 1*

virus performed at an offsite laboratory represent the gold standard for accurate coronavirus detection. The problem is that these tests are too costly and slow to meet the need for rapid screening.

The cost-effectiveness and speed of tests that identify the presence of antigens or toxins a virus produces that cause the body to produce antibodies are far more suited for rapid testing of the asymptomatic at the point of care. However, antigen tests lack the sensitivity of molecular assays. This creates the risk of false negatives and need for confirmatory testing. However, while antigen testing is not appropriate for diagnostic and treatment uses, they are sensitive enough for screening the asymptomatic or only mildly symptomatic for purposes of surveillance and infection control.

That, at least, is the contention of test producers, laboratories, policy makers and others that have carved out a stake in antigen testing. However, because the SARS-CoV-2 virus emerged without warning, there has been precious little time and opportunity to gather the scientific evidence needed to prove that those contentions are true.

The University of Illinois Study

Published on June 30, 2021, the new study is the work of a team of researchers from the University of Illinois at Urbana-Champaign that set out to evaluate the performance of rapid antigen and molecular SARS-CoV-2 tests over the course of mild and asymptomatic infections. They analyzed samples collected via the University's protocol requiring on-campus students and staff to undergo saliva-based SARS-CoV-2 molecular testing every two to four days.

The researchers formed a subset of 43 individuals who tested positive for COVID-19 and asked them to submit daily saliva and nasal swab samples over the course of 14 days. They then performed saliva- and swab-based PCR testing on the samples, as well as swab-based rapid antigen testing using Quidel's Sofia SARS Antigen FIA test run on the Sofia 2 device. The researchers also performed viral culture of the nasal samples to determine at what points throughout the 14 days of testing the patients were likely to have been infectious.

The Study's Finding

Predictably, the researchers found that PCR testing had higher sensitivity than antigen testing—roughly 98 percent for saliva- and swab-based PCR tests versus 80 percent for antigen testing. However, they also found that they could compensate for this difference by performing the antigen

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Testing Trends: New Evidence Supports Suitability of Antigen Testing for COVID-19 Screening, *from page 11*

tests more frequently. Thus, antigen testing subjects every three days raised antigen assay sensitivity to better than 98 percent, the equivalent sensitivity of molecular assays during testing once a week.

In addition, researchers found that PCR testing continued to flag samples as positive even after the viral cultures were no longer positive. This finding bolsters the argument made by some advocates of antigen testing that the high sensitivity of PCR tests may actually be a disadvantage in the screening context to the extent that it makes those assays more apt to return positive test results for patients who are no longer infectious and thus not a threat to spread COVID-19. By contrast, positive antigen tests offer a more reliable indication that the test subject is infectious at the time of testing.

Takeaway

Until now, the suitability of using antigen testing for COVID-19 screening has been taken largely on faith. The University of Illinois study is significant because it is among the first research projects providing scientific evidence to support this case.

"In general, serial antigen screening will be as effective as PCR in catching and assessing infectiousness," noted Bruce Tromberg, leader of the NIH Rapid Acceleration of Diagnostics Tech program, which provided funding for the study. He noted that the minimum cadence for effective antigen testing should be two times per week, with three times a week best for regular screening of people in high-prevalence areas or engaged in higher-risk activities.