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New Trends, Applications, and IVD Industry Analysis

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Inside the Lab Industry: Exact Sciences Scores Big as USPSTF Lowers Colorectal Cancer Screening Start Age to 45

Wouldn't it be great if a government health task force recommended that people use the kind of test you create every year? Something like that just happened to Exact Sciences, maker of the Cologuard home-based colorectal cancer screening test. It happened when the U.S. Preventive Services Task Force (USPSTF) changed its guidelines by recommending that screening for colon and rectal cancer start at age 45, rather than 50. In addition to saving thousands of lives by promoting earlier colorectal cancer detection, the USPSTF announcement is very good news for molecular screening test companies, especially but not exclusively Exact Sciences. Here is a breakdown of the new USPSTF recommendations and their potential impact on screening patterns and the molecular testing market.

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Testing Trends: Test Makers, Retailers Are Raking in Money from Direct-to-Consumer COVID-19 Diagnostics

There is no disguising the fact that COVID-19 testing has proven to be a windfall for laboratories and the diagnostics industry. And even though the massive testing revenues of the past year are not sustainable, there is still lots and lots of money to be made in COVID-19 in the next few years. Of course, the market has and will continue to evolve with direct-to-consumer (DTC) offering perhaps the most favorable opportunities, at least in the near term. The most recent next big thing in the DTC space is do-it-yourself (DIY) at-home COVID-19 testing using over-the-counter (OTC) test kits that do not require a prescription. Three of the nation's biggest

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The Diagnostic Challenge

Colorectal cancer is the third leading cause of cancer death among adults in the U.S., with more than 52,000 people projected to die from the disease in 2021. Most colorectal cancer cases are diagnosed in people ages 65 to 74. Only 10.5 percent of new cases occur in those below age 50. However, the case incident rate among this group has steadily increased—at a nearly 15 percent clip between 2000 and 2016.

Unfortunately, there has been no commensurate increase in colorectal cancer screening over this period. According to the USPSTF, in 2016, 26 percent of eligible U.S. adults had never undergone colorectal cancer screening; in 2018, 31 percent adults were not up to date with their screening.

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The New Colorectal Screening Recommendations

The USPSTF reviews its screening recommendations every four years. The new recommendations, which were published in the *Journal of the American Medical Association* on May 18, are an update to its previous 2016 guidelines and a final version of draft recommendations published in October 2020. The latest revisions are based on a systematic review evaluating the benefits and harms of screening for colorectal cancer in adults 40 or older. The review also examined whether these findings varied by age, sex, or race/ethnicity. As it did in 2016, the USPSTF commissioned a report from the Cancer Intervention and Surveillance Modeling Network Colorectal Cancer Working Group to provide information from comparative modeling on how estimated life-years gained, colorectal cancer cases averted, and colorectal cancer deaths averted vary by different starting and stopping ages for various screening strategies.

The headline of the new guidelines is the recommendation that asymptomatic adults at average risk start colorectal cancer screening at age 45, rather than waiting until age 50 as the 2016 guidelines recommended. The new recommendation is in line with the American Cancer Society, which also recommended starting routine colorectal cancer screening at age 45 in 2018. According to the USPSTF, adults ages 45 to 75 should undergo routine colorectal cancer screenings. It estimates that earlier screenings would be associated with up to an additional 27 life-years, two to three fewer colorectal cancer cases, and between 0.9 and 1 fewer deaths from the disease, compared to adults who begin screenings at age 50.

The task force assigns members of this age 45 to 49 group a "B" grade, as opposed to the "A" grade given to the age 50 to 75 members of the cohort. Even so, a B grade is enough to ensure members who have commercial insurance will not have to pay out-of-pocket costs to receive their screenings under Affordable Care Act rules. First-dollar health insurance

coverage for adults starting at age 45 could impact up to 15 million adults, according to the patient advocacy organization Colorectal Cancer Alliance.

Meanwhile, the USPSTF recommends that screening in adults ages 76 to 85 be offered selectively as determined by clinicians on the basis of the specific circumstances of the case, including the patient's overall health, screening history and preferences. Evidence indicates that the net benefit of screening all persons in this age group is small. The task force assigns this group a "C" grade.

USPSTF Colorectal Cancer Screening Recommendations

Ages	Recommendations	Grade
50 to 75	Screening for all members	A
45 to 49	Screening for all members	B
76 to 85	Screening for selective cases determined by clinician based on patient's health, screening history and preferences	C

Impact on the Laboratory Industry

Reducing the starting age for colorectal cancer screening to age 45 with a "B" classification will significantly boost sales of molecular screening tests. The real breakthrough came in 2016, when the USPSTF first added molecular colorectal cancer screening to its guidelines. In addition to Multitargeted stool DNA (mtDNA) tests like Cologuard, the task force recommends two other stool-based tests, namely high-sensitivity Guaiac-based fecal occult blood tests (gFOBT) and Fecal immunochemical tests (FIT), as well as direct visualization approaches like colonoscopy.

Stool-Based Tests

Test Type	Recommended Frequency
High-sensitivity gFOBT	Every year
FIT	Every year
mtDNA	Every 1 to 3 years based on manufacturer's recommendations

Direct Visualization Tests

Test Type	Recommended Frequency
Colonoscopy	Every 10 years
CT colonography	Every 5 years
Flexible sigmoidoscopy	Every 5 years
Flexible sigmoidoscopy with FIT	Every 10 years + FIT every year

While there is plenty of competition, Exact Sciences is the clear market leader in mtDNA at-home colorectal testing with the greatest visibility

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among the late-40 somethings who will now be able to get screened for free each year, especially if it means avoiding colonoscopy. The draft version of the guidelines said that screening with Cologuard every year "would result in more colonoscopies than annual screening with FIT." But USPSTF softened its position in the final text by adding new language stating that Cologuard "every 1 to 3 years is estimated to provide a reasonable balance of life years gained per estimated follow-up colonoscopy compared with no screening."

FDA WATCH

Newly Reintroduced VITAL Act Would Strip Agency of LDT Regulatory Authority

When history is written, acceleration of the longstanding effort to eliminate the authority of the U.S. Food and Drug Administration (FDA) to regulate Laboratory Developed Tests (LDTs) may be remembers as one of the unexpected impacts of the COVID-19 pandemic. The public health emergency underlined the need to bring innovative new diagnostic tests to market more expeditiously. In fact, many of the most significant COVID-19 tests to receive Emergency Use Authorization were LDTs created by Quest, LabCorp, Abbott and other major testing laboratories. And now the epicenter of the movement may be shifting back to Congress with the reintroduced of the so-called VITAL Act.

The VITAL Act

First introduced by Senator Rand Paul (R-KY) in March 2020, the *Verified Innovative Testing in American Laboratories* (VITAL) *Act* would transfer the source of regulation of LDTs from the FDA (under the Food, Drug & Cosmetics Act (FDCA)) to the Secretary of the US Health and Human Services (HHS) (under the Public Health Services Act). While it may sound like legal nuance, this is important because it would end once and for all the FDA's claims that its regulatory authority over medical devices under the FDCA extends to LDTs.

Paul, who also introduced the most recent version of the bill, and supporters of the bill believe that VITAL is necessary to update CLIA by removing LDTs from FDA oversight in light of the slow federal response to expand access to SARS-CoV-2 virus tests during the pandemic. The FDA has been criticized for requiring test developers and manufacturers

to get EUA from the agency prior to launching testing. "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.

Laboratory Industry Support for VITAL Act

The VITAL Act had and now continues to have widespread support from the diagnostics industry. The day after Senator Paul re-tabled the bill, the Association for Molecular Pathology (AMP) and Association of Pathology Chairs (APC) issued statements supporting its passage.

"This important support by members of Congress for the VITAL Act addresses the serious consequences experienced by our nation when laboratory tests are regulated like medical devices," noted APC president Lydia Howell.

"In the earliest and most frightening days of the pandemic, CLIA-accredited academic clinical laboratories could have used their valuable expertise and resources to expand SARS-CoV-2 diagnostic testing in their communities, but were unable to do so due to inappropriate FDA restrictions," she continued. "Priceless weeks were lost, making the urgency to address these issues now even more clear."

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Here are some of the key new FDA EUAs and clearances announced in May and late April:

New FDA Emergency Use Authorizations (EUAs) & Approvals

Manufacturer(s)	Product
LabCorp	EUA for Pixel by Labcorp COVID-19 PCR Test Home Collection Kit expanded to allow for use by children and adolescents at least 2 years of age

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FDA Watch, *from page 5*

Manufacturer(s)	Product
Molzym	Breakthrough Device Designation for molecular diagnostic test system for diagnosis of bloodstream infections
Zeus Scientific	EUA for ELISA SARS-CoV-2 Total Antibody Test System
Qiagen	EUA for QiaReach Anti-SARS-CoV-2 Total Test to identify if person has SARS-CoV-2 antibodies from a prior infection
InBios International	EUA for point-of-care SCoV-2 Ag Detect Rapid Test for SARS-CoV-2 antigens
Viome	Breakthrough Device Designation for mRNA analysis and AI saliva-based oral and throat cancer detection technology
Quadrant Biosciences	Breakthrough Device Designation for Clarifi ASD assay to detect markers of autism spectrum disorder
Roche	Clearance for Ventana MMR RxDx immunohistochemistry panel as companion diagnostic to select endometrial cancer patients for treatment with dostarlimab
PathogenDx	EUA for molecular DetectX-Rv SARS-CoV02test
Southern California Permanente Medical Group	EUA for SCPMG's Kaiser Permanente High Throughput SARS-CoV-2 Assay
Inova Diagnostics	EUA for Quanta Flash SARS-CoV-2 IgG chemiluminescent immunoassay
Immunodiagnostic Systems	510(k) clearance for IDS Cortisol assay to detect cortisol in human serum and plasma on firm's IDS system
Retractable Technologies	510(k) clearance for EasyPoint Blood Collection Plus blood collection tube holder
Immunalysis	510(k) clearance for Sefria PCP Oral Fluid Enzyme Immunoassay

Technological Breakthroughs: NASA Begins Testing of Handheld COVID-19 Breathalyzer Device

A portable, handheld, easy-to-use breathalyzer device capable of accurately detecting the SARS-CoV-2 at the point of care would represent a game changer for COVID-19 diagnostics. And while inventing such a device is not exactly rocket science, the U.S. has called on its rocket scientists to make it happen. Last month, NASA announced plans to begin testing a prototype of such a device.

The Diagnostic Challenge

With the coronavirus in retreat, the priority for COVID-19 diagnostics developers is to create rapid and accurate point-of-care testing performed on a mass basis on both the symptomatic and asymptomatic. The current tests addressing this need are based on technology for detecting SARS-CoV-2 antibodies and antigen. While suitable for screening purposes, antibody and antigen testing is relatively lacking in sensitivity and accuracy. The label "rapid" also belies the fact that these tests do take minutes to process and do not deliver results immediately the way many tests do.

All of this makes it worthwhile to explore the potential to develop new modalities using different biomarkers to detect the SARS-CoV-2 virus. One candidate is exhaled volatile organic compounds (VOCs) that could be detected via a rapid breath test.

The E-Nose Breathalyzer

The U.S. Department of Health and Human Services (HHS) gave NASA $3.8 million to test a prototype of such a device called the E-Nose that was originally developed measure the quality of air inside a spacecraft. But Tennessee subcontractor Variable Inc., the firm that created the device, has reconfigured it for COVID-19 screening. Specifically, the E-Nose is designed to "sniff out" the signature VOCs of the virus in the breath of people who are infected.

It took Variable six months to develop the electronics and packaging for the smartphone-based device and Bluetooth functionality and a paired mobile app that processes, displays and transmits sensor data. Variable created the original device with funding from the U.S. Department of Homeland Security (DHS) to detect toxic gases that terrorists might try to inject into the capsule of a manned spacecraft.

Like the original DHS version, the COVID-detecting E-Nose integrates nanosensor technology invented by NASA scientist Jing Li. But the bulky instruments used to detect harmful gases need to be streamlined into a lightweight, portable, hand-held device that could be used easily in both a clinical and home setting. The key to the conversion was scaling and packaging the sensors.

The Testing

Having received the device from Variable, NASA now has to refine the sensors so they can detect the target COVID-19 VOCs more effectively. The NASA team is working with researchers from Johns Hopkins University and the Lawrence Livermore National Lab to study the VOCs associated with SARS-CoV-2 infections. The prototype design allows for swapping out the sensor chips as necessary to make adjustments in response to what the

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Technological Breakthroughs: NASA Begins Testing of Handheld COVID-19 Breathalyzer Device, *from page 7*

research team learns about the VOCs. Once they identify what they believe to be the virus' biosignature, they will take readings of healthy individuals and people with other types of infection, followed by field testing and clinical trials to demonstrate the device's sensitivity and specificity.

Ultimately, data from the E-Nose would be incorporated with body temperature and other symptoms for analysis by NASA's advanced machine learning programs to yield an immediate and more accurate means of detecting COVID-19.

Takeaway

It may not be the final frontier, but VOC-based detection has the potential to take rapid COVID-19 screening to a new dimension in both speed and accuracy. And right now, the E-Nose occupies a prime position on the launching pad. If it all works out, the "E-Nose can be deployed in factories, airports, grocery stores, and businesses of all sorts to rapidly screen for active infections," says technology inventor Li. "It's a noninvasive and rapid way to keep our communities safe as this pandemic continues."

LDTs: AACC Guidelines Caution Against Using Serology Tests to Determine COVID-19 Vaccine Efficacy

Although SARS-CoV-2 serology tests have yet to live up to the hype, they are still expected to play a crucial role in coronavirus infection control efforts going forward. In addition to accuracy concerns, testing laboratories that develop and manufacture Emergency Use Authorization (EUA) and laboratory developed test (LDT) serology tests have been bedeviled by confusing and sometimes contradictory messaging and regulation. However, new guidelines from the American Association of Clinical Chemistry (AACC) may help clear up the confusion and get SARS-CoV-2 serology testing back on track.

The Diagnostic Challenge

When the pandemic first began, many hailed serology tests that detect antibodies the body creates to fight SARS-CoV-2 as holding the key to not only rapid widespread testing but also efforts of public health officials to track infection rates and prevalence in different communities. Among the early believers was the U.S. Food and Drug Administration (FDA) which initially allowed SARS-CoV-2 serology tests to reach the market without EUA. Literally hundreds of assays passed through the floodgates, many of which lacked anything close to the scientific reliability and accuracy required for EUA status. Dozens of these junk tests were recalled. Not until May 4, nearly three months into the public health emergency, did the FDA pull back and require EUA clearance for serology tests.

This limited FDA review process for EUA approval, the AACC guidelines note, coupled with all of the different types of available tests and wide variance in performance characteristics and "the incomplete understanding of the humoral immune response in COVID-19," created questions about how to utilize and interpret SARS-CoV-2 serology tests most effectively. Those questions remain, despite the interim guidelines published by the U.S. Centers for Disease Control and Prevention (CDC), International Federation for Clinical Chemistry (IFCC), Infectious Diseases Society of America (IDSA) and other organizations.

The AACC Guidelines

The new guidelines created by a panel of AACC experts are an attempt "to provide a comprehensive reference for laboratory professionals and healthcare workers to appropriately implement SARS-CoV-2 serologic assays in the clinical laboratory and interpret test results during this pandemic." They provide what the manuscript contends are "the most up-to-date understanding of host immune responses to SARS-CoV-2, the associated antibody kinetics, and the currently available EUA assays."

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LDTs: AACC Guidelines Caution Against Using Serology Tests to Determine COVID-19 Vaccine Efficacy, *from page 9*

Specifically, the guidelines address:

- Utility and limitations of SARS-CoV-2 serology as a science, including in monitoring vaccine response effectiveness;
- Performance verification of EUA and FDA-authorized assays;
- CLIA requirements for validation of LDTs;
- Quality management of serology tests; and
- Interpretation of serology test results.

Takeaway: Serology Testing & the COVID Vaccination

The AACC guidelines come at a pivotal time for the future of serology testing. Now that COVID-19 vaccinations are being rolled out, serology tests hold the promise for use in measuring their effectiveness. But the AACC pumps the brakes on this notion, at least for now. While serology testing can determine whether an individual has developed SARS-CoV-2 antibodies in response to the vaccine, the value of that data is tempered by the absence of universally accepted thresholds indicating the level of antibody response indicates vaccine efficacy. Unless and until such thresholds are established, serology testing "should not be used to determine vaccine efficacy and protective immunity," cautions the AACC.

Of course, this caveat applies to not only public health officials monitoring infection prevalence but also physicians who may rely solely on the results of a serology test to make decisions about how best to treat a vaccinated patient.

Testing Trends: Test Makers, Retailers Are Raking in Money from Direct-to-Consumer COVID-19 Diagnostics, *from page 1*

retailers—CVS, Walgreens and Walmart—have gotten the early jump in the race to lead this emerging market.

CVS Stakes Out Its Claim for OTC COVID-19 Testing

CVS Health Corp. was one of the first companies out of the gate when it began selling OTC COVID-19 tests in mid-April. Initially available to residents of Rhode Island and Massachusetts for in-store purchase, CVS

says that tests will be available in all CVS stores nationwide by the end of May. The CVS catalog currently includes three tests:

- Ellume COVID-19 Home Test (costing $30 per test);
- Abbott BinaxNOW COVID-19 Antigen Self Test ($23.99 per test); and
- Pixel by Labcorp PCR Test Home Collection Kit ($119 per test).

The pharmacy giant also plans to sell these OTC kits online.

Walgreens and Walmart Are Close Behind

Walgreens is also aggressively pursuing the OTC COVID-19 testing opportunity via its Boots Alliance. On April 19, the national pharmacy chain announced that it had reached an agreement with Abbott to sell the BinaxNOW Rapid Antigen Self Test on a non-prescription basis in stores nationwide via in-store purchase, curbside pickup and same day delivery at a cost of $23.99 (MRSP). Online sales began a week later.

Like CVS, Walgreens has a nationwide presence with over 5,500 pharmacies, nearly 50 percent of which are located in socially vulnerable areas where testing can be difficult to come by. Walgreens said it plans to expand testing to 6,000 drive-thru testing sites, with about half of them to offer the Abbott BinaxNOW test at no cost.

Retail powerhouse Walmart has also joined the party and is now offering the BinaxNOW test OTC at stores and online. Late last year, all three retailers inked agreements to sell at-home COVID-19 self-collection kits on a prescription basis.

Uber Gets in on the DTC Product Delivery Side

At-home COVID-19 testing and sample collection, both OTC and prescription-based, is becoming so big that it is also drawing players from outside the laboratory testing and retail pharmacy markets. Among the most notable of the new arrivals is Uber, which on April 26 announced that its health care arm was partnering with Clinical Enterprise, Inc. d/b/a empowerDX, a U.S. subsidiary of Luxembourg-based Eurofins Clinical Diagnostics, to provide on-demand delivery service of at-home COVID-19 testing kits to consumers.

empowerDX is an online shop affiliated with CLIA-certified clinical laboratories in the U.S. that offers at-home testing for men's and women's health, sexual health and general wellness. Its owner, Eurofins, was one of the many DTC businesses to expand into COVID-19 early in response to the pandemic. Developed by the company's Eurofins Viracor infectious disease testing laboratory, the empowerDX At-Home COVID-19 PCR Test Kit received Emergency Use Authorization (EUA) from the Food and Drug Administration (FDA) on October 15 for home collection and maintenance of nasal swab specimens to detect RNA from the SARS-CoV-2 virus. Four

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Testing Trends: Test Makers, Retailers Are Raking in Money from Direct-to-Consumer COVID-19 Diagnostics, *from page 11*

months later, the agency expanded the kit's EUA to include DTC use and screening.

The company claims that as of December 2020, the assay offers one of the best sensitivity rates of the 117 laboratories that submitted results to the FDA's SARS-CoV-2 Reference Panel. The empowerDX at-home test kit, which is 100 percent covered by most insurance carriers, includes step-by-step instructions, a shallow nasal swab, test tube and a pre-paid FedEx package for easy sample returns. Consumers need to activate their kits online before taking the test. Test results are delivered to a secure patient portal within an average of 24 to 48 hours from sample receipt at the company's CLIA-certified laboratory.

Starting in May, consumers in more than two dozen US cities, including Houston, Austin, Seattle, Denver, Phoenix, Minneapolis, Tampa and Fort Lauderdale, will be able to order the kit directly from empowerDX website without a prescription. Uber will make the kit available for delivery, hopefully in as little as one hour, from Monday through Friday between 8 a.m. and 4 p.m. If the project proves successful, the companies plan to expand it to additional cities in the coming weeks.

Takeaway

COVID-19 testing is proving more sustainable than many believed it would when the public health emergency began. However, the market is an amoeba with sudden and rapid form changes. Clearly, though, sale of tests and testing kits directly to consumers is likely to be a windfall for both testing companies and retailers for the foreseeable future.