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Infectious Diseases: Eliminating RNA Extraction Offers Promise of Faster COVID-19 RT-PCR Testing

Reverse transcription polymerase chain reaction (RT-PCR)-based molecular testing is universally recognized as the gold standard for COVID-19 testing accuracy. The downside of molecular testing is its reliance on RNA extraction, which makes testing cumbersome, costly and slow. But now comes word scientists at the National Institutes of Health (NIH) have developed a new sample purification method that is both simpler and faster.

The Diagnostic Challenge

Molecular tests detect COVID-19 by identifying the RNA from the SARS-CoV-2 virus. However, the RNA detection requires elaborate sample preparation. First, the sample must be purified via treatment with chemical solutions to remove substances such

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Testing Trends: AHA Calls for Individualized Approach to Pediatric Cardiovascular Genetic Testing

Genetic testing of children can play a key role in determining a child's risk of developing heritable cardiovascular disease. But testing should be limited to children with a high likelihood of disease. It should also be undertaken as part of a specialized multidisciplinary effort that involves pre- and post-testing. Those, at least, are the key points made in a new scientific statement from the American Heart Association (AHA).

The Diagnostic Challenge

Analysis of genetic alterations at the gene/chromosome or DNA sequence level is capable of detecting many common diseases

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as proteins and fats. The RNA must then be reverse transcribed to DNA by use of a specific enzyme, which are then enriched to offer a better target for detection. The mixture is then placed in an RT–PCR machine for cycling to trigger specific chemical reactions that create new, identical copies of the target sections of viral DNA. The cycle is repeated over and over to continue copying the target sections of viral DNA. Each cycle doubles the previous number: two copies become four, four copies become eight, and so on.

The process takes at least 24 to 36 hours. And it must be carried out at a laboratory using specialized equipment. All of this makes RT-PCR testing great for diagnosis of symptomatic or high-risk cases but ill-suited for asymptomatic screening and other applications requiring rapid, scalable testing at the point of care.

The NIH Sample Preparation Method

The new sample preparation method bypasses the RNA extraction part of the process. A team of scientists from the NIH Clinical Center, National Eye Institute (NEI) and National Institute of Dental and Cranofacial Research (NIDCR), were able to use Chelex 100 resin, a chelating agent produced by laboratory supplies company Bio-Rad, to preserve SARS-CoV-2 RNA in samples for subsequent quantitative RT-PCR detection.

"We used nasopharyngeal and saliva samples with various virion concentrations to evaluate whether they could be used for direct RNA detection," noted Bin Guan, Ph.D., a fellow at NEI's Ophthalmic Genomics Laboratory and lead author of the report describing the technique, which was published this week in the journal iScience. The team tested a variety of chemicals using synthetic and human samples to identify those that could preserve the RNA in samples with minimal degradation while allowing direct detection of the virus by RT-qPCR.

To validate the test, they collected patient samples in either viral transport media, or the newly developed chelating-resin-buffer at the NIH Symptomatic Testing Facility. The samples in viral transport media were tested using conventional RNA extraction and RT-qPCR testing. The samples in the chelating-resin-buffer were heated and the viral RNA was, then, tested by RT-qPCR.

The new preparation significantly increased the RNA yield available for testing, compared to the standard method. In addition to allowing for detection with "markedly high sensitivity," the preparation technique inactivated the virus, making it safer for laboratory personnel to handle positive samples.

DTET

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Takeaway

Elimination of RNA extraction would make qRT-PCR testing faster and less costly, without compromising test accuracy. The NIH project is exciting in supplying early evidence of the idea's feasibility by stabilizing the RNA at room temperature for easier transport, storage, and handling in clinical settings.

FDA WATCH

Agency Imposes 2.5 Percent Increase in 2022 Premarket Application User Fees

Although the FY 2022 fees increase is less than half of last year's increase, applying to the US Food and Drug Administration (FDA) for premarket review of medical devices will still be more expensive next year. On Aug. 2, the agency announced that it is raising premarket approval (PMA) user fees by 2.5 percent in FY 2022.

How PMA User Fees Work

FDA sets the fee rate for each type of submission based on a specified percentage of the standard fee for a premarket application. *The Medical Device User Fee Amendments of 2017* (MDUFA IV) gives FDA the authority to collect user fees from the industry for certain medical device submissions to help pay for the agency's review activities. The MDUFA IV requires the FDA to meet performance goals designed to improve the efficiency, speed and transparency of the PMA and 510(k) review process. In return, the medical technology industry provides the FDA $999.5 million in additional financial resources over a five-year period.

In FY 2022, the $329,000 base fee and $4,978 establishment registration fee will be adjusted "using the same methodology as that for the total revenue inflation adjustment," according to the agency. The good news is that the resulting 2.5 percent adjustment for the year, which officially takes effect on Oct. 1, 2021, will be considerably less than the 7 percent increase in the user fee that the agency implemented in FY 2021.

Here are some of the key new FDA Emergency Use Authorizations (EUAs) and clearances announced in August:

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FDA Watch, *from page 3*

New FDA EUAs & Approvals

Manufacturer(s)	Product
Kwokman Diagnostics	EUA for Kwokman Diagnostics COVID-19 Home Collection Kit
Roche	Clearance for Ventana MMR RxDx immunohistochemistry panel as a companion diagnostic to select patients for treatment with GlaxoSmithKline's newly cleared anti-PD-1 agent dostarlimab-gxly (Jemperli) for patients with previously treated, mismatch repair-deficient, or dMMR, solid cancers
Roche	EUA for RT-PCR-based Cobas SARS-CoV-2 nucleic acid test for use on the Cobas Liat system
STS Lab Holdco (Amazon subsidiary)	EUA for Amazon Multi-Target SARS-CoV-2 Real-Time RT-PCR Test
Cleveland Clinic	EUA for SelfCheck COVID-19 TaqPath Multiplex PCR test
Qiagen + Ellume	EUA for QiaReach SARS-CoV-2 Antigen Test
Pillar Biosciences	Premarket approval for OncoReveal Dx Lung and Colon Cancer Assay tissue-based companion diagnostic test for qualitative detection of somatic mutations in DNA from non-small cell lung cancer and colorectal cancer tissue samples
Thermo Fisher Scientific	EUA for COVID-19 Fast PCR Combo Kit 2.0 to detect SARS-CoV-2 nucleic acid in saliva samples
Thermo Fisher Scientific	EUA for TaqPath COVID-19 MS2 Combo Kit 2.0 PCR-based test
Access Bio	EUA for CareStart COVID-19 Antigen Home Test chromatographic, digital immunoassay
LumiraDx	EUA for SARS-CoV-2 Ab Test (total antibodies test)
Phase Scientific International	EUA for Indicaid COVID-19 Rapid Antigen Test
NYU Langone Health	510(k) clearance for Genome PACT genetic test for solid tumors

Report: Nearly 7 in 10 Physicians Now Employed by Hospitals and Corporations

Once upon a time, a medical degree was a ticket to life-time self-employment. That no longer seems to be the case—at least not the "self" part of the phrase. For years, hospitals and health networks have been gobbling up physician practices at increasing rates. And now a new study from the Physicians Advocacy Institute (PAI) finds that, as of the beginning of 2021, just 30 percent of all physicians in the U.S.

are practicing medicine independently. The remaining 70 percent are employed by hospitals, private equity firms, health insurers or other corporate entities.

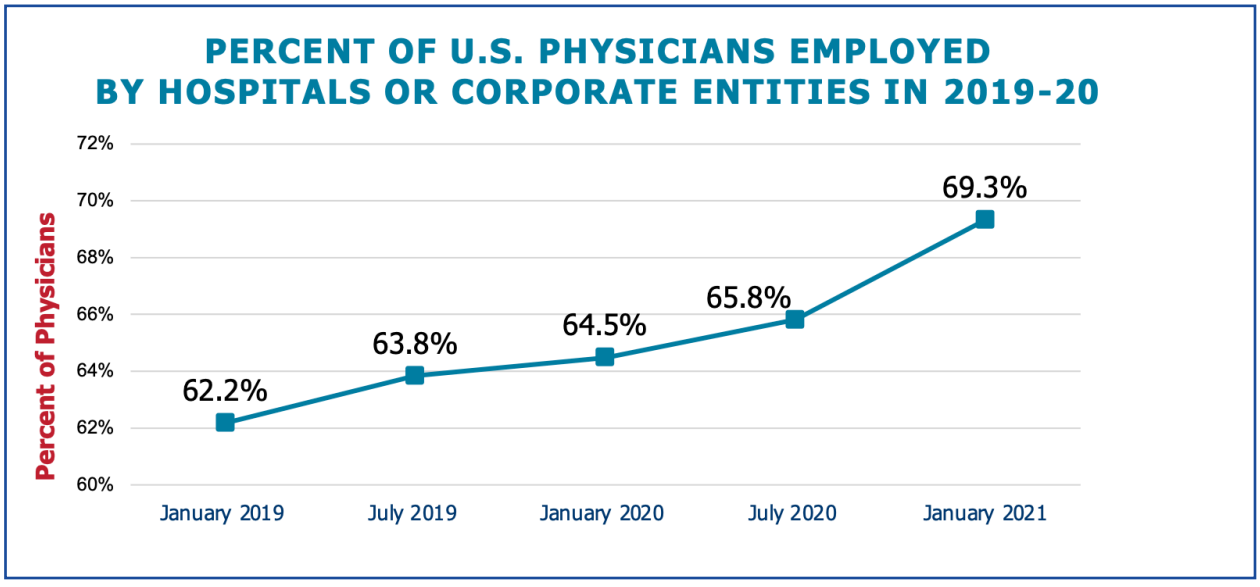
Whither the Independent Physician?

In addition to being a fixture of the U.S. health care system, the independent physician has been a part of Americana itself perhaps best captured in the paintings of Norman Rockwell. But now that familiar family doctor has become a nostalgic memory from a long bygone era. Thanks to consolidation, most of today's doctors are part of a corporate network. In addition to depersonalizing the physician-patient relationship, consolidation throttles competition, dampens medical practice innovation and drives up costs and health care spending.

The PAI Study

For nearly a decade, PAI has worked with Avalere Health to study the impact of hospital and health system acquisitions of physician practices in the U.S. Their collaboration began in 2012 when the mass exodus of physicians from independent practice began in earnest. By 2018, 44 percent of U.S. physicians were employed by hospitals or health systems, compared to just one in four back in 2012. The trend continued in 2019 to 2020, but with a new twist as hospital systems and corporation began aggressively scooping up independent physician practices.

The new PAI study documents the impact of the latest trend. The headliner is the finding that the percentage of physicians employed by hospitals and corporate entities has grown steadily since 2019 and now stands at 69.3 percent.



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Report: Nearly 7 in 10 Physicians Now Employed by Hospitals and Corporations, *from page 5*

Other key findings from the PAI study:

- From 2019 to 2020, 48,400 physicians left private practice and became employees of hospitals or corporate entities;
- Hospitals and corporate entities, including venture capital and private equity firms and insurance companies, now own nearly half of all the physician practices in the U.S.;
- The sharpest increases (32 percent) occurred during 2019 and 2020 driven by acquisitions of physician practices by health insurers, private equity firms and corporate entities;
- The COVID-19 pandemic accelerated corporate ownership of physician practices and physician employment by hospital systems and other corporate entities in the last half of 2020;
- There is a steady trend toward increased employment and hospital ownership of practices in every region of the nation, with some differences in the types of acquisitions driving regional consolidation.

The COVID-19 Impact

All regions of the country experienced continued growth in physician employment and practice acquisitions throughout the two-year study period that accelerated in the last half of 2020, suggesting a country-wide COVID-19 impact. During that period:

- The percentage of hospital or corporate-owned practices increased between 20 percent and 29 percent;
- The percentage of hospital or corporate-employed physicians increased between 9 percent and 15 percent;
- Acquisitions by corporate entities increased between 44 percent and 59 percent; and
- Corporate employment of physicians increased between 19 percent and 40 percent.

The Midwest led all regions in hospital employment at just over 60 percent, the study finds. The South has the highest percentage of corporate-employed physicians at more than 23 percent, and has also experienced the biggest increase in corporate-employment with more than 40 percent growth.

A Call to Action

Left unchecked, consolidation threatens to render the independent physician endangered, or even extinct, the study argues. To preserve the species and enable physicians who choose independent practice to sustain private medical practices, new government policies are needed to level the playing field. More transparency and oversight into corporate acquisitions

of medical practices is needed to protect patients, the study authors argue. "Regardless of the practice setting, physicians should retain clinical autonomy to provide high quality, cost effective care for their patients."

Takeaway

On July 9, just 10 days after the PAI published its study, President Biden issued an Executive Order calling on the Department of Justice (DOJ), Federal Trade Commission (FTC) and other federal government agencies to vigorously enforce the antitrust laws and rein in the corporate consolidation threatening competition in different markets, including health care. Although it does not specifically address medical practice acquisitions (since these transactions are typically too small to bring the DOJ and FTC into play), a strong federal policy to combat consolidation in the health care industry will provide impetus for state and local lawmakers to consider the kinds of policy changes the PAI study recommends.

Testing Trends: FDA Regulation of COVID-19 Testing Enters a New Phase

The public health emergency (PHE) is still in effect but the honeymoon has ended. The leniency that the U.S. Food and Drug Administration (FDA) has displayed toward COVID-19 tests and test makers through much of the coronavirus crisis has been replaced with a more business-as-usual approach. Simply stated, the agency is tightening up and increasing regulatory scrutiny over COVID-19 tests, including those that have received Emergency Use Authorization (EUA).

No More Mr. Nice Guy

Throughout the PHE, FDA officials have insisted that its extensive use of the EUA process and various measures to liberalize rules with regard to pooling, asymptomatic screening, at-home sample collection, non-laboratory setting validation and other aspects of COVID-19 test development and approval represent an expedient to bring desperately needed SARS-CoV-2 diagnostics to market rather than a fundamental change in regulatory approach and philosophy. But as the development of a robust pipeline for new tests obviates the need for flexibility, the agency has signaled its determination to resume normal scrutiny.

In a recent interview with Medscape magazine, Dr. Patricia Cavazzoni, Director of the FDA Center for Drug Evaluation and Research (CDER) acknowledged that EUA represents a "different sort of standard when it

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Testing Trends: FDA Regulation of COVID-19 Testing Enters a New Phase, *from page 7*

comes to deciding whether to make a therapeutic available." At the start of the pandemic "we had nothing." However, she continued, "we're in a very different place now where we have therapeutics. . . And so now we're in the space where our benefit/risk calculus also has to consider the fact that we have some effective therapeutics out there, and that obviously serves as context for how we look at the data."

FDA Takes Actions Against COVID-19 Tests

Although they address COVID-19 therapeutics and clinical trials, Dr. Cavazzoni's remarks apply equally to SARS-CoV-2 testing. Exhibit A is the agency's recent spate of enforcement actions targeting test makers. It began in late May, when FDA issued a Class I recall, the most serious kind, of the Lepu Medical Technology SARS-CoV-2 antigen test and Leccurate SARS-CoV-2 antibody rapid test. The agency cautioned against using the products, which were sold directly to consumers, because of their high risk of false positives.

In August, FDA issued a warning letter to Vivera Pharmaceuticals for marketing unapproved COVID-19 tests. The agency claims it found offerings for a pair of unauthorized tests on the Mission Viejo, Calif.-based company's websites, including the COVx-RDA Saliva Antigen Test and a COVx-RDA Nasal Antigen Test. Vivera's COVID-19 test kits are considered adulterated and misbranded, the agency said, adding that it is taking urgent measures to stop the sale of such products during the pandemic.

Revocation of EUAs

Starting in late May, the agency has also revoked about a half dozen EUAs for COVID-19 tests. In most cases, these actions were undertaken in response to the company's request. These revocations include (in chronological order):

- The RT-PCR assay developed by the US Centers for Disease Control and Prevention (CDC), the first COVID-19 test to receive EUA, after the agency actually withdrew the EUA, recommending that laboratories that were still using the test transition to a test that can differentiate the coronavirus from influenza viruses;
- Gravity Diagnostics' Gravity COVID-19 Assay, which the company had retired in favor of a modernized test methodology;
- Curative's Curative-Korva SARS-Cov-2 Assay, which received EUA in April 2020 as the PHE was beginning, but which was subject of an agency alert warning for false negatives earlier this year;
- BioFire Diagnostics' BioFire Respiratory Panel 2.1, which subsequently gained *de novo* clearance, making EUA no longer necessary; and

- Guardant Health's Guardant-19 COVID-19 assay, in response to the company's request following its strategic decision to get out of COVID testing and return its focus to oncology.

Takeaway

We have entered a new chapter in FDA regulation of COVID-19 tests. Although the EUA channel remains very much intact, the agency is signaling its intention to return to normal review procedures and standards as early as conditions permit. In the meantime, test makers are also reviewing their own COVID-19 testing products and strategies. In some cases, as with Guardant Health, that means withdrawing from COVID-19 and refocusing on core products. Others like BioFire and Curative are going in the other direction in favor of product evolution and improvement and shedding early EUA products along the path to innovation.

DTC: Quest Teams with Cloud-Based Platform to Provide COVID-19 Molecular Test Results to Travelers

As proof of COVID-19 vaccination and/or negative molecular test results morphs into a passport for air travel and attending live events, laboratories with the capacity to generate rapid and reliable tests and results on an expansive geographic scale will be in growing demand. Quest Diagnostics has been quick to recognize and take advantage of this opportunity by becoming a laboratory test provider for TrustAssure.

The TrustAssure Platform

Created by CLX Health, a developer of cloud-based solutions owned by SiriusIQ, the TrustAssure Global Testing Platform collaborates with physicians, clinics, hospitals and other providers in 5,000 U.S. and 15,000 global locations to provide test results to travelers and meeting attendees needing COVID-19 clearance to go through with their plans. Quest will become the first national provider of molecular COVID-19 testing to participate in TrustAssure.

The newly announced Quest/CLX Health collaboration will enable individuals to use the TrustAssure platform to schedule test appointments at Quest patient centers and more than 750 retail pharmacy partner locations across the country. Customers will know that they will get their results within 48 hours, which means they will have enough time to secure in advance the "passport" they need to fly or attend the event.

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DTC: Quest Teams with Cloud-Based Platform to Provide COVID-19 Molecular Test Results to Travelers, *from page 9*

The DTC Collaboration

The new deal is in many ways an ideal strategic collaboration: CLX Health secures Quest's massive molecular testing capabilities to bolster its solution. In turn, Quest gets to leverage the TrustAssure platform, which integrates the IBM Digital Health Pass, to reach the air travel and live events markets.

"COVID-19 testing is a powerful tool for providing insights that can foster safer environments," noted Cathy Doherty, Quest senior VP and group executive, clinical franchise solutions and marketing. "As COVID-19 restrictions are lifted around the country and world, our collaboration with TrustAssure will allow us to facilitate high-quality testing for individuals looking to get back to recreation and travel."

Takeaway

This is hardly Quest's first venture into consumer empowerment over laboratory test results. The company was among the first diagnostic information services provider to offer free online access to test results. The laboratory giant also offers the MyQuest mobile app and patient portal enabling consumers to access and track their test results, as well as the QuestDirect service providing tests for various health conditions, illnesses and infections.

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affecting the cardiovascular system, such as cardiac channelopathies, cardiomyopathies, aortapathies, hypercholesterolemias and structural diseases of the heart and major blood vessels. Accordingly, genetic testing is often used to inform diagnosis, clinical management and prognosis of cardiovascular disease. Tests can be performed diagnostically in individuals suspected of having a cardiovascular genetic disease or to gauge risk for a relative of someone with a pathogenic or likely pathogenic variant and cardiovascular disease.

There are a number of existing guidelines and best practices for cardiovascular genetic testing. But very few of them focus on the pediatric setting. That poses a problem to the extent that infants, children and adolescents are a vulnerable population that poses unique challenges. These include both ethical issues stemming from this population's lack of capacity to provide legal consent or assent and clinical issues associated conditions that might not pose a risk until adulthood.

The AHA Recommendations

With these considerations in mind, an AHA working group set out to analyze the existing literature and practices and develop a set of

recommendations for pediatric cardiovascular genetic testing. Their findings are set out in the scientific statement published in the August 2021 issue of *Circulation: Genomic and Precision Medicine*. Specifically, the statement makes five key points.

1. Need for a Multidisciplinary Approach

According to the statement, genetic testing should always involve comprehensive pre-testing and post-testing counseling. Ideally, such testing should occur in or in partnership with a specialized multidisciplinary setting that includes cardiology experts, medical genetic experts, genetic counselors and other healthcare providers. "Because of the central role that a patient-specific comprehensive clinical evaluation plays in determining whether gene testing should be done, and what scope of testing is ideal, engaging teams of specialists who can support this evaluation is important," noted first author Andrew Landstrom, a Duke University School of Medicine pediatric cardiologist and cardiovascular geneticist.

2. Limit Diagnostic Testing to Children at High Risk

The statement also cautions against improper utilization. In general, pediatric genetic testing for cardiovascular conditions should be guided by likelihood that the disease may present in childhood, the potential for mortality during childhood, the availability of therapies, and the family's values. "Genetic testing should be done in the context of a comprehensive clinical evaluation which is tailored to the child, their medical history, and their family's medical history," notes Landstrom. Specifically, genetic testing for purposes of diagnosis should be considered in children with a high likelihood of disease, to the extent that test results, in many cases, can help refine clinicians' diagnostic suspicions and guide treatment options.

3. Limit Risk-Predictive Testing to Children of Family Members with P/LP Variant

Risk-predictive genetic testing should be performed in children after identification of a pathogenic/likely pathogenic (P/LP) variant in a family member with disease. This is particularly true in cardiomyopathies that carry a high positive yield on diagnostic genetic testing, i.e., hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy. Similarly, risk-predictive genetic testing should be considered early in childhood, particularly when disease is likely to manifest before the child is able to provide assent, and therapies or other preventive measures can be implemented for at-risk children.

4. Timing of Testing Should Account for Disease Characteristics

According to the AHA working group, the timing of genetic testing in children should take into account disease-specific considerations of

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disease penetrance, the likelihood of pediatric disease presentation, the availability of effective therapies or lifestyle modifications, and the possibility of psychological distress in the family attributable to uncertainty.

The authors suggest that parents wait to conduct risk-predictive genetic testing for an adult-onset disease until the child reaches adulthood or is old enough to participate in the decision-making process and provide assent. However, some conditions can develop during childhood and even for adult-onset conditions, there may be lifestyle changes or therapies that can be started at a younger age. In the case of children with a family member with genetically confirmed familial hypercholesterolemia (FH), they suggested that risk-predictive genetic testing be conducted as well as lipid screening.

5. The Importance of Follow-Up

Finally, the statement stresses that continued follow-up of genetic test results is important to re-evaluate or confirm variant pathogenicity over time, as well as to address the changing needs of the patient and family as genomic and precision medicine evolves.

Takeaway

Genetic testing has proven its clinical value in detecting and informing treatment of heritable cardiovascular diseases. However, all patient populations are not the same. Specifically, the existing guidelines and practices that pertain to adult patients are not necessarily suitable for use in infants, children and adolescents. The value of the AHA scientific statement is in being among the first to recognize that and seek to adapt the general standards for use of genetic cardiovascular testing in a pediatric setting.