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Dennis J Dietzen.

Unleashing the Power of Laboratory Developed Tests: Closing gaps in COVID diagnosis and beyond.

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Randye Kaye:

Hello and welcome to this edition of "JALM Talk," from *The Journal of Applied Laboratory Medicine*, a publication of the American Association for Clinical Chemistry. I'm your host, Randye Kaye.

The COVID-19 pandemic has incurred a need for widespread diagnostic testing to rapidly identify and isolate patients with active SARS CoV-2 infection. However, commercially available test kits have proved insufficient to meet demand owing to limitations and manufacturer supplies as well as the timeline required for FDA review and authorization or approval of test products.

In contrast, Laboratory Developed Tests, or LDTs, are tests that are internally developed and validated at the performing laboratory. LDTs may allow clinical laboratories to fill the testing gaps during the COVID-19 pandemic and in other clinical scenarios where commercial tests are scarce.

An editorial published in *The Journal of Applied Laboratory Medicine* highlights the value of Laboratory Developed Tests in the context of the COVID-19 pandemic and warns of the dangers of overregulation of diagnostics. This article will appear in the September 2020 issue of JALM and is available online now.

The author of this article is Dr. Dennis Dietzen. Dr. Dietzen is a Professor of Pathology and Immunology and Pediatrics at the Washington University School of Medicine and is the Medical Director of Laboratory Services at St. Louis Children's Hospital. He is the immediate past president of AACC and is an Associate Editor for JALM. Dr. Dietzen was actually a guest on our very first JALM podcast. So, welcome back, Dr. Dietzen.

Dennis Dietzen:

Thank you.

Randye Kaye:

Let us begin here. Would you provide some background on Laboratory Developed Tests or LDTs, what are they and when and how are they used?

Dennis Dietzen: Sure. I would be happy to. So, LDTs--the old name, the old-fashioned name for these tests were homebrewed tests and some people still refer to them as such. But they are tests that are developed by individual laboratories for usually for a restricted local population and what that means is, all the ingredients, all the instrumentation that's necessary to perform a test is collected and put together by the laboratorians and then the test is validated on site and is maintained on site.

So, there are commercial reagents within those tests. But those reagents are deployed in an expert way by experienced laboratory technologists and scientists to make a laboratory test out of them. So, it is not something you buy off the shelf that has got all the ingredients in it and you push a button and make happen, it is much more complicated than that. So, that is typically what they are.

In my experience, they are used in at least three different situations. They are used in situations where there are no FDA-cleared or FDA-approved tests. I happen to work in a children's hospital. So, the rare diseases, the rare metabolic diseases that we diagnose, nearly all of the testing that are done to diagnose and follow those patients has to be done with Laboratory Developed Tests because there are simply no other alternatives to those tests.

Other circumstances where you might find yourself needing a Laboratory Developed Test are, if you have an FDA-approved test, but you know it has a significant flaw in it, you will not want to use that FDA-approved test. So, what you might end up doing is, creating your own test or modifying that FDA-approved test to serve better in your clinical population.

So, it might be as simple as running a set of reagents on an open channel on one of your automated chemistry analyzers. But again, you may be using a commercial piece of equipment and some commercial reagents, but you have varied that test enough that you need to redefine its performance characteristics and its diagnostic characteristics. So, that's situation number two.

Situation number three I think, is maybe the most important, and that is, laboratorians sit at the interface between medicine and technology, and within that that interface laboratorians know when there's a significant advance in the diagnosis or treatment of a disorder that may require a new test to help the physicians either prescribe treatment or follow the course of that disease. So, that is the third situation is in those gaps that develop and the pace of our improvement in the pathophysiology, understanding the pathophysiology of disease these days is tremendous.

So, laboratorians are charged with a lot of things. And one the things that we should be doing is monitoring the development of medicine and then plugging in diagnostics where they need to be plugged in.

Randye Kaye: All right, thank you. Wow. That is a lot of instances. So, when they are available, you know, how are the FDA-approved diagnostic tests different from the LDTs?

Dennis Dietzen: So, FDA-cleared or FDA-approved diagnostic tests are typically manufactured by companies that have a large installed instrument base, and they have to scale up the production of reagents to supply those instruments and they are supplied nationwide and they are supplied worldwide.

So, as part of the FDA approval process, the performance characteristics of those assays are gleaned from clinical studies, but the FDA approval process is also one that monitors the manufacturing capability of those reagents. So, multiple lots might be used in those studies. How accurate are those reagents from lot to lot? How precise are those reagents from lot to lot?

Some FDA-approved tests are approved on the basis of their equivalents to a preexisting FDA-approved test, but some FDA-approved tests go through a process called, a premarket authorization or a PMA or premarket approval. And those tests go through a little more rigorous clinical diagnostic accuracy assessment as well.

LDTs today, they are built and validated in a single laboratory for usually a restricted set of patients. So, all of the analytic performance characteristics and the clinical performance characteristics are determined by the performing laboratory and the FDA is typically not involved in that at this point.

Randye Kaye: All right, thank you. In light of all that, are the FDA-approved tests, are they safer to use than LDTs?

Dennis Dietzen: I think that is what some people would have you believe. Is the FDA process very rigorous and are those FDA-approved tests very safe? Yes, they are. But LDT is also are, there are many, many, LDTs that are in service today and thousands of tests every day get performed by LDTs and if you look hard enough, you can find situations where LDTs have been misused. Sometimes, you know, the validation process is at fault. Sometimes, there is a communication with physicians that is not optimal, that causes physicians to misinterpret those results, but FDA-approved test also have faults.

A decade or so ago, there was a problem with an HCG assay by one of the commercial manufacturers that caused false positive pregnancy diagnosis or false positive possibilities of

tumors. And so, this caused a big problem and every year there are dozens and dozens and dozens of FDA recalls every year on those reagents.

So, there is a lot of safeguards built into FDA-approved diagnostics, but they are not perfect. And the 510K process as it is known, which is used in situations where, a manufacturer can gain approval by comparing itself to a preexisting FDA-approved diagnostic, if that preexisting FDA-approved diagnostic is itself faulty, then you actually proliferate the problem in the FDA-approved test. So, I do not think it is fair to say that FDA-approved tests are safer than LDTs. There are risks in both setups.

Randye Kaye: All right. Thank you. And let us talk about the current COVID-19 pandemic, what role have the LDTs played in that?

Dennis Dietzen: I think the current situation and one of the things that prompted me to write the editorial for *The Journal of Applied Laboratory Medicine* was the spotlight that LDTs should get in this set of circumstances. So, usually LDTs are performed on a very small subset of patients, for example, for rare diseases. But in this pandemic the development and the light shone on the LDTs has been particularly intense because of this pandemic.

Early on in the pandemic, the only reagents made available to do diagnostic testing for the novel coronavirus COVID-19 were distributed to public health laboratories, and the supply was not great. It turns out there was some contamination in some of those reagents that hindered their development and hindered their use.

So, what happened is, a lot of laboratories in really record-breaking time, sourced reagents from various manufacturers to extract nucleic acid, to amplify nucleic acid, and detect the right amplified PCR products to detect COVID-19.

And this all happened—sometimes LDTs can take weeks to months to years to develop, and this all happened in a matter of days to weeks. And those LDTs, the local LDTs in many academic medical centers and in many private laboratories have been the only eyes that public health officials have had on the development of this test. The results from this test are incredibly important in determining how to treat patients, how to isolate patients and how to deploy caregivers in these situations with the proper protective equipment on them, so they can know who they are treating and if they are infected or not.

So, the role that LDTs have played in this current pandemic cannot be overstated any more than I am doing right now. It is just been incredibly important and it is been the only

eyeballs that we have had on most of this pandemic for a long time. Now, there are a number of commercial reagents approved under emergency use authorization by the FDA that are now coming into the marketplace that are helping with the capacity to test.

And importantly, the reopening of a lot of the of the economic activity of the country is going to depend on our capacity to do a lot more of these tests.

Randye Kaye: Yeah. Testing is huge, a huge issue in the news mentioned in almost every article. And your article mentions that there are some in Congress who have called for a greater FDA oversight of the LDTs. So, tell me a bit about this proposed regulatory framework?

Dennis Dietzen: Right. So, this has been percolating for a number of years in Congress. So, traditionally, the FDA has used what it calls enforcement discretion around Laboratory Developed Tests, which means, it pays attention to some but by and large, it does not pay attention to too many of these LDTs. But there have been some high-profile cases in which the use of LDTs has probably been abused.

So, a number of members of Congress are rightly concerned about the quality of laboratory testing and they have proposed that the FDA take a much larger role in regulating these particular tests. Typically, LDTs and the practice of LDTs in the laboratories is overseen by CMS via CLIA regulations, and those regulations stipulate what characteristics you need to understand about the test, the accuracy components, the QC components, and the proficiency testing components that are a critical part of any Laboratory Developed Test.

So, by bringing the FDA into this, it creates a second regulatory structure for those tests that has not existed before. Keep in mind that many of these tests are very, very, complicated. Some of them are very simple, but some of them are quite complicated. So, the questions that the AACC has and many of us that practice and deploy many LDTs, our concerns surround, you know, does the FDA have sufficient enough capacity to oversee this? Does the FDA have enough expertise to oversee this? What we think is at high risk of happening is, we're going to create a secondary regulatory structure that will require laboratories that do LDTs to develop another set of quality assurance, a parallel process for QA and QC of these particular tests, that will put a burden on the individual laboratories and the way that the FDA has proposed to accommodate this new regulatory oversight that they have, is to charge those laboratories user fees, which will drive up costs.

So, I think the key message here is that, many of these LDTs, you know, these are not highly profitable things. In the laboratory, developing LDTs is not for the faint of heart. We have to source reagents and we have to make sure that we have a supply line for those reagents; when we get new lots of an individual component of that reagent system, we have to be very, very, careful about what that does to the performance of the assay.

So, I think the risk here by bringing a second regulatory structure into this is that the two regulatory structures may not complement each other and they may contradict each other, in fact, and it will drive up the cost and burden of performing these tests, which again, are critically important in a variety of very specific patient populations. So, by driving up that cost, it may make it much more difficult for laboratories to build and maintain these LDTs and I think the people that suffer under those circumstances are patients.

Randye Kaye: Absolutely, and you may have already answered this, but I just want to check and see if you have anything to add, lastly about why this regulatory framework around the LDTs current and future is so important for clinical laboratorians?

Dennis Dietzen: Right. I think all laboratorians whether or not they deploy LDTs or not should be keenly aware of what is happening in this regulatory space. This is the ground, LDT is a ground where laboratorians innovate. Laboratorians are in a position to understand the developments in clinical medicine and the new needs for diagnostics and prognostic indicators in the practice of medicine.

Laboratorians are highly-trained individuals. To do an LDT, you must be certified to manage a high complexity laboratory. These are MDs, these are PhDs with years of experience in analytical chemistry and biochemistry. And so, giving them the tools to innovate is capable of driving better patient care and better innovation. This is the ground where laboratorians innovate and we want to be able to preserve that environment where laboratorians innovate. And in fact, many people say, that the LDTs of today will be the FDA-approved tests of tomorrow.

So, I think it is highly important that we are aware of what is going on in Congress around these regulations. And again, what we are not, both the FDA regulation of in vitro diagnostics at the FDA and the regulation of LDTs in CMS, I do not think that the Association and I do not think we are saying that those systems are perfect, and they probably do need to be refined. But I think, we have to be careful as we refine those, so as not to overburden laboratories and make it impossible to innovate when it comes to taking care of patients.

Randye Kaye: All right. Thank you. A very important and timely article. Thank you for joining us again, Dr. Dietzen.

Dennis Dietzen: You're very welcome.

Randye Kaye: That was Dr. Dennis Dietzen from the Washington University School of Medicine describing his JALM article, "Unleashing the Power of Laboratory Developed Tests, Closing Gaps in COVID Diagnosis And Beyond." Thanks for tuning in to this episode of JALM Talk. See you next time and do not forget to submit something for us to talk about.