FDA: Overseeing, Overarching, Overreaching

Article:
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Guest:
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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. My name is Randye Kaye, and I'm your host.

Today's podcast will focus on the issue of laboratory developed test, or LDT, regulation. This has been first and foremost in laboratorians' minds since October 2014, when the FDA released its draft guidance, a framework for regulatory oversight of laboratory developed tests. This document proposed that the FDA enforce oversight of LDTs using a risk-based approach. This could require laboratories that use LDTs to submit data to the FDA for independent review and evaluation of the assays' clinical and analytical performance claims in the population in which it will be used.

Now, while laboratories are committed to reporting the highest quality results, the concern is that this process could stifle implementation of new clinically important tests and thereby hindering patient care. Further, this could place a large burden on laboratories that may not have the personnel or the financial means to proceed with such a submission to the FDA.

Our guest today is author of the article titled, "FDA: Overseeing, Overarching, Overreaching," and that's published in the July edition of JALM which focuses on the use of LDTs in pediatric patients. He is Dr. Dennis Dietzen, Professor of Pediatrics and Pathology and Immunology at Washington University School of Medicine in St. Louis where he has directed the Core Laboratory and Metabolic Genetics Laboratory at St. Louis Children's Hospital since 2002. Welcome, Dr. Dietzen.

Dr. Dennis Dietzen: Thank you very much, Randye.

Randye Kaye: Dr. Dietzen, what are some of the ways pediatric laboratory medicine is different from adult practice?

Dr. Dennis Dietzen: So there are some really obvious ways it's different. I think the most obvious are things like, we deal with a lot less blood than adult laboratories, and that poses its own challenges. But the patients also cause a considerable number of challenges. Newborns in particular have physiologies that are changing on a minute by minute basis, so a cohort of one day old babies is very, very different from one another than it is to -- it's not a homogenous cohort of babies at all.

Many of the diseases that we deal with are very rare, so we see one of them a year or a handful of them in a month or so. It's not like you've got in an adult emergency setting, for example, wherein you have a lot patients coming in with chest pain that might signify myocardial infarction. The population is very heterogeneous in that way.

There's a considerable amount of pressure, too, in the pediatric laboratory world where the diagnosis and therapies that we have, they're not just short term things. If we don't do our jobs well, a misdiagnosis or lack or slow implementation of therapy or something like that, can have a long-lasting impact on the patient's cognitive capacity and physical capacity going forward. A lot of this is what is driving the AACC's focus on reference intervals for pediatrics.

We also have a fair number of specimen misadventures that adult populations have, but not at the frequency that we do. For example, newborn specimens tend to have a higher rate of hemolysis. And nurses in particular who are taking care of small babies are often, they understand the value of the circulating blood volume and they'll cheat a little bit and when they pull a sample out of a line, it will get diluted a little bit. So we always have to be on guard against specimen misadventures and other pre-analytic variables that might impact the quality of our data.

Those are just a few of the things that we have to keep our eyes open for in pediatrics.

Randye Kaye: Okay. Thank you. The variability's really high. The stakes are really high. So I can see there definitely are some differences there.

Dr. Dennis Dietzen: Absolutely.

Randye Kaye: Why are laboratory developed tests such an essential component of pediatric practice?

Dr. Dennis Dietzen: I think one of the primary reasons for this is the rarity of the diseases that we treat. It becomes a financial issue. The market size is very, very small. It's similar to therapeutics for rare diseases. There are programs to promote the development of therapeutics for rare diseases because there is often not very much of a profit motive, and the diagnostics world is no different. If there are specific disease-based tests that happen to a handful of babies in a year, no diagnostic manufacturer is going to be able to make a large sum of money off of that market.

In essence, in the laboratory, if there's a need for those diagnostics, we need to develop those ourselves. Furthermore, the interpretive criteria of those are awfully hard to come up with as well too. There are no huge clinical trials when you're dealing with a handful of cases in a year.

So we can use, and do use, diagnostics that are targeted for adults for some of these situations but none of them, typically, or very few of them have specific FDA clearance for pediatric populations. We have to do a little bit more work on those assays and techniques that are developed for adults, because the specimens are different and the clinical setting is different in the pre-analytical variables are different.

So anyway, virtually all of the tests we do on many of our automated platforms might be considered LDTs, because we're using them in a population for which they're not cleared. So just as diseases, as therapeutics for rare diseases require special attention, the diagnostics for those diseases also require special attention.

Randye Kaye: That's a lot of work then to get that done?

Dr. Dennis Dietzen: Absolutely.

Randye Kaye: So you're developing, validating, maintaining LDTs, can you give us an idea of what's involved in that, in a nutshell?

Dr. Dennis Dietzen: In a nutshell.

Randye Kaye: I'm sure there is a lot.

Dr. Dennis Dietzen: These are not simple projects to pull off. There are a number of things to consider. The first thing you need to consider, the materials that you need for a test. The laboratorian is the individual that has to make all these decisions and scour the literature and scour the commercial landscape for the materials that are necessary to do these things. Luckily, there are a large number of suppliers out there that can help us, but there are some issues.

For example, the starting materials, if it's an analyte, if it's a calibrator we need to worry about the quality of that. We need to worry about the purity of it. We often need solvents and buffers and calibrators. But in addition, when you start the project, you need to ensure that that supply chain of those reagents is going to be there on a long term basis. You can't start a project like this and then in three months have your supply of solvent that you're using dry up or your supply of calibrator that you're using dry up. And furthermore, you are the person that has to assess when a lot of one of these reagents changes from a manufacturer, you've got to do extra due diligence to make sure that that lot change doesn't have a negative consequence on the technique.

The second issue is the instrumentation that you use in these techniques. A lot of times, the instrumentation is not designed for the clinical laboratory. We have a lot of instruments that are designed for the clinical laboratory and designed to be very user-friendly and have minimal maintenance and have up times of days, weeks, months before they have to go down for maintenance. The instrumentation we use is often not designed with the clinical diagnostics in mind. So we need to make certain that we have maintenance folks nearby that are qualified to maintain these things, that can troubleshoot them when there are failures, and that are easy enough to use for technologists who are often doing many other things during the day. So the instrumentation, the materials are important.

Then the validation process is certainly like many other validation processes but it's much, much deeper because we have to characterize much more of the technique than we would if we bought a commercial product. We have to assess the accuracy, the traceability to other techniques. We have to make sure that the patient matrix and the calibrator matrix looks similar when we do this. We have to, for our accreditation purposes from the College of American Pathology and CLIA, we have to come up with a way to do proficiency testing for some of these things where there are not a large number of laboratories doing these things.

And finally, if you need it in a disaster situation, you need to have a backup plan. What are you going to do if one part of this process fails, what are you going to do? It's quite the undertaking already. It's not for the faint of heart, and it requires what I call a lot of care and feeding once it's built. But once it's built and people are trained on it and we get used to the characteristics of the method, we can usually perform these long-term without any undue consequences.

Randye Kaye: Right. It sounds like there is a lot more below the surface that people realize?

Dr. Dennis Dietzen: Yes.

Randye Kaye: It's a lot on your shoulders and unexpected obstacles can pop up all the time if you're not really careful.

Dr. Dennis Dietzen: Absolutely, at any time. Even after you're done characterizing it, those obstacles can pop up.

Randye Kaye: Wow. Is there anything else you can or want to tell me to describe the role of some specific LDTs in pediatric medicine?

Dr. Dennis Dietzen: I'll give you two examples of why we do this. And I mentioned both of these, I believe, in the article in *The Journal of Applied Laboratory Medicine* in the editorial that will be published in the summer. There are two prime examples that I'll mention. We do LDTs for two big reasons. One, is we generate methods where they don't exist and the other one is, we have to fix methods that don't work for us.

The first case, I'll give the first example, is a method where they exist, so I'll use the case of metabolic disorders. These are disorders that have a rather nonspecific phenotype but can have long-lasting damages for infants and small children depending on the disease and depending upon the age of presentation. These diseases are a series of hundreds of disorders, so you can't possibly have a single test for each one of these disorders. So what we do is we have a number of very large analytic profiles to detect as many of these diseases as we can. We do amino acid profiles, we do acylcarnitine profiles, and we do organic acid profiles, which detect hundreds of metabolites. These are not, for example, those three profiles are not three LDTs, those are hundreds of LDTs because many of these are quantitative and each one of those analytes represents a specific quantitative analysis for the diagnosis of one of these diseases. We have to build these from scratch.

So we happen to do many of these on a mass spectrometer so the selection of a mass spectrometer is important. The selection of standards and extraction solvents is important. We do this now in the context of confirming disorders that are presumptively diagnosed on newborn screening. And we also diagnose many of these in many patients in a de novo sort of situation for diseases that aren't covered by newborn screening.

So again, missing these has bad consequences. Missing these will result in a delay in dietary treatment or other

specific therapy that will often allow kids to grow and develop normally despite these metabolic disorders.

The second example that I will use is where we have to fix a method that's not appropriate for our patient population. And the one that I note in the editorial is clinical drug screening. Drug screening has been done in our hospital and in many hospitals, pediatric and adult alike, for decades using immunoassay-based detection. These immunoassays are imperfect for a number reasons, one reason is that they cross-react with a number of legal substances and therapeutic substances that might look like they're illicit on a drug screen. So all screen-positive immunoassays specimens must undergo a second round of testing which results in delays and can potentially -- action sometimes has to be taken before those secondary results are returned.

The situation in a pediatric hospital for example puts -- that situation puts our population of physicians that we refer to as child protection physicians in a very ugly quandary. For example, if they choose to believe that the child has been exposed to an illicit substance, they have to do something about that. They have to investigate where that might have come from. In some cases, they may decide to temporarily remove the child from the home environment. And if they're wrong, they might get sued. On the other hand, if they ignore that particular result that suggests this child has been exposed to something and they're wrong then harm can come to the child and eventually, they might get sued again.

The solution we have here is we have done away with immunoassay screening, and we've gone to a mass spectrometry-based screen that in one round of testing, it detects a broad number of substances. So the menu of substances that we can detect is much larger than the typically immunoassay menu. We can turn it around in real-time, in an hour to two hours or so. So the child protection physicians and other physicians have that information at their fingertips when they're making these important decisions.

So those are just two examples of the LDTs that we employ here to take care of kids.

Randye Kaye: Great, and you've really spelled out the value of those and how important they are.

Dr. Dennis Dietzen: I hope so.

Randye Kaye: Definitely. So with all the value and importance of these LDTs, if the new regulations imposed by the FDA, how would that impact pediatric patient care?

Dr. Dennis Dietzen: I think the main fear that has been noted in the literature is the fear of more requirements for registration and documentation and data generation, but we're already experiencing something very different. What we have experienced here in the last few months is the threat of new FDA regulation has sent manufacturers into a corner where they are hesitant to provide the instruments and the reagents that we need to perform these particular tests. These tests have been and are part of everyday patient care. And when manufacturers are now starting to pull out of a commitment, that leaves us in a very unfavorable situation when it comes to taking care of our patients.

So we've run into two situations already where we've tried to replace a couple of pieces of instrumentation that are very old and prone to failure. In some cases, instrument manufacturers will note that we are a pediatric institution and that their particular piece of equipment, despite the fact that we're already using an older version of their piece of equipment, they are citing the FDA regulation as a reason that they cannot sell us that piece of equipment. Despite the fact that these regulations have not been adopted yet and not been published in any formal way, they're already having an impact on what manufacturers will sell to us.

Another manufacturer who -- we have their equipment in our laboratory now and we use it to assess the hemostatic state of many patients who are on artificial circulatory devices like ECMO for example. We use these in protocols that are spelled out throughout the hospital in a very, very formal way. And we wanted to add to our number of instruments that we're using for this purpose because of the volumes that we're encountering and they simply, without saying it verbatim, they have delayed the process and indicated to us that they would rather not sell us that instrument, because of the threat of the FDA coming after them for selling into an environment where they're not supposed to sell in. We might potentially be hit on both sides, from the supply side and from the regulatory side. It already has made our life here exceedingly difficult and then promises to make it even more difficult going forward to the point where many laboratories, I suspect, will think twice about offering this sort of testing, which will be a detriment particularly in the case of metabolic disorders where timely diagnosis is extremely important. It will lead to the detriment of patient care.

Randye Kaye: All right. So ultimately, the patient and their family will suffer and already possibly suffering even from the threat of these regulations. Is that right?

Dr. Dennis Dietzen: We are. I can't point to a specific instance at this point where it's harmed a patient, but we've been in situations where we lack the capacity to do a few of these tests and data has certainly been delayed by this.

Randye Kaye: Okay. Thank you so much. The rest I guess is in the article.

Dr. Dennis Dietzen: Yes. I think you got a good taste for what we've encountered recently. It's frustrating because as manufacturers, they're not interpreting the FDA's intent here in a consistent way. A number of manufacturers, when one manufacturer says, "No, I cannot sell you this," I will go ask another one and they say, "Yeah. We have no problem doing that." But it becomes important when a change in manufacturer is not necessarily a very simple thing to do. You can't swap out one manufacturer's instruments for another set, and expect to proceed in a seamless fashion without interrupting the supply of data. I think this is becoming a level of frustration where we have to ask before we do anything, "Will you sell us this piece of equipment?"

Randye Kaye: Dr. Dietzen, thank you so much for being with us today.

Dr. Dennis Dietzen: You're very welcome. I'm happy to help.

Randye Kaye: That was Dr. Dennis Dietzen from St. Louis Children's Hospital at Washington University School of Medicine in St. Louis, talking about the JALM article, "FDA: Overseeing, Overarching, Overreaching" for this podcast.

Thanks for tuning in for "JALM Talk" and we'll see you next time. Don't forget to submit something for us to talk about.