Point: The Need for Additional FDA Regulations in Laboratory Medicine. Counterpoint: Why the FDA Should Not Regulate Laboratory-Developed Tests

Articles:
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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 Association for Diagnostics & Laboratory Medicine. I'm your host, Randye Kaye.

While many routine tests performed in U.S. clinical laboratories are regulated by the FDA, other tests, referred to as laboratory developed tests, or LDTs, are modified or developed, validated, and performed in a single laboratory. Laboratories often use LDTs to fill clinical needs that cannot be met with commercially available tests that have gone through FDA review. Currently, LDTs are not regulated by the FDA, but fall under CLIA regulations. CLIA, which has not been substantially modified since 1988, requires that laboratories assess specific performance characteristics of LDTs in order to use them for patient testing. Due to significant advances in testing methodologies over the past few decades, the FDA has sought to enforce regulation of LDTs similar to the way that it regulates commercially available in vitro diagnostics. The introduction of this type of regulation could be burdensome and expensive for clinical laboratories, and therefore, controversy exists as to the most appropriate way to regulate LDTs.

The January 2024 special issue of *JALM*, entitled "Molecular Testing in Medical Practice: Challenges and Triumphs of the Genomic Age," features a Point-Counterpoint article pair that debates FDA regulation of LDTs. Today, we're joined by the authors of the Point-Counterpoint articles. Dr. Eric Konnick is an Associate Professor and Associate Director of the Genetics and Solid Tumors Lab at the University of Washington in Seattle. Dr. Konnick authored the Point article, "The Need for Additional FDA Regulations in Laboratory Medicine." Dr. Marco Leung is a Clinical Director at the Steve and Cindy Rasmussen Institute for Genomic Medicine at Nationwide Children's Hospital and an Assistant Professor at the Departments of Pathology and Pediatrics at the Ohio State

University College of Medicine in Columbus, Ohio. Dr. Leung authored the Counterpoint article, "Why the FDA Should Not Regulate Laboratory-Developed Tests."

Welcome, Dr. Konnick and Leung. Firstly, what are some of the arguments that have been made as to why laboratory developed tests should be regulated by the FDA?

Eric Konnick: So, there have been a lot of arguments that the agency has made as to why laboratory developed tests should be regulated by the FDA, and one of the key ones is accuracy of results. And so there have been multiple claims that the FDA has made over the years that there are LDTs that are on the market that have provided incorrect results where it could have affected patient care. Some good examples, there was a document the FDA released back in 2015 that was citing 20 examples of tests that they said performed poorly. Unfortunately, some of those examples were tests that were actually never used on patients or the examples they used, it was actually a medical decision that was being made, it wasn't actually the test result that impacted things. So whether or not the agency would even have jurisdiction over something like that is uncertain. But again, those are the claims that have been made.

Another example that has been cited is what has been called the different playing fields argument, where basically manufacturers have to go through the FDA in order to market and distribute their devices to laboratories for them to use, versus laboratories that develop their own tests don't have to go through that same process. They, under CLIA, are allowed to modify FDA-approved or -cleared kits and if they go through validation processes for that or for tests that they create, they can use those on their patients as well. So there's this perception that that gives laboratories advantage over manufacturers, if you will. I think it kind of neglects the fact that going through the FDA is a really expensive and time consuming process, and it may work for a manufacturer that has a limited number of tests. But many laboratories have thousands of tests on their menu with hundreds of laboratory developed tests. And so the scale is quite different. It's looking at a test-specific lens rather than a practice-specific lens. But again, those are two of the common arguments you'll hear.

Randye Kaye: All right, thank you. So let's get to those. So, Dr. Leung, what are some of the arguments for maintaining the current regulatory structure under CLIA?

Marco Leung: Yeah, so the FDA traditionally regulates manufacturers who produce kits that are mass produced, box marketed, and distributed. However, laboratories performing LDTs, they're not manufacturers and they do not distribute a product, but

instead, they're really performing a professional service using laboratory methods performed by laboratory personnel who render the diagnosis and are liable if there is an incorrect result.

So, for this reason, CLIA's regulation focusing on processes and credentialing are much more important, whereas the FDA's regulation focusing on manufacturing activities are not really appropriate in the LDT setting. Second, the addition of the FDA regulation would really increase the cost to develop and launch new diagnostic assays. This, in the grand scheme of things, may be a minor fraction of the total development cost for common analytes for a large market, however, the high cost would be a disincentive for rare disease assays, especially in community hospital or academic centers, where these tests are performed a few times a month. Another argument for maintaining LDT regulation under CLIA is the feasibility of additional test review workload by the FDA. If the FDA were to review all the high-risk testing, including most of the genomic assays, it is very unlikely that the FDA has the adequate resources to process test application. And that was the case during the pandemic. The FDA could not handle the high volume of the emergency use authorization application for SARS-CoV-2 testing, leading to delays in application reviews and patient access and testing. So, these are just some of the examples of arguments for maintaining the current regulatory structure under CLIA.

Randye Kaye: All right, thank you. So, we have your arguments, let's talk about the data, what data are available, Dr. Konnick, to support the claims that increased FDA regulation is needed.

Eric Konnick: Yeah. So this is actually kind of a difficult area, because recently, back in October, the FDA released a proposed rule to regulate laboratory developed tests under the medical device authorities. And in that extensive document, they cited a couple of papers that they said really provided justification. And so if you just look at their justification, yeah, it may sound like there's data out there, but as you actually dive into the papers that they cited as strong evidence, it gets a little murky. For example, one of the papers they cited was looking at mutations in lung cancer and whether or not tests that had gone through the FDA would do a better job than the laboratory developed test that was used in the clinical trials. On its surface, it looked like maybe the manufactured test did slightly better and would identify more patients. But the hard part was that it really wasn't an apples-to-apples comparison, because the test that was used in the clinical trial, yeah, it was a laboratory developed test, but it was in Europe. And so it actually wasn't even subjected to the CLIA regulations. And as best I could tell, going through all the original data and manuscripts, I couldn't tellif

it was in a CLIA certified lab. So to say that's a laboratory developed test is a little disingenuous.

And then the other part that was kind of interesting is that to adjudicate differences, they actually used a laboratory developed test to decide the winner, if you will. But it wasn't clear if the test was actually validated for the use that they wanted. So they were using an unvalidated LDT to decide whether or not an LDT performed well. So it's just one of those things where the data just aren't clear. And every single example you go through in that document there are problems as you get into the data. So I think just backing up and saying, well, if this is a proposed rule that's going to go through the executive branch and impact the industry, this is probably the best data that's available. I assume that the FDA has done their homework and really tried to find the best examples, and there really aren't a whole lot of examples. There aren't a whole lot of data in the literature that we can find, especially once you peel back the headlines. So it is a challenge.

Randye Kaye: Okay. So on the other hand, are there data to support the effectiveness of the current regulatory system? Dr. Leung?

Marco Leung: Yeah, I would say in addition to data, there are actually a lot of different real-life examples that would support the effectiveness of the current regulatory system. The current system really allows clinical laboratories to update the testing while maintaining patient safety. As you guys know, we have new literature that comes out all the time and the current LDT mechanism really allowed laboratories to reliably translate new scientific discoveries into clinical care. And this really allows patients to benefit from the latest breakthroughs in medical science without sacrificing test quality. Also, in addition to innovation, the current regulatory system also allows laboratories to adapt and pivot, especially during the various challenges in desperate time. During the pandemic, a lot of different items on the shelves, including reagents and consumable, like pipette tips and nasal swap collection kits, they were all impacted by the supply chain issues, and many of them were not available for laboratories.

So that really delayed the testing results and negatively impact patient care. Now, under the current CLIA regulatory framework, many laboratories were able to find alternative reagents and consumables and able to quickly validate them to ensure test quality and continue availability. So this approach allows laboratories to minimize delay to patient care. So in other words, the effectiveness of the current LDT system really enables this flexibility. While the IVD, in vitro diagnostic kits, under the FDA regulation would not allow that.

Randye Kaye: All right, thank you. Now, many who are against FDA regulation of LDTs, they still support some type of updates to the current system. What alternatives to an FDA centric regulatory scheme have been proposed?

Eric Konnick: Yeah, so, many in this area have recommended updates to the CLIA program for many, many years, including ADLM and Association for Molecular Pathology, Association for Medical Genetics, et cetera. And so that's been something that's been advocated for a long time. But we really didn't have a solid proposal until recently, when the Association for Molecular Pathology got together a group of experts in this area and recommended some changes to the CLIA regulation. So that's something that's just been released within the last month or so for public review. And so I think that something to recognize is that we already have quite a bit of regulation that laboratories are subject to, and we've been subject to it for decades. And unfortunately, the regulations were created back in the 1980s with some minor adjustments, but for the most part, they're pretty much the same. And I think both Dr. Leung and myself could attest that the things that we do every single day for our patients didn't even exist when the current regulations were conceived of. So really just taking a look at those regulations and making them more applicable to modern practice, I think, as most practitioners would agree with.

The other thing is to look at what are the things that we do well and what are potential changes that need to be made so that any potential concerns can be addressed. And we already have a very robust proficiency testing requirement for most of our laboratory tests, whether they're FDA cleared or approved or laboratory developed, they're all subject to proficiency testing multiple times per year. And so really making that program much more robust and making it required for a lot of the testing that we do routinely now, I think, would be really critical. And one of the shortcomings that the group saw with CLIA is that, again, it hasn't been updated. So really make that part of the program going forward, that, get the experts together on a regular basis and cadence and look at the practice and make it so that when we're practicing in 15 or 20 years, the regulations have kept up with the practice.

And so that's the most recent thing that we've seen. We've also seen calls for CLIA modernization going back almost a decade. There have been proposals that have been floated in Congress. They haven't gone through the entire process, but it's been something on people's minds for a very, very long time. A reasonable alternative, and again, splitting the regulation between multiple agencies, it's going to be very difficult for laboratories to navigate because they're going to have requirements that are different between the two

regulatory agencies and having to have duplicate infrastructure and increased costs and things like that. So a lot of us who are in this space think that updating the current regulatory paradigm is the most efficient way to move forward and provide our patients with the accurate and rapid results that they've become accustomed to.

Randye Kaye: Thank you. Yes, change happens for sure and the 80s were a long time ago. So, finally, how do you think this FDA regulatory framework will affect medical education?

Marco Leung: Yeah, so, as mentioned earlier, the FDA's plan to regulate clinical tests as devices would unequivocally incur additional financial strain to the laboratories, especially to the non-profit laboratories and the academic medical centers. Now, the residents and fellows in pathologies and genetics, they spend a significant amount of time of their training in academic medical center laboratories, and this is the place where they learn test development for different diseases. And because academic medical center laboratories are already operating on small margins with low reimbursement rates, the financial strain created by the FDA regulation would force many of the laboratories to halt testing, to halt offering the low volume tests, such as the test for the rare diseases, or the labs would even shut down altogether. So this would consequently affect the training programs and therefore the available workforce and pipeline of the board certified laboratory personnel in this country.

Randye Kaye: That was Drs. Eric Konnick and Marco Leung discussing their Point-Counterpoint articles on FDA regulation of laboratory developed tests from the January 2024 special issue of *JALM* entitled "Molecular Testing in Medical Practice: Challenges and Triumphs of the Genomic Age." Thanks for tuning into this episode of *JALM* Talk. We'll see you next time. And don't forget to submit something for us to talk about.