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# Help Us to Help You: Recommendations for Continued Enforcement Discretion for Common Infectious Disease Test Modifications under the FDA Final Rule

**Article:**
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**Guests:** Dr. Kyle Rodino from the Perelman School of Medicine and the Hospital of the University of Pennsylvania and Dr. Erin Graf from the Mayo Clinic Arizona.

Bob Barrett: This is a podcast from *Clinical Chemistry*, a production of the Association for Diagnostics & Laboratory Medicine. I'm Bob Barrett. In May 2024, the FDA released its Final Rule that defines clinical and public health laboratories as test manufacturers and classifies laboratory-developed tests as devices requiring approval by the FDA. The Rule further states that modifications to FDA-approved tests, including use on a specimen type not included in the manufacturer's instructions for use, also require FDA approval. This has profound implications for clinical laboratories as most have insufficient resources to shepherd their laboratory-developed or modified tests through the FDA approval process.

While many areas of the clinical laboratory are affected, the impact on clinical microbiology labs would be particularly severe. Determination of antimicrobial susceptibility, evaluation of specimens from patients outside the manufacturer-defined age range, testing of specimens not defined in the manufacturer's instructions for use--all of these play an essential role in patient care but would be discontinued to comply with the FDA Final Rule.

Now, in a late-breaking development, just before this podcast was recorded, the Final Rule was vacated in U.S. District Court, which stated that the FDA lacked statutory authority to regulate laboratory-developed tests.

A new opinion article, appearing in the May 2025 issue of *Clinical Chemistry*, highlights the ways the proposed Final Rule would have negatively impacted clinical microbiology laboratories and advocates for the exclusion of common tests from FDA oversight. With the rule now having been vacated, the regulatory landscape looks dramatically different. How should laboratorians respond to this news and how can we learn from this experience to improve dialogue between clinical laboratories and regulatory bodies?

In this podcast, we welcome the article's lead and senior authors. Dr. Kyle Rodino is an Assistant Professor in the Perelman School of Medicine and Assistant Director of Clinical Microbiology at the Hospital of the University of Pennsylvania.

Dr. Erin Graf is an Associate Professor and Co-Director of Microbiology at the Mayo Clinic in Phoenix, Arizona. And Dr. Graf, let's start with you. This FDA Final Rule amending regulation of laboratory developed tests is complex. Can you give a high-level overview of the Rule?

Erin Graf: Sure, and thank you for having me on this podcast. I'm sure the *Clinical Chemistry* audience is quite familiar with the LDT Final Rule. But just briefly, the document published by the FDA that spends more than 100 pages justifying the change really boils down to just a simple phrase that expands their prior definition of in vitro diagnostic products to now include when the manufacturer, and I'll use air quotation marks, "manufacturer," is a laboratory.

So, in essence, under the Final Rule, FDA equates individual laboratories who internally validate testing procedures, equates them to commercial manufacturers, who then become subjected to all the financial and administrative burdens associated with FDA clearance or approval.

So, of course, this is a massive problem as the vast majority of institutions that perform LDTs for patient care simply can't afford such a burdensome regulatory structure. So, this has generated tremendous concern and outreach and then obviously, lawsuits, which we'll get to coming up.

Bob Barrett: So we are recording this the first week of April. And just this week, there was news on two lawsuits challenging the FDA Rule. Can you summarize the ruling, Dr. Rodino, and how that impacts enforcement of the Rule?

Kyle Rodino: Absolutely, and thanks as well for giving me the opportunity to join the podcast. So, the lawsuits that you're referencing were brought by the Association for Molecular Pathology and American Clinical Laboratories Association. And they challenged that the FDA actually has the authority to implement the referenced Rule. On March 31, the U.S. District judge that was overseeing the case ruled to quote, "vacate and set aside the rule in its entirety," which means that they've ruled in favor of the two societies challenging the lawsuit and stated essentially that the FDA does not, in fact, have the regulatory authority over laboratory-developed tests, and challenged the definitions they used as LDTs being devices, and also as these individual laboratories being manufacturers. And essentially said that those definitions were inaccurate and linking the regulatory oversight of in vitro diagnostics to LDTs by using that premise was false.

So, they effectively ruled that the FDA misinterpreted their authority or used some sort of agency overreach in putting together this new rule and kicked it back basically to the

secretary of HHS, recommending that the Rule not be implemented.

Now, the final, I guess, outcome of this ruling is unclear. There could be multiple things that follow. There, of course, could be an appeal, there could be something new from FDA, there could be something new from the secretary of HHS. But at least in the moment, I think the win that we're all celebrating here is that minimally, the deadlines for compliance that were placed upon us in those timelines are at least paused, but effectively erased at this point.

Bob Barrett: What was the genesis of this opinion article?

Erin Graf: The genesis of the article came from a meeting, a scientific meeting called the Clinical Virology Symposium that took place in October of 2024, around the time that the lawsuit was filed. And I think it's also worth pointing out there were a number of societies that signed an amicus brief, including ADLM, as well as the American Society of Microbiology, the group that runs the Clinical Virology Symposium, ASM.

And so, at that time, we knew that the lawsuit was filed, but weren't sure how things were going to go from there. There was a panel discussion on the Final Rule, including myself and Dr. Jonathan Genzen from ARUP, and others, and Kyle. Actually, Dr. Rodino asked a great question about the Final Rule is overly rigid in terms of the scope for which FDA would regulate LDTs as devices, including even minor modifications to FDA cleared tests. So, things like an alternative sample type would be considered actually an LDT under this Final Rule, and therefore, subject to the full weight of that FDA oversight.

So, the thought from Kyle was, "Can we get together as professionals and make a case for what we consider standard-of-care modifications?" So, these are not modifications for which clinical validity needs to be established. These are modifications that have well established clinical validity in the literature. And so, that focus became this opinion piece, which includes a discussion of a lot of those modifications in a table format in that article.

We broadened the ask of our community to say, "You know, what are we missing? What are we not thinking about? What should we be including in this? What is not esoteric testing, but what is really truly standard-of-care modifications?" So, a great example would be *Mycobacterium tuberculosis* PCR. *Mycobacterium tuberculosis* is obviously a very significant global pathogen and something you want to diagnose rapidly. There's only one FDA-cleared test that's commonly used in the United States and it is limited to sputum specimens. So, many labs across the US and globally have modified that

assay to include alternative sample types like bronch lavages, which is a different method of collecting a lower respiratory tract specimen, as well as things like cerebrospinal fluid for diagnosis of tuberculosis meningitis.

So, these are again well established in the literature in terms of their clinical validity. And so we made an argument that these should continue to be under what FDA called enforcement discretion, whereby they would not actively regulate, but they would sort of hold and reserve the power to potentially regulate downstream. Now, of course, with the vacating of the Final Rule, some of this may become not as relevant as it directly ties to that Final Rule. But it is food for thought, which we'll get to for how we might want to approach future types of LDT-associated regulation.

Bob Barrett: The opinion article proposes enforcement discretion for common modifications to FDA-approved and -cleared infectious disease diagnostics. Can you explain modification in this context and summarize your proposal?

Kyle Rodino: Absolutely. So, Erin did a great job of introducing that concept. But a modification in this context is really defined as any deviation from the manufacturer instruction for use, or package insert, of a test that has been approved by the FDA. When they go for FDA approval, all of the exact details of what types of samples, on which patient populations, in which clinical context, all of the nitty-gritty technical details are outlined in the submission to the FDA. And then when approved, those become basically set in stone in those package inserts or instructions for use.

And the intention there is that the laboratory running the test follows that direction to the letter. So, a modification is anytime you deviate from that. So, Dr. Graf already referenced expanding acceptable sample types for the TB example, but you could also modify say, the stability. Maybe it says that the sample is good for seven days and you can test within a seven-day window, but your laboratory for some need may validate an extended window, say 14 days. Or, really detailed items like sometimes package inserts come with manufacturer-specific approved transport medias.

And theoretically, if you use a different manufacturer's transport media, like a different viral transport media, you are off the label, and that could be a modification, although a minor one. And a really big one that's included in the article is about patient populations. Many assays are evaluated only in adult populations because evaluating them in children would be overly burdensome or in some cases ethically questionable. And so, they say that this assay has not been evaluated in patients under the age of X. However, we need

to use those tests in those patient populations and when you do so, that is a modification.

So, again, to sort of reiterate the proposal is that there are lots of examples of standard-of-care modifications. There are expectations from our patient facing colleagues that we have these tests available to perform that type of testing on these, sometimes guideline indicated cases. And really the point here is to outline what our field collectively agrees are acceptable modifications that could really be potentially, in the future, you could imagine a pathway where they could be additions to the instructions for use and reduce that burden on the individual laboratory to validate them themselves.

Bob Barrett: Well, finally, now that the Rule has been vacated, what are your laboratories doing in response? How have your efforts shifted with, with this news?

Erin Graf: So, you know, everyone's kind of taking a breath and celebrating this victory. And I think the importance here is to not just let down our guard and go back to business as normal. You know, this has been looming for quite some time. I want to say I was in fellowship when the first round of these kind of heavy-handed attempts came out. And luckily that was struck down, but then there was VALID that circulated and so something is definitely going to bubble up next. So, we have to be ahead of what that is.

I think it's a time with our professional societies, as well as our institutions, to decide what we think regulation of LDTs, if necessary at all, should look like. Should we be looking at CLIA and the language within CLIA to help us potentially better capture some of the laboratories that may need some quality improvement? I think across our different disciplines, we could all point to some commercial for-profit independent reference laboratories that probably need some additional scrutiny and some regulatory oversight, but certainly not under something as burdensome as what the FDA had proposed.

I think working within professional societies to further parse out exactly what Dr. Rodino and I discuss in this document, which I should also acknowledged as supported by ASM, by the American Society for Microbiology, and something we're actively working on, is what do we think we need in the future? Do we need any regulation at all? Or, can we continue to sort of self-regulate under CLIA with the accreditation procedures that we have?

Kyle Rodino: Yeah, and those are all great points and I share that focus now too. I'll say that locally, we had been mapping out our timeline to compliance and we made it here. Just a month from now, we would be talking about phase one compliance

deadline. So, we had been putting in place our plan of a stepwise fashion of addressing compliance for May 6, 2025. And while we did put some effort there, I want to say that I feel like that was in no way wasted with the news. It actually, I think, brought this conversation really to the forefront. Talking about it in the department a lot more than we were in the past, really getting somewhere, I think, from our regulatory and compliance group on what it would take to comply and just where we sit in thinking about what was being asked of us and what may be asked of us in the future.

How can we continuously improve? And while, I think, we were in a great place to be compliant with this phase and some of the next ones, because we've been putting that effort in all along, it has given us the opportunity to ask like, "Where could we do better in our everyday work?"

And then just to add on to sort of what you were mentioning about globally, the focuses now shift to like what's next, and what is better, and where could further regulation help? I think my focus has shifted to what is at the crux of this whole issue. Could we very clearly define the problem we are trying to solve? And could we answer what regulatory addition solves that problem and provides benefit to patients? Because I think ultimately this is about quality and patient safety and exemplary diagnostics. And I think we really need to look at what we can do in a more surgical fashion.

So, the FDA quoted a number of sort of examples and popular culture situations. There are some anecdotes and published studies that really did have patient impact or bad outcome. But we need to recognize that, of course, that is the minority of the diagnostic process and laboratory medicine, that the vast majority of our clinical laboratories are implementing, running, and resulting fantastic diagnostic assays. So, I think the focus is really like, instead of this sort of blunt object approach to regulation, where do we need to improve the most? How do we set up a fair system in order to do that? And, is there a way to have a really refined, and again, like surgical approach, to improving laboratory-developed tests where they need to be?

Erin Graf: I'm glad you said that, Dr. Rodino. And I do want to emphasize that point, that there's a missing perception of quality, and lab is always the behind-the-scenes partner in patient care, but there is a misperception of the high-quality testing and care that we provide every single day.

And so, how do we, I think that's part of this too, is how do we, again, I think through our professional societies, help change that view? How do we help patients understand better what we do, how we do it, the care and the quality that we put into the work that we do? I think that will be key as

well in kind of the future state of things, is how do we change that perception to recognition of the high-quality work that we do?

Bob Barrett: That was Dr. Erin Graf from Mayo Clinic Arizona in Phoenix, Arizona, and Dr. Kyle Rodino from the University of Pennsylvania in Philadelphia. They authored an opinion article in the May 2025 issue of *Clinical Chemistry,* recommending continued FDA enforcement discretion for certain commonly modified infectious disease tests, and they've been our guests in this podcast on that topic. I'm Bob Barrett. Thanks for listening.