LDT thoughts offer nuance, and advice

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August 2024—Two roads diverged in a regulated wood—and here comes Joe Lennerz, MD, PhD, happy not to be traveling both.

As Dr. Lennerz, chief scientific officer of BostonGene, considers this spring's final rule from the FDA that regulates laboratory-developed tests as medical devices, he's also kept an eye on the range of responses to the agency's actions.

One path is, broadly speaking, reactive; the other, proactive.

He sees himself as a traveler on the latter road. This is perhaps unsurprising; he readily acknowledges he has professional sympathies with oversight agencies. He's on the federal advisory panel for the Centers for Medicare and Medicaid Services. He also helped launch a group, the self-evidently named Pathology Innovation Collaborative Community, that includes FDA participation. "So I've been involved—let's call it active collaborating—in this with the agency [FDA] for a number of years, at least since 2018," he says.

His motive is simple, his stride confident: "You can wait for regulation—guidance, final rules—to drop. Or you can become proactively involved. I am not reactionary. I always look to talk to the agency rather than criticize them."

Dr. Lennerz knows his views will not win him many votes. "I realize my position isn't always the most popular," he says with a laugh, "because it aligns closely with the FDA's perspective. I believe it's the right approach."

Dr. Lennerz may be one of the more sanguine voices that have emerged on the topic. Others are feeling quite bilious. But like everyone else, he too is searching for answers and guidance and trying to predict what changes might lie ahead. As the dust settles, what is the best foot forward?

That first step might be to take a closer look at the final rule, with its rough-edged realities, rather than dashing into action.

Dr. Lennerz says the current version of the final rule evolved into a much more meaningful version than prior versions, including what was put out for public comment last fall. It is longer and more detailed than he expected it to be. "But it still leaves a lot of room for interpretation." In his read of the situation, the FDA took seriously comments from laboratory professionals, leading to unanticipated and welcome changes.

Nevertheless, he adds, "There are certainly some glaring, underappreciated complexities."

William G. Morice II, MD, PhD, president and CEO of Mayo Clinic Laboratories and professor of

laboratory medicine and pathology, Mayo Clinic College of Medicine and Science, has likewise been cogitating on the topic for some time. He chaired Mayo's Department of Laboratory Medicine and Pathology from 2015 to 2023, and he's the board chair of the American Clinical Laboratory Association. ACLA and member company HealthTrackRx filed a lawsuit against the FDA in late May, challenging the final rule.

Dr. William Morice of Mayo Clinic: "The challenge we have is the clinical laboratory lives very much at the intersection of technology advancement and health care advancement." That calls for a more collaborative approach, he says, if laboratories are going to work with regulators. Photo: Dean Riggott

It should surprise no one that the FDA has stepped up its game, Dr. Morice says, adding that many were disappointed when the VALID Act didn't pass at the end of the 2022 legislative session, including the FDA.

He refers to the waiting period between last fall and the final rule's publication as a roller coaster. The proposed rule seemed onerous, and the comment period was, in his view, short. "I think labs across a number of organizations, including CAP, did a great job of getting comments to the FDA." But the silent

period between the proposed and final rules was knuckle-biting.

Diana Cardona, MD, MBA, associate professor of pathology and associate director of Duke Health clinical laboratories, recalls waiting and worrying with her colleagues. “At Duke alone it probably would have been well over 600 tests that we would have to figure out, okay, what level of risk are they? Do we need to submit something to the FDA? Do we just stop offering that test?”

“We were,” Dr. Cardona says, “just trying to understand the scope of what that lift was going to be.”

Many fears diminished somewhat when the final rule was published. “There were things that were surprising,” Dr. Morice says, including the continued enforcement discretions. “So when the final rule came out, I think there was a sense of—I don’t want to say ‘relief,’ that might be too strong of a word—but there were things that labs wanted to see” that are indeed part of the final rule.

But the ride isn’t over. Dr. Morice says the four-year phaseout is short. “It’s still a very tight implementation timeline, probably to line up with the next funding cycle for the FDA. And there’s still a lot of administrative burden on laboratories.”

And even though the final rule might seem similar to what was proposed with VALID, legislative action would have created a helpful framework for the FDA to abide by, Dr. Morice says. Now, with the FDA asserting LDTs are medical devices, “all those different enforcement discretions are exactly that. The reality is, with the final rule, it’s still within the FDA’s purview to end any of those things at any point in time. The rules could change, essentially.”

Also worth noting is that even as these specifics are playing out in laboratory medicine, the broader regulatory landscape is also shifting. Two recent U.S. Supreme Court decisions (*Loper Bright Enterprises v. Raimondo and Relentless, Inc. v. Department of Commerce*) overturned the Chevron deference doctrine, which will likely reshape the authority of federal agencies, including the FDA. This could have implications for device regulation, among many other health-care–related matters.

Against this larger backdrop, laboratories are delving into definitions.

What sort of parley can unfold when one group is speaking the language of laboratory medicine, and the other the jargon of regulation?

For labs, says Dr. Cardona, “It’s not just the fact that we’ve got something new as far as regulation to consider. It’s a whole new language. Laboratories historically have not had to submit for IVD 510(k) clearance. That’s not what laboratory medicine is focused on. There’s going to be a steep learning curve for anybody involved in this.”

Take the word “grandfathered.” Like a weary member of the Académie Française taking on the *le brunch*, Dr. Lennerz says it has no place in the current discourse, though the word pops up repeatedly in conversations “when you colloquially talk to colleagues” about whether current tests are affected by the final rule. It implies that certain tests will stay the same. “But that’s a large oversimplification,” he says, noting that “grandfathered” doesn’t appear in the final rule.

The first step to comprehending the final rule, he says, echoing Dr. Cardona, is knowing regulatory language. “You need that to have a meaningful conversation. That, from my perspective, is an extremely important call to action to the field: We must learn these terms. Speaking as a pathologist, we will be

affected by this, be it in industry, academia, or private practice. And you cannot just blurt something out without knowing the context."

Dr. Lennerz wades in further. In practical terms, he says, some LDTs can indeed continue to be used without going through formal 510(k) submission. "The FDA would have the right to insert themselves at any time, but they opt not to do so," he says. "That's the enforcement discretion."

But to be clear, Dr. Lennerz explains, "These are not grandfathered tests." And since the FDA considers them to be IVDs, they are subject to medical device reporting. "So you're not asked to stop your testing. You're not asked to take down your formerly known LDT, which the FDA calls IVD previously marketed as LDT. But they're asking you to at least register them.

"They want to—which I think is a logical thing to do—capture the landscape of these high-complexity tests that currently exist in the United States," Dr. Lennerz continues. "Almost like, *Let's size the issue.* Once it's captured, at least it's trackable."

And while the New York Clinical Laboratory Evaluation Program exemption offers another route for test approval, it's hardly the fast track for tests that some might have assumed it could be. Mayo Clinic Laboratories, which uses CLEP, is focused on understanding the requirements for all its LDTs and "evaluating the investment needed to do all the listing and administrative work to be compliant," Dr. Morice says. The lab offers more than 4,000 tests, about half of which are LDTs, "so we have to get all that work prioritized and accomplished and understand the workforce we have."

Mayo also develops about 100 new tests a year, Dr. Morice says. "We'll have to think about which of those tests are our highest priority items. There's going to be more investment required now for new tests that are in development. So we're reevaluating that list as well."

These tests could be tricky for the FDA to manage, too, Dr. Lennerz says. He sketches out a scenario a half-dozen years or so in the future, where premarket authorization is now the norm. What will be the approval route for emerging tests that are research use only? "Even if you would make it part of a clinical trial, you need to come up with a framework that serves this intermediate step before you can submit it to the FDA." It could be called an investigational diagnostic device, he suggests, but it would need its own pathway. "Which I haven't seen proposed yet."

It would need to be a multistep process, he says. "So you would have to do a clinical trial to see whether the test works. You discuss it with the FDA. You show them some sort of data, to be determined. Then you start executing it." Unless this gets addressed, he worries, test development could be stifled.

What other concepts will require clarification as laboratories and the FDA hike deeper into the woods?

Dr. Lennerz is quick to answer. "I think one of the most complicated issues is, what is affected and what is not? And that term 'complexity'—high-complexity versus not. That requires that you understand the CLIA categorizations." Even the term "CLIA categorizations" is interesting, he says. "It is effectively combining CLIA and FDA," with their nuanced differences.

Dr. Joe Lennerz of BostonGene says the Food and Drug Administration's laboratory-developed tests final rule is longer and more detailed than he expected it to be but still leaves room for interpretation. "There are certainly some glaring, underappreciated complexities," he says. Photo: Webb Chappell

He offers the example of what the FDA is calling a manual test, such as IHC, which is well established, backed by decades of experience. Would this require registration?

At first glance the answer appears to be "no." Nonetheless, Dr. Lennerz says, recent developments and newer markers—he cites PD-L1, folate receptor 1, and HER2-low—"have a conceptually different risk." When established technologies are coupled with weightier decisions, or when technologies are combined, "it makes sense to take individual differences into account" when assessing registration.

"If you just stain cytokeratin, and you read these manually, these new rules would not apply," he says. "However, if you stain PD-L1 and you make a companion diagnostic decision, or you scan IHC slides with a whole slide imaging system, upload them, and do a digital read, and then apply an AI tool to add an interpretation, these different layers of complexity might affect the validity of the result."

It might even seem like an existential crisis. "A cytokeratin stain might be just a cytokeratin stain," he says. But when it's applied to render a hugely impactful decision—for example, ALK translocation-specific IHC—"that is a huge deal."

By starting with the higher complexity level during the phaseout, the FDA's framework—as currently put forth—focuses on "things that might have unintended consequences" that might be caused by using newer technologies—next-gen sequencing combined with AI, for example. "So you can't just say, 'Is IHC in or out?' Because you have to know the end-to-end solution you're proposing," Dr. Lennerz says.

It's caused a lot of confusion, understandably so, he says. "People may have very practical and reasonable questions, based on their immediate area of interest: 'Can I use my Dell monitor?' That is not an easy, yes-or-no answer," depending on how it's being used. The FDA, on the other hand, "thinks about it as the quality of the whole process," with complexity linked to the intended use of a device.

"Specifically, any deviation from an approved device, such as replacing the approved monitor in a whole slide scanning system with an alternative high-resolution Apple monitor, would—under the new rule—make you the 'manufacturer' of the device, even though you didn't manufacture the monitor." That poses numerous questions that are not currently addressed in the final rule, he says.

"I would venture to say," Dr. Lennerz adds, "that many laboratories know why they use a test or device," but they haven't had to articulate it in official FDA-friendly terms.

Mayo Clinic has been looking at several major areas since the final rule dropped, Dr. Morice says.

The first is the internal preparedness of the academic department that performs clinical testing.

The second is working with academic medical centers and other labs across the country. "Many of them have not been as engaged on this issue as we have, because of our position," he says. "So we're trying to help educate other laboratories."

Labs that have a blood bank within their department already have a sense of FDA compliance, Dr. Morice notes. But for those who don't—and that's quite a few—"we're just trying to help educate and work with our colleagues and collaborators to help them understand what the lift will be, the basic know-how that's going to be needed. It's an educational component we owe our colleagues," he says, noting that groups such as ACLA and the CAP are doing similar work.

Last but not least is continuing to keep an eye on what happens with the final rule. "There's already talk that the health system exemption might be too broad," says Dr. Morice. "Do they need to have additional guidance around that?"

His colleagues in other fields—especially the pharmaceutical industry—"tell me that once the FDA steps in and starts regulating an area, it typically does not do less in terms of regulation; it does more," he says. "So we need to be watching that as well, and understanding how to advocate for the uniqueness of clinical laboratories."

That includes continuing to work with Congress to achieve a legislative solution, Dr. Morice says. "If the FDA is to regulate laboratory-developed tests, having a legislative framework specific to that task—because it's much different, in my mind, than producing a medical device—would be the ideal."

He and others will also be watching for any momentum behind reintroducing VALID.

It's even possible, he says, that momentum may build behind a lab-specific legislative package that would guide FDA regulation of LDTs. "This would give us much more surety and security than the current situation, where everything we have in terms of leniency, if you will, from FDA, is completely based on enforcement discretion, not on something specific to labs per se."

It's quite possible the FDA doesn't fully understand what it has bit off, Dr. Lennerz says. "My

speculation is the FDA will need to establish third-party review programs." Ultimately, he says, it might make sense for the agency to review the highest-complexity tests and bump tests that are less critical to other groups.

The templates and tables the FDA put out, specifying how a submission should look, will also be helpful, he says. Both might make it possible for the FDA to handle this new larger task without greatly expanding its own workforce.

(On July 10, the House Appropriations Committee approved the fiscal 2025 spending bill covering agriculture, rural development, and the FDA and related agencies and directed the FDA "to suspend its efforts to implement the rule and continue working with Congress to modernize the regulatory approach for LDTs." It's a nonbinding recommendation.)

In addition to tackling the multi-stage phaseout, the laboratory field finds

itself moving through multiple stages of acceptance (or not). "And while some are complaining," says Dr. Lennerz, "I think it's important that laboratories move toward a stage of assessment."

This entails posing the obvious questions: What tests do we have that would fall into these higher and highest risk categories? How mission critical are they for us? And then how would we report those?

Behind them lurks an even more critical query, Dr. Lennerz says.

If labs are asking, *What do we need?*, he offers an answer: "You need people who are interested in this topic."

He speaks passionately about the need for regulatory science to become part of the educational curriculum and residency programs.

The final rule not only is lengthy but also contains, by Dr. Lennerz's estimate, hundreds of concepts that are likely unfamiliar to the majority of laboratory directors. "Not because they don't want to, but because they've never learned it." And in the laboratory, "we have our own jargon." The middle of this particular Venn diagram is alarmingly slim.

He cites an example involving the many approaches that can be used to train and optimize an AI algorithm. The FDA uses the term "multireader studies," as an example, a familiar term in radiology and many other specialties. In pathology, the more usual term is "consensus studies," he says. "But consensus sometimes is a regression to some sort of abstract middle, not independent readers providing independent results." Even though these terms are well understood within different groups, the details around protocols and definitions can be applied differently.

Another example is proficiency testing. The term means one thing to those in the laboratory but something else to the FDA, which views matters through the prism of a layperson, Dr. Lennerz says—is someone proficient in a skill? (Whereas labs would use "competency" to make that people-centered assessment, he says.) "When some people read these documents, they think with their pathology hat on, without necessarily questioning if that works."

"The term 'validation' is also confusing," Dr. Lennerz says. "In the FDA world, it usually means you establish something, and verify it, and then provide the data." But in pathology, he notes, validation "is

heterogeneous from one laboratory to another."

There are also gaps in understanding the meaning of clinical validity and clinical utility, he notes. "People call something useful, but that doesn't mean you have formally proven clinical validity or utility."

When it comes to words, in short, "There's a gigantic rift between the words in the field and the agency," says Dr. Lennerz. "We must bridge that. Right now, we have four years to do it. It's a huge issue."

It's possible that both the FDA and laboratories are reluctant travelers.

But for those who insist the journey should have never begun—that the FDA shouldn't be doing this at all—"I think we've moved past that point of complaint and denial," Dr. Lennerz says.

"In my personal opinion, I've had many fruitful interactions with the FDA. They're always listening—you just have to present the data with the right words." There may be value in reforming CLIA, or suing the FDA, or reviving the VALID Act. "But I think we need to learn a lot more about the intricacies of the existing regulations, and how they would interface within this new framework, before we can make any sort of statement like, 'We should just revise CLIA.'"

"And to be honest, if you look at it from the outside, it's just looking as if we're trying to avoid something that everyone else already has to comply with," he says. "So my suggestion would be, instead of putting the effort, money, and time into those actions, it would be wiser to [be] actively looking and helping the FDA [as to] how to make this regulation meaningful."

AI's imminent arrival is reason enough for pathology to help set up the guardrails, he says. Until now, evolution has come primarily from within the profession. "But once tech giants, with all their money, absorb pathology data and put it through some sort of wringer, the errors and mistakes made by that, I think currently we're not equipped to react to that."

Nor is the FDA, Dr. Morice says, at least not now. For labs like Mayo that offer a lot of esoteric testing, there are no FDA-approved platforms for technologies such as mass spectrometry and NGS that generate a lot of data and then use AI to help guide interpretation. "How will the FDA approach that in the clinical laboratory?" he asks. "Especially as digital pathology is adopted, and large language models. The field is moving so quickly. It's more and more a part of routine laboratory testing, honestly. And there's nothing out there right now on the topic."

The arguments around lab exceptionalism can be tied back to technology, says Dr. Morice.

"The challenge we have is the clinical laboratory lives very much at the intersection of technology advancement and health care advancement." That calls for a much more collaborative approach if labs are going to work with regulators, he says.

"Laboratory-developed tests are really, in my mind, a medical service that I as a physician have been trained to provide," Dr. Morice continues. "So what's the best way to ensure quality, to ensure that patients and providers can be confident in the results they're getting? And that also includes continuing to educate the public and physicians and the provider community on the best way to use tests. We saw this a lot with COVID."

Remarkably, having testing take front and center during the pandemic has had little educational carryover, he says. “It’s kind of amazing to all of us, really. But that’s the way it is, I guess.”

If tech firms are one Bigfoot in this unfolding story, another possible partner lingers nearby, says Dr. Lennerz: the pharmaceutical lobby.

“Pharmaceutical manufacturers will definitely look toward people who can work with them on those pathways,” Dr. Lennerz says. With the FDA regulating high-complexity tests, labs face one future, two choices: “You either become a lab that is complaining and sits there, and nags about the rule. Or you have more partners in powerful positions, because you suddenly comply with the end-to-end rules of the FDA.”

In other words? “Adapt or become irrelevant,” Dr. Lennerz says.

Others are listening well beyond the lab, he suggests. As the field becomes more digitized, and bioengineers and bioinformaticians view how impactful pathology is, “having our collective workforce complaining about something that is complete standard of care in other fields might not have the intended effect.”

“I’m not saying we must embrace the rule, or embrace working with the FDA,” Dr. Lennerz hastens to add. “We should definitely continue to fight meaningless things.” But to harness newer technologies, the field needs to end any isolationist tendencies that might still linger.

“Trust me, I love my microscope,” he says. But pathology is “more of a collective. And how to regulate that to make it safe has not been the purview of traditional pathologists. Sorry, those days are over—we work in multidisciplinary teams. We have scanning technologists, NGS experts, and deal with stains. Our revenue cycle management has changed. You cannot blame any single person for doing something right or wrong. You have to have processes; you have to have quality management systems.”

All of these changes—the quality movement, explosive growth in technology, the data wave, the advent of AI—have created tremendous stress in the field, Dr. Lennerz concedes. It’s even possible that some of that stress “has been projected onto the final rule,” he says.

Which might explain another language phenomenon he’s seen. As labs respond to the final rule, their language has been unusually vibrant. In a survey Dr. Lennerz and colleagues conducted as part of the collaborative community, respondents were asked to be open in describing the problems they foresaw with the final rule. “It went all the way to frank profanity,” Dr. Lennerz says.

“If something reaches that level of emotion, there’s either something completely misunderstood, or—*or*—there is probably something very meaningful happening.”

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