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The VALIDity of Laboratory Developed Tests: Leave it to the experts?

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Clinical laboratory results influence more than 70 % of medical decisions and are a critical component of healthcare. Clinical laboratory tests may be manufactured commercially or developed within a clinical laboratory setting. In the current landscape, commercially manufactured assays, which are considered *in vitro* diagnostic (IVD) devices, go through the United States Food and Drug Administration's (FDA) regulatory submission process, and are classified based on risk. Vendor-manufactured assays may be submitted as Class I, II, or III IVD devices. Class I devices, such as rapid group A streptococcal tests, are low risk assays that may be eligible for exemption, thus circumventing the need for FDA pre-market approval. The majority of tests available in Core Laboratory settings, such as glucose, creatinine, and thyroid stimulating hormone tests, are submitted under the Class II 510(k) pre-market notification process; the 510(k) process is appropriate for tests that are low to moderate risk and complexity. High risk or high complexity tests, including molecular assays for infectious pathogens or *KRAS* and *BRAF* testing, are typically submitted as Class III devices and go through the pre-market approval (PMA) process.

Laboratory developed tests (LDTs) are designed, validated, and utilized within a single clinical laboratory to meet specific and unmet medical needs. LDTs may also encompass modifications to commercially manufactured assays, such as validating a test for an alternate specimen source (e.g., body fluid testing). Importantly, LDTs cover a spectrum of analytical methodologies and applications, and specific validation requirements and performance metrics are based on test design, methodology, and application. Subject matter experts, like board-certified clinical laboratory directors, are best poised to evaluate the methodologic, fiscal, and logistic considerations associated with LDT design, validation, and implementation. Currently, LDTs are subject to federal Clinical Laboratory Improvement Amendments (CLIA) regulations, which apply to all clinical laboratory testing performed in the United States with the exceptions of non-human and basic research, as well as clinical trials.

Historically, the FDA has exerted enforcement discretion of LDTs. Under enforcement discretion, while the agency has oversight of LDTs, it does not require LDTs to undergo the PMA process. However, over the last several years, there have been efforts to increase oversight of LDTs. The Verifying Accurate Leading-edge IVCT (*in vitro* clinical test) Development (VALID) Act of 2022 is a legislative proposal that would place all LDTs under FDA oversight. Such a change would have an impact on the patient, provider, and population level. Each LDT would need to meet both CLIA and FDA regulatory requirements, adding

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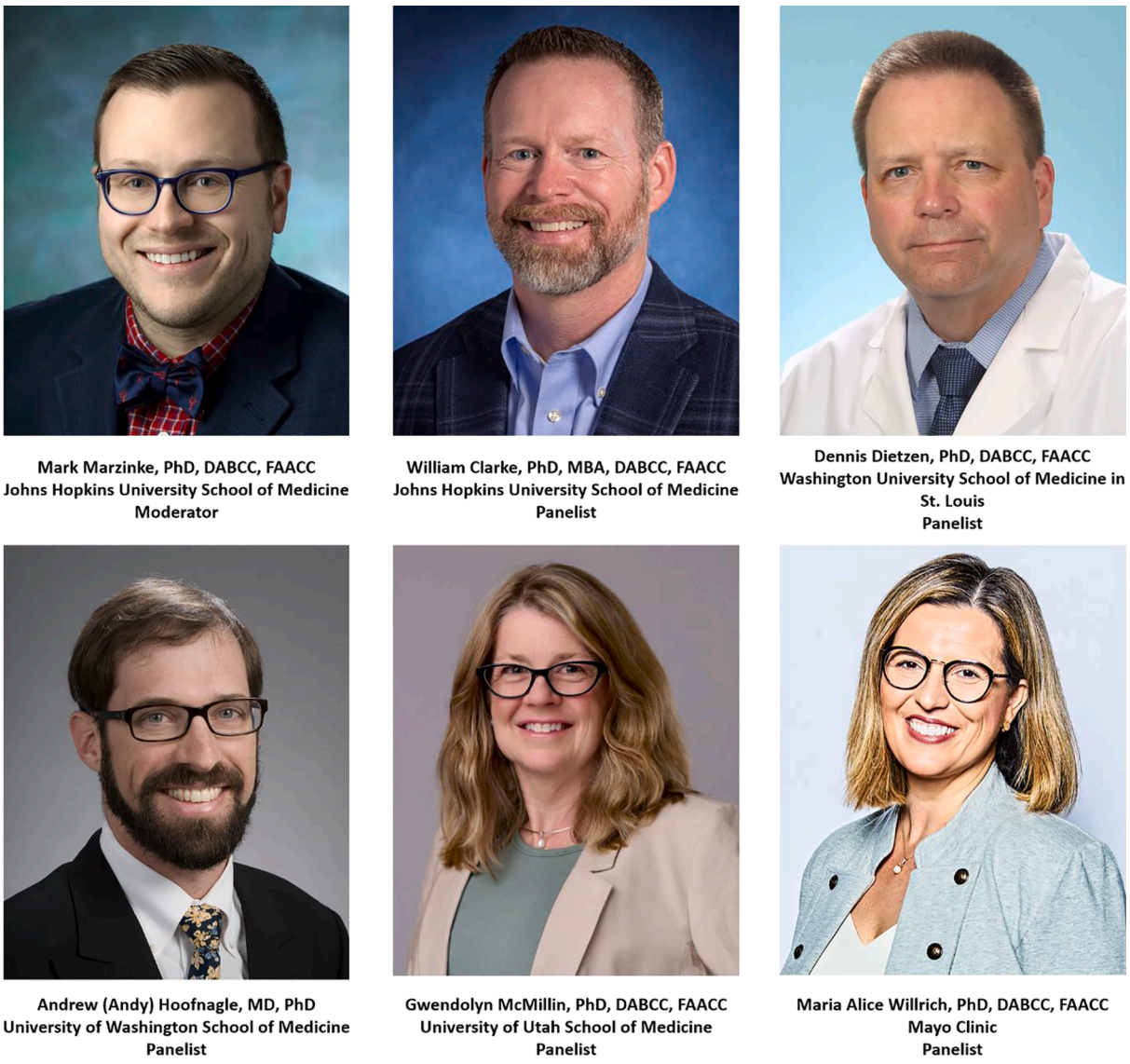

Fig. 1. Q&A Moderator and Panelists.

further logistic and oversight complexity to the LDT landscape. Due to the seismic shifts that may occur in the delivery of laboratory services under the VALID Act, or similar, future legislature, we have invited several experts in the field to share their perspectives on the utility and management of LDTs, as well as their insights on how future oversight could, or should, look (Fig. 1).

Broadly, what types of LDTs do you use in your laboratory? From your own practice, can you provide an example that demonstrates the utility of LDTs and their impact on clinical diagnosis or decision support?

William Clarke: We have many types of LDTs in our laboratory, including off-label use of moderately complex tests for body fluid testing, mass spectrometry-based tests, flow cytometry, and gas chromatography-based assays. An illustrative LDT example in our group is the use of liquid chromatography-tandem mass spectrometry (LC-MS/MS) for toxicology screening to support pain management or substance use treatment patients. In these patients, it is critical to know the drugs and metabolites present for proper interpretation, which is not possible solely with commercially available immunoassay-based screening. With LC-MS/MS, we have the flexibility to add new substances as they emerge, which is particularly important for substance use treatment.

Dennis Dietzen: The LDTs in my laboratory have a pediatric focus. Pediatric labs depend on LDTs more than other laboratories because conditions are rare, test volumes are low, and financial rewards are minimal for IVD manufacturers. Most of our LDTs employ various forms of mass spectrometry, including expansive metabolic profiles to detect inborn errors of metabolism (e.g., amino acids, carnitine esters, organic acids) and drug screening. We are nimble enough to have developed and deployed a direct-to-mass spectrometry drug testing scheme that minimizes the occurrence of false negative and false positive results associated with immunoassays. We have detected concentrations of drugs in a number of at-risk infants that would certainly have been missed using FDA approved assays, and children are safer because we can do this.

Andrew (Andy) Hoofnagle: We have developed assays using a variety of methodologies, including spectrophotometry, electrophoresis, molecular and immunohistochemical techniques, and mass spectrometry. LDTs in our laboratory are used for multiple applications, from nutritional assessments to therapeutic management of cancer to the diagnosis of infectious disease, and everywhere in between. For example, due to the recognized issues with all of the FDA-cleared or approved immunoassays, we have developed a method that uses LC-MS/MS to measure serum thyroglobulin as a tumor marker in patients after therapy. Also, due to an absence of appropriate FDA-regulated devices, we developed flow cytometric assays to monitor for residual disease in

patients treated for leukemia and lymphoma. These assays are now cornerstones of our oncology practice. Having these methods available within our hospital system allows rapid turnaround times and fosters close consultation with multidisciplinary teams to optimize patient management across the spectrum of care.

Gwendolyn McMillin: As a Medical Director at a large reference laboratory, we are involved in the development, validation, operation and maintenance of hundreds of clinical LDTs. LDTs are a major part of my daily life! One area of testing that I have been focused on for the past 20 years is newborn drug testing, intended to detect and document *in utero* drug exposures. The specimens utilized most often, due to relatively high diagnostic yield in reflecting fetal drug exposures during the last few weeks of pregnancy, are meconium and umbilical cord tissue. There are no commercially available test kits, quality control material, proficiency testing (PT) options, or even blank matrix; thus, all meconium and umbilical cord drug tests are LDTs. Test results are widely used to make important social and medical management decisions for infants, parents, and care takers. Results may influence treatment decisions for an infant experiencing symptoms of drug withdrawal, how a mother is counselled on breast feeding, and proposing post-partem monitoring plans.

Maria Alice Willrich: So many—LDTs are fundamental to our practice of medicine! For instance, at my institution, we measure kappa free light chains using a modified version of an FDA-approved test validated on an alternative specimen type (cerebrospinal fluid; CSF). This approach serves as an automated alternative to oligoclonal band testing and is used in the clinical work-up of multiple sclerosis. Additionally, we also use matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry for the identification and interrogation of patients with monoclonal gammopathies and evaluation of AL amyloidosis. This LDT has largely replaced serum immunofixation and allows our laboratory to provide better care to our patient population.

What are some of the advantages and disadvantages of the current CLIA regulatory structure for LDTs? If additional oversight is needed, are there any mechanisms, institutional committees, professional societies, or other outside organizations that should be involved?

William Clarke: One advantage of the current CLIA regulatory structure is that it allows maximum flexibility to quickly respond when a clinical need is identified and no commercial assay is available. Unfortunately, this structure also allows underqualified doctoral-level folks (e.g., a physician with one year of laboratory training) to set up LDTs. Further, the current structure does not require demonstration of LDT clinical utility, only analytical validation of the method. While the assessment of utility is often implicit when a lab director is determining whether a test is needed, formal evaluation of clinical use is not required. Since the quality of LDTs can be quite variable, I find it desirable to strengthen the oversight required for LDTs. However, my opinion is that it should be done under the existing CLIA and accreditation structure, and not by creating a new structure with overly burdensome requirements.

Dennis Dietzen: The current CLIA regulatory structure is actually quite stringent. Test developers must assess fitness of equipment, evaluate continuity of hardware, software, and reagent supply lines, then document accuracy, precision, clinical sensitivity and specificity, and fiscal feasibility. Accountability through CLIA alone is admittedly superficial, but, for those labs that have the extra layer of certification by the College of American Pathologists (CAP), the burden of documentation and continuous quality assessment is significant. The education, training, and ethical expectations of high-complexity lab directors add another layer of safety and effectiveness to the mix. That said, for the unscrupulous and profit-driven, CLIA oversight alone is a weakness. Without some strategically applied regulatory caulk, this hole will continue to be exploited. During the Disruptive Technology Competition at the 2022 American Association for Clinical Chemistry (AACC) Annual Scientific Meeting, one of the participants with clear goals to manufacture, market, and sell their technology widely, confessed to using the "LDT pathway" to avoid early regulatory oversight. This sort of misbehavior threatens the academic settings where LDTs fill gaps in clinical care.

Andy Hoofnagle: Because CLIA provides a holistic view of each laboratory, the practice of medicine that is embodied by the development of novel assays is included in the greater context of a laboratory's operation. Unfortunately, the current bar for being CLIA-certified might be lower than necessary for a high complexity laboratory running novel LDTs. Also, the assessment of a laboratory's competence may be evaluated by individuals who are insufficiently trained to adjudicate that a laboratory running a specific type of technology is competent to do so. The main disadvantage with CLIA is that it has not been significantly updated for decades, and many of the analytical approaches that we commonly use today were not even contemplated when the law was last updated. One way that CLIA could be modernized is to provide more details about what is expected of laboratories that invent their own assays, with respect to the background and competence of the medical and technical directors of the laboratory. However, even in the absence of legislation modernizing CLIA, organizations like CAP, other deemed organizations, professional societies, and standards organizations could: (1) make checklists for laboratories performing LDTs, (2) develop specific training and trainer-assessments to ensure a strong knowledgebase for inspectors, and (3) ensure that well-trained inspectors are present and asking the right questions during inspections. I would hope that the Centers for Medicare and Medicaid Services (CMS) would be willing to collaborate with organizations like CAP, AACC, the Association for Molecular Pathology (AMP), and others, to help write the legislation that would modernize CLIA in this manner. What needs to be avoided is individual laboratory societies siding with commercial interests that promote legislation that would stifle innovation and restrict the practice of medicine by laboratorians and physician pathologists.

Gwendolyn McMillin: Because the FDA, CMS and the Centers for Disease Control and Prevention (CDC) are currently responsible for CLIA, the theoretical regulatory oversight of clinical laboratories already incorporates safety, payment, and diagnostic perspectives. In addition, the accreditation and licensure status of clinical laboratories provides further assurance that the testing process is evaluated by external experts. Guidance documents by the Clinical and Laboratory and Standards Institute (CLSI), which are utilized by numerous organizations, are also key components to promote appropriate LDT validation. LDTs are by definition high complexity, and should not be attempted by laboratories who are not accredited and licensed appropriately. A major disadvantage of the current system is that the details surrounding laboratory oversight are considered private. Most end-users (e.g., clinical providers, patients) do not know whether the testing laboratory is appropriately skilled to offer a specific LDT. While a laboratory as a whole may be accredited as "high complexity", an individual test may not have been appropriately vetted.

Maria Alice Willrich: While not perfect, the current CLIA regulatory structure allows for timely deployment of a test after validation experiments and internal review processes are complete. Following appropriate validation assessments, test modifications may be implemented to further refine and optimize a method. For example, our laboratory has an LC-MS/MS method to quantify infliximab in serum; we have modified the method several times, resulting in improved precision and shortened turnaround times (48 h to 4 h). Additional oversight, including external data review and demonstrated clinical utility, would be a paradigm shift and impact how and when we implement an LDT. If additional oversight is needed, I envision all laboratory professional societies being called to action. Societies may create expert panels for various technology areas to develop checklists or validation tools; these experts could even take part in the review process of LDTs. If finding reviewers for publications is challenging, identification of subject matter experts to review LDTs would be a herculean task, and delay patient care.

The end users for LDTs are the providers and, ultimately, the

patients. What strategies do you recommend to educate other stakeholders about the value of LDTs and the impact of external regulations on essential medical services currently available to them?

William Clarke: I would suggest that one identify some high-impact, key clinical scenarios and work through patient advocacy groups for those diseases or conditions. These groups are often highly motivated and leverage multiple platforms for both patient and government representative education.

Dennis Dietzen: In my experience, providers take LDTs for granted. Most patients likewise do not know much about the tests that keep them healthy. Lab administrators with an eye on the financial bottom line see LDTs as a significant burden. I have come to learn that regulators view LDTs with a fair degree of skepticism despite the fact that thousands of laboratory-developed procedures are tremendously effective tools for a wide variety of patients. We don't do a good job of communicating our success to clinicians and administrators in our own institution, much less with regulators and the public at large. We need to get better at this. Our respective professional societies can be valuable conduits for getting the message to regulators and policy makers. AACC, the American College of Medical Genetics (ACMG), and AMP have been driving this narrative for the past several years. Lab practitioners must learn to hone a simple LDT message and repeat it loud and clear in front of the right audiences. Memories tend to be short on Capitol Hill.

Andy Hoofnagle: This is a wonderful question and I don't have a good answer. At the University of Washington, we have been unable to convince our own Senator (and sponsor of the VALID legislation) that these changes could be detrimental to our state-owned medical system. For years, we have invited FDA regulators and advisors, who do not have first-hand clinical laboratory experience, to come to our laboratory for tours and discussions; no one has taken us up on these offers.

Gwendolyn McMillin: Education of providers that order testing, and education for patients affected by LDT results, would be ideal. PT performance is not provided publicly, and most clinical providers and patients wouldn't even know to inquire about PT; perhaps it should be? An example of regulatory oversight that may be worth critical evaluation is the New York Department of Health (NYDOH) model, which has historically required that laboratories offering clinical testing to patients who reside in the state of New York be certified by the NYDOH, and in many cases, participate in PT provided or accepted by the NYDOH. Another possible strategy would be to require that laboratories indicate, as a required reporting element, some index of ongoing regulatory compliance per test, and/or when a specific test was approved for clinical use. Looking for a 'stamp of approval' or other classification indicative of test quality and satisfactory PT performance could be required for all tests, and this can be made publicly available and disseminated to relevant stakeholders, educating them on the quality of a test.

Maria Alice Willrich: The value of clinical laboratory medicine was highlighted by the SARS-CoV-2 pandemic; we must continue to advocate and amplify our professional contributions to healthcare. Even with an increased spotlight on laboratory diagnostics, details on how laboratories work or are regulated are not known to the public. Social media is a powerful tool and most people are immersed in online activities. In general, the online laboratory medicine presence has not been amplified, when compared to other healthcare areas. I have found myself learning new things online when I was not necessarily looking for the information, and a brief "teaser" on a given topic may be impactful and drive interest. Communication is key. For instance, a personal email to professional colleagues with key points on the value that LDTs play in the management of their patients could be impactful and help promote education and advocacy around LDTs and clinical laboratory medicine.

If oversight of LDTs fell to the FDA or another designated organization, how could it impact patient care?

William Clarke: This really depends on the structure – oversight is important and should be improved, but the question is: How will it be structured? If FDA oversight will carry a significant administrative burden, then patient care will absolutely be negatively impacted. Very few hospital laboratories will be able to offer LDTs, and there may be fewer LDTs in reference labs – or at least the pace of development will be slower. This will result in reduced access for patients.

Dennis Dietzen: Despite some tantalizing mitigation proposals in the VALID Act, like grandfathering, technology certification, and exceptions for "rare" conditions, patient care would undoubtedly suffer. Grandfathering works until you need to make changes to the LDT. Good LDTs should always be changing and improving. Technology certification allows a laboratory to demonstrate proficiency in a specific technology, such as mass spectrometry, but does this include all types of mass spectrometric platforms and applications? Although the process is not yet defined, technology certification will likely be just as onerous as a single method submission to the FDA. How many small labs have the extra resources to take this on? The result is that smaller labs will have to get out of the LDT business. Test volumes may funnel into larger, better-resourced reference laboratories and turnaround times will grow very long. Further, the FDA is not known for punctuality. How long would a regulatory review take? New advances in medicine will still happen, but the capacity to translate these into laboratory practice will be halted. Patients will be the victims.

Andy Hoofnagle: We have witnessed recent issues with respect to the technical expertise available at the FDA, the bureaucratic hurdles that stymie progress, the costs of submitting documents for review by the FDA, and the very long turnaround times in reaching a decision. So, if the FDA began regulating LDTs tomorrow, I would be very nervous about our ability to provide quality and essential clinical care. At its most extreme, our hospital system would be overburdened, and would very likely stop making new tests. More realistically, I expect that the decisions governing LDT implementation would be influenced by the financial return on investment rather than the medical necessity of a particular test. Given that some of the most important current diagnostic methods, such as PCR and next-generation sequencing, did not seem economically or technically viable initially, it is worrisome that they may not be prioritized with a VALID-like framework in place. At the very least, it would add cost and inconvenience, and would certainly limit progress on new diagnostics at our institution. That said, I believe if LDT oversight fell more explicitly into the CLIA-framework, we could overcome current challenges. This would place oversight squarely with CMS and its deemed organizations, where the practice of medicine belongs.

Gwendolyn McMillin: The primary focus of the FDA is on safety. The definition of safety as it relates to the impact of laboratory testing on public health is not always clear, and has often been an ancillary (or accidental) focus. For example, the FDA definition of an LDT is more about where the test is manufactured and performed than about patient care. Designation of a test as an LDT does not ensure its safety, validity, or clinical utility. Some sort of classification indicative of test quality would be helpful on a per-test vs per-laboratory basis. I feel that appropriate classification could address quality and promote consistency of testing/results; however, no organization can universally define how a single test or test result would impact patient care. Increased oversight of LDTs will not improve patient care. If increased oversight is to be discussed, the costs of oversight must be realistic, because offering new LDTs will be cost-prohibitive for laboratories if every new test requires an approval process similar to the FDA's current 510(k) or PMA pipelines. Costs and administrative delays are likely to negatively impact patient care by reducing test access, particularly in areas with the greatest unmet needs.

Maria Alice Willrich: I echo the sentiments of other panelists; patient care would be impacted, depending on the requirements for a given LDT.

If the VALID Act, or a future policy with similar regulatory goals, passes, how can laboratory leaders work to ensure that patient care is not compromised while maintaining compliance? Can all types of clinical laboratories meet such benchmarks?

William Clarke: I think that day-to-day operation of LDTs will be

very similar under any type of policy; we will perform method validation, conduct preventative maintenance, and follow our quality procedures. Compliance will be maintained under the standard laboratory accreditation system within CLIA. The biggest difference would be the administrative work necessary to qualify and register LDTs under the new legislation, as well as any associated cost with that process. In my mind, any compromise in patient care will not be related to day-to-day compliance, but instead would be related to availability of LDTs when they are needed.

Dennis Dietzen: During the debate over the VALID Act, its critics have been depicted as bereft of any other rational alternative. Laboratory proponents of the VALID Act see the bill as the least objectionable alternative to inevitably heightened regulatory scrutiny. I believe there is a middle ground and laboratory practitioners must be part of the solution. LDT regulation via CLIA has been effective, but there are vacuums in the regulations that allow bad tests to fester and flourish. This should be remedied. It seems reasonable to add an extra layer of oversight for LDTs. One monolithic agency cannot possibly possess both the expertise and responsiveness to fill this space without stunting the practice of medicine. A peer-to-peer review scheme might be far more effective. Requisite supplementary certification beyond CLIA might be another way to ensure proper review of LDTs. Such an approach works only when high-complexity laboratory directors meet the highest technical, clinical, and ethical standards. Newly proposed CMS regulations that relax requirements for high complexity laboratory directors would be a step backwards. Avoiding overly prescriptive and restrictive solutions like the VALID Act requires the lab community to provide a strengthened layer of regulation. Benchmark standards should be stringent. Laboratories that cannot meet them should be held accountable. Laboratories must police themselves.

Andy Hoofnagle: This legislation will increase the cost of doing business, simply by increasing the documentation associated with our practice, while not improving quality. There has to be a new focus on hiring personnel specialized in regulatory affairs so that we can navigate this new environment. The FDA speaks a completely different language than those of us practicing laboratory medicine. It is highly unlikely that we will be able to expand our current regulatory affairs/compliance group to meet the expectations that are laid out in the VALID Act for all LDTs. We are also unlikely to be able to expand educational programs to adequately inform our laboratories of the new regulatory requirements and definitions.

Gwendolyn McMillin: Laboratories that have high standards for quality, operations, and transparency should not immediately be threatened by the concept of VALID, or similar legislation. There are many examples of poor-quality laboratory tests that became available clinically and led to patient harm, such as the highly publicized issues at Theranos. There are also examples of high-quality tests that are misordered, misinterpreted, or not utilized appropriately, also impacting patient care. As experts in laboratory medicine, we are best poised to propose solutions and educate non-laboratory stakeholders. In my opinion, the goals for the future should be to promote awareness and understanding of what a test is designed to do (LDT or otherwise), the strengths and limitations of a particular test or testing approach, and whether evidence exists to support clinical claims. It is unlikely that more regulations can accomplish those goals. Instead, we need a stronger voice.

Maria Alice Willrich: Depending on the specific LDT and the scope of oversight, there will be heavy administrative, analytical, and fiscal burdens incurred by laboratories. Smaller laboratories will be unable to support LDTs, and impactful tests that would be ordered at low volumes for a small cohort of patients may fall by the wayside. If LDTs are funneled to larger reference laboratories that may have the administrative capacity to continue to implement LDTs, there would be an impact on result turnaround time, and decisions may shift towards a financial bottom-line, as opposed to delivering timely and actionable results.

The VALID Act is not the first initiative to increase LDT regulation, and likely will not be the last. As a laboratory community, what strategies should we employ to demonstrate our expertise in this arena?

William Clarke: I think that the need is not for the laboratory community to demonstrate our expertise, but to demonstrate our willingness to improve quality and oversight of LDTs. Most of us agree that treating an LDT like a commercial IVD is not the answer, but we must acknowledge that there are LDTs of varying quality. The current system, under CLIA, must be strengthened to ensure sufficient quality measures are taken and that individuals with oversight responsibilities for LDTs have sufficient expertise and experience to carry that responsibility.

Dennis Dietzen: The debate over VALID has exposed the complacency of the lab community, but also presented lessons for future engagement. It is easy to get wrapped up in the technical minutiae of the laboratory, but broad engagement with medical practitioners, administrators, regulators, and policy-makers is essential. The challenge to demonstrate expertise is not limited to the laboratory world. Laboratorians must engage both the medical and administrative hierarchy. Invite administrators into the lab. Share your success stories. That one-in-a-million diagnosis delivered by an LDT could have been one of their family members. Share strategies with laboratory colleagues. Publish and highlight the novelties of new LDTs. Finally, continued engagement with regulators and policy-makers is necessary. One spectacular LDT failure is enough to taint thousands of success stories. Work with respective professional societies to make sure that the last message policy-makers hear highlights the value of innovation in the laboratory.

Andy Hoofnagle: I think that working with our professional organizations that are working to improve the practice of medicine, rather than make it more difficult, would be most helpful. They will need our expertise to properly envision the future and a more effective CLIA framework.

Gwendolyn McMillin: One of the sources of doubt about laboratory test quality and equality is attributed to a lack of understanding. Other sources of concern are the proprietary nature of most laboratory tests (IVD and LDT), and limited published information about test utilization. Few clinical studies evaluate testing the way that pharmaceuticals are evaluated, and laboratories are not in a good position to manage clinical judgement. Further, PT data are also proprietary. Would more transparency on laboratory performance data benefit providers and help guide decision making? Should there be more investment in harmonization of testing? The laboratory community could work together to provide more information about LDTs, including harmonization of content, thresholds for decision making, and demand. Partnering with clinical organizations to endorse clinical value of LDTs is also needed.

Maria Alice Willrich: With great power comes great responsibility. Our role in healthcare is often seen as a “black box”. While a provider or patient may see a final result in a health record, a clear understanding of the process, and people, involved in generating that result, is rarely considered. While it is difficult to convey the complexity of laboratory services, we must continue to advocate and communicate the importance of LDTs in delivering high quality care. Participation in open forum discussions focused on laboratory medicine, leveraging relationships with professional societies, and presenting in non-laboratory focused venues are some of the ongoing strategies we can implement now to demonstrate the critical need of LDTs in healthcare.

Different technologies are used for a variety of clinical applications, including chromatographic-mass spectrometric identification of analytes, analysis of alternative specimen sources (e.g., body fluid testing), and PCR-based molecular assays. Do you recommend stratified oversight requirements based on the complexity of the LDT, or should requirements be agnostic of the type of LDT? With a stratified approach, how would you determine requirements for different types of LDTs?

William Clarke: I think that LDTs should be stratified not only by the complexity of the LDT, but also by the type of technology or method that is the basis for the LDT. An LDT that is the result of using a cleared,

moderately complex test outside of its intended use would not require any specialty expertise, and would simply require validation of the new conditions. However, for more complex technologies, there should be demonstrated expertise and experience relative to the specific technology and the person responsible for test development and oversight. In addition, consensus guidelines for various categories of tests (e.g., genetic sequencing, LC-MS/MS) should be developed by the laboratory community, and incorporated into accreditation requirements.

Dennis Dietzen: I personally do not think a technology approach is the right strategy. Let experts be experts. I cannot walk into a molecular genomic lab and design a primer set and then develop an amplification, detection, and quality control scheme for the next emerging viral pathogen. Nor would I expect virologists to walk into my laboratory and be familiar with how to develop an LC-MS/MS assay. Regulators seem to have forgotten the astounding amount of education, training, and experience possessed by those who build LDTs, and instead focus on oversight of the development process. The VALID Act proposes a clinical risk-based approach to stepped up oversight, but clinical risk is in the eye of the beholder. I suspect this approach is because the FDA is unable to assess all of the LDTs that are in use today. Are we all OK with oversight that responds primarily to the number of a patients that might experience harm? How many patients have to be harmed for the FDA to step in? I personally think that one is too many. I think every LDT needs tailored, standardized oversight. Stratification by risk or technology is too blunt an approach in my opinion.

Andy Hoofnagle: I think that the medical and technical directors of high complexity laboratories performing LDTs need to be competent to perform the testing that they oversee, which requires specific training, board certifications, state licensure (in some cases), and maintenance of certification. Their collective education, credentials, and resumes should be reviewed during laboratory certification and considered carefully based on the laboratory's menu of assays. In addition, this background and competence should be reviewed by knowledgeable inspectors at each inspection. The most important way to ensure quality in the clinical laboratory is the competence and diligence of the testing personnel. Thus, having competent, thoughtful, and dedicated people at all levels is crucial. It seems that the safest laboratory culture should start from the top of the organization structure, and ensuring that the medical director responsible for an LDT has the background and experience necessary to properly implement and apply laboratory results under their purview is a reasonable place to start. Required background and experience would be dependent on the technologies being deployed.

Gwendolyn McMillin: I absolutely support development of a stratified approach to assign risks associated with LDTs. Risk could reflect accuracy/traceability, analytical inconsistencies/harmonization, as well as clinical validity/utility. However, testing should not be restricted to the point of inaccessibility. There is always a place for conducting clinical research with novel testing, and/or developing and offering biomarker panels that include analytes with tiered evidence, per biomarker (e.g., pharmacogenetics panels).

Maria Alice Willrich: I see value in a tiered approach. The NYDOH has a risk attestation form that may serve as a roadmap for stratifying LDTs. While there will be limitations in the external determination of risk and prioritizing test reviews and approvals without input from vetted subject matter experts, a codified, tiered approach may serve as a mechanism for better defining requirements for LDTs depending on their methodologic or clinical applications. However, there would be important considerations in operationalizing and gatekeeping such an approach.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Clarke W: Thermo Fisher Scientific; Roche Diagnostics; Shimadzu Instruments, Inc. Dietzen DJ: Roche Diagnostics; Waters, Inc.; Becton-Dickinson; Danaher; Abbott; Ascensia. Marzinke MA: No relevant disclosures. Hoofnagle AN: Waters, Inc. McMillin GA: No relevant disclosures. Willrich MAV: Myeloma360; Sebia, Inc.; patents on the use of mass spectrometry for immunoglobulin quantification.