

How the VALID Act will impact the practice of medicine primarily in academic health systems:

Prepared April 25, 2022 by the Association of Pathology Chairs, on behalf of affected member laboratories and their affiliated hospitals

The VALID Act proposes implementation of an FDA-based regulatory system over a potentially unsafe “wild west” of diagnostic test development. Laboratory-developed tests or procedures (often referred to as LDTs or LDPs) are the focus, even though many of the laboratories and medical professionals who perform them are already carefully regulated by the Clinical Laboratory Improvement Amendments Act (CLIA) under CMS.

In hospital-based laboratories, LDPs are performed to address the needs of the patients at that hospital. LDP development, validation, and interpretation is directed by physicians (primarily pathologists) and PhD clinical laboratorians with extensive medical training and certification in their specialties. In academic medical centers, for example, many patients need expert care for rare diseases or complex conditions. Clinicians need LDPs performed in academic clinical laboratories in order to diagnose and treat their patients.

Ironically, the VALID Act exempts the practice of medicine from oversight, but it does not recognize hospital-based pathologists and laboratory professionals as engaging in the practice of medicine in the provision of LDPs. In hospital-based laboratories of all types, the majority of testing is done as part of a larger process, which frequently does not use any FDA-approved kits (sometimes referred to as in vitro diagnostics or IVDs) as a component. The entire diagnostic process, and the physicians and medical directors who manage it, operates under the oversight of CLIA, with extensive quality guidelines to ensure the safety of the entire process, including any FDA-approved kits that may be incorporated. CLIA dictates an extensive framework of operational requirements, which spans the entire testing procedure from sample collection to reporting, and includes laboratory inspections, competency assessment and training requirements for staff, and participation in proficiency testing programs to make certain they are performing tests and procedures correctly.

All diagnostic tests begin as LDPs. Generally, once the clinical application of an LDP is recognized, if the potential market is large enough, a company will develop and manufacture a kit. Some LDPs are developed at independent laboratories and marketed broadly as reference tests, but they are not mass-produced as devices or kits for commercial sale to clinicians or patients. Many diagnostic processes are too complex to be made into a kit (microbial culture, examination of tissue samples, toxicology testing) and will continue to be performed as procedures under CLIA guidelines. Others have become routine and automated, and for those, FDA-approved kits are ideal.

FDA review is important for devices and kits that will be marketed broadly and utilized in a variety of settings where they must consistently produce accurate results. A sizable market is needed to cover the expense of FDA approval; therefore, the companies that pursue FDA approval do so for the most common disorders or diseases, tumors or sample types.

If a lab needs to deviate from the details of the FDA approval for a kit—to test for the identical gene mutation in a different tumor, for example-- the lab must use the kit as an LDP, performing the same validation and quality procedures as under CLIA guidelines as they would for any LDP. Additionally, in rapidly evolving fields such as oncology or genetics, LDPs can be modified to include a new gene or mutation fairly quickly under CLIA; whereas, once a kit is FDA-approved, it rarely is modified or updated due to the expense of the approval process. “Grandfathering” of tests under VALID would similarly discourage improvement and advancement of tests.

Under VALID, laboratories would be required to submit their LDPs and any modifications to them to the FDA, in addition to continuing the quality activities they currently perform under CLIA. The expense and burden of such dual compliance would be a major obstacle to academic clinical laboratories, whose limited profits are reinvested into medical research and education. Many academic clinical labs would simply have to stop offering LDPs to their hospital systems’ patients. Those labs that continue would pass the cost of FDA regulation on to the hospitals and, ultimately, to patients, to generate revenue to offset the new regulatory expense. Such expense would be in addition to CLIA oversight by CMS and, in New York and Washington states, their states’ current additional laboratory regulatory systems.

FDA is trying to address a genuine concern. Pew Research and others make note of tests that escaped thorough regulatory oversight and had negative consequences for patients. For example, Theranos is often cited. Theranos created a device that did not work and was not properly reviewed before going to market. The CLIA proficiency testing program and their inspectors detected the issues and halted the testing. CLIA *does* protect patients. Further, CLIA-accredited, academic clinical labs warned about the potential issues and public health consequences for *not* vetting Theranos more thoroughly.

There are bad actors in all industries, but they are rare among those physicians and laboratory professionals practicing medicine in clinical environments connected to patients, without profit as their primary motivation. Their health systems and CLIA licenses will hold them accountable in the same way that any other clinician is monitored and held accountable.

Pausing now to seriously reflect on the implications of the VALID Act, which provides broad FDA regulation where it has questionable authority, is vitally important. This is complex legislation addressing a very complex issue. Without understanding the specifics of how the VALID Act would be implemented, it is impossible to fully understand the impact it would have at an operational level in hospitals and health systems. However, it is reasonable to believe, based on the bill in its current form, that the additional administrative burdens on academic and other health system laboratories (without any obvious added benefit) would cause both a scaling back and a slowing down of LDP development. Increased reliance on outside reference laboratories would increase turnaround times, slow down the pace of innovation, decrease the ability to adapt testing platforms to local clinical needs, and disrupt the peer-to-peer consultation between laboratorians and their clinical peers that adds real value to the optimal use and interpretation of laboratory testing in the management of complex patients. Downstream consequences to clinical care would likely include increased length of stay, inappropriate utilization of alternative laboratory tests, delays in critical interventions, inappropriate therapeutic interventions, decreased access to appropriate testing and, ultimately, increased morbidity and mortality. It has been estimated that 70% of medical decisions rely on laboratory testing. Consequently, crippling clinical laboratories cripples healthcare delivery in general. Some specific examples to illustrate the importance of a robust laboratory LDP infrastructure are provided below.

Clinical Examples of LDP Use¹

1. Antimicrobial Susceptibility:

Antimicrobial susceptibility testing is performed widely in microbiology laboratories and indicates whether or not antibiotics will be effective for bacterial infection. FDA publishes interpretive criteria at the time of antibiotic approval and periodically updates these afterward to address antibiotic resistance ². The FDA also clears automated instrumentation used to determine antibiotic resistance (via the 510k process) ³. Updates to the instrument interpretive software require a revised 510k application. Because the FDA does not have the authority to require manufacturers to submit data for revised breakpoints, manufacturers may elect to use outdated breakpoints rather than face the expense of a 510k resubmission. A recent example was the 3-year delay between the publication of updated breakpoints for diagnosing carbapenem-resistant Enterobacteriaceae and the inability to use these breakpoints in the clinical laboratory.

This delay was used to calculate that as many as 1,821 additional carriers of multidrug resistant Enterobacteriaceae occurred in Orange County, CA because of this delay⁴. The disastrous spread of MDRO Enterobacteriaceae can be mitigated by laboratories validating testing methods that enable use of updated antimicrobial breakpoint interpretations before FDA-cleared testing is available. Specifically, interpreting results differently than listed in the product insert using update criteria is a change that renders the procedure an LDP. Without the option of using a laboratory developed procedure, one is left reporting outdated interpretations that miss resistant strains leading to unacceptable patient care.

2. Inherited Cardiomyopathies:

Inherited cardiomyopathies (including hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and restrictive cardiomyopathy (RCM)) are common conditions with more than 1 in 500 individuals carrying a disease-causing gene variant for HCM alone^{5, 6}. Inherited cardiomyopathies have strong genetic associations ^{7, 8}, a long pre-symptomatic phase, and a predisposition to sudden cardiac death (SCD). A recent study showed that 16% of SCD cases are due to an underlying inherited cardiomyopathy⁹, sadly covered by media reports on many cases of sudden death in young competitive athletes¹⁰.

Genetic testing for these disorders started in the 1990s and is now offered by many molecular diagnostic laboratories. Clinical heterogeneity requires the use of large multi-cardiomyopathy gene panels (covering genes for all disorders) with exome sequencing being increasingly used. Importantly, the identification of pathogenic variants in affected individuals can inform medical management of family members and can identify those at risk early and release negative individuals from clinical screening⁷. Genetic testing can also identify other diseases which can masquerade as HCM and thus lead to appropriate treatment.

With exome and genome sequencing being increasingly implemented, guidance has been issued by the American College of Medical Genetics and Genomics (ACMG) on how to deal with the incidental identification of variants known to cause inherited cardiomyopathy and other so called "actionable" genes in patients tested for unrelated conditions^{11, 12}.

3. Herpes Simplex Virus:

Encephalitis is the most serious complication of herpes simplex virus (HSV) infection⁴³. It is critical to rapidly and accurately diagnose HSV infection of the brain and initiate acyclovir treatment to reduce morbidity and mortality. Culture of CSF is insensitive for the diagnosis, so for many years brain biopsy, a very invasive procedure with significant morbidity, was required, with results not available for days afterward. A landmark study in 1995 showed that detection of viral DNA in CSF samples by PCR performed better and faster than culture of brain biopsy^{44, 45, 46}. Given the relative ease of collecting CSF samples, the lower risk of complication, and the lower cost and speed of results, PCR became the standard of care for diagnosing HSV CNS infections in the mid-1990s; these LDPs were used for nearly twenty years. It was not until 2014 that the first FDA-cleared PCR test for the diagnosis of HSV encephalitis became available, with a second test cleared in 2015. LDPs dramatically improved the quality of care for many patients, and continue to be used successfully today, since the cleared tests have limitations, including the instrumentation required.

HSV can also cause infections in newborns with a frequency of 1:3500 to 1:5000 deliveries in the United States. Again, rapid diagnosis is essential to prevent morbidity. The diagnosis of encephalitis is made via PCR of CSF samples, while testing of plasma or serum is critical to diagnose disseminated HSV disease. There are no assays cleared for testing serum and plasma, so LDPs continue to play a critical role in the diagnosis and management of disseminated HSV infection in newborns.

LDPs have performed with a high degree of accuracy and inter-laboratory agreement. Unknown proficiency testing samples distributed to 383 labs as part of a CAP proficiency testing survey for analysis of HSV; 91.6% correctly identified HSV-2, and 7.8% identified HSV, but did not specify the subtype; an overall accuracy of 99.4 % was obtained. Previous proficiency surveys showed similar results for samples containing HSV1. Over 90% of the laboratories used LDPs.¹⁷

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