



# The Neverending LDT vs IVD Debate:

by Hannah Mamuszka

How we can streamline our industry to encourage innovation and investment and aim for the broadest patient access to democratize the best care?

**T**he biggest debate in the diagnostic industry for the last 30 years has been Lab Developed Test (LDT) vs In Vitro Diagnostic (IVD).

Both are types of diagnostic tools that providers may use to determine health status, diagnosis and/or monitor a disease, and inform treatment decisions. An LDT is a type of diagnostic test that is designed, performed, and used within a single laboratory.

An IVD refers to an FDA-cleared diagnostic test sold as a complete kit that a laboratory purchases from a manufacturer, and comes with all of the procedures and controls to perform the test. Some IVDs are used in the clinical setting, while others, such as blood glucose testing for diabetes, are for home use. There are many similarities between LDTs and IVDs, and some test for the same thing.

But the differences are the controversy in our industry.

This column isn't taking sides; I've spent 20 years in this industry and can expertly argue for either. But the conversation in Washington D.C. does seem to be trending towards pushing for more IVDs, and there are some underappreciated obstacles to consider.

First, a quick history refresher on how this got (re)started. Since 1976, FDA has had oversight responsibility over IVDs based on the Medical Device Amendments Act. However, this was thought to be excessive for the basic laboratory testing that hospitals were already routinely performing. This led to the Clinical Lab Improvement Amendments (CLIA) of 1988, which defined federal regulatory standards that apply to all clinical

laboratory testing performed on humans in the United States, with the exception of clinical trials and for basic research purposes, and allowed certain qualified laboratories to apply for a CLIA license as an exemption from having to pursue an IVD path for every test. A CLIA license comes with demonstrated proficiency testing, certificates for laboratory operators and directors, and criteria for test validation. In accordance with the CLIA, the CLIA Program sets standards and issues certificates for clinical laboratory testing, and performs audits on laboratories with licenses. Centers for Medicare and Medicaid Services (CMS) has the primary responsibility for the operation of the CLIA Program, and so allows for submission to the CMS via local Medical Administrative Contractors (MACs) for reimbursement determinations. ▶

An objective of the CLIA is to ensure the accuracy, reliability, and timeliness of test results regardless of where the test was performed. In 2014 the FDA started a public discussion about regulating some LDTs due to their increased complexity, as well as in response to both issues with some laboratories not being compliant, falsifying results, manipulating records and defrauding Medicare, as well as pressure from the IVD industry, who would like to see stronger regulations and restrictions on labs running LDTs. This discussion continues to wax and wane.

Back when CLIA was defined in 1988, LDTs were generally routine assays run by hospital labs on patient samples, to assist in diagnosis and treatment management. As technology has developed, sample collection methods and preparation methods have allowed for easier and more stable transport of patient samples and analysis platforms and methods have become more sensitive and accurate, LDTs are increasingly utilizing more complex technology and represent tests that are perceived as more risky for the decisions they inform. Historically, FDA has exercised what they refer to as 'enforcement discretion', limiting their premarket review, adverse event reporting, and other regulatory concerns to tests that they have deemed high risk and/or without sufficient evidence to support their clinical use. This has led to some confusion and to some laboratories receiving unexpected warning letters to cease providing their tests. A recent confounding case was that of Inova Labs who was offering pharmacogenomic (PGx) testing supported by guidelines from the Clinical Pharmacogenomic Implementation Consortium (CPIC), and is similar to many other laboratories offering PGx testing as LDTs who did not receive FDA warning letters.

As within any industry, there are bad players who take advantage of the (perceived) more lax oversight that the CLIA system provides, either performing tests for which they are not certified, improperly overbilling

Medicare (and other payers), or various other infractions. Those laboratories represent a danger to patients, and should be ferreted out with significant consequences. Some have pointed to Theranos as an example of why LDTs should not be allowed to exist, but Theranos illegally misrepresented their activities and circumvented many rules and laws that had nothing to do with their clinical lab itself, (and their CLIA license was revoked).

On the other side, are IVDs, which undergo FDA premarket review to ensure that they meet the rigorous standards for analytical and clinical validity. IVDs are kitted tests, which means they come as a kit in a box with the reagents and controls that allow a laboratory to perform the assay with relatively little training, as compared to LDTs. The intention is that a trained technician should be able to run an IVD out of the box (whereas developing an LDTs requires multiple PhD and MDs). Because the test comes ready to go, IVDs have the opportunity to be used in thousands of labs around the world, and impact many more patients than could be handled in a single CLIA laboratory running a single or small number of tests. Additionally, IVD kits enable hospitals in more rural or community settings who may not have the scale of personnel or capabilities to internally develop and validate LDTs, to run more tests in their hospitals, to the benefit of their patients. (Diagnostic tests don't benefit patients if they don't have access to them.) Financially, hospitals and physicians may view their laboratories as a revenue generator, and are inclined to run as many tests in house as possible, which IVD kits enable more easily, as opposed to sending tests out to be run in an external CLIA lab, where they do not participate in the economics. The best way to get diagnostic tests out to benefit as many patients as possible is to do so in a way that incentivizes all physicians to use them, and makes it easy to do so.

The timelines for validation and commercialization and the investment

required for LDTs and IVDs different greatly, as do the practical requirements. Depending on the clinical data that needs to be developed (how long a trial may need to run to determine outcome results; whether or not retrospective samples are available to analysis or whether all collection must be prospective) an LDT can go from technical validation, CLIA laboratory validation and commercialization in less than a year, while filing for a Premarket Approval Application (PMA) takes significantly longer, not because of the FDA process itself, which has been more efficient in recent years, but because of what is required of diagnostic companies to file.

Using a broad example in current Precision Medicine in oncology, say you have a short actionable mutation sequencing panel using blood (sometimes referred to as liquid biopsy) that you have validated in a CLIA lab, have analytical and clinical validity for, and you realize that your test would be more broadly accessible as an IVD, so you want to pursue a PMA path to IVD clearance. The first hurdle is platform selection- hopefully you have done all of your development and validation work on a platform that is already FDA cleared. (If you haven't, and you are really tied to that machine for performance or other reasons, you will need to work with the platform manufacturer to go to the FDA together and apply to get a platform cleared based on your test, and your test will be completely dependent on the manufacturers ability to get their platform certified, and then distributed in the market.) But let's assume you have done all of your development and validation work on a platform that is FDA cleared.

To demonstrate and prove your analytical validity and reproducibility to FDA, you will need access to the device manufacturer's design history files (DHF). These are files that instrument manufacturers must maintain and update that describe how a platform works, to what specifications and limits of detection, including any software updates. Any problems

with the platform must be reported to the FDA, along with modifications to correct. The diagnostic developer does not control any of these, but must rely on the platform manufacturer to access. The diagnostic developer is also at the absolute mercy of the platform manufacturer to maintain the platform; to make sure it is distributed broadly, since a test can only be run on the platform for which it is approved; to address, correct and update any software or hardware issues that are found on a platform, since a bug in a software update can stop a diagnostic test in its tracks. Platform selection is one of the most critical choices a diagnostic developer can make, because it is effectively a partner for life. This becomes problematic when there are few choices of platform to analyze a particular analyte available in the market; the fewer the players, the stronger they hold the major player has. Consider the current landscape in clinical sequencing, where Illumina has complete market dominance, especially if you consider FDA-cleared platforms and distribution, there are essentially two players: Illumina's MiSeqDx and ThermoFisher's Ion PGM Dx. In terms of instrument placement, which is a key deciding factor for diagnostic developers as it gates market access, and sensitivity, which is needed for developing liquid biopsy tests, a diagnostic developed is effectively limited to one- which gives all of the power to Illumina.

For certain, the investment that the diagnostic platform manufacturer makes in bringing a platform through FDA clearance is significant, and the additional investment in distribution and maintenance requires years (or decades) of planning and maintenance. When companies agree to develop a test on a cleared platform, they are ensured access to that platform for essentially the life of the test, in exchange for revenues derived from running the test. If a platform manufacturer decides to sunset a platform, all of the diagnostics still running on that platform would have to be re-validated on another platform.

However, the investment for a diagnostic company developing a test on a cleared platform is easily \$20-30M from validation through FDA approval- not a trivial investment in an uncertain reimbursement environment. Even if a test were to garner \$1000 reimbursement (for average benchmarks, Cologuard is \$650, Mammaprint is \$3500, KRAS is \$180), that would take selling 20,000 tests in the middle of those benchmarks of the clinical trial budget just to cover the costs of the investment, not including actually running the test, and running the company that develops and supports it.

Now say you want to use a blood collection tube with a preservation substance in it to keep analytes in the sample stable longer, as are used in thousands of clinical trials and LDTs everyday, including Non-Invasive Prenatal Testing (NIPT). There is currently no FDA cleared blood collection tube with a preservative, so the test developer would also need to bring the desired tube under their own cGMP processes, and certify each batch of tubes that the tube manufacturer makes OR undertake the responsibility of taking a tube through the FDA clearance process themselves.

Just between the potential problems with controlling the sample collection tube, and the potential problems with selecting a platform partner, it's no wonder innovative companies tend to develop LDTs.

A final major consideration is adaptability to new discoveries. Current IVD requirements limit the ability to modify a test once it has been approved, without essentially restarting the PMA process de novo. In healthcare in the next-generation sequencing era, the rate of discovery of biomarkers is rapid, and once a company is locked into a biomarker signature or panel and begins moving through the PMA process with the FDA, there is little ability to change, even if new data suggests adding or changing biomarkers could improve patient outcomes.

In oncology, one of the most glaring examples of this problem is KRAS testing for colon cancer. Patients who have colon cancer may be candidates for EGFR therapies, but only if they are negative for a defined set of biomarkers downstream of EGFR. When the first EGFR inhibitors were approved, FDA realized this, and required the development of companion diagnostic tools to determine patients who had mutations on codons 12 and 13 on KRAS. Qiagen and Roche each developed companion diagnostic tests, which were/are still the only IVD kits available for testing for KRAS in colon cancer. But the clinical data has developed, and now all academic guidelines suggest that patients will do significantly better (25% higher response rate) when assigned EGFR therapies if they are tested with an extended RAS panel, which includes KRAS, NRAS, BRAF, and PI3K, as opposed to just the codons 12 and 13 found on the IVD kit. But there is no simple way for Qiagen or Roche to add the additional markers onto their test, so there is a significant disparity in outcomes depending on which type of test a patient is tested with, and no extended RAS kit in sight that will be developed to close the gap.

Technology in healthcare is advancing at a rapid rate, and advanced diagnostic tools can help inform major decisions around disease management and treatment. Considerations around the LDT → IVD conversation need to take into account the major hurdles for technology developers to pursue an IVD path, while also remaining focused on patient safety and accountability objectives. ■

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