Laboratory-Developed Tests Account for a Small Minority of Tests Ordered in an Academic Hospital System

Jenna Rychert, PhD,[1,2] *Robert L. Schmidt, MD, PhD, MBA,*[1,2,*] *and Jonathan R. Genzen, MD, PhD*[1,2]

From the [1]Department of Pathology, University of Utah Health, Salt Lake City, UT, USA, and [2]ARUP Laboratories, Salt Lake City, UT, USA.

ABSTRACT

Objectives: To determine the frequency of use of laboratory-developed tests (LDTs) in an academic medical center system.

Methods: Retrospective analysis of 2021 test order data from an academic medical center (hospital, outpatient clinics, and cancer center) was done. Measures included assay type, assay methodology, regulatory status, test order volume, inpatient vs outpatient setting, and provider medical specialty.

Results: Of the 3,016,928 tests ordered in 2021, 2,831,489 (93.9%) were tests cleared, approved, and/or authorized by the US Food and Drug Administration (FDA); 116,583 (3.9%) were LDTs; and 68,856 (2.3%) were standard methods. These test orders were performed using a total of 1,954 distinct assays. Of these, 983 (50.3%) were FDA assays, 880 (45.0%) were LDTs, and 91 (4.7%) were standard methods. Laboratory-developed tests were more commonly ordered in the outpatient vs inpatient setting and represented a higher proportion of the test volume at the cancer center compared with the university hospital (5.6% vs 3.6%, respectively). The top 167 LDT assays accounted for 90% of the LDT volume (104,996 orders). Among the 20 most frequently ordered LDTs were mass spectrometry assays and tests used in the care of immunocompromised patients. Internal/family medicine placed the greatest number of orders (1,044,642) and ordered one of the lowest proportions of LDTs (3.2%).

Conclusions: Laboratory-developed tests made up a small percentage of the total laboratory tests ordered within the academic health system studied.

INTRODUCTION

The US Food and Drug Administration (FDA) is authorized under the Medical Device Amendments of 1976 (MDA) to regulate medical devices, including in vitro diagnostics (IVDs), which are introduced into interstate commerce for commercial distribution.[1] The MDA and subsequent federal regulations established the framework under which manufacturers of IVDs are required to obtain clearance or approval prior to distributing test kits or instruments used to diagnose human disease. The FDA officials have described this as the "commercially distributed pathway" for IVD regulatory oversight.[2]

However, some clinical laboratory assays are developed within a single laboratory and are not distributed as kits for other laboratories to use. The FDA defines these

KEY POINTS

- Laboratory test orders at an academic medical center were reviewed to determine how frequently laboratory-developed tests were ordered by clinicians.
- Laboratory-developed tests were more commonly ordered in the outpatient vs inpatient setting and represented a higher proportion of the test volume at a cancer center.
- Laboratory-developed tests made up a small percentage of the total laboratory tests ordered within the academic health system studied.

KEY WORDS

Laboratory-developed tests; Food and Drug Administration; Clinical Laboratory Improvement Amendments; Laboratory regulations

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Corresponding author: Jonathan R. Genzen, MD, PhD; jonathan.genzen@aruplab.com.

*Current affiliation: LabCorp, Burlington, NC, USA.

laboratory-developed tests (LDTs) as "an IVD that is intended for clinical use and designed, manufactured, and used within a single clinical laboratory."[3] The FDA has asserted that it has the authority to regulate LDTs but that it has followed a policy of enforcement discretion.[3] Although the FDA announced its intention to exercise oversight over LDTs in 2010 and released a draft regulatory framework in 2014, this framework was ultimately not implemented.[3-7] The regulatory landscape surrounding LDTs remains controversial.[8-10] In addition, federal regulations from the Centers for Medicare & Medicaid Services (CMS) enacted under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) have specified the performance standards for LDTs that clinical laboratories must follow prior to their use in high-complexity clinical laboratory settings.[11,12]

The Verifying Accurate Leading-edge IVCT Development Act (VALID Act) is a bill that was introduced into the US Congress. If enacted, it would provide a unified regulatory oversight system for all in vitro clinical tests, a new definition that includes both IVDs and LDTs.[13,14] A concern raised by the supporters of diagnostic reform is that the number of LDTs currently on the market and being used in patient care is not known.[15,16] Clinical laboratories are specifically exempt from device registration with the FDA under current federal regulations.[17] However, they do maintain and submit information about test menus to regulatory and accreditation agencies. For example, when applying for a CLIA certificate of compliance, a clinical laboratory must provide the CMS with a full list of all assays performed, including their manufacturers.[18] Furthermore, laboratories accredited by the College of American Pathologists are required to maintain a laboratory activity menu and a separate list of LDTs to assist in the process of biannual inspections, but this list is not submitted to the CMS.[19] Finally, the New York State Department of Health (NYSDOH) maintains a database of all LDTs approved by the Wadsworth Center.[20]

As an academic health system with a university-owned national reference laboratory, our institution maintains information on all clinical laboratory testing performed within our facilities, including assay type, test volumes, and regulatory compliance status. As such, the present study was conducted to determine how frequently LDTs were ordered in inpatient and outpatient settings.

MATERIALS AND METHODS

Health Care Setting

ARUP Laboratories is a not-for-profit enterprise of the University of Utah Department of Pathology. Along with serving as a national clinical reference laboratory, ARUP operates inpatient and outpatient clinical laboratories for the University of Utah, an academic medical center that includes the University Hospital, the Huntsman Cancer Institute, and more than a dozen community health centers and clinics.

Sample

Throughout the article, the term *assay* is used to refer to a distinct type of laboratory diagnostic method available in our test directory, whereas *test* refers to the performance of the specific assay method on a unique patient specimen under a clinician's order. Under an institutional review board exemption protocol (University of Utah, #00082990), a deidentified data set was obtained for tests ordered by providers at the University of Utah Health from January 1 to December 31, 2021. The data set included assay name, volume of test orders by year, patient admission status (inpatient and outpatient), location (University Hospital and Clinics [UH] and Huntsman Cancer Institute), and ordering department. Ordering departments were categorized according to the medical specialty. A subset of information on test orders collected at outpatient phlebotomy sites that could not be attributed to specific ordering departments in this data set was categorized as unclassified. The data set was then cross-referenced to the compliance status of the assay as an FDA assay (ie, FDA cleared, approved, or exempt), emergency use authorization (EUA) assay, LDT (subclassified as in-house developed, analyte-specific reagent, or modified FDA), or standard assay.[21] The classification of standard methods adhered to the NYSDOH definition of "a standardized protocol that is universally applied in laboratories that employ the method for the analyte" (eg, immunohistochemical stains and in situ hybridization probes with pathologist-guided processes, microbiological cultures, manual microscopy, manual differentials).[22] Tests using research use only (RUO) reagents are included as a subset of in-house developed tests but are not subcategorized as RUOs in our data warehouse, thus precluding separate analysis. The EUA assays are included as a subset of FDA tests throughout the article, as they were subject to review and authorization by the FDA under Section 564 of the Federal Food, Drug, and Cosmetic Act.[23] For clarity, individual assay names were shortened throughout the article to reflect the analyte (and specimen type, as applicable).

Under a separate institutional review board exempt protocol (University of Utah, #00161484), the number of scanned external test reports categorized as "genetic test results" in our electronic health system (Epic) in 2021 was also retrieved. These results represent assays requested by providers directly to third-party laboratories.

Design

The total and proportional number of ordered tests and unique assay types were tabulated according to compliance category. These values were then analyzed by patient admission status, ordering location, and ordering department's medical specialty. The frequency distributions of the most commonly ordered LDTs were then analyzed overall and for each specialty. Data analysis was conducted using Stata 17 (StataCorp), Excel 365 (Microsoft), and SigmaPlot 14 (Systat).

RESULTS

Providers within our health system ordered 3,020,260 tests through our laboratories in 2021. Of these, 3,332 (0.1%) were for send-out tests performed by outside laboratories. As these did not have compliance categories available for review, they were excluded from further analysis. An additional 5,572 scanned test reports categorized as "genetic test results" were identified in our hospital electronic health record system in 2021, representing tests ordered directly by

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providers to third-party laboratories. Among these, 1,223 had corresponding referral documentation in our laboratory information system that enabled categorization by compliance category. These are analyzed separately, however, as they are not included in our original data set of test orders.

Of the remaining 3,016,928 tests, 2,831,489 (93.9%) were for FDA assays, 116,583 (3.9%) were for LDTs, and 68,856 (2.3%) were for standard methods **TABLE 1**. These test orders were performed using a total of 1,954 distinct assays. Of these, 983 (50.3%) were FDA assays, 880 (45.0%) were LDTs, and 91 (4.7%) were standard methods. Among the FDA tests ordered, 24,385 (0.8% of total orders) were for EUA assays, with more than 99.9% of these orders for SARS-CoV-2 testing. Among the LDT orders, 6,301 were for modified FDA assays (0.2% of total orders), which included 49 unique assays. A change in the specimen type, preservative, or collection device was the reason for the modification of most assays (40 of 49 assays, representing 5,068 of the 6,301 modified FDA tests ordered).

Test volume and regulatory status were then evaluated by the ordering location and setting **TABLE 2**. Overall, total test order volumes were higher at UH compared with the cancer center (2,559,594 and 457,334, respectively). Across these 2 settings, more tests were ordered in the outpatient (2,207,630, 73.2%; combined) than in the inpatient (809,298, 26.8%; combined) locations. The odds ratio of exposure to either an LDT or standard test order vs an FDA test order (cancer institute vs UH) was 2.07 (95% CI, 2.01-2.09; $P = .001$).

The most commonly ordered LDTs and standard assays across the health system were then evaluated. Ninety percent of the LDT order volume was represented by 167 assays (19.0% of the total number of LDT assays). These assays used predominately 4 methodologies, including mass spectrometry (60 assays), various immunoassay techniques (33 assays), several nucleic acid amplification techniques (27 assays), and flow cytometry (11 assays) (see Supplemental Figure 1; all supplemental materials can be found at *American Journal of Clinical Pathology* online). The remaining 36 assays used 11 different methodologies. All of these methodologies are well established in the literature and used as part of cleared, approved, or authorized test systems by the FDA. The 20 most frequently ordered LDTs accounted for 53.3% of the total LTD volume (62,095 orders) **TABLE 3**. Among the 20 most frequently ordered LDT assays, 12 used mass spectrometry, including assays that measure drugs/therapeutics, hormones, vitamins, and trace elements. Seven of the most frequently ordered LDT assays are used in the clinical care of immunocompromised individuals or in the setting of transplantation for the detection of tacrolimus, cytomegalovirus (CMV) viral load, CD4 lymphocyte subset, Epstein-Barr virus (EBV) viral load, BK virus viral load, cyclosporin A, and everolimus. Two of the most frequently ordered LDT assays are used for the diagnosis and monitoring of hematopoietic neoplasms (leukemia/lymphoma phenotyping and chromosome analysis). Eight standard assays accounted for 95% of the total standard test volume **TABLE 4**.

Test volumes according to the ordering location of the medical specialty were then evaluated **FIGURE 1** (see Supplemental Table 1). Among the orders that could be directly attributed to a specific specialty, internal/family medicine and emergency/intensive care had the highest absolute total numbers of orders (1,044,642 and 456,590, respectively), of which a small percentage were LDT orders (3.2% and 1.4%, respectively). The LDT orders, as a percentage of total test volumes for the specialty, were the highest in radiology (27.0%), infectious disease (10.4%), and neurology (8.9%). Supplemental Table 2 shows the most common LDTs by medical specialty. Each specialty (except dermatology) included at least one of the top 20 most common LDTs.

Orthopedics, radiology, and oncology ordered proportionally more standard methods than other specialties (14%, 12.8%, and 6.3%, respectively; Supplemental Table 2). In orthopedics, the standard methods ordered were primarily erythrocyte sedimentation rates (80.2%) and body fluid cell counts (19.0%); in radiology, the most frequently ordered standard methods were body fluid and cerebrospinal fluid cell counts (89.4%); and in oncology, the most

TABLE 1 Categorization of Tests by Regulatory Status

Characteristic	Volume of Tests Ordered, No. (%)	Distinct Assays, No. (%)
FDA assays	2,831,489 (93.9)	983 (50.3)
FDA	2,807,104 (93.0)	979 (50.1)
EUA	24,385 (0.8)	4 (0.2)
LDT assays	116,583 (3.9)	880 (45.0)
LDT	110,282 (3.7)	831 (42.5)
Modified FDA	6,301 (0.2)	49 (2.5)
Standard methods	68,856 (2.3)	91 (4.7)
Total	3,016,928	1,954

EUA, emergency use authorization; FDA, Food and Drug Administration; LDT, laboratory-developed test.

TABLE 2 Test Volumes by Location, Setting, and Regulatory Status

Characteristic	FDA, No. (%)	LDT, No. (%)	Standard, No. (%)	Total No.
University of Utah Health	2,422,142 (94.6)	91,133 (3.6)	46,319 (1.8)	2,559,594
Inpatient	611,060 (95.9)	13,255 (2.1)	12,911 (2.0)	637,226
Outpatient	1,811,082 (94.2)	77,878 (4.1)	33,408 (1.7)	1,922,368
Cancer center	409,347 (89.5)	25,450 (5.6)	22,537 (4.9)	457,334
Inpatient	154,602 (89.8)	6,698 (3.9)	10,772 (6.3)	172,072
Outpatient	254,745 (89.3)	18,752 (6.6)	11,765 (4.1)	285,262
Total	2,831,489 (93.9)	116,583 (3.9)	68,856 (2.3)	3,016,928

FDA, Food and Drug Administration; LDT, laboratory-developed test.

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TABLE 3 Most Frequently Ordered Laboratory-Developed Tests

Test Name	Specimen	Method	Test Volume, No.	% LDT Volume
Tacrolimus	WB	MS	12,662	10.9
Cytomegalovirus, viral load	P	RT-PCR	5,226	4.5
Estradiol	S, P	MS	4,527	3.9
Leukemia/lymphoma phenotyping	WB	FC	4,410	3.8
Targeted drug profile	U	EIA, MS	3,394	2.9
CD4 lymphocyte subset	WB	FC	3,373	2.9
Vitamin B_1	WB	MS	3,222	2.8
Zinc	S, P	MS	2,858	2.5
Copper	S, P	MS	2,635	2.3
Epstein-Barr virus, viral load	S, P	RT-PCR	2,584	2.2
Progesterone	S, P	MS	2,279	2.0
Vitamin A	S, P	HPLC/UV	2,144	1.8
Chromosome analysis	BM	GB	1,954	1.7
Testosterone, total	S, P	MS	1,822	1.6
Vitamin B6	S, P	MS	1,784	1.5
Selenium	S, P	MS	1,618	1.4
BK virus, viral load	WB, S, P	RT-PCR	1,546	1.3
Everolimus	WB	MS	1,445	1.2
Albumin, body fluid	BF	IT/SPEC	1,342	1.2
Cyclosporin A	WB	MS	1,270	1.1

BF, body fluid; BM, bone marrow; EIA, enzyme immunoassay; FC, flow cytometry; GB, Giemsa band; HPLC/UV, high-performance liquid chromatography/ultraviolet absorbance; IT/SPEC, immunoturbidimetry and spectrophotometry; LDT, laboratory-developed test; MS, mass spectrometry; P, plasma; RT-PCR, real-time polymerase chain reaction; S, serum; U, urine; WB, whole blood.

TABLE 4 Most Frequently Ordered Standard Methods

Assay	Specimen	Method	Test Volume, No.	% Standard Volume
Differential cell count (manual)	WB	M	25,861	37.6
Erythrocyte sedimentation rate	WB	V	21,209	30.8
Urinalysis	U	SPEC	7,133	10.4
Cell count	BF, CSF	M	5,120	7.4
Blood smear with interpretation	WB	M	2,416	3.5
Gram stain	BF, CSF	M	1,331	1.9
Ova and parasite exam	Stool	M	1,276	1.9
Wet prep, vaginal	G	M	747	1.1

BF, body fluid; CSF, cerebrospinal fluid; G, genital; M, microscopy; SPEC, spectrophotometry; U, urine; V, visual; WB, whole blood.

frequently ordered standard methods were differential cell counts (62.2%) and urine pH (23.2%) (data not shown).

The frequency of orders for all noninfectious disease molecular tests was then evaluated. In our data set of test orders, a total of 143 different assays were identified for this category, 6 of which are FDA cleared/approved and included only 62 orders. The remaining 137 were LDT assays accounting for 10,233 orders, representing 8.8% of the total LDT volume and 0.3% of the total order volume (data not shown). Among the most frequently ordered tests in this subclassification were chromosome analysis (1,954 orders), myeloid malignancy panel by next-generation sequencing (NGS) (1,138 orders), and quantitative assay for *BCR-ABL1* major (p210) fusion forms (839 orders), all of which are used for the diagnosis, prognostic determination, and monitoring of hematopoietic neoplasms. In the analysis of the additional 1,223 genetic test reports for assays ordered by providers directly to outside laboratories (for which we had sufficient information to assess compliance category), 137 (11.2%) were for FDA assays and 1,086 (88.8%) were for LDTs.

DISCUSSION

The present study demonstrated that LDTs account for a relatively low percentage of all diagnostic tests ordered in an academic hospital and outpatient system (3.9% of tests ordered). While 45% of the assays that were ordered were LDTs, a relatively small number

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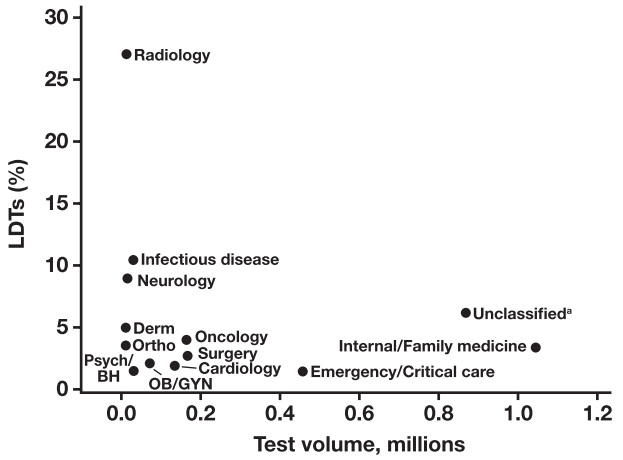

FIGURE 1 Test volume vs percent laboratory-developed tests (LDTs) by medical specialty. Total volume includes US Food and Drug Administration assays, LDTs, and standard tests. See Supplemental Table 1 for complete information. Derm, dermatology; Psych/BH, psychiatry/behavioral health; OB/GYN, obstetrics and gynecology; Ortho, orthopedics. [a]Unclassified includes orders collected at walk-in outpatient phlebotomy locations.

of these accounted for the majority of the volume of LDTs ordered (167 assays, 90% of LDT order volume). If device registration was required for all these tests, it would be a significant burden on clinical laboratories. If standard tests were classified as LDTs, then the combined overall percentage of non–FDA-cleared/approved/authorized tests would be 6.1% of all diagnostic tests ordered.

Analysis of our data identified some common themes. First, assays that use mass spectrometry are the most common and most frequently ordered LDTs. While clinical mass spectrometers are classified by the FDA as class I (low risk) and exempt from premarket review,[24] many of these analytes are currently classified as class II (moderate risk) and would likely require a 510K submission for an assay kit that was commercially distributed by a manufacturer.[25] While a mass spectrometry assay for the quantitative determination of 25-OH-vitamin D was cleared by the FDA through the De Novo pathway in 2017 and classified as class II (exempt),[26] for some analytes, including vitamin B_1, vitamin B_6, zinc, and selenium, there are no FDA-cleared/approved assays and no regulations specifying their risk classification. There are FDA-cleared or exempt assays for estradiol, progesterone, and copper, but there appears to be an analytical benefit to using mass spectrometry for these analytes.[27,28]

The second theme identified was that several of the most frequently ordered LDTs were assays used in the clinical management of immunosuppression and transplantation. These assays are routinely used in evidence-based practice guidelines for these patient populations.[29] While there are FDA-cleared immunoassays for tacrolimus, everolimus, and cyclosporin A and viral load assays for CMV, EBV, and BK virus, unmet clinical needs appear not to be addressed by these assays, including nonapproved specimen types and workflow modifications.[30]

The third theme we identified in our data analysis was the need for modification of an existing assay for testing alternative specimen types. For example, commonly ordered LDTs in dermatology included polymerase chain reaction testing for herpes simplex virus and varicella-zoster virus, for which there are no FDA assays approved for testing specimens other than urogenital or anogenital skin lesions. Because the assays use an alternative specimen type (ie, a swab from a nonurogenital or nonanogenital lesion), this makes the assay an LDT under current regulatory structures. The same is true for some of the commonly ordered LDTs in emergency medicine (eg, body fluid total protein, glucose, and lactate dehydrogenase). VALID Act submission requirements related to test modifications due to source and/or specimen type could burden clinical laboratories with significant additional regulatory requirements and costs.[31] More broadly, given the common themes we identified, it is essential that any impact on overall health care costs is considered in the context of regulatory reform efforts.[32]

The present study showed that across specialties, genetic testing such as NGS and other noninfectious disease molecular testing are currently not among the most commonly ordered methodologies in our health system. This testing made up less than 0.3% of the total testing volume and only 8.8% of the LDT test volume. The regulation of molecular diagnostics has been a particular focus of reform efforts in both the United States and the European Union.[33] Next-generation sequencing and genomic testing, particularly for use in oncology and prenatal screening, are often referenced as justifications in support of diagnostic regulatory reform efforts.[34] Ultimately, the potential burden and cost of regulatory reform efforts may have a disproportionate impact on the ability to develop and sustain assays that are not frequently ordered.

The differentiation between LDTs and standard tests has not received much attention in diagnostic reform discussions. For example, in the current draft of the VALID Act, "manual tests" are exempt from certain regulatory requirements but only if they are not considered high risk and if no component or reagent of such tests is introduced into interstate commerce.[13] While pathologist interpretations of immunohistochemistry or in situ hybridization may qualify as manual testing, manufacturers of reagents used for manual tests may be subject to new regulatory oversight requirements under the VALID Act.

Limitations of the present study include the fact that data from only 1 health network were available for the analysis of LDT volumes. In addition, the presence of a national reference laboratory as part of the university health system may also have contributed to more LDTs being available for ordering than at other institutions. If this were the case, the present study's findings may overrepresent LDT orders vs those placed at other institutions. Alternatively, the present results may represent the combined proportion of LDTs that a large health system would either perform in house or send to referral laboratories. Finally, the present report cannot exclude the possibility of other types of uncategorized scanned test reports in the electronic health record from third-party laboratories.

The observation that only a small percentage of total ordered tests were LDTs and that a relatively small proportion of LDT assays made up most of the LDTs ordered has practical implications for the potential impact of diagnostic reform efforts on clinical

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laboratories. For example, an increase in regulatory costs associated with low-volume, low-margin tests could make ongoing clinical offerings unsustainable in certain settings. Regulatory reform efforts should consider all approaches to ensuring the most appropriate and cost-effective patient care is available.

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