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Research Article

Impact of the loss of Laboratory Developed Mass Spectrometry testing at a major academic medical center

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ABSTRACT

Background: Our laboratory historically performed immunosuppressant and definitive opioid testing in-house as laboratory developed (LDT) mass spectrometry-based tests. However, staffing constraints and supply chain challenges associated with the COVID-19 pandemic forced us to refer this testing to a national reference laboratory. The VALID Act could impose onerous requirements for laboratories to develop LDTs. To explore the potential effect of these additional regulatory hurdles, we used the loss of our own LDT tests to assess the impact on patient care and hospital budgets.

Methods: Laboratory information systems data and historical data associated with test costs were used to calculate turnaround times and financial impact.

Results: Referral testing has extended the reporting of immunosuppressant results by an average of approximately one day and up to two days at the 95th percentile. We estimate that discontinuing in-house opioid testing has cost our health system over half a million dollars in the year since testing was discontinued.

Conclusions: Barriers that discourage laboratories from developing in-house testing, particularly in the absence of FDA-cleared alternatives, can be expected to have a detrimental effect on patient care and hospital finances.

Introduction

Laboratory developed tests (LDTs) play a valuable role in diagnostic laboratory medicine. They are used for a variety of purposes, such as therapeutic drug monitoring (TDM) of medications. Clinical laboratories can develop and validate LDTs to increase access to testing, reduce turnaround time, and enable them to quickly adapt to new diagnostic challenges, such as the recent SARS-CoV-2 pandemic.

The development and validation of LDTs are currently limited to high-complexity laboratories regulated by the Clinical Laboratory Improvement Amendments (CLIA) [1–4]. Despite a long history of successful LDT use in clinical laboratories, the VALID Act, or the "Verifying Accurate Leading-Edge IVCT Development" Act in its initial form, submitted for congressional approval in March of 2022, would change the regulatory oversight of LDTs by empowering the United States Food and Drug Administration (FDA) to enforce oversight of LDTs in the same manner as the FDA approves in vitro diagnostic (IVD) tests.

The final bill is still being debated, and the final regulatory landscape is not yet defined. Numerous publications in both popular press and scientific journals have outlined the potential effects that the VALID Act could have on diagnostic laboratory medicine [3,5–7]. One frequently-cited effect is the potential for increased turnaround time for test results, as smaller laboratories will be forced to send patient testing to reference laboratories. This is because only reference laboratories have the resources needed to submit the required documentation and have enough volume and revenue to justify the increased cost of regulation.

Due to the loss of key personnel in a short time frame, we were forced to send out all testing performed by mass spectrometry (MS) beginning in February 2022. This impacted both TDM of our immunosuppressant drugs (ISDs) and our opioid testing panel.

Post-transplant, solid organ and bone marrow transplant recipients require life-long management with ISDs such as tacrolimus, sirolimus, and cyclosporine to prevent organ rejection [8]. TDM is required in such patients, as ISDs have a narrow therapeutic window. Insufficient

Abbreviations: CLIA, clinical laboratory improvement amendments; Cyclo A, cyclosporine A; EUA, emergency use authorization; FDA, food and drug administration; ISD, immunosuppressant drug monitoring; IVD, In-vitro diagnostic; LCMS, liquid chromatography mass spectrometry; LDT, laboratory developed test; MS, mass spectrometry; TAT, turnaround time; TDM, therapeutic drug monitoring; VALID, verifying accurate leading-edge IVCT development.

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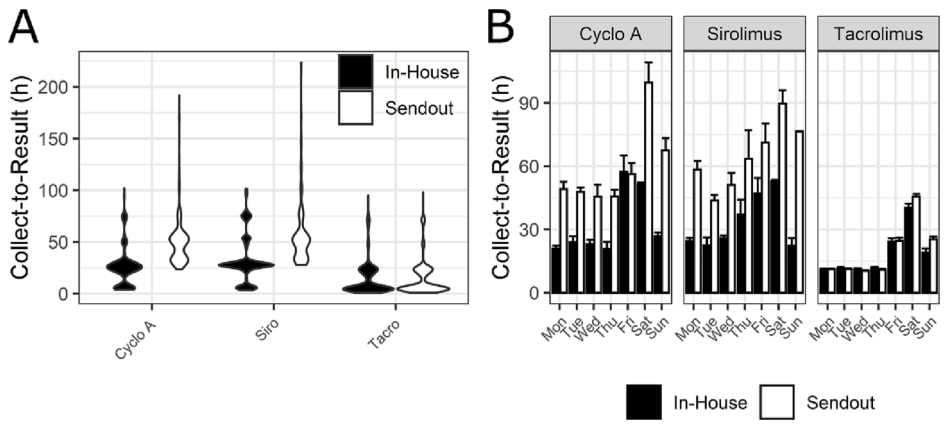

Fig. 1. A) Distribution of turnaround times by assay during the In-House and Sendout periods. As shown in Table 1, cyclosporine A ("Cyclo A") and sirolimus ("Siro") saw significantly longer turnaround times during the sendout period, while tacrolimus ("Tacro") was unchanged. B) Mean turnaround time by test and day of specimen collection during the In-House and Sendout periods. Bars represent mean +/- standard error. Open bars represent the Sendout period.

Table 1
Turnaround times for immunosuppressant drug measurements prior to and after sendout.

Test	Period	n	Mean TAT[a] (h)	Median TAT (h)	95th %ile (hours)	P[b]
Cyclosporine A	In-House	162	26.90	24.89	74.37	$<2 \times 10^{-16}$
	Sendout	184	51.52	50.41	101.52	
Sirolimus	In-House	111	33.29	27.73	76.57	$<2 \times 10^{-16}$
	Sendout	97	57.90	51.64	124.26	
Tacrolimus	In-House	2120	14.57	5.98	60.47	1.000
	Sendout[c]	2182	14.79	5.98	60.05	

[a] TAT, turnaround time.
[b] Bonferroni-corrected P values for In-House and Sendout values within the same test. Means for sirolimus and cyclosporine A were not significantly different in the In-House (P = 0.062) or Sendout (P = 0.073) periods.
[c] Sendout refers to the period during which cyclosporine A and sirolimus have been referred to an outside laboratory; tacrolimus was not sent out but serves as a control for test volumes and other affects not due to externalizing the test.

concentrations are associated with increased risk of organ rejection, while concentrations above the therapeutic window can damage the organ they are meant to preserve [9]. Timely analysis and reporting of these ISDs is needed both immediately post-transplant as well as during follow up visits, particularly in the setting of acute illness when pharmacokinetics may differ from baseline.

Opioids challenge immunoassays because of their structural variety and necessitate availability of multiple immunoassay screens. Conversely, their sometimes unexpected cross-reactivities to related drugs [10] limit the utility of these screens when assessing patient compliance. Because of high volumes of patients on opioid compliance contracts, we internalized LCMS opioid testing in October 2020. Testing continued until supply chain issues paused testing in late 2021, and it was not revived prior to suspension of MS testing in February 2022.

The discontinuation of LCMS testing provides us an opportunity to examine the impact of the loss of these LDTs on our facility in accordance with their priorities. This change in testing site allows us a view into what laboratories and medical providers might expect should the VALID Act lead to the discontinuation of established and regulated LDTs or impede their development at medical centers.

Materials and methods

Numbers of tests and times of collection and verification were identified for ISDs from June 15, 2021, through October 13, 2022, approximately the eight months before and eight months after transition to referral testing on February 14, 2022, using reports within Cerner Millennium. Tacrolimus was moved to an automated immunoassay approximately five months prior to the study period and served as a control for volumes and turnaround time (TAT).

Turnaround time was calculated as the time from specimen collection to verified result. Numbers of tests and originating locations were identified for the in-house LCMS opioid panel for the period from November 3, 2020, to November 10, 2021 (a period of 371 days), and for the LCMS opioid sendout panel from November 10, 2021, to November 16, 2022 (also a period of 371 days). Cost and reimbursement information were obtained from our departmental business manager; test volumes and specific cost and reimbursement figures are presented only in aggregate form.

Statistical analyses and data visualization were conducted in R using the R Studio integrated development environment. Unless specified, means were compared with two-sample, two-sided t-tests assuming unequal variances.

Institutional Review Board (IRB) approval was not required for this study.

Results

Switch to referral testing adversely impacted immunosuppressant turnaround times

Prior to sendout, ISDs other than tacrolimus (i.e., cyclosporine A and sirolimus) were performed Monday through Friday, typically in two batches per day. Saturday and Sunday runs required director approval and made up approximately 1% of the total test volume for these ISDs. Tacrolimus was moved to immunoassay on our automated chemistry line and offered Monday through Friday on day shift (with Saturday and Sunday runs again requiring director approval). Tacrolimus served as a control for turnaround time assessment during the study period; the sendout of cyclosporine A and sirolimus should have no impact on

tacrolimus test volume or turnaround time.

Distributions of turnaround-time data are presented in Fig. 1A, and sample sizes and selected summary statistics for turnaround time by assay are presented in Table 1. Similar proportions of each test were observed in the In-House and Sendout periods (P = 0.333, Fisher's Exact Test). The mean and median turnaround times for cyclosporine A and sirolimus lengthened significantly by approximately 24 h each (Table 1), and 95th percentile turnaround times extended by 27.15 h for cyclosporine A and 47.69 h for sirolimus. Turnaround time for tacrolimus did not differ significantly between periods, consistent with its performance by automated immunoassay being unaffected. The lessened impact at the 95th percentile for cyclosporine A is unclear; on average, Cyclosporine A results were verified later in the day (12:37 pm vs 11:52 am, P = 0.035), but a mean difference of 45 min seems unlikely to fully explain the gap. No meaningful differences were observed for collection times or time in-lab (P = 0.351 and P = 0.764).

The distributions of data exhibited periodicity (Fig. 1A), with the greatest densities of turnaround times occurring at approximately 24-hour intervals. We observed that delays in turnaround time had the greatest impact on specimens collected during weekdays, and these likewise had the greatest impact on the mean turnaround time due to the relative paucity of such orders over the weekends. This delay logically accounts for the approximately 24-hour mean difference in turnaround—an additional day is required for transit to and routing at the reference laboratory.

Specimens collected after shipment on Friday, or on weekends, when our referral laboratory department is closed, were also affected; they were not shipped until the following Monday, arriving at our reference laboratory on Tuesday instead of in the special chemistry laboratory on Monday. Of the longest 10% of cyclosporine A turnaround times, 10 out of 19 samples were received in lab between 3:30 PM Friday (our shipment cutoff) and midnight Monday morning, whereas only 3 out of 17 were received during the in-house period (P = 0.041, Fisher's Exact Test). Lower weekend volumes for sirolimus precluded analysis, and no impact due to weekend collections was identified for tacrolimus.

Switch to referral testing adversely impacted opioid testing costs

Assessing the budgetary impacts of externalizing a test is not straightforward due to differences in insurance provider reimbursement. Additionally, labor costs per test may be difficult to assess if the loss of a test does not result in changes to the number of full-time equivalents required to perform other laboratory testing. Nevertheless, it is still beneficial to explore the impact of externalizing these tests within these limitations.

While we have incurred increased costs due to the referral of ISDs (sirolimus costs are approximately threefold and everolimus costs are approximately fivefold), the relatively low volumes lessen their financial impact. Conversely, the annual test volume for the urine opioid panel is approximately 10 times the number of ISD samples and could represent a much greater impact on our budget.

In analyzing the financial impact of sending our opioid testing to a reference laboratory, two aspects became clear. The first was unexpected: our volume of opioid panel testing for the 371 days prior to discontinuing testing was 169% of what it was in the 371 days after. Upon investigation, we realized that the source of the disparity lay in the handling of sendout tests at our affiliate hospitals; in most cases, they sent their samples directly to the referral laboratory. When we internalized opioid testing, we captured not only our own referral volumes, but those of our affiliate sites, which accounted for approximately 38% of our volume during the in-house period.

The price our institution is billed for the opioid screen is 2.5 times our cost of performing the testing, not including labor. This difference amounts to approximately $52,000 in costs since we converted to sendout testing from our facility. When accounting for anticipated reimbursement, reduced costs, and the sendout costs we captured from our affiliate sites—one of which produces 50% of our sendout volumes—we estimate that the sendout has cost our health system approximately $564,000 over these 371 days.

Discussion

The extended turnaround times for sirolimus and cyclosporine A, along with updates to their therapeutic ranges, have impacted our solid organ and bone marrow transplant programs at DHMC. Although our transplant program is relatively small, it is the only solid organ transplant center in New Hampshire; since its inception, it has performed approximately 1,050 renal transplants, with a total of 47 organ transplantations occurring between calendar years 2020 and 2021 [11]. As a health system, we currently follow approximately 300 post-kidney transplant patients, according to the most recent Scientific Registry of Transplant Recipients report [11]. This number of monitored patients does not include those who have received allogeneic bone marrow transplants at the Norris-Cotton Cancer Center at DHMC. That population is of a similar size, and approximately 20 patients undergo allogeneic bone marrow transplantations annually (personal communication with Christi Ann Hayes, MD).

At our small transplant center, the change in turnaround time for sirolimus and cyclosporine A has not gone unnoticed by the clinical treatment team. In particular, our providers have conveyed to us that the delayed reporting of cyclosporine A has complicated the initial dosing of pediatric patients in the hematology service (personal communication with Angela Ricci, MD).

Unfortunately, we were unable to transition sirolimus and cyclosporine measurements to an FDA-cleared method due to the paucity of approved methods for the commonly used ISDs (tacrolimus, sirolimus, and cyclosporine). Tacrolimus currently has the largest number of FDA-cleared automated laboratory methods available, with offerings from Abbott Diagnostics, Roche Diagnostics, and Siemens Healthineers. Reagents from Thermo Scientific and Syva EMIT are available but considered LDTs when used on automated analyzers for which they were not designed. For the other ISDs, there are fewer FDA-cleared methods. The Abbott Architect *i* and Siemens Dimension are the sole platforms with automated FDA-cleared assays for all three drugs. In the absence of readily available FDA-cleared assays, many clinical laboratories are forced to choose between sending testing to a reference laboratory or establishing LDTs via third-party reagents or MS.

As with many medical centers, our healthcare system has continued to face difficult financial headwinds, most recently announcing a $22.1 million budget shortfall [12]. Unfortunately, our facility finds itself in good company with approximately 53% of hospitals expected to post a financial loss in 2023 [13]. Although the loss of our LDT MS testing was not a consequence of the VALID Act, it does demonstrate that there was an annual financial shortfall of approximately $600,000 due to its absence. As an academic medical center, these LDTs are only two of many, and the potential financial impact can have wide-reaching reverberations throughout the healthcare system.

Even in situations where it is possible to use an FDA-cleared method for testing, there may be valid reasons to prefer an LDT. For example, a review of the instructions-for-use for a whole-blood sirolimus assay on the Siemens Dimension analyzer reveals substantial cross-reactivity of 6–89% with O-demethylated or hydroxylated sirolimus metabolites [14]. This cross-reactivity may lead to reporting of a falsely elevated or biased concentration as compared to a specific LCMS method, as has been demonstrated previously [15]. Other immunoassay manufacturers offer similar disclaimers with respect to cross-reactivity in their product inserts [14,16–18].

Our experiences and data can be generalized to predict the effects on many laboratories for a majority of commonly performed chemistry tests on pathological accumulations of body fluids, not discussed here. Light's criteria for the determination of transudative vs. exudative effusions rely on measurement of fluid total protein and/or lactate dehydrogenase

[19], and neither of these widely used tests are available as FDA-cleared methods. Likewise, tumor marker detection in body fluids (e.g., hCG or AFP in cerebrospinal fluid [20]), most toxicology testing by definitive methods (e.g., toxic alcohols, drugs of abuse), and many endocrine tests (e.g., testosterone) are often performed via LDTs. A system in which clinical laboratories are compelled to submit their validation data for routinely available tests for FDA review would likely result in numerous submissions, potentially delaying approval for months or even years.

Conclusions

The loss of key LDTs at our facility has had detrimental impacts on both patient care and the financial health of the hospital. Though not caused by the VALID Act, our experience highlights potential consequences should laboratories struggle to maintain or develop new LDTs. A final form of VALID that erects high barriers for the development of LDTs may force laboratories to make difficult decisions about the investment of resources into their development. If this final form requires laboratories to send all existing LDTs through a laborious and time-consuming submission and approval process at the FDA, it jeopardizes the care of vulnerable patient populations, such as transplant recipients and oncology patients, whose physicians depend on these tests. Moreover, even a brief period of such losses could exacerbate an ongoing financial crisis. Therefore, lawmakers should exercise caution when evaluating what role, if any, the FDA should play in overseeing LDTs.

Funding information

This study was not funded.

Ethics statement

Institutional Review Board (IRB) approval was not required for this study.

CRediT authorship contribution statement

K. Aaron Geno: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing, Visualization, Software, Formal analysis, Investigation, Resources, Supervision. **Mark A. Cervinski:** Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing, Visualization, Formal analysis, Investigation, Validation, Resources, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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