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Mini-Review

How the VALID Act could affect patient access to laboratory developed testing for therapeutic drug monitoring

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1. Introduction

Therapeutic drug monitoring (TDM) is an area of clinical laboratory medicine that provides accurate, quantitative drug concentrations in patient samples [1]. These samples are typically collected in whole blood, serum or plasma and drawn immediately before the next drug dose (trough), and their quantitative result is used by pharmacists and other medical personnel to adjust the following dose of the drug [1]. TDM is particularly important for drugs with narrow therapeutic windows, unusual pharmacokinetics, or patient-to-patient variability in metabolism or protein binding [2]. Immunosuppressant drugs (ISDs), antiepileptic drugs (AEDs), antimicrobials, antidepressants, antipsychotics, antiarrhythmics, and antihypertensive drugs are all drug classes where TDM is routinely employed [3]. In the United States, 2.5–3 % of Americans are estimated to be prescribed ISDs [4,5], and over 1 % of Americans are estimated to have epilepsy [6], with the vast majority being treated with AEDs [7]. Published protocols for evaluating efficacy and safety of ISD and AED therapies include routine TDM, the analytical results of which are produced by complex assays in clinical laboratories [8].

Although the Food and Drug Administration (FDA) has cleared immunoassays for some specific TDM targets, Liquid Chromatography-Mass Spectrometry (LCMS)-based assays have provided foundational support for the quantitation of many of the clinically necessary TDMs and are considered the reference method for patient testing [9]. A PubMed search of "Therapeutic Drug Monitoring Mass Spectrometry" in October 2022 yielded 7,056 publications within the past 10 years. Currently, there is only one LCMS-based TDM assay that has ever been FDA cleared; it was only cleared to quantify tacrolimus. This makes the vast majority of current LCMS-based TDM assays in the United States laboratory-developed tests (LDTs). The clinical utility of LCMS-based LDTs, particularly those supporting TDM, is met by providing high sensitivity and high specificity [9], while also allowing creators to adjust assay parameters to meet their unique patient populations' needs [10]. An example of this flexibility is how the creators of one LCMS-based tacrolimus quantitation LDT validated a new calibration protocol that enabled patient samples to be extracted without needing a full calibrator set extracted concurrently [11]. This strategy improved turn-around times (TAT) for single patient testing compared to waiting for an entire calibration curve to be acquired and evaluated first [11]. Other examples of improved clinical utility based on the flexibility of LDTs include: (1) Rapidly validating a new or different collection device or tube type when supply chain issues cause delays in shipping, (2) Extending the analytical measurement range (AMR) of a pre-existing clinical assay to capture more elevated results without needing to perform additional dilutions, and (3) Developing and validating new drug targets on an existing LCMS method to improve test menu options and patient access to testing.

LDTs are currently managed under the regulatory umbrella of CLIA; however, the updated 2022 Verifying Accurate Leading-Edge IVCT Development (VALID) Act proposal submitted to Congress in its current form pushes for FDA regulation of LDTs in all clinical laboratories [12,13]. If passed, these changes would alter the regulatory landscape of LDTs and potentially have significant impacts on patient care and access to important laboratory testing. This analytical overview will review the current regulatory landscape, discuss the proposed changes, and consider how they may directly impact patient care in the United States.

2. Regulatory background

Understanding the origins of the VALID Act, and its potential impacts, necessitates a brief overview of the current regulatory landscape. Through the Clinical Laboratory Improvement Act of 1988 (CLIA), the Centers for Medicare and Medicaid Services (CMS) regulates human clinical laboratory testing in the United States [12]. This regulation is organized by the complexity of the testing performed, and in order for laboratories to develop LDTs or make changes to any FDA-cleared assays, they must be classified as high complexity laboratories. The FDA provides oversight for commercial in vitro diagnostics (IVDs), but oversight for LDTs is unclear. Although all LDTs are considered IVDs, the

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FDA has historically deferred to CMS to regulate them through CLIA. Through CLIA, or organizations such as the College of American Pathologists (CAP) or the Joint Commission (TJC), LDTs are regulated based on analytical performance through validation requirements that must be provided upon inspection [12].

Two main gaps of concern in this regulatory structure have been raised by the FDA:

1. These laboratory inspections through CLIA, or CLIA accredited bodies, typically occur every-two years, which means new LDTs can begin to be offered for patient testing before they are reviewed during inspection [13].
2. Clinical validation claims that an individual laboratory produces to diagnose disease are typically not part of the CLIA regulatory scope for evaluation [13].

In 2018, an initial draft of the VALID Act was created to address the FDA's concerns [14]. Since its introduction to congress in 2020, the VALID Act has been revised multiple times and as of February 1, 2023, has yet to be passed in any form. Some key components of the VALID Act that would directly affect clinical laboratories that manage or create LDTs include:

1. Language to grandfather current LDTs already created and on the market prior to the VALID Act enactment [14].
2. Proposed infrastructure to create a third-party review program which would manage the many thousands of LDTs on the market [14]. This infrastructure is proposed because the FDA, in its current state, would not have the resources to oversee LDTs on their own.
3. A certification program proposal, allowing certain clinical laboratories to market specific LDTs without a full submission to the FDA [14].
4. An undefined time allowance for clinical laboratories to fully transition to this new regulatory framework [14].

3. Current perspectives

This new framework proposed in the VALID Act has a spectrum of perspectives ranging from full support of the VALID Act to full rejection of the entire proposal [15].

Some specific points in favor of the passing of the VALID Act in the context of LCMS-based LDTs for TDM include:

1. Aid in the standardization and harmonization of LDT clinical assays

Standardization and harmonization of clinical assays has become an important objective of many clinical laboratories and laboratory organizations. The prospect of improving these metrics through the passing of the VALID Act is welcomed by the community.

2. Aid in improving patient safety and reducing patient harm

Proponents of the VALID Act argue that this framework improves patient safety and harm reduction by standardizing all IVDs under one regulatory body. The lobbying organization AdvaMedDx, which represents IVD manufacturers, strongly supports LDT regulation under the FDA. They argue that FDA review of LDTs would directly improve patient safety and test effectiveness [15]. Some focus has been placed on Noninvasive Prenatal Testing (NIPT) and Direct-to-consumer genetic testing LDTs and the concerning variability of results that these LDTs produced from different manufacturers [16]. The concern is that this variability could have devastating consequences to patients making decisions on potentially inaccurate or inconsistent results [16]. Specifically, the following concerns were discussed based on the current use of LDTs without FDA oversight:

3. Patients experiencing negative health effects from receiving unnecessary or inappropriate treatments [16].
4. Patients experiencing missed treatments or delay in receiving proper medical care as a result of unregulated LDT results [16].
5. Emotional burden experienced by a patient being wrongly diagnosed using an unregulated LDT [16].
6. Unnecessary confirmatory diagnostic procedures that may be painful or invasive to the patient based on an initial incorrect LDT result [16].
7. Support from large regulatory and accreditation bodies like the CAP

In their position statement, the CAP outlines support for passing of the VALID Act. Specifically, the CAP strongly supports the use of the proposed risk classification framework for LDTs in the VALID Act, which would address some of the concerns of patient safety and harm. The CAP also supports the grandfather provisions to help protect current LDTs on the market [17].

Within many clinical communities, the proposed VALID Act is believed to be deeply flawed in its current form and concerning for the future of patient access to important clinical testing [18,19]. A letter to leaders of congress was drafted in July 2022 and signed by over 125 academic universities, health systems and professional health organizations, including AACC, ACLPS, AAMC, AMP and MSACL, who opposed the VALID Act as written. In the letter, specific concerns were outlined [20]:

1. Decreasing innovation and limiting patient access to healthcare.

Based on language in the current VALID Act of 2022, the process for approving new LDTs in a rapid and efficient manner appears cumbersome and onerous. The direct impact to patient care would materialize as slower patient access to important clinical testing. The way that the VALID Act is structured, clinical laboratories wishing to offer LDTs would be required to submit annual user fees. These user fees may force many laboratories, especially smaller laboratories, to reduce their testing menu or eliminate their LDTs entirely, decreasing access to localized patient care. These cumbersome processes coupled with a new added cost to create LDTs may ultimately decrease the exploration of new and innovative testing that would have otherwise been implemented. These changes will almost invariably decrease the number of LCMS-based TDM assays offered to patients, which, at best, will increase TAT for TDM results and at worst prevent patients from being tested as recommended by published clinical guidelines [21].

2. Duplicative processes that are already covered in the current CLIA.

Some of the proposals in the VALID Act, such as updated quality systems, adverse event reporting, and laboratory inspections are highly duplicative to what clinical laboratories are required to comply with under CLIA. The language in the VALID Act [14] outlining these changes is also vague on how to de-convolute these duplicative processes, and which regulatory body would ultimately be responsible for enforcement. These discrepancies highlight a likely cumbersome set of regulatory requirements that, ultimately, will bottleneck the creation of innovative and important TDM LDTs for patient care.

3. Lack of clarity in the proposed risk categorizations, definitions, and eligibility criteria for technical certification programs.

The VALID Act attempts to define high, moderate, and low risk categories of LDTs. Based on the risk, different sets of regulatory requirements and standards may be applied to each category. These risk categories, however, remain vague and unclear, making it difficult for laboratorians to understand the requirements that would further compromise the continuity of patient care. Although the FDA has commented specifically that LCMS-based LDTs would likely be in the

low-risk classification, LCMS-based TDM assays are still undefined based on language in the VALID Act [14]. The criteria for the proposed technical certification program also remain unclear in terms of which types of tests are eligible for authorization, including LCMS-based testing.

4. Clinical LDT Creators, are not eligible to participate in the proposed accreditation process.

The VALID Act specifically clarifies that clinical laboratorians who create LDTs are not allowed to become or act as third-party reviewers of new LDTs. This approach is markedly different from those of many accredited bodies under CLIA, such as CAP, which encourage peer-review inspections by fellow clinical laboratorians to be part of the inspection process. If an inspection program were to be implemented, clinical laboratorians would be the most qualified to evaluate and determine the validity of new LDTs, as they are the subject matter experts [21]. This is especially important when focusing on LCMS-based assays. LCMS testing requires significant scientific and clinical training to understand the complexities and nuances of assay development, validation and implementation, which only highly specialized laboratorians understand [22].

4. Discussion

Reviewing the currently available devices on the FDA website of common ISD and AED assays, there is concerning evidence that development, innovation, and use of LCMS-based TDM assays would be stifled if the VALID Act were to pass in its current form. Although at least one FDA-cleared device is available for each of the common ISDs, tacrolimus is the only ISD which has an LCMS-based method that has been FDA-cleared [23]. This extremely low number of FDA-cleared LCMS-based TDM assays is not surprising, as reimbursement for clinical testing continues to decrease, thereby lowering the manufacturer's margin of profit to sell FDA-cleared LCMS assays. This situation will be even more extreme if these same barriers were applied to all clinical laboratories. Although current language in the VALID Act proposal suggests that previously created LDTs would be grandfathered in, the greatest risk would be for laboratories attempting to develop and offer new LDTs, potentially causing a significant decrease in available TDM testing. Furthermore, many specific TDM targets have only one single FDA-approved immunoassay available. This is true for AED targets such as Lacosamide, Gabapentin, Topiramate, and Oxcarbazepine metabolite, all of which are FDA approved by ARK Diagnostics. Because Ark Diagnostics only produces the calibrators and QC in an FDA-approved kit, the assays themselves must be validated on a third-party analyzer [24–27]. Based on the vague language in the VALID Act, FDA-cleared assay kits placed on third-party analyzers may be considered laboratory developed, thereby subjecting entire assay options available to clinical laboratories to transform into LDTs [14].

Reviewing many of the FDA 510 K submissions provides even more striking evidence of the flaws in the VALID Act. When providing method comparison data to prove an immunoassay functions with high accuracy, the predicate assay is usually an LCMS-based LDT [24–26]. This implies that although LCMS assays can be used as a reference method to FDA approve a new immunoassay, the LCMS assay itself remains an LDT, a conundrum which has yet to be addressed by the FDA. Additionally, FDA-cleared immunoassays for TDM have also been known to have analytical flaws which may translate into inaccurate clinical interpretations. When compared with LCMS, patient results for tacrolimus tended to be positively biased (up to 40 %), indicating potential active or inactive tacrolimus metabolites cross-reacting in the immunoassay [28]. Because of direct mass detection along with multiple quality measures, LCMS is far less prone to interference from structurally similar metabolites, reinforcing why LDT LCMS-based assays are the reference method for testing and essential for precision medicine [22,28,29].

5. Conclusion

If the VALID Act were to pass in its current form, it may take many months, if not years, for clinical laboratories to experience any changes to their LDT menus. However, the most obvious effects that clinical laboratories would likely experience following the passing of the VALID Act include:

1. Implementation of user fees that laboratories would be required to pay to support FDA oversight.
2. Existing LDTs will likely be grandfathered in and not subject to the new regulatory oversight; however, any new LDTs would be subjected to the new regulatory landscape.
3. LCMS-based LDTs are still considered foundational for supporting ISD and AED testing, so they will continue to exist after the VALID Act is passed. It is unclear, however, what extent the new regulations will impose on clinical laboratories that are attempting to create and implement new LCMS-based LDTs for ISD and AED testing.

FDA-cleared assays are essential for clinical laboratory testing, and the passing of the VALID Act may help to standardize LDTs and reduce patient harm. However, patient populations may be at risk of experiencing diminished access to critical laboratory testing if the VALID Act is passed as currently written. LCMS-based LDTs provide much-needed flexibility to safely adjust analytical parameters to meet the needs of highly specialized and delicate patient populations for fast and accurate TDM [22]. As the healthcare model continues to shift towards providing quality care through personalized medicine [29,30], passing the VALID Act in its current form would be a step backward. The language of the VALID Act needs to be clarified and revised to maximize patient safety while maintaining patient access to critically important TDM that LDTs have successfully and effectively contributed to improving patient outcomes for years.

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.

References

[1] J. Kang, L. Min-Ho, Overview of therapeutic drug monitoring, Korean J. Intern. Med. 24 (2009) 1–10, https://doi.org/10.3904/kjim.2009.24.1.1.
[2] M. Hallworth, I. Watson, K. Poyser, R. Sherwood, Therapeutic drug monitoring and laboratory medicine, ACB Venture Publications, 2008.
[3] R. Ghiculescu, Therapeutic drug monitoring: which drugs, why, when and how to do it, (2008). 10.18773/austprescr.2008.025.
[4] R. Harpaz, R. Dahl, K. Dooling, Prevalence of immunosuppression among US adults, 2013, JAMA 316 (2016) 2547–2548, https://doi.org/10.1001/jama.2016.16477.
[5] B. Wallace, B. Kenney, P. Malani, D. Clauw, B. Nallamothu, A. Waljee, Prevalence of immunosuppressive drug use among commercially insured US adults, 2018–2019, JAMA 3 (2021) 1–4, https://doi.org/10.1001/jamanetworkopen.2021.4920.
[6] M. Zack, R. Kobau, National and state estimates of the numbers of adults and children with active epilepsy United States, 2015, Morb. Mortal. Wkly Rep. 66 (2017) 821–825, https://doi.org/10.15585/mmwr.mm6631a1.
[7] K. Kim, D. Kim, K. Yang, S. Lee, J. Byun, J. Seo, Y. No, K. Kang, D. Kim, Y. Cho, Refining general principles of antiepileptic drug treatments for epilepsy, Journal of, Clinical Neurology 16 (2020) 383–389, https://doi.org/10.3988/jcn.2020.16.3.383.
[8] M. Vogeser, From therapeutic drug monitoring to total drug monitoring and drug-omics, Clin. Chem. Lab. Med. 59 (2021) 287–290, https://doi.org/10.1515/cclm-2020-0339.
[9] C. Seger, L. Salzmann, After another decade: LC–MS/MS became routine in clinical diagnostics, Clin. Biochem. 82 (2020) 2–11, https://doi.org/10.1016/j.clinbiochem.2020.03.004.
[10] D. Dietzen, Unleashing the power of laboratory developed tests: closing gaps in COVID diagnosis and beyond, The journal of applied laboratory medicine 5 (2020) 844–846, https://doi.org/10.1093/jalm/jfaa077.
[11] A. Brister-Smith, J. Young, A. Saitman, A 24-Hour extended calibration strategy for quantitating tacrolimus concentrations by liquid chromatography-tandem mass

spectrometry, J. Appl. Lab. Med. 6 (2021) 1293–1298, https://doi.org/10.1093/jalm/jfab048.
[12] J. Genzen, J. Mohlman, J. Lynch, M. Squires, R. Weiss, Laboratory-developed tests: a legislative and regulatory review, Clin. Chem. 63 (2017) 1575–1584, https://doi.org/10.1373/clinchem.2017.275164.
[13] K. Graden, A. Shannon, S. Bennett, H. Delaney, G. Willrich, M. Willrich, A high-level overview of the regulations surrounding a clinical laboratory and upcoming regulatory challenges for laboratory developed tests, Lab. Med. 52 (2021) 315–328, https://doi.org/10.1093/labmed/lmaa086.
[14] U.S. Congress, House, Verifying Accurate Leading-edge IVCT Development (VALID) Act of 2021, HR 4128, 117th Cong., 1st sess., introduced in House June 24, 2021, https://www.congress.gov/117/bills/hr4128/BILLS-117hr4128ih.pdf.
[15] D. Borfitz, Current Perspectives On The VALID Act, Diagnostics World News, (2022) https://friendsofcancerresearch.org/news/diagnostics-world-news-current-perspectives-on-the-valid-act/.
[16] E. Khatami, Clinical Lab Tests Need Stronger FDA Oversight to Improve Patient Safety, Pew Trusts, (2021) https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/01/clinical-lab-tests-need-stronger-fda-oversight-to-improve-patient-safety.
[17] College of American Pathologists (CAP), Letter to Chair Murray and Ranking Member Burr, https://documents.cap.org/documents/cap-may-2022-valid-act-comments.pdf.
[18] American Association of Clinical Chemistry (AACC), Oversight of Laboratory Developed Tests, (Position Statement). https://www.aacc.org/-/media/Files/Health-and-Science-Policy/Position-Statements/2020/LaboratoryDevelopedTests_PS_20201001.pdf?la=en&hash=6323D93ED0098BC92EAC1D3289626BF085357269.
[19] American Association of Medical Colleges (AAMC), Letter to Chair Murray and Ranking Member Burr, https://www.aamc.org/media/61121/download.
[20] American Association of Clinical Chemistry (AACC) Letter to Chair Murray and Ranking Member Burr, https://www.aacc.org/-/media/Files/Health-and-Science-Policy/Legislative-Issues/2022/Sign-on-Letter-re-VALID-Act-May-22-2022-Final.pdf?la=en&hash=BCC031B9A00200B1652FF7A914D9BA478CF344DD.
[21] K. Denhaerynck, F. Dobbels, I. Cleemput, A. Desmyttere, P. Schäfer-Keller, S. Schaub, S. De Geest, Prevalence, consequences, and determinants of nonadherence in adult renal transplant patients: a literature review, Transpl. Int. 18 (2005) 1121–1133, https://doi.org/10.1111/j.1432-2277.2005.00176.x.
[22] V. Gaspar, S. Ibrahim, R. Zahedi, C. Borchers, Utility, promise, and limitations of liquid chromatography-mass spectrometry-based therapeutic drug monitoring in precision medicine, J. Mass Spectrom. 56 (2021) 1–13, https://doi.org/10.1002/jms.4788.
[23] FDA 510K Submission Approval Summary, MASSTRAK Immunosuppressants KIT, Waters Corporation, K063868, https://www.accessdata.fda.gov/cdrh_docs/pdf6/K063868.pdf.
[24] FDA 510K Submission Approval Summary, Ark Lacosamide Assay, Ark Diagnostic Inc, K201089, https://www.accessdata.fda.gov/cdrh_docs/pdf20/K201089.pdf.
[25] FDA 510K Submission Approval Summary, Ark Gabapentin Assay, Ark Diagnostic Inc, K101574, https://www.accessdata.fda.gov/cdrh_docs/pdf10/K101574.pdf.
[26] FDA 510K Submission Approval Summary, Ark Oxcarbazepine Metabolite Assay, Ark Diagnostic Inc, K153596, https://www.accessdata.fda.gov/cdrh_docs/pdf15/K153596.pdf.
[27] FDA 510K Submission Approval Summary, Ark Topiramate Assay, Ark Diagnostic Inc, K083799, https://www.accessdata.fda.gov/cdrh_docs/pdf8/K083799.pdf.
[28] A. Saitman, I. Metushi, D. Mason, R. Fitzgerald, Evaluation of the Waters MassTrak LC–MS/MS assay for tacrolimus and a comparison to the Abbott architect immunoassay, Ther. Drug Monit. 38 (2016) 300–304, https://doi.org/10.1097/FTD.0000000000000252.
[29] G. Ginsburg, K. Phillips, Precision medicine: from science to value, Health Aff. 37 (2018) 694–701, https://doi.org/10.1377/hlthaff.2017.1624.
[30] A. Towse, L. Garrison, Economic incentives for evidence generation: promoting an efficient path to personalized medicine, Value Health 16 (2013) 694–701, https://doi.org/10.1377/hlthaff.2017.1624.