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The regulatory landscape of precision oncology laboratory medicine in the United States – Perspective on the past 5 years and considerations for future regulation

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ABSTRACT

The regulatory landscape for precision oncology in the United States is complicated, with multiple governmental regulatory agencies with different scopes of jurisdiction. Several regulatory proposals have been introduced since the Food and Drug Administration released a draft guidance to regulate laboratory-developed tests in 2014. Key aspects of the most recent proposals and discussion of central arguments related to the regulation of precision oncology laboratory tests provides insight to stakeholders for future discussions related to regulation of laboratory tests.

1. The current regulatory environment in the United States

The current state of laboratory test regulation in the United States (US) is complex and the prospect of changes in the current paradigm has been continually on the horizon since 2014. Briefly, clinical laboratories in the US are regulated under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88)[1] of the Public Health Services Act, which are administered by the Center for Medicare and Medicaid Services (CMS). These regulations were put in place to improve the quality of the processes in clinical laboratories, but the regulations allow for organizations that have received certification from CMS to inspect laboratories as a deemed entity. This status allows deemed entities to place additional requirements in place, so long as the underlying CLIA requirements are met. CLIA regulations have a flexible framework that allows individual medical directors and laboratories to have some leeway in how the specific requirements are met, which allows for accommodation of unique population-, laboratory-, and test-level factors that can improve the overall quality of testing and allows for the development of tests by laboratory medicine practitioners within certain bounds. Testing kits that are manufactured and shipped across state lines are regulated by the United States (US) Food and Drug Administration (FDA) via the Medical Device Amendments of 1976 [2] to the Food, Drug, and Cosmetic Act of 1938. The FDA has several review and approval pathways where the manufacturer submits documentation and data to the FDA for review, and if the data fulfill the FDA's requirements, the test recieves marketing authorization. Manufacturers can then sell their products to laboratories, who wish to perform that testing. Testing kits which are cleared or approved by the FDA are regulated under CLIA when they are performed in a certified laboratory. In addition, under the current structure, laboratories are expected to verify the performance of these products and, under CLIA, are allowed to modify them if deemed necessary by medical leadership. If a manufactured product is modified by the user laboratory, the test is considered a laboratory developed test, and such modifications are frequently made to improve assay performance, use the assay in a way different from the use claimed by the manufacturer (e.g. diagnostic instead of screening applications), or allow acceptance of additional sample types that were not submitted to the FDA for approval. This regulatory flexibility allows medical laboratories to offer tests that are accurate and medically relevant to their patients. Currently, many high-complexity clinical laboratories are accredited by the College of American Pathologists (CAP), which conducts unannounced biannual laboratory inspections and administers a multitude

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of proficiency testing programs to evaluate the accuracy and agreement between laboratories across the spectrum of laboratory tests. The FDA has maintained that they have the statutory authority to regulate all laboratory tests, including tests that are developed and offered in a single lab, but have chosen to operate under a policy of enforcement discretion.

2. Emergence of new regulatory proposals

2.1. 2014 Draft guidance and evolution to legislation

In October of 2014, the US FDA released a draft guidance [3] that proposed to dramatically change the regulatory landscape of tests that were developed and offered in a single laboratory, or so called Laboratory Developed Tests (LDTs). There was a large amount of feedback from academic, community, commercial, and professional stakeholders, with several hundred comments submitted to the FDA docket [4]. After the 2016 presidential election, the US FDA publicly stated that the Agency will defer to the legislative branch of the US government to update the regulatory landscape of LDTs and manufactured laboratory tests, also know as *in vitro* diagnostic devices [5]. Although the FDA has stated that it will not wholesale change the regulatory requirements for LDTs in the interim, the Agency has continued to release guidance documents, in both draft and final forms, that touch on the regulation of laboratory diagnostics that are used in the care of oncology patients.

During this same period of time, several groups proposed alternative regulatory approaches, including professional organizations, including the CAP [6] and the Association for Molecular Pathology (AMP) [7]. In addition, a consortium of commercial laboratories, test manufacturers, and large reference laboratories with academic affiliations helped draft the basis for the Diagnostic Accuracy and Innovation act (DAIA) [8] which was made available for red-line comments by representatives in the US House of Representatives in 2017. This proposal introduced a new term of *in vitro* clinical tests (IVCTs) as a common term for both manufactured and LDTs, and as a term to differentiate such tests from medical devices. As part of the feedback process, the legislative sponsors requested technical assistance (TA) and comments from the FDA.

2.2. VALID act of 2020 and VITAL ACT of 2020

The process of obtaining the FDA TA document for DAIA took over a year, and the TA document that was received by the sponsors was not a commentary on the draft legislation that was provided to them, but an entirely new legislative discussion draft that outlined an almost entirely different regulatory scheme from DAIA. The legislative sponsors quickly evaluated the TA document and released the Verifying Accurate, Leading-edge IVCT Development (VALID) Act [9,10]. Over the following years, the VALID Act was the topic of many meetings between stakeholders, FDA, and legislative staff, and a final version was introduced into the US House of Representatives and US Senate on March 5, 2020 [11] during the early days of the SARS-CoV-2 pandemic in the United States. On March 17, 2020, an alternative regulatory bill, the Verified Innovative Testing in American Laboratories (VITAL) Act of 2020[12], was introduced into the Senate.

The approach outlined in VALID Act of 2020 continues the US FDA's long-standing assertion that the Agency be the central arbiter of laboratory test analytical accuracy and validity. Key components of VALID include extensive grandfathering of existing LDTs, a new classification scheme for new tests, and a framework for a precertification scheme that is designed to allow laboratories to create, validate, and offer certain tests without FDA review in certain circumstances. While many previous approaches to regulation included 3 categories of tests (low, moderate, and high), the VALID Act of 2020 only has 2 categories of low- and high-risk. Tests in the low-risk categorization would be allowed to be developed and used for patient care through individual submission to FDA or use of the pre-certification pathway. Tests that were considered to be in the high-risk category would not be eligible for using the precertification pathway and would require the test to be submitted to the FDA via a pathway similar to the current the premarket approval (PMA) pathway. Given that many current molecular oncology LDTs are used to select therapy regimens or could be used to decide prophylactic surgeries, most of these tests are expected to be classified in the high-risk category, requiring a time-consuming and expensive PMA, were VALID to be come law. While there is the provision for high-risk tests to use "mitigating measures" that would allow a different regulatory pathway, it is unclear how this might work in practice, and none of the examples cited in the legislation reference professional practice or expertise. The proposed precertification is similar in concept to some existing programs, including the conditional approval process utilized by the New York State Department of Health (NYDOH) [13], but uses a technology classification system to allow laboratories or manufacturers to develop within a certain scope of expertise. The technological categories have underlying scientific principles that are considered generally similar by the FDA. The technology categories are clot detection, colorimetric, enzymatic, fluorometry, immunoassay, mass spectrometry/chromatography, microbial culture, nephlometric/turbidimetric, next generation sequencing (NGS), non-NGS nucleic acid analysis, slide-based technology, and spectroscopy. The Valid Act of 2020 stipulates that laboratories would become precertified for a specific technology by submitting an initial assay through the stand-alone pathway, and if successful would obtain a multi-year permission to develop and modify tests within that technology class. At the end of a certification term, the lab could submit a new assay for review and could receive an extension of the precertification. While tests developed in the precertification window would not need to be submitted for review, documentation would have to be maintained for inspection by FDA or 3rd-party reviewers.

A key provision of VALID is the extensive grandfathering provision that is included in the legislation where tests that are available before the legislation enactment can continue to be offered after the law is in effect. This grandfathering was included to prevent the sudden loss of laboratory tests as the law is enacted. A key aspect of this grandfathering is that tests cannot be modified after VALID becomes law, and the FDA has the authority to order any test off the market if they choose.

While the VALID act of 2020 has numerous provisions over 245 pages and ensconces many aspects of regulation of LDTs in statute, the VITAL act of 2020 takes the opposite approach. The VITAL act of 2020 is only 7 pages in length, and simply states that all development and performance of LDTs will be under the jurisdiction of the Public Health Services Act and cannot be regulated under the Medical Device Act. These two legislative bills are indicative of the extreme differences that people, companies, and institutions have taken on the issue of regulation of laboratory services and the methods that are used to provide data to inform patient care. The key regulatory prosals and legislation are presented in Table 1.

The fates of the current legislation are uncertain, given the current state of the US political climate, but evaluation of key underlying concepts related to the logic of regulation may benefit the stakeholders who are interested in this regulation.

3. Commentary on the scope of regulation

There are numerous manufacturers who have developed targeted precision oncology tests and companion diagnostics that have achieved FDA approval. Despite the availably of these manufactured tests, many laboratories continue to develop and use LDTs for oncology testing, especially at academic institutions. There are several examples of specific comprehensive tests that were developed and used as LDTs that have sought both PMA (Foundation medicine) and 510(k) (MSK-IMPACT) approval [14]. While the exiting FDA regulatory pathways are clearly available to all laboratories that develop LDTs, the observation that these pathways have not been used except by a handful of large and well-funded organizations suggests that the burdens of seeking such approvals are sufficiently large and complex [15,16] to dissuade laboratories from undertaking, despite any benefits. Laboratories that develop LDTs often state that the ability to modify tests without needing to seek regulatory approval allows for tests to be continuously improved and updated to meet patient needs. In the setting of precision oncology, laboratory tests are undergoing constant revision and updating as new discoveries in science and medicine are applied to routine patient care.

In many discussions and talking points related to the need for regulation of LDTS, several topics are consistently raised as key reasons for increased regulation of LDTs. These factors include: Risk of patient harm, the changing nature of LDTs, accuracy and interchangeability of results, encouraging innovation, and the requirement for a single regulatory pathway.

3.1. Risks to patients and the changing nature of LDTs

A commonly cited reason for additional regulation of laboratory testing is the to reduce the risk of patient harm due to tests that do not perform as expected [17]. Although many assertions of patient harm due solely to laboratory developed tests are often easily debunked [18], the possibility of patient harm is a serious possibility that should be considered. Manufactured products that are produced and shipped across state lines may require more extensive regulatory oversight because the manufacturer has no control over the specific skills or expertise of the laboratory staff and directors who are implementing the test. Thus having a test that can be understood and used by novices and experts alike may be a reasonable requirement, which is the current state of manufactured tests in the United States. LDTs are often developed and implemented in laboratories that have specific expertise and patient needs that require specialized testing. LDTs are also commonly used in areas of medicine where there is rapid increase in knowledge (e.g. oncology), or where testing methods must be nimble due to changing analytes (infectious disease). The ability to rapidly adapt testing methods and implement new scientific and medical findings with LDTs is in contrast to the extensive and costly process required for tests taken through the FDA, which have been estimated to result in multiple years delay in test availability compared to other western countries, with potential costs of tens of millions of dollars per FDA sumission [19]. Given the costs associated with obtaining FDA approval for laboratory tests, there will be significant costs that laboratories will have to bear under the VALID proposal, both in terms of submitting tests for consideration of precertification and in maintaining that certification. In addition, tests that are in the high-risk classification will be less likely to be laboratory developed and will either need a commercial solution or require referral to an outside laboratory.

A concern that has been repeatedly raised by the FDA and other groups is that the nature of LDTs has changed over the past decades. Where LDTs were once mostly performed in hospital laboratories for local patients, in the present day, LDTs are often performed in central laboratories that are removed from the site of patient care. These labs can fall into several general categories: reference laboratories for hospital systems, regional reference laboratories, national reference laboratories, and commercial, for-profit entities. While these laboratories are all likely to adhere to high standards and perform analytically sound tests, the change of LDTs from a primarily local to a regional or national scale has been suggested by the FDA to be a rationale for no longer applying enforcement discretion. Although not explicitly stated in the FDA's statements, is the potential for decreased patient safety, not due to the type of test performed

Table 1
Timeline of key developments in the regulation of laboratory testing.

Date	Document	Relevant Statute
1976	Medical Device Regulation Act	Food, Drug, and Cosmetic Act of 1938
1998	Clinical Laboratory Improvement Amendments (42 USC 263a)	Public Health Services Act
2014	Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)	Food, Drug, and Cosmetic Act of 1938
2017	Diagnostic Accuracy and Innovation Act (DAIA)	Food, Drug, and Cosmetic Act of 1938
2018	Verifying Accurate Leading-edge IVCT Development Act of 2018 (FDA technical assessment of DAIA)	Food, Drug, and Cosmetic Act of 1938
2019	Verifying Accurate Leading-edge IVCT Development Act of 2018 (FDA technical assessment of DAIA)	Food, Drug, and Cosmetic Act of 1938
March 2020	Verifying Accurate Leading-edge IVCT Development Act of 20201	Food, Drug, and Cosmetic Act of 1938
March 2020	Verified Innovative Testing in American Laboratories Act of 2020	Food, Drug, and Cosmetic Act of 1938

(LDT vs. FDA cleared/Approved), but due to decreased interaction of the laboratory experts with the team caring for individual patients.

When any tests are performed in centralized laboratories with limited access to clinical records, there is a higher risk of making pre-analytical, post-analytical, and cognitive errors that can impact patient care. In addition, incentives such as the payment structure of the laboratory can incentivize behaviors that are divergent from the best interest of patients and the health system. Many decentralized laboratories use a fee-for-service payment model which has been suggested to increase overutilization [20,21], and can potentially lead to situations where analytical and clinical validity claims may overreach the available data [22]. Analyses have suggested that laboratory testing done remotely from the patient may lead to increases in cost, turnaround time, duplicative orders, unnecessary studies, and increased errors [23,24]. Ironically, the addition of additional and costly regulations under VALID may actually drive further consolidation of the centralization model of laboratory testing, which could lead to additional errors as previously described. As complex testing is removed from regional and academic centers and concentrated in centralized laboratories, the ability of laboratory medicine experts to interact with their patient-facing colleagues is likely to decrease, resulting in further degradation in care.

In contrast, integration of laboratory medicine experts in the clinical care team has been suggested to improve diagnostic yield, especially in the setting of complex and nuanced laboratory data, and the potential benefits of integration with clinical details to improve diagnostic yield, have been proposed as a valuable service for pathologists [25] that can provide insight to the clinical care teams. As precision oncology has become more reliant on numerous biomarkers and mutations to direct treatment, systematic studies have demonstrated that interpretations of results may benefit from expert consultation [26], which may not be available when the testing is performed remotely. While it is true that the type and complexity of tests that have been developed as LDTs has changed, the more critical aspect that has changed is the decentralization of care that has simultaneously occurred, and that is an aspect of medical practice that cannot be regulated by the FDA.

3.2. Accuracy and equivalency between laboratory tests

A commonly cited rationale for the need to regulate LDTs is the need to ensure that results are equivalent between assays, especially in the area of oncology tests that are used to direct oncologic decision-making and treatments. While the rhetoric is often that the accuracy of LDTs is not known, there are many studies and programs in place that laboratories use to evaluate the performance of their LDTs and manufactured kits, with proficiency testing and comparative studies being key tools. Many published scientific studies have demonstrated good equivalence between molecular oncology tests, both LDTs and FDA approved [27–32], including studies examining assessment of important recurrent oncologic mutations that are frequently assessed in proficiency testing. It is also critical to remember that even when the same test is used to assess identical samples, but in different labs, there will be slight differences in performance due to statistical factors [33]. There are publications citing disagreement between specific laboratory methods, but investigation of the methods and biology relevant to specific comparisons often reveal that the apparent differences may actually be do to biological phenomena [34,35], or specific disease biology [36–38], highlighting the importance of the expertise of medical practitioners in interpreting testing data and applying the results of these studies.

Proficiency testing is required under CLIA, and CAP develops proficiency testing programs using content experts to devise appropriate challenges [39], in addition to developing accreditation checklists [40], and clinical guidelines [41]. Multiple studies examining CAP proficiency testing data using well-characterized reference materials demonstrated that real-world challenges of total assay performance showed excellent agreement between a variety of FDA-approved, FDA-cleared, and LDTs precision-oncology assays across a broad range of technologies [42–46]. As the field of precision oncology diagnostics has evolved, new technologies and approaches such as next generation sequencing (NGS) present additional problems, including the need for sometimes complex bioinformatics pipelines to analyze and interpret large volumes of data. To complicate the scenario, some laboratories use outside services for bioinformatics, which allows for decreased internal resources for this specialized field, but opens the possibility for errors that may be difficult to diagnose and detect. Studies have demonstrated the feasibility of using *in silico* manipulation of data to simulate variants in data generated in the laboratory under evaluation [47], indicating that innovative approaches to new problems using existing structure can quickly address new problems as they emerge. These common practices of comparisons of different laboratories using blinded, standardized materials demonstrates the analytical accuracy of the methods and provides a mechanism for identifying laboratories and tests that are not preforming up to the standard, and offer a route to problem resolution. The participation in proficiency testing programs is another mitigating measure that allows for continuous quality improvement and should also be considered in any regulatory scheme.

3.3. Regulatory certainty and innovation

Regulatory certainty has been stated as a key component to encouraging innovation in the realm of laboratory testing. This argument is often framed in as regulatory certainty provides a financial incentive for investing in innovation, which focuses on the financial and business aspects of laboratory testing, but neglects the medical needs that often drive test development. Regulatory certainty has been present for manufactured kits for many years, but the long developmental timeline for many assays has led to assays being obsolete when they finally become availble [31], which can be problematic if the state of scientific and medical understanding change in the intervening years. In order to decide to undertake long regulatory approval processes, entities must have not only the resources to undertake the process, but will also need to have a return on investment in order to proceed. In contrast, many LDTs are developed to assess a specific medical or operational need that is not possible of practical to address by alterative means. Having a regulatory framework that allows for both scenarios will allow for patients to have the maximum access to important diagnostic tests. Many manufacturers and regulators have stated that a single regulatory pathway is the most appropriate and efficient approach, but that view focuses on the needs of those constituencies, but neglects other considerations. A chief concern is the reality that most laboratories are responsible for

managing thousands of tests that are required for patient care, while manufacturers and specialty laboratories generally have a limited portfolio of tests that they maintain. Having a single regulatory path could result in much higher regulatory burden for professionals that are providing medical care to patients, potentially reducing the number of test available for patient care and diverting monetary and personnel resources from patient care activities to administrative tasks. While both arguments have some merit, the convenience of the regulatory body and special interests need to be balanced against the need for flexibility to provide appropriate services to patients and providers.

4. Recommendations for policymakers, regulators, and stakeholders

As of this writing, the political landscape in the United States is such that comprehensive reform of laboratory regulations does not seem likely to advance under the current climate. In addition, the events surrounding the delayed rollout of laboratory diagnostics to address the initial encounter with the SARS-CoV-2 pandemic in the United States has brought new attention to the issue of regulation of laboratory tests [48]. Reflecting on the half-decade that has elapsed since the FDA's draft guidance to regulate LDTs, several key observations can be made with regard to the common themes in the public discussion and proposals for the regulation of laboratory tests:

- The level of risk to the patient should be taken into account
- Most laboratories involved in testing of biomarkers related to precision oncology have comparable results.
- Precision oncology relies on the ability of laboratories to rapidly innovate to provide optimal patient care

4.1. Assessment of risks to patient

Manufactured tests, tests provided by for-profit laboratories, or labs that have a profit motive (startup laboratories, public companies, etc.) may require additional regulation to ensure that the primacy of analytical accuracy and clinical validity are appropriate for the claims of the laboratory. The observation that fee-for-service can result in increased utilization and errors suggest that additional scrutiny may be needed in these situations. Laboratories that are integrated with the patients they serve, including oncology patients, have the opportunity to embrace the role of diagnostic consultant, utilizing the professional services of expert medical directors to aid in the interpretation and dissemination of understanding of complex test results, and hence requiring less regulation.

4.2. Addressing analytical concerns

While data have demonstrated that precision oncology assays have excellent accuracy and concordance, the concern that disparate assays should be able to be accurately evaluated during development is a valid. Rather than a rigid regulatory construct, this specific concern can be addressed through establishment professional practice guidelines and recommendations, and though development of standards that can be used for assay development and quality control [49,50] for established biomarkers. As scientific knowledge and medical understanding are constantly evolving, the role of professionals is critical to investigate and understand the technical, biological, and medical variables that impact laboratory tests, and that will require deep involvement and expertise. Such resources are especially important in the setting of precision oncology as some highly-actionable alterations are also extremely rare and difficult to detect by many technologies [51–53]. When such standards are in available and routinely used, the risk that an incorrect result will be generated in the analytical process decreases. Similarly, tests that use proprietary algorithms or artificial intelligence should have a higher level of scrutiny because the ability to compare individual tests using a standard material may not be appropriate. Development of physical and performance standards by professional societies should be leveraged to allow for test development and comparison. Utilizing professional societies will allow for integration of the most recent scientific and medical findings, is potentially more nimble than a process embedded in a federal agency.

4.3. Innovation and application

Patients expect that the assay that is being used to provide information to care for them is the most up to date method possible, as such, tests must be able to updated as necessary to maintain their performance and relevance. For manufacturers and commercial laboratories, a precertification pathway as delineated in VALID may be a sensible approach for precision oncology applications, if such tests can be assigned an appropriate risk classification. With regards to laboratories that are closely associated with physicians providing patient care, a more flexible approach akin to that currently under CLIA provides an optimal balance between the ability of laboratory medicine physicians to practice medicine, protect patients, provide relevant laboratory results, and regulatory burden.

5. Summary

The regulatory environment of precision oncology tests in the US is complex, and multiple legislative proposals to update the regulatory environment have been introduced. As discussions around laboratory regulation proceed, careful consideration of the risks, benefits, and costs of various regulatory approaches must be considered. In order to deliver the most appropriate care to patients in difficult circumstances, broader evaluation of the implications of test regulation should be contemplated. Many assertions and assumptions have been made as to why additional regulation of laboratory tests is required, but the likely effects of that regulation on

patient care have not been evaluated with regards patients and the full spectrum of stakeholders. Identifying tools that can be leveraged to improve laboratory test quality may offer many benefits that do not necessarily require a burdensome regulatory framework.

Declaration of competing interest

I have no relevant conflicts related to this manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.plabm.2020.e00172.

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