April 2, 2024

The Honorable Bill Cassidy, MD
Ranking Member
Committee on Health, Education, Labor & Pensions
828 Hart Senate Office Building
Washington, DC 20510

Dear Senator Cassidy,

The Association for Diagnostics and Laboratory Medicine (ADLM) appreciates the opportunity to provide input on legislative reforms to the diagnostic industry. As your questions correctly indicate, there are two distinct areas of oversight:

- Centers for Medicare and Medicaid Services (CMS) regulation of the clinical laboratories that perform laboratory testing; and
- Food and Drug Administration (FDA) supervision of the manufacture and distribution of test kits that are used within laboratories.

Each segment has separate, distinctive missions.

ADLM agrees Congress should evaluate and update the underlying statutes that govern each of these regulatory processes. In the case of CMS and the Clinical Laboratory Improvement Amendments (CLIA), it has been nearly 40 years since legislators passed the historic legislation. ADLM was part of those efforts and looks forward to working with you to modernize CLIA.

We believe that any changes to the statute must ensure the accuracy of testing, while also encouraging innovation and continuous improvements—two of the pillars of laboratory medicine—that are vital to providing quality, and timely patient care, particularly to our underserved and marginalized communities. Below are our answers to the questions you posed regarding diagnostic reform.

CLIA Regulatory Framework for LDTs

1. What updates to the clinical laboratory regulatory structure under CLIA should Congress consider to reflect the latest scientific practices and safety standards?

The CLIA standards work well. They were designed to unify existing federal standards and to give assurance to consumers that their tests, wherever they were performed, were of high quality. In addition to LDTs, ADLM believes other areas in need of review include: near-patient testing; proficiency testing; the test categorization process, and the use of data-driven decision-making,

among others. After a thorough assessment of the program, it may be that the standards only need slight modifications. ADLM looks forward to being part of this process.

2. What are your views on the effectiveness and use of the Clinical Laboratory Improvement Advisory Committee (CLIAC) in providing scientific and technical guidance to inform potential updates to CLIA standards?

ADLM is supportive of CLIAC. The advisory panel is comprised of a wide variety of stakeholders and therefore serves as a good venue for discussing changes to the current laboratory standards. One disturbing development in recent years is that the committee has been barred from discussing issues about LDTs (see Attachment 1). This is nonsensical since the panel is responsible for recommending updates to the CLIA standards, which includes oversight of LDTs.

In November 2021, ADLM and 17 other groups, including the American Medical Association and Children's Hospital Association wrote to CLIAC urging the panel to take up the LDT issue (see Attachment 2). We find it perplexing that a topic that is of the utmost public importance cannot be talked about by the experts who know the issue best and can address any concerns. Unfortunately, the FDA appears to be using its veto power over what issues the panel discusses to prevent it from taking up this issue.

3. Do the proficiency testing (PT) programs currently approved by the Department of Health and Human Services (HHS) reflect the latest clinical standards of laboratory medicine? Are there specialties, subspecialties, or analytes that should receive greater consideration for HHS approval?

The PT programs meet the needs for commonly available analytes. For rare disorders or drugs of abuse testing for which there are few FDA approved or cleared tests, laboratories must develop alternative PT methods to demonstrate accuracy. Additional guidance could be helpful for alternative PT methods. Revisions to the CLIA PT regulations go into effect on July 11, 2024. They include 29 newly regulated analytes and gather PT acceptability limits for many currently regulated analytes, along with changes to grading and reporting. These revisions are an appropriate first step, but additional guidance and work is needed.

4. How well does the existing enforcement structure under CLIA work in ensuring compliance with regulatory requirements and taking action against noncompliance? What should be improved, if anything at all?

The CLIA oversight structure works for moderate and high complexity laboratories. These facilities, in addition to having to successfully participate in PT three times a year, are subject to biannual inspections and self-inspections.

One element of the process that can be improved is to make sure that inspection teams include inspectors who understand, and can properly assess, LDTs. The development and

application of LDTs can be a very complex process and, therefore, requires an individual with expertise to conduct the review.

It is important to note that most LDTs are not directly inspected by CMS, but by its third-party accrediting organizations, such as the College of American Pathologists. These entities must also ensure that individuals familiar with LDTs are part of the inspection teams.

ADLM also believes that high complexity laboratory directors should document their ability to oversee the LDTs they perform. While board certification is sufficient in most cases, newer, more specialized technologies (e.g., next-generation sequencing, mass spectrometry, and flow cytometry) require additional credentials to demonstrate competency. Such a change would be consistent with current CLIA policy and could be done through the existing regulatory process.

Another issue that needs to be addressed is the oversight structure for laboratories performing near-patient (also known as point-of-care) or waived testing. Over the past few decades, there has been a significant increase in near-patient laboratory testing sites outside of the traditional clinical laboratory. These sites, which often perform only waived testing, include physician offices, pharmacies, home health care agencies, and skilled nursing facilities, among others.

The number of registered facilities performing only waived testing has grown from 67,294 in 1993 to 244,791 in 2024 – more than a three-fold increase. A benefit of near-patient testing is that test results are typically available more quickly than if the test is sent to an off-site laboratory. However, studies have shown that many near-patient testing sites perform clinical tests incorrectly. More research is needed to assess the extent and impact of these problems and to determine where improvements are necessary.

We also suggest that additional penalties be explored for laboratory directors who intentionally violate the law. A two-year ban and civil monetary penalties may not be a sufficient deterrent. ADLM believes that all laboratories, regardless of where they are located and the level of testing performed, should have processes in place that facilitate reliable testing and quality patient care.

5. Should legislative reforms address CLIA's quality system requirements? If yes, which of those changes would require Congressional action, and which could be effectuated by CMS alone?

Throughout the LDT discussion, government, medical and professional societies, and consumer organizations have advocated for clinical laboratories to demonstrate the clinical validity of LDTs before introducing these tests. CMS does not currently require clinical validation. The FDA has stated that it has serious concerns regarding the lack of independent review of the evidence of clinical validity of LDTs. This assertion is itself not entirely valid.

More than 8,000 laboratories are accredited by the College of American Pathologists (CAP) or the Joint Commission (both deemed accrediting organizations under CLIA), both of which require clinical validation of any claim relating to the use of LDTs for patient care. The New

York State Department of Health similarly requires that all laboratories licensed to perform testing for their residents provide evidence of clinical validity for each registered LDT. Such evidence can take a variety of forms, including published studies in the peer-reviewed literature and the use of clinical guidelines.

Expanding clinical validity to all LDTs under CLIA appears to be a viable regulatory option that would achieve the goal of ensuring clinical validity without the prohibitive administrative burden of dual oversight by FDA and CMS. ADLM supports requiring laboratories to demonstrate the clinical validity of a test. This could be done by CMS under its existing authority.

6. Where does redundancy exist, if at all, within the current CLIA regulatory structure with respect accreditation standards under federal and state licensure programs, as well as through CMS-approved accreditation organizations?

In addition to CLIA certification, some states have their regulatory structures for clinical laboratories. While these state programs may have unique requirements tailored to their jurisdiction and may overlap with some aspects of the CLIA standards, this is not generally a major issue for the laboratory community. Of much greater concern is FDA's plan to oversee laboratory testing, which would create a duplicative regulatory structure that would overlap with CMS registration, quality, inspection, and user fee requirements and will undoubtedly have an adverse effect on patient access to care.

7. In considering legislative reforms to CLIA, should LDTs be defined in statute? What aspects of test development would characterize such a definition?

While ADLM has concerns about the way LDTs are currently defined, we do not believe these tests should be defined in statute. Rather, a group such as CLIAC, which is comprised of laboratory professionals, clinicians, consumers, and industry representatives, as well as government representatives should be directed to develop a reasonable definition. If LDTs are defined in statute, it will be exceedingly difficult to update the definition to reflect changes in technology or the healthcare environment.

While it is generally accepted that a new test developed and used in one laboratory without FDA clearance or approval is an LDT, there is considerable uncertainty around whether the modification to an approved or cleared test (which is also considered an LDT) warrants the label of LDT.

ADLM believes that a modification to an FDA cleared or approved assay, which does not change the assay itself, should <u>not</u> be considered an LDT if the laboratory demonstrates that the modification does not adversely affect the analytical performance of the assay. The very definition of an LDT requires clarity so that proper regulatory guideposts can be employed.

8. How should Congress consider issues relating to the practice of medicine and its relationship with labeling for LDTs? Should there be additional oversight of the information conveyed to patients serviced by LDTs?

LDTs are an invaluable tool for physicians and other healthcare providers caring for patients. The laboratory director works with the ordering provider to determine the information needed to diagnose and treat the patient. The laboratory director then develops the test and obtains the needed data. This interplay between clinician and laboratorian is the practice of medicine in action. Over regulation will inhibit pathologists and laboratorians from playing their vital role in patient care.

While LDTs are highly complex, labs must follow certain regulatory steps in both developing and reporting this information. There is no need to segment out an LDT test result for a patient and treat it differently from any other test. That would heighten patient concerns about a test that is often well characterized and understood by the clinical community.

ADLM does suggest that Congress explore issues involving direct-to-consumer testing, where patients may receive results without guidance from a clinician or other qualified healthcare providers. While increasing patient involvement in their care is good, sometimes entities marketing these tests have overstated their value leading patients to make bad healthcare choices (see Attachment 3). Legislators should focus particular attention on the marketing of these tests.

9. Should certain CLIA regulations be updated, would it necessitate a reevaluation of the CLIA fee schedule?

The reassessment of the CLIA fee schedule would be dictated by the changes made to the program. However, consideration should be given to requiring waiver laboratories to pay for some form of oversight, even if limited. While we understand the value of near patient testing, no test is foolproof, and certainly not when performed by someone not familiar with the testing process. This is an area that warrants further investigation.

10. What compliance challenges would legislative reforms to CLIA create? How should new regulatory requirements apply to tests currently available to patients?

The compliance challenges would depend on the changes made to the regulatory structure. We believe any changes to the CLIA standards should apply to new as well as existing tests.

FDA Regulatory Framework for Diagnostics

1. How well is FDA's medical device framework working for the regulation of diagnostic products? Are there improvements that should be made?

a. Of these specific changes, which would require Congressional action, and which can be effectuated by FDA alone?

In general, the FDA review process for medical devices works. However, it needs reform. The clinical trials process has become overly prescriptive and the underlying premise of 510(k)s needs to be reassessed. Too often a new device is cleared using a predicate that is decades old, flawed, or obsolete. There needs to be some assurance that the original device was truly "safe and effective." In some instances, better test kits may lead to fewer LDTs.

3. What, if anything, makes diagnostics distinct among FDA-regulated medical products to warrant specific attention to how AI may be used in the review of product submissions?

Any medical product, whether a diagnostic or therapeutic product, warrants careful attention to the use of AI and its overall effect on the risk profile of the product. AI may enable complex diagnostic interpretations by integrating multiple diagnostic modalities (laboratory, radiology, physical, demographic data), that require a holistic review in addition to a review of the parts of the diagnostic product. These diagnostic-specific risks for in vitro diagnostics are not different than the risk of AI in other medical products.

4. Are the regulatory pathways intended to evaluate diagnostics for special populations (i.e. rare diseases or genetic disorders) working?

a. How could they be enhanced to accelerate and authorize products for special populations, for example, certain companion diagnostics for rare biomarkers?

There are virtually no pathways for obtaining a test for rare diseases or special populations. That is why LDTs are so critical to some populations. Without LDTs some conditions would never be diagnosed and treated. There are also significant limitations with pediatric testing. Few test kits are developed for younger populations. Therefore, the laboratory must develop a new test to diagnose the condition or modify an existing test kit developed for the adult population, thus making it an LDT. There are a variety of reasons that contribute to the dearth of pediatric tests, including its limited market size, difficulty in obtaining healthy pediatric samples for testing, and the need for tests that capture their continually changing biology.

As described by one of our members *"There is no profit motive to re-engineer platforms for kids or to include kids in clinical and analytic validation studies. They will get approved based on adult data and we (pediatric people) will adopt them for our use because we don't have any other option. Assay dynamic ranges are often inappropriate for kids (immunoglobulins, sex*

hormones, to name a few). If available at all, reference intervals are inappropriate for kids. Resistance to high levels of interference that we see in kids is inadequate. Blood collection devices are inappropriate. For once, I would like to see a platform developed from the bottom up that starts with the needs of pediatric population."

LDTs, as developed by clinical laboratories, are a vital element of patient care. Limiting access to these tests will harm many, particularly the most vulnerable in our society – our children.

ADLM appreciates the opportunity to provide input on diagnostic reform. We look forward to working with you as you consider methods for improving the delivery and quality of patient care through laboratory medicine. If you have any questions, please email Vince Stine, PhD, ADLM's Senior Director of Government and Global Affairs, at vstine@myadlm.org.

Sincerely,

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President, ADLM