ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

April 3, 2024

The Honorable Bill Cassidy, MD
United States Senate
455 Dirksen Senate Office Building
Washington, D.C. 20510

Dear Senator Cassidy,

The American College of Medical Genetics and Genomics (ACMG) appreciates the opportunity to respond to the Request for Information (RFI) on Regulation of Clinical Tests. ACMG is a prominent authority in the field of medical genetics and genomics and the only nationally recognized medical professional organization solely dedicated to improving health through the practice of medical genetics and genomics. As the only medical specialty society in the US that represents the full spectrum of medical genetics disciplines in a single organization, the ACMG provides education, resources and a voice for more than 2,500 clinical and laboratory geneticists, genetic counselors and other healthcare professionals. ACMG's mission is to improve health through the clinical and laboratory practice of medical genetics as well as through advocacy, education and clinical research, and to guide the safe and effective integration of genetics and genomics into all of medicine and healthcare, resulting in improved personal and public health. This includes ensuring that patients have access to high-quality, accurate genetic testing services.

FDA Regulatory Framework for Diagnostics

As an association representing healthcare professionals providing genetic services, we largely defer to test manufacturers regarding improvements that could be made to regulation of in vitro diagnostics (IVDs). However, it is important that IVDs not be confused with laboratory developed tests (LDTs). LDTs are procedures offered as part of clinical testing services provided by highly trained, board-certified laboratory professionals. Federal regulations of LDTs have to be appropriate for provision of clinical services, including allowing flexibility for laboratory professionals to modify tests to meet physician orders (such as those to meet the unique needs of the local patient population or special specimen type), to rapidly validate new test components when supply shortages arise, to update tests in a timely manner to keep pace with advances

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in scientific advances (e.g., evidence of gene-disease relationships), and to provide laboratory interpretations of results in line with their professional training and certification.

Even manufactured, FDA-approved/cleared IVDs often have to be modified by laboratory professionals to ensure that the tests perform as intended while meeting unique patient needs. Such modifications are regulated the same as LDTs. For example, many IVDs are approved/cleared for use in a typical adult population. Pursuing expanded indications, such as for use in pediatrics, would require additional studies and costs. Because many IVD manufacturers often do not pursue label expansions, laboratories must perform their own validations for off-label use of an IVD to meet the needs of ordering healthcare professionals and specific patient populations (e.g., pediatrics). Limiting this ability, as the proposed FDA LDT regulations would do, will cause diagnostic delays and thus significant patient harm.

Past legislative proposals to improve the regulatory pathway for manufactured IVDs have been muddied by efforts to treat LDTs like IVDs and treat laboratory professionals like manufacturers who supply finished goods for distribution. Unlike manufacturers selling finished goods for profit, the vast majority of clinical laboratories are severely resource constrained and would not be able to perform the work necessary or afford the fees associated with the premarket approval (PMA) or 510(k) process. FDA regulation of LDTs would force many laboratories to reduce their test menu or even shut down altogether. This, in turn, would reduce access to genetic testing for patients with genetic diseases and cancers. The devastating effects of such approaches have been established and ultimately prevented passage of efforts to reform IVD regulations. Moving forward, regulatory improvements for LDTs and IVDs must be considered separately and done in a way that improves, rather than harms, patient access to accurate clinical genetic testing.

CLIA Regulatory Framework for LDTs

Clinical testing laboratories have been successfully regulated by CLIA for decades. The CLIA framework sets a floor to ensure that laboratories, including the tests they develop, operate appropriately while also allowing the flexibility needed for such clinical services. However, the ACMG believes that there are some updates that can be made to ensure that CLIA continues to be robust and account for advances in clinical testing technology.

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For many of the questions in this RFI on the CLIA framework, we defer to the attached draft legislative proposal on modernization of CLIA. ACMG supports the proposed legislation which addresses many of the questions in this RFI. We have also provided some additional feedback for certain questions below.

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

   - There are several updates to the CLIA regulations that should be addressed through legislation, starting with review of tests' clinical validity. CLIA already requires review of tests' analytical validity, but clinical validity should also be reviewed, standards for which should be developed by CMS. Improvements should also be made to the inspection process, including requiring that CMS inspect new laboratories in a timely manner. Further, CMS should maintain a database of tests being used in clinical care, and laboratories should be required to submit and update such information to CMS as test menus change. CMS should also inspect any marketing materials of LDTs used by laboratories to ensure that such marketing materials accurately reflect the performance and intended use of the tests.

     For additional details, see the attached draft legislative proposal for modernization of CLIA.

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?*

   - The CLIAC is a good resource for issues related to clinical testing laboratory operations and regulations. However, they have not been used to the extent needed. For example, CLIAC has not been given the opportunity to weigh in on the appropriateness of various regulatory proposals, including the impact of FDA oversight of laboratory testing. As another example, CMS has recently made notable changes to personnel requirements under CLIA without first seeking input from the CLIAC. This includes recent regulatory changes that lighten the eligibility requirements that must be met to be a high complexity laboratory

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director. It is unclear as to why CMS would make significant changes like this without first seeking the expertise of the CLIAC.

3. *Do the proficiency testing 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 College of American Pathologist (CAP), an HHS-approved accrediting agency, is used by most clinical laboratories across many specialties, including molecular pathology, cytogenetics, microbiology, histology, etc. In order to be CAP-accredited, laboratories have to meet the requirements described in the CAP checklists, which are more stringent than the requirements listed in CMS CLIA. However, not all laboratories pursue CAP accreditation, and the Secretary may consider adopting CAP proficiency testing (PT) guidance to apply more broadly to labs with different accreditation/inspection organizations.

     The attached draft legislative proposal for modernization of CLIA includes additional details about updates to proficiency testing requirements and the Secretary's responsibility for maintaining a list of analytes for proficiency testing.

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?*

   - When an inspector is examining a laboratory, many aspects of the laboratory are scrutinized such as testing personnel qualification, laboratory safety environment, test validations, clinical reports, proficiency testing results, etc. A citation is given to the laboratory if a specific requirement is not met or deemed deficient. Depending on the scale of the deficiencies, inspectors can order the laboratory to stop testing. For example, in 2016 CMS revoked the CLIA certificate of Theranos, who had previously been inspected by FDA with no deficiencies identified, due to a faulty test and stated that "the deficient practices of the laboratory pose immediate jeopardy to patient health and safety".

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While there are many examples of successful CLIA enforcement, consideration could be given to the frequency of inspections. This is especially important for new startup laboratories that are allowed to operate under a certificate of registration until an inspection for accreditation can be obtained. In some cases, laboratories can operate under a certificate of registration for long periods of time before undergoing their first CLIA inspection. CMS should be required to inspect a new laboratory as soon as possible after they receive a request for a certificate of registration. The CLIAC could be a good resource for developing suggestions in the frequency of inspections and the timing of an initial inspection for new laboratories.

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

   - Yes, LDT should be defined in statute. The definition should make clear what is or is not an LDT and how LDTs are distinct from manufactured IVDs. There are several factors that should be considered when developing the definition, such as the role of board-certified laboratory professionals, who the results are being returned to, and distributive testing models.

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?*

   - Board-certified and/or licensed laboratory directors are responsible for validation of all assays performed on human samples in an accredited lab. Laboratory reports include statements pertaining to test performance characteristics. For more complex tests, the reports may also include a laboratory interpretation of results in the context of the unique patient tested. These laboratory interpretations are based on the judgement of board-certified laboratory professionals. They rely on the most up-to-date scientific evidence which is constantly evolving. While they are not practicing medicine, they are working at the interface of medicine and science and must have the flexibility to use their professional training to develop a laboratory interpretation of results. Such reports are provided to the ordering healthcare

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professional and are one of several pieces of information that the treating physician uses to make a diagnosis or management decisions.

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

   - Reevaluation of the CLIA fee schedule may be necessary to ensure that CMS is able to increase staffing as needed. For example, review of clinical validation, examination of marketing claims, and increasing the frequency of inspections may require more financial and human resources. Updates to the CLIA fee schedule are currently handled through the rulemaking process which allows for public comment by laboratories. This process may be suitable to continue moving forward to ensure the CLIA program has the monetary resources necessary to enforce the regulations.

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

    - Ideally, new regulatory requirements should be applied to all LDTs currently in use. However, this must be done in a way that does not disrupt the availability of current tests and does not place unreasonable or unmanageable levels of burden on clinical testing laboratories. Likewise, if any sort of grandfathering approaches were to be considered, even if temporary, they must be done in a way that does not discourage laboratories from updating or improving their current tests. Past legislative proposals have included grandfathering provisions that disincentivize laboratories from updating their tests due to the enormous costs that would be associated with the regulatory process that would be required following any updates to the tests. This freezes tests in time and discourages laboratories from making changes to improve their tests.

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ACMG welcomes the opportunity to discuss these issues further. For questions or comments, please contact Dr. Michelle McClure, Director of Public Policy, at mmcclure@acmg.net.

Sincerely,

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President
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