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September 14, 2026

Mehmet Oz, MD
Administrator
Department of Health and Human Services
Centers for Medicare & Medicaid Services
Attention: CMS-3485-NC
P.O. Box 8013
Baltimore, MD 21244-8013

RE: Request for Information; Clinical Laboratory Improvement Amendments of 1988 (CLIA) Regulations; CMS-3485-NC

Submitted electronically via regulations.gov

Dear Administrator Oz:

On behalf of the Association for Molecular Pathology (AMP), thank you for the opportunity to submit comments in response to the Request for Information; Clinical Laboratory Improvement Amendments of 1988 (CLIA) Regulations; CMS-3485-NC. AMP is an international medical and professional association representing approximately 3,100 physicians, doctoral scientists, and medical laboratory scientists (technologists) who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from academic medicine, hospital-based and private clinical laboratories, the government, and the *in vitro* diagnostics industry. AMP members are highly involved in the development, validation, and interpretation of molecular diagnostic tests, including biomarker tests for the diagnosis and management of inherited disorders, cancers, rare and infectious diseases.

Clinical laboratory tests, including laboratory-developed testing procedures, are an essential component of medical practice and rapidly translating medical and scientific advances into diagnostic services. AMP staunchly supports the principle that only high-quality, clinically and analytically valid laboratory tests should be used in clinical practice and that all laboratories performing clinical testing should meet, if not exceed, CLIA standards; adhere to established professional society and laboratory practice guidelines; and obtain required and optional professional and facility certifications, licensure, and accreditations as appropriate for their particular settings. The combined effect of the CLIA program, laboratory accreditation, and board certification and licensure of laboratory directors and other laboratory personnel has engendered safe, effective, high quality, accessible, patient-oriented test services. Recognized proficiency testing surveys include challenges for the commonly tested analytes and have demonstrated excellent performance of laboratory-developed testing procedures in the area of molecular pathology for a decade or more.[1,2,3]

[1] Weck KE, Schrijver I. A panoramic view of the accuracy of molecular genetic testing. Genet Med. 2016 Dec;18(12):1188-1189. doi: 10.1038/gim.2016.116. Epub 2016 Aug 18. PMID: 27537703.

[2] Kim AS, Bartley AN, Bridge JA, Kamel-Reid S, Lazar AJ, Lindeman NI, Long TA, Merker JD, Rai AJ, Rimm DL, Rothberg PG, Vasalos P, Moncur JT. Comparison of Laboratory-Developed Tests and FDA-Approved Assays for BRAF, EGFR, and KRAS Testing. JAMA Oncol. 2018 Jun 1;4(6):838-841. doi: 10.1001/jamaoncol.2017.4021. PMID: 29242895; PMCID: PMC6145687.

[3] Merker JD, Devereaux K, Iafrate AJ, Kamel-Reid S, Kim AS, Moncur JT, Montgomery SB, Nagarajan R, Portier BP, Routbort MJ, Smail C, Surrey LF, Vasalos P, Lazar AJ, Lindeman NI. Proficiency Testing of Standardized Samples Shows Very High Interlaboratory Agreement for Clinical Next-Generation Sequencing-Based Oncology Assays. Arch Pathol Lab Med. 2019 Apr;143(4):463-471. doi: 10.5858/arpa.2018-0336-CP. Epub 2018 Oct 30. PMID: 30376374; PMCID: PMC6910717.

Maintaining nimble innovation that allows laboratory professionals to draw on their experience, medical training, and scientific expertise in new test development is crucial to a laboratory's ability to provide high-quality patient care and respond to emerging public health challenges. The current regulatory oversight system enables molecular pathologists and other laboratory professionals to rapidly incorporate new findings into practice, and to modify existing laboratory tests and their usage in accordance with advances in clinical knowledge. This has allowed timely and appropriate introduction of innovative testing into practice, and it has also helped foster patient access to the most up-to-date treatment options. **AMP commends CLIA officials for the successful implementation of this program and for establishing federal quality standards to ensure that the millions of laboratory tests Americans rely on every day – from routine bloodwork to cancer diagnostic testing – are accurate and reliable. AMP urges CMS to continue recognizing the value of the system that has served patients and providers well over the past three decades, and to preserve the same flexibility in any new or modified regulation.**

Laboratory Developed Testing Procedures and CLIA Modernization

We also commend CMS on their efforts to update CLIA to reflect advancements in medical practice, laboratory workflow, and clinical laboratory testing. AMP also sincerely appreciates the time CMS staff spent with our leadership to discuss the CLIA program earlier this year. We look forward to continuing this dialogue and welcome the opportunity to meet with CMS following the comment period's close and CMS' review of all received comments.

As CMS is aware, AMP formed a Task Force to develop a proposal that clarifies certain aspects of the CLIA program. The most recent version of AMP's proposal[4] was released on November 9, 2023, which encompasses many of the organization's perspectives on how the CLIA program should be legislatively adapted to accommodate advances in laboratory medicine and ensure the quality of clinical laboratories, services, and personnel. Some perspectives from this proposal are shared below as we believe it is appropriate and feasible to implement many of these changes through regulation, given the existing authorities.

A central aspect of this proposal reinforces that laboratory-developed testing procedures (LDTs/ LDPs) are federally regulated solely through the CLIA program. This position was affirmed by the recent decision in the *Association for Molecular Pathology v. FDA,* which determined that LDPs are not a medical device and therefore, not subject to regulatory requirements in the Food, Drug, and Cosmetic Act. To acknowledge this important distinction, AMP prefers the appellation LDP, in lieu of LDT, because AMP believes that the term "Laboratory Developed Procedure" more appropriately reflects the nature of these medical services. **AMP strongly urges CMS to modify its regulation to reflect that the program is responsible for ensuring the quality of all LDPs.**

In support of this aim, CLIA regulations should be amended to explicitly require clinical laboratories to establish the clinical validity of any LDP they offer. The proposal further details how clinical validity can be established by the following evidence:

(i) peer-reviewed scientific or medical literature;
(ii) clinical guidelines;
(iii) reports of significant human experience with an in vitro diagnostic or laboratory developed testing procedure;
(iv) case-control studies;
(v) case studies or histories;

[4] https://www.amp.org/advocacy/clia/

(vi) clinical data;
(vii) consensus standards;
(viii) reference standards;
(ix) data registries;
(x) postmarket data;
(xi) real world data;
(xii) clinical trials; or
(xiii) other evidence deemed appropriate by the Secretary.

When selecting the most appropriate testing procedure for a given clinical scenario, molecular laboratory professionals already take responsibility for confirming a test's clinical validity. Codifying this expectation in regulation would align CLIA requirements with standard laboratory practice. This modification also fits comfortably within CLIA's existing statutory authority: the CLIA statute requires certified laboratories to adhere to standards to assure that all laboratory examinations and other procedures are valid and reliable.[5] AMP believes this authority should be implemented through regulatory standards addressing both analytical and clinical validity, ensuring optimal and consistent laboratory performance nationwide. We believe this commonsense regulatory change is essential to assure the public that all laboratory testing procedures are consistently clinically meaningful for patients.

AMP will address the RFI's general and specific comments in the remainder of our letter, with sections labeled correspondingly to the RFI's nomenclature.

B.4. Laboratory Processes and Procedures

Molecular laboratory professionals use rigorous, structured analytical validation processes before a test is used in patient care. As the RFI notes, under CLIA's federal regulatory standards, laboratories must establish and document their own performance specifications for testing procedures to confirm accurate and precise results before implementation, addressing characteristics such as accuracy, precision, reportable range, reference interval, analytical sensitivity, and analytical specificity. In practice, this means optimizing every step of the assay individually and test performance as a whole. There are a myriad of guidelines, references, and regulatory resources that inform and describe how professionals should approach this aspect of their work, as demonstrated by the examples throughout this letter, and AMP believes CLIA should consider established best practices when amending its regulations. However, we wish to emphasize that validation processes are highly specific to the test type, methodology, clinical application, specimen type, etc. CLIA establishes baseline performance standards that allow for the regulatory flexibility laboratory professionals need to meet the needs of the patients they serve, within their specific practice environment. There is no single prescriptive way that laboratories should approach testing validation, which is highly dependent on professional medical practice, and one reason why CLIA's holistic approach of regulating facilities, testing services, and laboratory personnel is so essential to its success in assuring testing quality. **Because the CLIA program currently allows for variation of analytical validation to reflect clinical context and test methodology, AMP's resolute position is that CMS' CLIA program is the most effective and appropriate regulatory mechanism to oversee laboratory testing, and that CMS should maintain this flexibility**.

B.4.2.a. Testing Methods & Unique Performance Characteristics

CMS is seeking input on what testing methods, and/or specific applications of those methods, have unique performance characteristics that need to be established and are not already addressed in the CLIA regulations or guidance. Respectfully, professional societies representing the pathology and laboratorian professions are constantly evaluating new methodologies & applications and developing guidelines and best practices as new

[5] 42 U.S. Code § 263a

methods are introduced into clinical practice and evolve over time. Such efforts have already established or addressed performance characteristics for major testing methods that have not been explicitly defined or captured in CLIA regulation. Examples of this include the College of American Pathologists (CAP), Clinical and Laboratory Standards Institute (CLSI), and AMP-led national guidelines establishing performance characteristic guidelines such as the following:

- Next-Generation Sequencing (NGS) for Oncology Panel Validation Guidelines[6]
- NGS Bioinformatics Pipelines Validation Guidelines[7]
- Interpretation and Reporting of Cancer Sequence Variants Guidelines[8]
- Analytical Validation of Tumor-Informed Circulating Tumor DNA Assays for Molecular Residual Disease Generic Protocols[9]
- Establishing Molecular Testing in Clinical Laboratory Environments; Approved Guideline (MM19-A)[10]

AMP appreciates CMS' efforts to engage stakeholders in identifying potential gaps in CLIA related to unique test performance characteristics. **Given the extensive consensus-based guidelines already developed by professional organizations and accrediting bodies, AMP urges CMS to work closely with these stakeholders to ensure that: (1) existing standards are leveraged and duplicative efforts are avoided; and (2) any updates to CMS' analyte list are aligned with current laboratory practices and established guidelines, preventing unnecessary inconsistencies between regulatory requirements and real-world testing.**

B.4.2.b. Examples of Performance Characteristics

As previously stated, in addition to performance characteristics required under CLIA, recommendations for methodology-specific performance characteristics for many tests are already thoroughly addressed by professional guidelines created by engaged and informed stakeholders. Examples include:

- Stability Studies:
    - CLSI EP25: Evaluation of Stability of In Vitro Medical Laboratory Test Reagents[11]

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[6] Jennings, L. J., Arcila, M. E., Corless, C., Kamel-Reid, S., Lubin, I. M., Pfeifer, J., Temple-Smolkin, R. L., Voelkerding, K. V., & Nikiforova, M. N. (2017). *Guidelines for validation of next-generation sequencing-based oncology panels: A joint consensus recommendation of the Association for Molecular Pathology and College of American Pathologists*. *The Journal of Molecular Diagnostics, 19*(3), 341-365. https://doi.org/10.1016/j.jmoldx.2017.01.011.

[7] Roy, S., Coldren, C., Karunamurthy, A., Khetarpal, S. A., Kuderer, N. M., Knapp, D. J. H. F., Longshore, J. W., Lowery, A., Voelkerding, K. V., Wang, C., & Carter, A. B. (2018). *Standards and guidelines for validating next-generation sequencing bioinformatics pipelines: A joint recommendation of the Association for Molecular Pathology and the College of American Pathologists*. *The Journal of Molecular Diagnostics, 20*(1), 4-27. https://doi.org/10.1016/j.jmoldx.2017.11.003.

[8] Li, M. M., Datto, M., Duncavage, E. J., Kulkarni, S., Lindeman, N. I., Roy, S., Tsimberidou, A. M., Vnencak-Jones, C. L., Wolff, D. J., Younes, A., & Nikiforova, M.N. (2017). Standards and guidelines for the interpretation and reporting of sequence variants in cancer: A joint consensus recommendation of the Association for Molecular Pathology, American Society of Clinical Oncology, and College of American Pathologists. Journal of Molecular Diagnostics, 19(1), 4–23. https://doi.org/10.1016/j.jmoldx.2016.10.002.

[9] Baden, J., Lin, C.-H. J., Anfora, A. T., Beer, J., Bisselou, K., Bungo, J., Corner, A. S., Danek, T., Dickey, J., Godsey, J. H., Johann, D. J., Jones, G., Lee, J. S. H., Liu, L., Karlin-Neumann, G., Larson, J. L., Lopez Ramos, D., Merriam, D., Palomares, M., ... Leiman, L. C. (2025). Generic protocols for analytical validation of tumor-informed circulating tumor DNA assays for molecular residual disease: The Blood Profiling Atlas in Cancer's Molecular Residual Disease Analytical Validation Working Group consensus recommendation. JCO Precision Oncology. https://doi.org/10.1200/PO-25-00267.

[10] Clinical and Laboratory Standards Institute. (2025). MM19: Establishing molecular testing in medical laboratory environments (2nd ed.). Clinical and Laboratory Standards Institute. https://clsi.org/shop/standards/mm19.

[11] Clinical and Laboratory Standards Institute. (2023). EP25: Evaluation of stability of in vitro medical laboratory test reagents (2nd ed.). Clinical and Laboratory Standards Institute. https://clsi.org/shop/standards/ep25/.

    - CLSI MM13: Collection, Transport, Preparation, and Storage of Specimens for Molecular Methods[12]
- Carry-Over: CLSI EP10: Preliminary Evaluation of Quantitative Medical Laboratory Measurement Procedures[13]
- Internal Standards:
    - CLSI MM09: Human Genetic and Genomic Testing Using Traditional and High-Throughput Nucleic Acid Sequencing Methods[14,15]
- Clinical Validity
    - COM.40620 Body Fluid Analysis Phase II[16]

B.4.3. How Labs Design, Develop, and Prepare Reagents for Laboratory Developed Testing Procedures

Laboratories validate and offer LDPs solely for use in their laboratory. Reagent preparation is part of the LDP and its performance is included in the end-to-end validation under §493.1253(b)(2), which states:

> **Establishment of performance specifications.** *Each laboratory that modifies an FDA-cleared or approved test system, or introduces a test system not subject to FDA clearance or approval (including methods developed in-house and standardized methods such as textbook procedures), or uses a test system in which performance specifications are not provided by the manufacturer must, before reporting patient test results, establish for each test system the performance specifications for the following performance characteristics, as applicable:*
>
> *(i) Accuracy.*
> *(ii) Precision.*
> *(iii) Analytical sensitivity.*
> *(iv) Analytical specificity to include interfering substances.*
> *(v) Reportable range of test results for the test system.*
> *(vi) Reference intervals (normal values).*
> *(vii) Any other performance characteristic required for test performance.*

As addressed in previous sections, one reason CLIA has worked so well in the past three decades is its flexible framework that creates a baseline series of requirements. Setting new reagent-specific requirements would undermine this flexibility. **AMP recommends that CMS not create any new reagent-specific requirements.**

B.4.4. Common Types of Laboratory Modifications to FDA-Cleared or Approved Test Systems

In the RFI, CMS asks for input related to the types of common modifications that a laboratory might make to an FDA-cleared or approved *in vitro* diagnostic device. A nimble environment that promotes innovation and allows testing services to be quickly adapted and improved is essential to the continued advancement of genomic medicine, and there are numerous examples of common validated modifications that a laboratory might use with an FDA-authorized test. One study demonstrated that IVDs are often modified based on

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[12] Clinical and Laboratory Standards Institute. (2020). MM13: Collection, transport, preparation, and storage of specimens for molecular methods (2nd ed.). Clinical and Laboratory Standards Institute. https://clsi.org/shop/standards/mm13/.

[13] Clinical and Laboratory Standards Institute. (2024). EP10: Preliminary evaluation of quantitative medical laboratory measurement procedures (4th ed.). Clinical and Laboratory Standards Institute. https://clsi.org/shop/standards/ep10/.

[14] Clinical and Laboratory Standards Institute. (2023). MM09: Human genetic and genomic testing using traditional and high-throughput nucleic acid sequencing methods (3rd ed.). Clinical and Laboratory Standards Institute. https://clsi.org/shop/standards/mm09/.

[15] CLSI MM09 is comparable to § 493.1255: Standard: Calibration and calibration verification procedures.

[16] College of American Pathologists. (2025). *All Common Checklist; COM.40620, Body Fluid Analysis/Validation, Phase II Requirement).* Northfield, IL: College of American Pathologists.

patient need; 60% of participants using the FDA-authorized test reported adapting their assay from the approved procedure to allow for a greater breadth of sample type, a greater number of tumor types, to accept a lower level of tumor content, and to use instrumentation specific to their laboratory.[17] The examples outlined below illustrate how modifications are made due to clinical necessity.

- Many FDA-authorized tests are not intended for use with specimens typically used in children. For example, many laboratories use gastric aspirates as the specimen for nucleic acid amplification tests in pediatric patients suspected of having tuberculosis because it is extremely difficult to gather a sputum sample that most test kits are validated for.[18] Additionally, the IVD could be limited or are limited to only formalin-fixed, paraffin-embedded cancer tissue samples. Because of that limitation, laboratories can choose to validate other samples for use with the test kit that are appropriate for their practice setting, such as pediatric samples and non-fixed specimens obtained by minimally invasive procedures.
- Molecular laboratory professionals frequently modify interpretative criteria of FDA-authorized panels by analysis of variants as evidence supporting disease association matures. Such approaches are necessary because manufactured products are cleared by regulators at a single point in time and are generally not updated at the pace at which clinically actionable gene-disease relationships are identified, particularly in oncology and inherited disease testing.

Moreover, testing platforms and instrumentation often require considerable capital investment, and laboratories often cannot justify the additional cost of new proprietary equipment tied to a single IVD kit each time a new test becomes available. Rather than duplicating capital investment for every manufacturer-specific system, laboratories draw on their professional expertise to develop and validate an LDP that performs reliably on the equipment already in use within the facility. For example, an immunohistochemistry IVD requires specific staining equipment to use the provided antibodies. If a laboratory has a different type of staining equipment, use of the existing machinery is outside the IVD's FDA approval and the offered test is classified as an LDP. Many cleared/approved assays have been a complex manual process that are not amenable to high throughput laboratories or place laboratory staff at high risk for repetitive stress injuries. In these situations, laboratories may choose to automate or replace a manual with an automated method that improves performance or ameliorates shortcomings of the approved procedures. This approach allows laboratories to expand their testing menus and adopt new clinically relevant assays without the recurring capital costs of platform-specific instrumentation, helping to control the overall cost of testing while preserving patient access to the technology already available on-site.

Existing CMS quality regulations ensure that the processes and methodologies for every LDP (whether new or modified) are fully documented and that the laboratory follows the validated processes via documented protocols.[19] These protocols must specify each LDP's requirements for "patient preparation; specimen collection, labeling, storage, preservation, transportation, processing, and referral; and criteria for specimen acceptability and rejection," as well as the following:

1. step-by-step performance of the procedure, including test calculations and interpretation of results;
2. preparation of slides, solutions, calibrators, controls, reagents, stains, and other materials used in testing;
3. calibration and calibration verification procedures;
4. reportable range for test results for the test system;
5. control procedures;

[17] Kim AS, Bartley AN, Bridge JA, et al. Comparison of Laboratory-Developed Tests and FDA-Approved Assays for BRAF, EGFR, and KRAS Testing. JAMA Oncol. 2018;4(6):838-841. doi:10.1001/jamaoncol.2017.4021

[18] See Amplified Mycobacterium Tuberculosis Direct (MTD) Test and Xpert MTB/RIF Assay as examples.

[19] § 493.1251(a) A written procedure manual for all tests, assays, and examinations performed by the laboratory must be available to, and followed by, laboratory personnel.

6. corrective action to take when calibration or control results fail to meet the laboratory's criteria for acceptability;
7. limitations in the test methodology, including interfering substances;
8. established reference intervals (normal values) and the standards for identifying imminently life-threatening test results, or panic or alert values;
9. pertinent literature including references to support the LDP; and
10. a system for entering results in the patient record and reporting patient results including the protocol for reporting imminently life-threatening results, or panic, or alert values.[20]

CMS also mandates in current regulations that any changes in procedures must be approved, signed, and dated by the current laboratory director before use,[21] and the laboratory must maintain a copy of each LDP with the dates of initial use and discontinuance.[22]

Any changes to the existing regulatory framework should allow appropriately qualified professionals to modify an FDA-approved or -cleared *in vitro* diagnostic to better suit the needs of the patient or the laboratory. AMP urges CMS to re-affirm that modifications to FDA-approved or cleared *in vitro* diagnostics - with appropriate validation establishment of performance specifications - will continue to be permitted within the CLIA framework, and such appropriate practices will remain within the scope practice of laboratory medicine.

B.6. Postanalytic Interpretation and Use of Artificial Intelligence (AI)

AMP generally supports CMS' efforts to understand and categorize how post-analytic services fit within the existing CLIA framework, and its proposal to term such services as "Software as a Medical Service (SaMS)" from "Software as a Service (SaaS)." Regardless of how software is otherwise regulated, software that ultimately impacts a laboratory clinical report, including but not limited to analysis, interpretation, report construction, result integration, or any other aspect of preanalyic, analytic, or postanalytic phases of a laboratory procedure, should be considered to be within the CLIA framework. AMP's long held position is that laboratory analytics, including SaMS, encompass algorithms (including those powered by artificial intelligence or machine learning), software, mathematical formulae, clinical decision support tools, clinical calculations, risk calculations, and other tools that are used to clarify or enhance the clinical usefulness of the laboratory procedure. Furthermore, AMP has advocated for legislation that would further clarify that genomic, molecular, and "dry bench" laboratories should be regulated within CLIA's jurisdiction.[23] This approach allows for laboratory director oversight of the entire laboratory procedure and allows for accountability for information that is being used for patient care. Regardless of how data analytic methods are created – via commercial production or custom development – when such components are used as part of a continuous diagnostic testing procedure, they become a part of that procedure and must be subject to appropriate oversight under the CLIA regulation.

AMP believes such tests should be conducted under the oversight of the CLIA regulations. Specifically, when software is used to generate a reportable laboratory result, is necessary to generate the result, is an integral component of the testing process required to interpret the result, or is related to patient care, a CLIA-certified laboratory should remain responsible for ensuring the validity of the result. **Therefore, AMP urges CMS to clarify the definition of "laboratory" within the CLIA regulations to include facilities that produce, examine data, produce interpretations, and or summarize laboratory information obtained through analysis of such materials derived from the human body.**

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[20] § 493.1251(b).
[21] § 493.1251(d)
[22] § 493.1251(e).
[23] https://www.amp.org/advocacy/clia/

B.7. Data-Only Facilities

AMP's position on facilities that only process analytical data or provide specialized data interpretation is that if that data-only facility is receiving data from a laboratory performing wet-bench testing for post-analytic data analysis, that data-only facility should be CLIA-certified. The underlying principle for this is the same as it is for SaMS generally to be regulated under CLIA - data analysis functions as a component of a continuous diagnostic testing service. This is consistent with how physical specimens are handled between laboratories, where samples that are being used for production of clinical results should only be sent to CLIA certified laboratories. A consistent approach across all patient-derived samples and data will enable more efficient operations and regulation of laboratories. **AMP recommends CMS clarify that data-only facilities generating reportable clinical results that will inform patient care derived from laboratory results should require CLIA certification.**

B.2. Specimen Preparation Activities and Personnel

CMS asks stakeholders if the CLIA definition of "laboratory" should be updated to include facilities only collecting or preparing specimens (or both) or only serving as a mailing service and not performing testing. AMP's position is that it is impractical for all aspects of collection to fall under CLIA regulations. Laboratories cannot necessarily or easily verify what happened to the specimen before arriving at the laboratory, i.e., when a phlebotomist performs collection, but there are consensus-informed quality assurance steps to ensure appropriate collection and handling of samples. **AMP recommends that CMS reference CLSI QMS101 and CLSI GP41 for specimen collection in any possible regulations that address facilities only collecting, preparing, and/or mailing specimens.**

B.3. Suboptimal Specimens

Similar to AMP's recommendations related to collection, preparing, or mailing-only facilities, AMP recommends that CMS take a flexible approach with regard to the permissibility of suboptimal specimens should be addressed in CLIA regulations. One of the primary benefits of regulating LDPs under CLIA is the laboratory director's ability to adapt a protocol to facilitate testing on suboptimal specimens that are an unavoidable reality of medical practice. How to handle suboptimal specimens is highly test specific, and regulations need flexibility to allow for incorporation of medical judgment. Real world examples of clinical necessity requiring the use of suboptimal specimens may include cancer patients unable to undergo further biopsies or irreplaceable samples such as bone marrow samples pre-transplant and swabs from patients with suspected bacterial infections who were treated with antibiotics after sample collection. Another example is chorionic villus sampling (CVS) or testing amniotic fluid from a specific gestational window during pregnancy. In those circumstances, the benefit of results from testing, even from a non-ideal specimen, may still be clinically desirable and beneficial to test a suboptimal sample when no alternatives are available, rather than not generating a result at all.

Existing CLIA regulations anticipate the possibility of predictable and unpredictable events that would lead to suboptimal specimens, requiring laboratories to build validation processes that address such likelihoods. Additionally, as in other areas, professional guidelines can be helpful in guiding validations (e.g., CLSI MM09: Human Genetic and Genomic Testing Using Traditional and High-Throughput Nucleic Acid Sequencing Methods). In situations where the test is an FDA-approved device that is being performed exactly to manufacturers procedures, there may not be as many avenues to account for and adapt when the specimen is suboptimal, reinforcing the important role of LDPs, i.e., modified IVDs, in medicine and the benefits of CLIA's flexibility. **AMP recommends that CMS preserve laboratories' discretion under CLIA to establish and implement test-specific or patient situation-specific policies for the evaluation and use of suboptimal specimens.**

D.1. Specialty Testing Areas

As discussed earlier, AMP strongly recommends that CMS adopt an updated and inclusive definition that would modernize CLIA:

> *"The term "laboratory" or "clinical laboratory" means a facility for the biological, microbiological, serological, chemical, immuno-hematological, hematological, biophysical, cytological, pathological, flow cytometric, molecular, genetic, genomic, or other examination of materials derived from the human body or information obtained through analysis of such materials, for screening purposes or for the purpose of providing information for the prognosis, diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings."*

Adoption of this updated definition would align CLIA with advances in laboratory science and diagnostic technologies and promote regulatory consistency across testing methodologies. It would also ensure that patients continue to benefit from high-quality, innovative diagnostic services.

D.1.1. Specialty Testing Areas

The RFI also asks for respondents to contemplate what challenges or limitations that laboratories currently experience with specialty or subspecialty categories in CLIA regulations**. AMP urges CMS to expand CLIA's specialty areas to formally encompass flow cytometric, molecular, genetic, and genomic analyses.** The current regulations do not include a dedicated category for molecular genetic testing, flow cytometry, or genomic analyses. This omission is increasingly consequential given the volume and clinical significance of molecular and genomic testing performed today, from companion diagnostics to hereditary cancer panels to flow cytometric evaluation of hematologic malignancies. As CMS is aware, laboratory medicine has grown and evolved substantially since CLIA was enacted nearly 40 years ago, and molecular and genomic technologies that barely existed at the time of the statute's passage are now central to routine clinical care. **CMS should update the CLIA regulations to reflect current laboratory practice by establishing specialty and subspecialty categories, for these fields, ensuring that oversight keeps pace with the technologies laboratories now use to diagnose and manage patients.**

C.1. Emergency Preparedness

Academic and community molecular diagnostic laboratories, together with public health and reference laboratories, play an indispensable role during infectious disease outbreaks. The 2020 SARS-CoV-2 pandemic remains the most significant and impactful public health emergency in recent memory, and laboratories employing AMP members were integral to the pandemic response, providing visibility into the emergence, spread, and eventual molecular evolution of the virus.

AMP continually solicits qualitative and quantitative data from its members with the objective of creating professional resources and informing policymaking, and the pandemic years were no exception. AMP surveyed its membership multiple times over the course of the pandemic to understand the successes and hurdles they experienced when providing crucial and timely diagnostic services for patients during the public health emergency (PHE). You may access the full survey results here, but we highlight a few notable results below.

AMP's survey identified inefficiencies in the deployment of laboratory testing during the COVID-19 pandemic in the United States. Certified public health laboratories are essential to early testing during an outbreak and conduct surveillance in nonemergent times but faced challenges meeting the demand due to limited testing capacity and lack of integration with the medical system. Due to their direct physical proximity to patients, hospital laboratories and other local community clinical testing laboratories are optimally positioned on the frontlines during pandemics to meet testing capacity needs and to provide appropriate turnaround times necessary to manage patients that need immediate care. Unfortunately, our 2020 surveys found that academic medical centers and community health laboratories were underutilized and

deprioritized throughout the COVID-19 PHE with regard to accessing limited testing supplies. This was despite the fact that approximately 90% of academic medical centers and community hospital or health system laboratories performing SARS-CoV-2 diagnostic testing reported a turn-around time of less than 24 hours, compared to only 57% of commercial laboratories having a turn-around time of less than 24 hours. The fast turn-around times of near-to-patient laboratory testing is especially important because it allows for more rapid decision making as it relates to patient treatment plans, the protection of frontline healthcare workers, curtailment of community transmission, and decisions regarding utilization of scarce personal protective equipment.

All of the sectors of the clinical testing landscape need to be supported to ensure a complete laboratory response effort during a pandemic. **AMP encourages CLIA to recognize the importance of incorporating the full range of clinical laboratories in response to a PHE and not limit testing, to a limited number or type of laboratories.**

AMP's surveys also found that in the COVID-19 PHE, laboratory professionals simultaneously employed multiple SARS-CoV-2 testing methods to address supply-chain disruptions and ensure that access to testing and patient care was maintained despite problems with procuring certain materials and components. The surveys found that not only did supply chain shortages for SARS-CoV-2 testing impact a laboratory's ability to obtain reagents for other tests (72 percent), a majority of labs also had to divert staff (68 percent) and laboratory space and instruments from other life-critical testing to SARS-CoV-2 testing (48 percent).[24] For instance, laboratories validated use of saline instead of extremely limited viral transport media (shortages experienced by 53% of respondents) or used saliva as a specimen type to alleviate the swab shortage (experienced by 60% of respondents). This redundancy in testing methods and flexibility to modify and validate tests as needed was made possible via the CLIA regulations. **AMP is hopeful that in future PHEs, clinical laboratories will have the support of the CLIA program to fully utilize LDPs in response, surveillance, and other applications.**

Last, the unprecedented surges in testing capacity in recent PHEs highlight the importance of maintaining an adequate and resilient laboratory workforce. The Department of Labor defines hazard pay as "additional pay for performing hazardous duty or work involving physical hardship. Work duty that causes extreme physical discomfort and distress which is not adequately alleviated by protective devices is deemed to impose a physical hardship."[25] While outside the purview of CLIA directly, support for hazard pay and other incentives for these frontline workers will help maintain an adequate workforce during future infectious disease outbreaks. **Given its role in laboratory practice standards, AMP encourages CLIA to work with its colleagues at other agencies to support this critical healthcare workforce.**

Above all, AMP urges CMS to affirm that a flexible regulatory framework is critical to ensuring laboratories can swiftly and adeptly launch LDPs and other test systems to respond to the public health emergency and ensure that any implemented updates to CLIA reflect this.

Conclusion

Thank you again for the opportunity to engage with CMS on this important first step for modernizing CLIA at the regulatory level. AMP appreciates CMS' efforts to ensure that CLIA regulations reflect current laboratory practices and concerns. For ease of reference, AMP has provided a summary of its recommendations to CMS in the attached Appendix A. We welcome the opportunity to continue working with you and should you have any

[24] Association for Molecular Pathology. (2021). *Cancer diagnostic testing amidst COVID-19 pandemic survey results*. https://www.amp.org/AMP/assets/File/advocacy/AMPSurveyResults-CancerandCOVID-FINAL-2-2021.pdf

[25] https://www.dol.gov/general/topic/wages/hazardpay

questions or require additional information, please direct your correspondence to Gail M. Reese, JD, Public Policy and Advocacy Director, at greese@amp.org.

Respectfully,

Aaron D. Bossler, MD PhD
President
Association for Molecular Pathology

APPENDIX A:

Summary of AMP Recommendations in Response to CMS' Request for Information; Clinical Laboratory Improvement Amendments of 1988 (CLIA) Regulations; CMS-3485-NC

RFI Section / Topic	AMP Recommendation to CMS
Laboratory Developed Testing Procedures Generally	Continue to recognize the value of CLIA and preserve the same flexibility that has served patients and providers well over the past three decades.
Laboratory Developed Testing Procedures and CLIA Modernization	Modify CLIA regulation to reflect that the program is responsible for ensuring the quality of all LDPs. Specifically, CLIA should explicitly require laboratory professionals to establish clinical validity of any LDP, via the options listed.
B.4. Laboratory Processes and Procedures	Preserve CLIA's flexible, performance-based framework and continue allowing laboratories to establish validation approaches appropriate to the specific test, methodology, specimen type, and clinical context.
B.4.2.a. Testing Methods & Unique Performance Characteristics	Leverage existing consensus-based standards and collaborate with professional organizations and accrediting bodies to address existing gaps in CLIA with regard to unique performance characteristics in order to avoid duplicative efforts and ensure that any CLIA updates to analyte-specific requirements align with current laboratory practice.
B.4.2.b. Examples of Performance Characteristics	Recognize that performance characteristics for major testing methodologies are already comprehensively addressed through established professional guidelines and should inform any future regulatory updates.
B.4.3. Design, Development, and Preparation of Reagents for LDPs	Do not establish new reagent-specific requirements and instead continue relying on CLIA's existing validation framework to assess reagent performance as part of the overall testing process.
B.4.4. Modifications to FDA-Cleared or Approved Test Systems	Reaffirm that laboratories may continue to modify FDA-cleared or approved test systems and validate those modifications under CLIA when necessary to meet patient and laboratory needs.
B.6. Postanalytic Interpretation and Use of AI	Clarify that software, algorithms, machine learning tools, and AI systems used to generate or interpret reportable laboratory results fall within CLIA oversight and laboratory responsibility.
B.7. Data-Only Facilities	Require CLIA certification for data-only facilities that generate reportable clinical results used in patient care.
B.2. Specimen Preparation Activities and Personnel	Reference established CLSI collection and specimen-handling standards rather than imposing extensive new CLIA requirements on collection, preparation, or mailing-only facilities.
B.3. Suboptimal Specimens	Preserve laboratory director discretion to evaluate and test suboptimal specimens when clinically appropriate.
D.1. Specialty Testing Areas	Modernize the definition of "laboratory" to include molecular, genomic, flow cytometric, and data-analysis functions associated with clinical testing.
D.1.1. Specialty and Subspecialty Categories	Establish molecular, genomic, and flow cytometry specialty/subspecialty categories.

RFI Section / Topic	AMP Recommendation to CMS
C.1. Emergency Preparedness **(Regulatory Challenges)**	Integrate all sectors of the clinical laboratory system into public health emergency response planning and avoid restricting testing, even with *in vitro* diagnostic testing kits, to a limited number or type of laboratory.
C.1. Emergency Preparedness **(Supply Chain Challenges)**	Preserve CLIA's regulatory flexibility so laboratories can rapidly validate and implement LDPs and alternative testing approaches in response to emerging public health threats and supply chain disruptions.
C.1. Emergency Preparedness **(Resilient Workforce)**	Support development and retention of a resilient laboratory workforce capable of responding to future public health emergencies.
C.1. Emergency Preparedness **(Generally)**	Maintain a flexible CLIA framework that supports innovation, professional judgment, and timely patient access to high-quality laboratory testing while preserving robust quality standards