P.O. Box 92, Dundee, Michigan, 48131
301.478.6379 • www.ascls.org

The American Society for Clinical Laboratory Science (ASCLS) appreciates the opportunity to comment on this Request for Information on behalf of its members and other stakeholders drawn from a broad representation of the clinical laboratory community.

Guiding Principals

Through this Request for Information, CMS will be gathering information from a broad cross section of the clinical laboratory community. As this information is processed, ASCLS urges CMS to apply time-honored principals that align with the highest ethical principles of the health professionals caring for patients in our country.

Assuring the highest-level patient safety, well-being, and care should be the guiding standard of any regulation. Patients are not to be balanced against any other concern.

CMS must resist pressure to lower standards out of convenience or the perception that access may be compromised because of a self-inflicted "personnel shortage" by the clinical laboratory industry. While there are challenges attracting qualified medical laboratory professionals to some areas of the country, there is no evidence that widespread shortages of medical laboratory professionals exist. Regulatory changes that compromise patient care or increase risk to patients based on a false narrative should not be considered.

Finally, professional organizations in our community are doing extraordinary work developing practice guidelines and references that will always be more current scientifically than regulatory regimes can address. Where possible, and when those guidelines have broad professional support and consensus, CMS should reference those external resources rather than self-develop them within the agency. These organizations are best equipped to respond to changes in scientific knowledge and clinical practice.

Breath Testing

Breath testing is an evolving area that spans well-established clinical applications, such as *Helicobacter pylori* urea breath testing, and emerging or frontier applications, including breath-based assessment of liver function and investigational disease detection such as oncology-related volatile organic compound analysis. ASCLS supports regulatory modernization that recognizes breath as a clinically relevant human-derived specimen type when test results are used for diagnosis, prevention, treatment, or health assessment.

What breath tests are facilities performing for clinical use?

P.O. Box 92, Dundee, Michigan, 48131
301.478.6379 • www.ascls.org

Facilities currently perform several categories of breath testing for clinical use. The most established example is the urea breath test for active *H. pylori* infection and post-treatment eradication confirmation. Gastrointestinal breath testing is also used to evaluate small intestinal bacterial overgrowth (SIBO), intestinal methanogen overgrowth (IMO), carbohydrate malabsorption or intolerance, and related gastrointestinal symptoms such as bloating, gas, abdominal discomfort, diarrhea, and constipation. These tests commonly include hydrogen and methane breath tests using substrates such as lactulose, glucose, lactose, fructose, or sucrose. Some commercial offerings also measure hydrogen sulfide in addition to hydrogen and methane, as reflected by products such as the Trio-Smart SIBO Breath Test. Liver function breath analysis, such as LIBRA®, represents another marketed example. In contrast, breath-based cancer detection and broader volatile organic compound profiling remain frontier applications that require additional clinical validation, standardization, and appropriate regulatory oversight before widespread clinical implementation.

What methodologies and technologies do facilities use in breath testing for clinical use?

Methodologies vary by clinical indication. Urea breath testing generally uses an isotopically labeled urea substrate, followed by measurement of labeled carbon dioxide in exhaled breath to detect urease activity associated with active *H. pylori* infection. Hydrogen and methane breath testing generally uses a carbohydrate substrate, timed serial breath collections, and measurement of exhaled gases produced through microbial fermentation. Technologies may include infrared spectroscopy, isotope ratio analysis, gas chromatography, electrochemical sensors, or other validated gas-detection platforms. Emerging platforms may use multi-gas detection, volatile organic compound profiling, mass spectrometry, sensor arrays, or other analytic technologies.

What type of facilities perform breath testing for clinical use?

Clinical breath testing is performed across a range of settings, including hospitals, health system laboratories, gastrointestinal and motility clinics, physician office laboratories, outpatient specialty clinics, and independent or reference laboratories. In practice, many gastrointestinal breath tests are collected in gastrointestinal clinics, outpatient settings, or at home using manufacturer- or laboratory-provided kits and then analyzed by specialty or reference laboratories. Some facilities perform testing directly on site, while others collect or facilitate collection and refer specimens to laboratories with the appropriate instrumentation and expertise.

How do facilities collect, transport, and store clinical breath specimens? What challenges are encountered?

P.O. Box 92, Dundee, Michigan, 48131
301.478.6379 • www.ascls.org

Collection practices vary by test system but generally involve patient preparation, baseline breath collection, administration of a substrate when applicable, and one or more timed post-substrate breath collections. Hydrogen and methane tests often require serial collections over several hours, while urea breath testing commonly requires baseline and post-dose specimens. Specimens may be collected into bags, tubes, vials, or device-specific containers supplied by the manufacturer or testing laboratory.

Common challenges include inconsistent patient preparation; timing errors during serial collection; incomplete or improperly labeled specimens; sample leakage or contamination; gas instability during storage or transport; variable ambient temperature exposure; delayed shipment; lack of harmonized cutoffs or interpretive criteria across platforms; and limited availability of standardized calibrators, controls, proficiency testing, and external quality assessment materials for some breath testing technologies.

ASCLS recommends that when breath test results are used for clinical diagnosis, treatment decisions, disease monitoring, prevention, or health assessment, they should be subject to an appropriate quality framework under CLIA. Before regulations are fully implemented, CLIA and FDA should work collaboratively with manufacturers, proficiency testing providers, and other stakeholders to define appropriate requirements for calibration, calibration verification, quality control, method validation or verification, specimen stability, personnel competency, proficiency testing, and standardized reporting. ASCLS supports a balanced approach that protects patients by ensuring accurate, reliable, and timely results while allowing continued innovation in validated breath-based diagnostics.

Specimen Preparation Activities and Personnel

What activities does the laboratory consider to be part of specimen preparation (for example, centrifuging, aliquoting, loading on analyzers, adding chemicals for preparation, tissue processing, slide staining, inoculating culture plates, DNA/RNA extraction)?

Any and all activities required to prepare a specimen for testing is part of specimen preparation, including all the examples cited.

What is the education and experience of the personnel who perform specimen preparation activities for your laboratory?

The backgrounds of the personnel who are responsible for the preanalytical process include phlebotomists, medical assistants, laboratory assistants, and other individuals with at least a high school diploma. They are educated and trained by community

colleges, technical education programs and medical laboratory technicians, and scientists. ASCLS supports the creation of a new personnel category with reasonable personnel qualifications (not requiring an associate or bachelor's degree) that would establish a training and competency-based pathway for these personnel.

How does the laboratory ensure that personnel who perform specimen preparation activities remain competent?

As required for all positions in the laboratory, regular annual competency assessment is conducted. In-service sessions and morning huddles are used to ensure that the personnel have the latest information.

Suboptimal Specimens

All compromised specimens put patients at risk because we have no assurance that the result provided is valid. Current systems for laboratory reporting do not ensure clinicians are seeing, much less interpreting, notes properly.

Providing results from suboptimal specimens is, by default, a risk to patients. Annotating the results with interpretations and/or qualifiers is always provided to communicate the issues with the results, but they are often overlooked or ignored by clinicians. Unless communications systems force clinicians to see and react to the clarifying notations, using suboptimal specimens presents an unacceptable and avoidable risk to patients.

ASCLS acknowledges that under some circumstances it is appropriate to use suboptimal specimens to perform the requested testing. This occurs when recollection is not possible (the patient is no longer alive) or getting another specimen is very invasive, impractical, or puts the patient at risk, such as biopsies and spinal fluid, or specimens that were obtained during a surgical or radiologic procedure. Laboratories will also proceed with testing on a suboptimal specimen if some of the results are valid, withholding results that are below optimal standards.

Several of the accreditation agencies include provisions for the special handling of suboptimal specimens that we all follow. At the very least the report should indicate that status of the specimen and how that might affect the result.

ASCLS agrees with accreditation requirements that specimens must be rejected when mandatory criteria are not met—such as a blood specimen drawn in the wrong tube or not appropriately filled (such as in a citrate tube), or when patient or specimen identity is doubtful.

Calibration Verification

What technical and operational challenges does the laboratory face when performing calibration verification on FDA-cleared or approved manufacturer-calibrated devices?

Most devices designed for POC testing cannot be calibrated, which is in the best interest of patient care. When the devices are not within calibration, a failsafe is triggered and the device is returned for replacement by the manufacturer. Very few medical laboratory professionals would have the appropriate competencies to perform calibration verification correctly on these devices. Even in situations where this testing has oversight of laboratory professionals, it is still preferable that systems not within calibration cannot operate.

If this needs to be addressed under CLIA, CMS should carefully provide an exception clarifying the types of test systems that require calibration verification, as many test systems do not.

Data-Only Facilities

ASCLS believes it is appropriate to have data only facilities for bioinformatics and interpretation only, but they should have a CLIA certificate. The Society sees no justification for waving this requirement and opening a loophole.

Remote Direct Observation Competency Assessment

ASCLS believes that in the appropriate situation and using the appropriate methodology that virtual competency assessment can be helpful, especially for rural and remote facilities. If it is to be allowed, standards should be set that describe the visual and audio fidelity of what the assessor must see and hear.

Emergency Preparedness, Biosafety and Biosecurity, and Cybersecurity

Most clinical laboratories have standalone emergency preparedness plans required by their accreditor already. Those that don't, likely are integrated into plans required by institutional accreditors like The Joint Commission.

ASCLS believes it reasonable for all laboratories to have emergency preparedness plans and urges CMS to build on the clinical laboratory community's strong foundation that exists already.

Cybersecurity

ASCLS recognizes cybersecurity as a significant and increasing threat to clinical laboratory operations, patient information, and ultimately patient care. Modern laboratories are highly interconnected data environments that depend on laboratory information systems (LIS), electronic health record (EHR) interfaces, middleware, automated instrumentation, vendor-supported software, remote connectivity, and

increasingly cloud-based technologies. A cybersecurity event affecting any part of this infrastructure can disrupt testing, delay results, compromise data integrity, and interfere with the laboratory's ability to support timely clinical decision-making.

Cybersecurity is also a rapidly evolving area. For this reason, ASCLS supports a risk-based and flexible approach rather than highly prescriptive CLIA requirements for specific technologies or security controls. Laboratories vary considerably in size, structure, resources, and institutional support. In many hospital and health-system laboratories, cybersecurity infrastructure is managed at the organizational level by information technology (IT) and information security departments rather than by laboratory personnel alone. Independent, physician-office, rural, and smaller laboratories may have substantially different resources and may rely on external vendors or contracted IT services. CLIA requirements should recognize these differences while establishing an expectation that laboratories participate in protecting the confidentiality, integrity, and availability of laboratory information and operations.

Appropriate cybersecurity practices may include unique user identification, role-based access, multifactor authentication where appropriate, periodic review of user access, prompt removal or modification of access when employment or responsibilities change, network segmentation, firewalls, secure remote access, system monitoring, data backup and recovery procedures, and controls governing vendor access. Access from outside the United States should similarly be governed by institutional risk assessment and appropriate security controls rather than categorically prohibited. Legitimate remote access may be necessary for qualified laboratory professionals, vendor support, and other operational needs.

ASCLS also recognizes a particular challenge involving laboratory instrumentation and vendor-supported systems. Laboratory professionals may be responsible for operating systems that cannot be patched, upgraded, or modified without vendor authorization. Vendor requirements may also conflict with institutional cybersecurity practices, including requirements related to administrator privileges, user accounts, remote access, or software configuration. ASCLS encourages CMS to recognize these limitations and avoid placing laboratories in the position of being held solely responsible for cybersecurity controls they are contractually or technically unable to implement. Cybersecurity expectations should promote collaboration among laboratories, healthcare organizations, information security professionals, manufacturers, and software vendors.

Cybersecurity incident response should be incorporated into laboratory emergency preparedness and continuity planning. Plans should address identification and escalation of an incident, containment of affected systems, communication

responsibilities, preservation and recovery of laboratory data, verification of data and result integrity following restoration, downtime testing and reporting procedures, regulatory or legal notification when required, and post-incident evaluation. Laboratories must be prepared to maintain essential testing when electronic systems are unavailable, particularly for time-sensitive and critical patient care services.

Responsibility for cybersecurity will vary among laboratory settings. Institutional information security and IT professionals may have primary responsibility for technical cybersecurity infrastructure, while laboratory leadership, LIS personnel, laboratory IT specialists, and other laboratory professionals provide critical expertise regarding laboratory workflows, instrumentation, interfaces, patient safety, and operational consequences. The laboratory director retains an important role in ensuring the confidentiality and integrity of laboratory information and should be involved in laboratory-specific cybersecurity planning and response.

Finally, laboratory personnel should receive cybersecurity education appropriate to their responsibilities. At minimum, training should address secure access practices, phishing and social engineering, protection of patient information, appropriate use of laboratory systems, recognition and reporting of suspected cybersecurity events, and laboratory downtime procedures. Personnel with responsibility for LIS, middleware, interfaces, instrumentation, or other laboratory information systems should receive additional role-specific education.

ASCLS encourages CMS to recognize cybersecurity as an essential component of modern laboratory quality and patient safety while maintaining sufficient regulatory flexibility to accommodate rapidly changing threats and technologies. Cybersecurity is a moving target, and overly specific technical requirements risk becoming outdated quickly. CLIA should establish clear expectations for cybersecurity preparedness, accountability, training, and continuity of laboratory operations while allowing laboratories and their organizations to implement controls appropriate to their size, complexity, technology, and identified risks.

Specialty Testing Areas

ASCLS supports modernization of the CLIA specialty and subspecialty framework to better reflect contemporary laboratory practice. Many of the existing categories were established before molecular diagnostics, genomics, advanced informatics, and other technologies became routine components of laboratory testing. As laboratory medicine continues to evolve, the terminology and scope of these categories should evolve to accurately reflect current practice.

ASCLS recommends that CMS and the CDC review existing specialties and subspecialties to identify outdated terminology and areas where current definitions no

longer adequately represent the testing being performed. However, modernization does not necessarily require the creation of a new specialty each time a new technology or methodology is introduced. In many cases, newer methodologies can appropriately remain within an established specialty when they serve the same clinical purpose. Histocompatibility is one example. The field now incorporates advanced molecular and immunologic methods that extend well beyond the testing historically associated with the specialty, but these methods remain integral to the practice of histocompatibility.

At the same time, ASCLS believes there are areas of laboratory medicine that warrant consideration for more specific recognition within the CLIA specialty and subspecialty framework. Molecular diagnostics and genomic testing are particularly important given their continued growth and increasing role in patient care. Molecular testing is now routinely used in inherited disease, oncology, infectious disease, pharmacogenomics, transplantation, and other areas of laboratory medicine. Some of these areas, particularly molecular oncology, inherited genetic and genomic testing, and pharmacogenomics, have distinct bodies of knowledge, technical requirements, interpretive complexity, and significant implications for patient care.

ASCLS cautions against defining specialties based on methodology alone. The same technology, such as next-generation sequencing, may be used for tumor profiling, inherited disease testing, infectious disease identification, or histocompatibility testing. Although the analytical technology may be similar, the expertise required to validate, perform, interpret, and clinically apply the results can differ substantially. Specialty and subspecialty categories should therefore consider the clinical purpose of the testing, its complexity, and the expertise required rather than the methodology alone.

ASCLS also encourages CMS and the CDC to consider existing standards and consensus guidance developed by organizations with recognized expertise in specialized areas of laboratory medicine. The Association for the Advancement of Blood and Biotherapies (AABB), the American Society for Histocompatibility and Immunogenetics (ASHI), the Foundation for the Accreditation of Cellular Therapy (FACT), and other professional and accreditation organizations have established standards and quality frameworks for specialized laboratory testing. CMS should avoid unnecessarily recreating technical standards where well-established, evidence-based frameworks developed by experts in the field already exist.

Federal requirements should establish appropriate expectations for quality, personnel competency, validation, patient safety, and laboratory accountability while recognizing the value of specialty-specific standards developed by experts within those disciplines. As CMS and the CDC consider revisions to the current specialty and subspecialty

P.O. Box 92, Dundee, Michigan, 48131
301.478.6379 • www.ascls.org

categories, engagement with the professional organizations representing these areas can help ensure that any changes accurately reflect current laboratory practice, testing complexity, and patient safety needs.