WHITEPAPER

Beyond the Status Quo

The Structural "Glow Up" of Next-Generation Lateral Flow Architectures

Christina Holloway, RN, LNCC
Inventor & Founder, Point-of-Care Diagnostics
Patent Holder, U.S. Patent No. 10,386,376
ORCID iD: 0009-0002-2264-7668
cdhollowayllc@gmail.com

Background:

Point-of-Care Testing (POCT) has revolutionized healthcare delivery by shifting diagnostic analysis to the bedside. However, a systemic “workflow bifurcation” persists: while assay biochemical sensitivity has advanced, sample collection, volumetric transfer, and reagent mixing remain heavily reliant on manual, pre-analytical steps. Research indicates that 60% to 70% of all diagnostic errors occur in this unmonitored pre-analytical phase [1, 2], driving operator-dependent false-negative, invalid, and concentration-dependent “hook effect” results.

Objective: This paper presents a paradigm shift in decentralized diagnostics through *structural automation*- the integration of specimen collection, volumetric self-metering, and dry-reagent storage into a contiguous, closed-system architecture. By embedding passive capillary fluidic logic directly into the device’s physical geometry, the human hand is decoupled from the fluidic pathway. This architecture structurally mitigates natural sample viscosity variances, guarantees stoichiometric reagent-to-sample ratios, and replaces non-commutable, error-prone external Liquid Quality Controls (LQCs) with specimen-activated structural controls.

Impact: Incorporating structural automation drastically reduces pre-analytical operator error, which has been shown in field evaluations to improve diagnostic sensitivity from 31.3% to 85.7% [11], while maintaining invalid rates under 1% [16]. Economically, this unified model reduces clinical labor overhead (which constitutes up to 31% of POCT costs) [13], minimizes biohazardous waste, and eliminates the cost of refrigerated external controls. Regulatorily, minimizing the device’s use-error profile significantly de-risks human factors validation under IEC 62366-1, establishing a robust, predictable pathway toward a direct FDA 510(k) clearance and CLIA waiver status.

Keywords: Point-of-Care Testing (POCT), Lateral Flow Assay (LFA), Pre-Analytical Error, Structural Automation, Liquid Quality Control, CLIA Waiver.

Executive Summary

Point-of-Care Testing (POCT) has long promised to democratize medicine by shifting the diagnostic center of gravity from highly centralized, slow-turnaround core laboratories directly to the patient's bedside. Within this decentralized movement, the Lateral Flow Assay (LFA) remains the most widely deployed diagnostic technology globally, valued for its simplicity, speed, and low unit cost. However, a widening paradox threatens the clinical utility of modern POCT: while the biochemical sensitivity of lateral flow test strips has advanced exponentially, the physical workflows used to deliver samples to these strips remain trapped in archaic, manual processes.

This mismatch manifests as a critical "workflow bifurcation." A standard LFA is not a singular test. Rather, it is a multi-step clinical procedure involving separate specimen collection, manual volumetric transfer, liquid reagent mixing, and precise gravity-driven dispensing. Because these steps occur entirely in the pre analytical phase and unmonitored by the test strip itself, they introduce a massive vector for human error.

**** Studies consistently demonstrate that 60% to 70% of all diagnostic errors occur in the pre-analytical phase, driven primarily by manual handling, specimen quality degradation, and incorrect volume transfers [1, 2]. ****

While core laboratories mitigate these variables through high-throughput, automated liquid-handling robotics and rigorous, closed-loop quality control protocols, decentralized point-of-care environments shift this procedural complexity entirely onto non-laboratory operators — effectively forcing bedside clinicians or patients to perform precise manual fluidics with zero automated oversight.

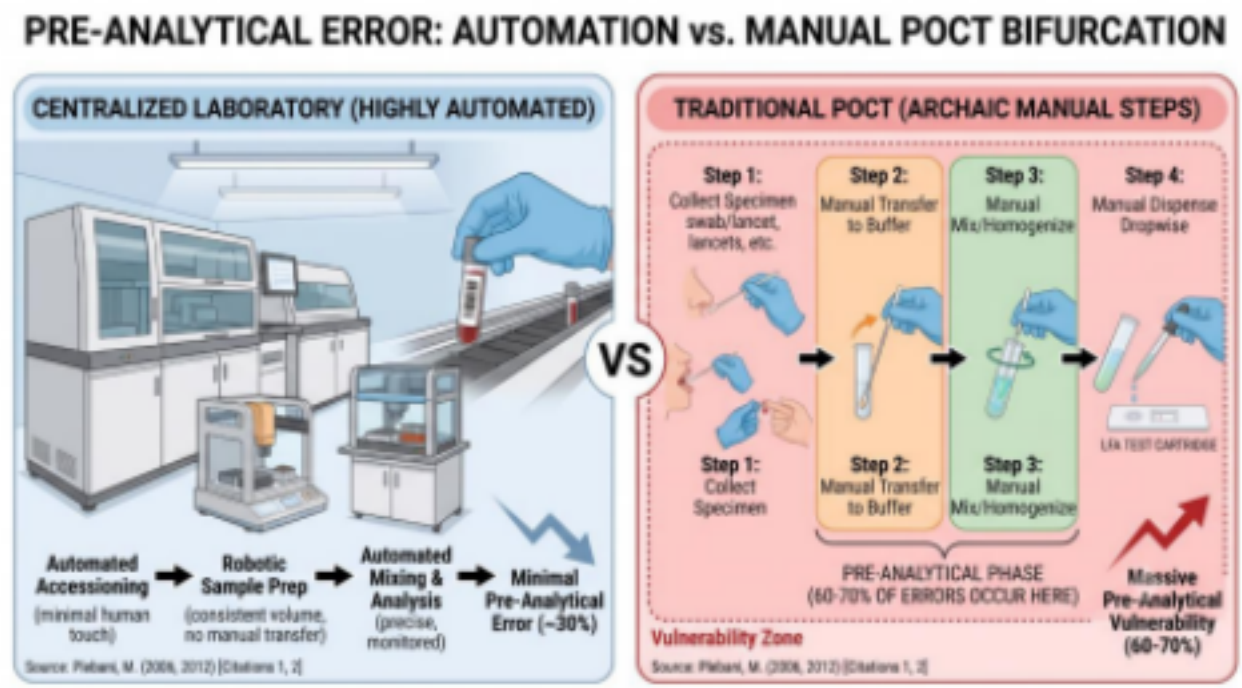
This paper examines the critical need for a paradigm shift in decentralized diagnostics: the transition from manual, multi-step fluidic handoffs to integrated, single-unit structural automation. By physically uniting sample collection directly with the assay membrane in a single, closed-system

The Status Quo & The Critical Flaw: Workflow Bifurcation in LFAs

To understand why decentralized diagnostics suffer from high rates of false-negative and invalid results, one must analyze the physical path of a specimen. The "workflow bifurcation" refers to the literal separation of specimen collection (often a swab, lancet, or cup) from the analytical reaction chamber (the test cartridge).

The Hazard of Manual Fluidics

In a typical CLIA-waived clinic or home testing environment, a non-laboratory operator must execute a highly coordinated sequence of manual actions: collecting the specimen, transferring it to a buffer vial, mixing and homogenizing the sample, and dispensing it dropwise onto the test cartridge.



~Figure 1. Pre-analytical error: automation in the centralized laboratory versus manual bifurcation in traditional POCT. Source: Plebani, M. (2006, 2012) [1, 2].~

According to human factors engineering guidelines (such as IEC 62366-1 and FDA Usability Guidance), each manual handoff is classified as a “critical task” — an action where a minor user deviation can lead to complete diagnostic failure.

1. Volumetric Under-filling: Insufficient sample volume fails to trigger lateral flow migration, resulting in weak or absent control lines.

2. Volumetric Over-filling: Excess sample floods the conjugate pad, causing “hook effects” or washing away detection antibodies before target binding can occur.

3. Viscosity & Homogenization Failures: Improper sample-to-buffer mixing yields non-homogeneous samples, which block fluidic flow or produce false-negative readouts.

While core laboratories mitigate these variables using automated liquid handling robotics, the POCT market has historically forced the bedside nurse, medical technician, or patient to act as the “robot.”

The Liquid Quality Control (LQC) Mirage

To catch these manual errors, regulatory frameworks like the Clinical Laboratory Improvement Amendments (CLIA) encourage and often mandate the use of external Liquid Quality Controls (LQCs). However, in decentralized settings, LQCs present severe economic and clinical limitations:

• The Matrix Effect & Non-Commutability: Commercially prepared liquid controls are chemically stabilized, lyophilized, or modified to extend shelf-life, meaning they do not behave like authentic, fresh clinical specimens. This “non-commutability” creates a clinical blind spot. A liquid control may produce a perfect “pass” result on a device that would otherwise fail when processing highly viscous, fresh patient samples [3, 4].
• High Operational & Hidden Costs: Purchasing, storing (often requiring refrigeration at 2–8°C), and manually running external controls vastly increases the cost-per-test of POCT

programs. In busy clinical environments, the burden of running daily or weekly LQCs leads to widespread non-compliance, jeopardizing facility accreditation and patient safety [5, 6].

• User-Induced QC Failures: Because liquid controls require the exact same manual mixing and dispensing steps as patient specimens, the controls themselves are highly prone to false-failure readings caused by operator handling error, rather than true device malfunctions [6, 7].

The Unified Architectural Paradigm: Structural Automation at the Point of Care

To resolve the systemic pre-analytical vulnerabilities of modern lateral flow assays (LFAs), the diagnostic industry must move away from expecting non-laboratory operators to perform complex liquid handling. Instead, we must transition to structural automation.

Conventional lateral flow assays rely on open-strip architectures that are highly vulnerable to environmental factors and irregular sample migration rates [17]. While chemical modifications have been used to stabilize these membranes, physical and structural barriers remain the bottleneck to achieving consistent bedside performance.

In decentralized clinical environments, the clinician, bedside nurse, or patient is routinely forced to act as a manual fluidic processor. Under high-pressure clinical conditions, they must manually collect, meter, mix, and transfer liquids. Structural automation addresses
these operational pain points by embedding fluidic logic directly into the physical geometry of the testing device itself. To bypass the inherent weaknesses of legacy liquid handling, next-generation architectures must integrate sample collection directly with fluidic routing. Transitioning from manual fluid manipulation to embedded physical logic represents a paradigm shift in minimizing operator-dependent diagnostic variability. By unifying specimen collection, sample preparation, and analytical detection into a contiguous, closed-system architecture, the human hand is decoupled from the fluidic pathway, subsequently insulating the entire diagnostic process from operator variance.

Passive Capillary Dynamics & Viscosity Mitigation

The foundational design pillar of a unified point-of-care testing (POCT) architecture is the direct specimen to-membrane interface. Rather than collecting a sample on an isolated swab and performing manual extraction steps in an external vial, the collection interface is structurally integrated directly with the assay's membranes.

• Fluidic Velocity Regulation: Upon sample collection, fluid transition is driven entirely by passive capillary forces engineered into the device's internal micro-environment, eliminating manual pipetting, shaking, or dropwise dispensing. This design directly addresses the Lucas–Washburn physical laws governing fluid flow on porous membranes, where natural variations in patient sample matrix viscosity (e.g., mucins, lipids, or cellular rheology) alter capillary flow velocity by 10% to 40% [8]. By structurally regulating the physical interface, the device prevents the "fluidic lag" and downstream timing errors that traditionally lead to false or uneven capture.

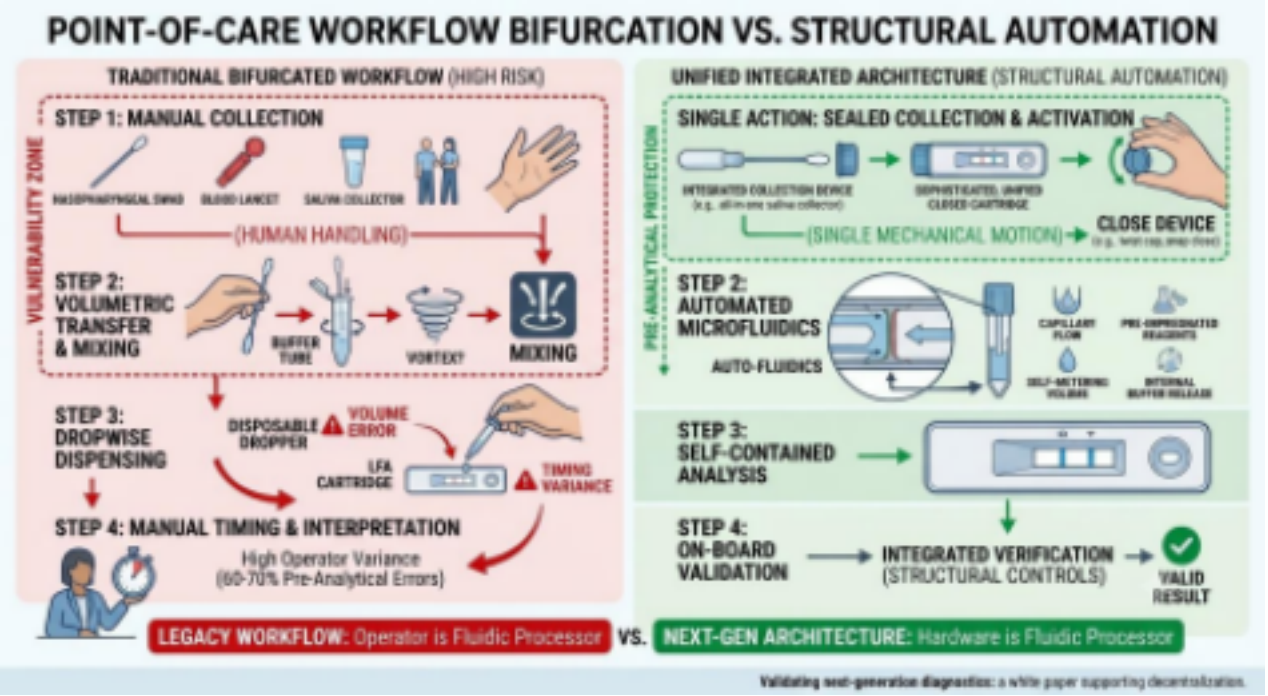
• Volumetric Self-Metering: By controlling the physical geometry and absorption capacity of the capillary channels, the architecture inherently self-meters the specimen. Utilizing integrated hydrophilic capillary geometry and passive, self-filling thermoplastic structures, the device autonomously draws and seals precise microliter volumes. This mechanical isolation completely bypasses the volume inaccuracies, edge-pooling, and sample flooding (such as the hook effect) caused by human pipetting mistakes.

• Pre-Impregnated Reagent Liberation: Necessary buffers, lysing agents, and running reagents are dry stored directly within the internal microfluidic channels. Physical activation of the device automatically hydrates and releases these reagents at precise stoichiometric ratios [10]. This achieves uniform sample-to-reagent homogenization passively, removing

the operator's mixing technique as a clinical variable.

Mechanical Fluidic Integration

In traditional testing, the transition from specimen collection to reagent dispensing represents a high-risk "vulnerability window" where specimen degradation or contamination can occur. A unified architecture closes this window by substituting manual handoffs with integrated mechanical actions (e.g., securing a cap, sliding a sleeve, or sealing a chamber). This single, highly reproducible physical motion triggers a controlled cascade of internal fluidic events [10].



~Figure 2. Point-of-care workflow bifurcation versus structural automation- legacy manual workflow compared to a unified integrated architecture.~

Structural Controls and Self-Contained Verification

If the physical architecture of the device inherently guarantees volume precision, reagent ratios, and capillary migration, the clinical reliance on external Liquid Quality Controls (LQCs) is fundamentally shifted. Instead of running expensive, chemically altered, and non-commutable external liquid controls to test whether the user performed the steps correctly, a unified system relies on built-in structural controls.

These consist of integrated procedural lines and parallel on-board capillary paths containing dry controls that only activate upon successful, volumetric hydration by the clinical specimen. This design-level safety net matches the error-mitigation capabilities of core laboratory automation.

Replacing loose manual transfer steps with calibrated, built-in fluidic collection and capillary interface elements has been shown to drastically reduce pre-analytical operator error, driving clinical sensitivity in field evaluations from 31.3% up to 85.7% [11].

Clinical, Economic, and Regulatory Impact

Transitioning from a bifurcated, manual point-of-care testing (POCT) model to a unified, structurally automated architecture resolves physical engineering challenges as well as drives compounding clinical, economic, and regulatory advantages. By decoupling the human hand from the fluidic pathway, healthcare facilities can simultaneously protect patient safety, lower operational overhead, and streamline the path to regulatory clearance.

1. Clinical Impact: Eradicating the Human Factor and False Results

The most immediate consequence of structural automation is the drastic reduction of pre-analytical errors, which directly translates to improved diagnostic accuracy and patient outcomes.

• Elimination of Operator-Induced False Negatives: In traditional assays, insufficient sample volume or incomplete buffer mixing routinely leads to weak signal development, which is frequently misread by tired or busy clinicians as a false negative. By automating capillary-driven flow and self-metering, the test membrane receives the exact stoichiometric ratio of sample and reagent every single time. Large scale, peer-reviewed evaluations of structurally automated point-of-care devices in real-world distributed service models demonstrate that mitigating operator-dependent step complexities results in exceptionally low invalid/error rates (<1%) and laboratory-equivalent accuracy [16]. Decoupling the user from the fluidic pathway ensures that clinical decision-making is driven entirely by standardized, physical hardware rather than variable operator technique, transforming point-of-care testing into a truly robust, lab-grade diagnostic tool.

• Mitigation of the Hook Effect (False Negatives at High Concentration): Over-saturation of an assay due to manual over-dispensing can cause a “prozone” or “hook” effect, where excess target antigen blocks antibody binding sites and yields a flat, false-negative result. A self-metering physical architecture physically excludes excess sample volume, protecting the test’s analytical upper limit without requiring complex manual dilutions [12].

• Prevention of Cross-Contamination and Biohazard Exposure: In manual workflows, open-vial mixing and dropper dispensing expose operators to raw, potentially infectious clinical specimens. A contiguous closed-system design traps the sample entirely within the internal plastic microfluidics, protecting the clinical environment and the operator from pre-analytical cross-contamination or biohazardous exposure [2].

2. Economic Impact: Labor Efficiencies and Waste Reduction

While developers often focus on raw material costs, the true cost of POCT is heavily driven by clinical labor and waste management in decentralized settings.

• Reduction in Clinical Labor Time: Traditional LFAs require clinicians to perform a multi-step sequence of collecting, pipetting, mixing, timing, and interpreting. These tasks keep highly paid clinical staff anchored to a workbench. Because personnel time constitutes up to 31% of the total cost of POCT delivery, reducing this entire process to a single mechanical action directly lowers labor constraints and allows personnel to be redirected to direct patient care [13].

• Minimization of Biohazard Facility Waste: Because traditional workflows rely on multi-piece consumables (disposable swabs, transfer pipettes, buffer vials, and assay cartridges), they generate a large volume of loose, contaminated clinical waste. A single-unit, closed-system architecture consolidates the sample, the buffer, and the test strip into a single solid piece of plastic, significantly reducing the volume and weight of biohazardous waste that facilities

must pay to incinerate.

• Savings from Unused and Failed Liquid Quality Controls: Facilities routinely lose thousands of dollars annually on purchasing, refrigerating, and manually running external liquid quality controls (LQCs) — many of which fail purely due to operator handling errors rather than device defects. By using built-in, dried-down structural controls that verify hydration and volume, facilities can drastically decrease their reliance on costly, non-commutable external liquid sets.

3. Regulatory Impact: De-risking the FDA 510(k) and CLIA Waiver Pathways

For any next-generation diagnostic developer, the path to commercialization is dictated by the complexity of regulatory submissions. Designing a device that inherently prevents human error simplifies this journey.

• Mitigating Human Factors Engineering Hurdles: To secure an FDA clearance, manufacturers must prove through robust usability testing that non-laboratory users cannot easily make a mistake that alters the clinical outcome. By structurally automating the fluidics (eliminating the steps where 60–70% of errors occur), the device's use-error profile is practically minimized, drastically simplifying global Human Factors (HF) validation protocols [15].

• Feasibility of a Direct CLIA Waiver: Under the Clinical Laboratory Improvement Amendments (CLIA), tests that utilize direct, unprocessed specimens and require only basic, non-technique-dependent manipulations are eligible for a CLIA waiver [14]. A closed, automated system is the gold standard for waiver eligibility; because the system relies on built-in, fail-safe mechanisms that physically prevent the user from executing incorrect volume transfers or mixing ratios, the FDA can then easily categorize the test as "simple" with an insignificant risk of erroneous results [13].

Conclusion & The Future of Decentralized Diagnostics

The long-term success of decentralized medicine relies on a simple truth: point-of-care testing (POCT) cannot reach its full potential if the device's accuracy depends on the manual skill of the operator. For decades, the lateral flow assay (LFA) has been the cornerstone of rapid testing. Yet, as the chemical sensitivity of these test strips has advanced, they have remained bottlenecked by manual, error-prone preparation steps. Forcing clinical staff and patients to act as manual fluidic processors is the primary driver of the industry's 60% to 70% pre-analytical error rates.

By moving past the legacy bifurcated workflow and embracing structural automation, we can eliminate these human variables entirely. Integrating specimen collection directly with the assay membrane in a closed, capillary-driven architecture transforms POCT from a multi-step clinical chore into a single, highly reliable mechanical action. This architectural shift protects patient safety by eliminating false results, reduces labor and biohazard waste overhead for healthcare facilities, and de-risks the regulatory path to FDA clearances and CLIA waivers.

**** This is the structural evolution "Glow Up" that point-of-care testing has been waiting for , and the only way to build a truly reliable foundation for decentralized healthcare.****

The future of point-of-care diagnostics belongs to systems that are inherently fail-safe. By replacing manual liquid-handling steps with smart, physical hardware design, the industry can deliver laboratory-grade diagnostic precision directly to the bedside.

Competing Interest Statement:

Christina Holloway is the Inventor and Co-Founder of UraSure™ Point-of-Care Diagnostics and the sole patent holder of U.S. Patent No. 10,386,376, which describes the structural LFA architectures discussed in this manuscript. Beyond this corporate affiliation and intellectual property ownership, the author declares no other financial, commercial, or personal relationships that could be perceived as competing interests or as having influenced the submitted work.

Funding Statement:

This work was supported entirely by internal operational funds from UraSure™ Point-of-Care Diagnostics. The author received no external grants, corporate sponsorships, or third-party payments from any public or private funding agencies in the past 36 months to support the development, writing, or publication of this research.

References

[1] Plebani, M. (2006). Errors in clinical laboratories or errors in laboratory medicine? Clinical Chemistry and Laboratory Medicine (CCLM), 44(6), 750–759.

[2] Plebani, M. (2012). Exploring the true value of laboratory medicine. Clinica Chimica Acta, 413(1–2), 319–323.

[3] Miller, W. G., et al. (2011). Commutability of reference materials and quality control materials. Clinical Chemistry, 57(3), e1–e29.

[4] Nichols, J. H. (2014). Risk management for point-of-care testing. eJIFCC, 25(2), 154–161.

[5] Halverson, K., et al. (2016). IQCP without agony at the point of care. CAP Today, College of American Pathologists.

[6] Shaw, J. L. V. (2016). Practical challenges of quality assurance in point-of-care testing. Clinical Biochemistry, 49(18), 1317– 1324.

[7] Meier, F. A., & Jones, B. A. (2005). Point-of-care testing error: sources and clinical significance. Clinics in Laboratory Medicine, 25(2), 263–288.

[8] Huynh, T.-T., Vo, D.-T., & Le, T.-N. (2026). Evolution of Next-Generation Multiplex Lateral Flow Immunoassays: From Engineered Nanomaterials to AI-Driven Detection. Biosensors, 16(5), 269.

[9] Czilwik, G., et al. (2016). Rapid real-time PCR and high-resolution melt analysis in a self-filling thermoplastic chip. Lab on a Chip, 16(18), 3345–3354.

[10] Plebani, M. (2022). Errors in laboratory medicine and patient safety: the road ahead. *Clinical Chemistry and Laboratory Medicine (CCLM)*, 60(8), 1165-1173.

[11] Kularatne, R., et al. (2018). Use of rapid point-of-care diagnostic tests for the elimination of congenital syphilis: what is the evidence? Southern African Journal of Infectious Diseases, 33(1), 1–6.

[12] PMC Diagnostic Review (2020). Unraveling the Hook Effect: A Comprehensive Study of High Antigen Concentration Effects in Sandwich Lateral Flow Immunoassays. MDPI Biosensors / PMC7711776.

[13] BMJ Sexually Transmitted Infections Costing Study (2025). Point-of-care screening in antenatal care: a costing study. Sexually Transmitted Infections, doi:10.1136/sextrans-2025.

[14] U.S. Food and Drug Administration (2020). Recommendations for CLIA Waiver Applications for Manufacturers of In Vitro Diagnostic Devices. FDA Guidance Document.

[15] IEC 62366-1:2015/AMD 1:2020. Medical devices — Part 1: Application of usability engineering to medical devices. International Electrotechnical Commission.

[16] Rebbapragada, A., et al. (2023). Performance of the Cue COVID-19 point-of-care molecular test: insights from a multi-site clinic service model. Microbiology Spectrum, 11(5), e01355-23.

[17] Posthuma-Trumpie, G. A., et al. (2023)**.** Lateral Flow Assay: A Summary of Recent Progress for Improving Assay Performance. *MDPI Biosensors*, 13(9), 837.

[18] Jankelow, A., et al. (2026)**.** Machine learning-augmented and structural lateral flow assays for point-of-care infectious disease diagnostics. *Lab on a Chip (Royal Society of Chemistry)*, 26(2), d5lc01124h.