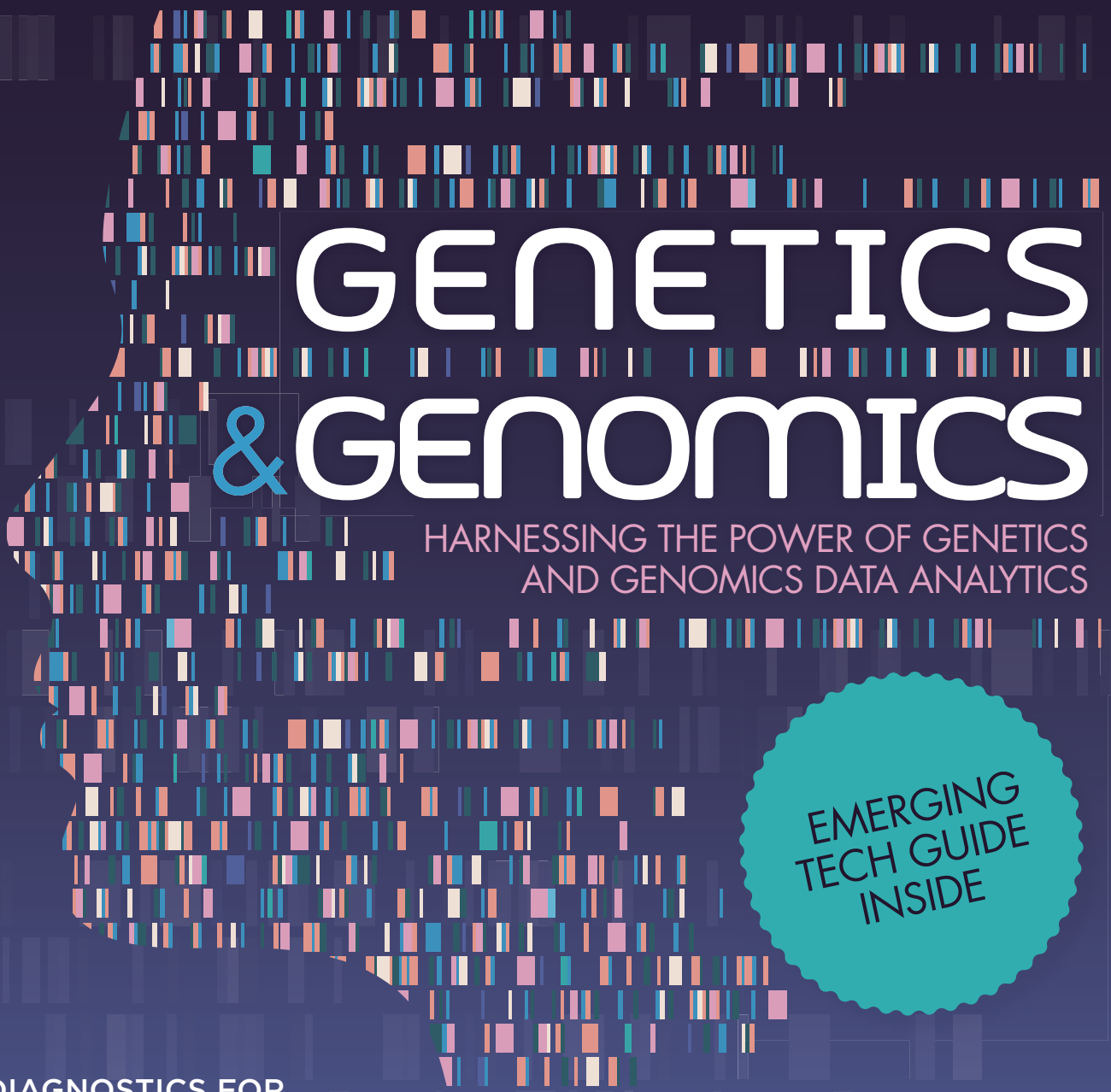
TODAY'S CLINICAL LAB

November 2024 | Volume 25



GENETICS & GENOMICS

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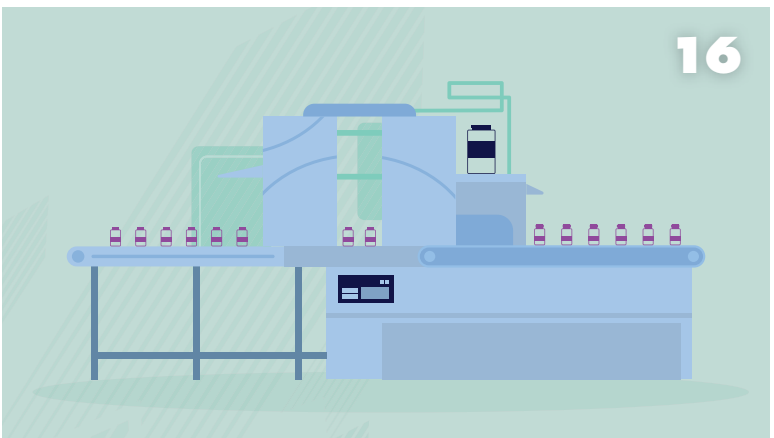

the age of artificial intelligence

The Nobel committee recently awarded the 2024 Nobel Prize in Physics to Hopfield and Hinton for foundational work on machine learning and artificial neural networks, which *The New York Times* noted as "an acknowledgement of AI's growing significance in the way people live and work." The decision emphasizes how data analytics, computational science, and machine learning now form the basis of many modern scientific tools.

This recognition echoes recent advancements in genomics, where researchers are using data-driven AI tools to analyze vast datasets in search of new insights to improve diagnostics and personalized medicine. To explore some of these insights, turn to our Advances section on page 6.

Similarly, our Genomics feature on page 10 highlights the power of combining computational and genomics methods to characterize new ultrarare diseases and greatly reduce diagnostic delays for the people living with them.

As recent innovations and regulatory changes are rapidly altering the landscape of diagnostic testing and disease treatment, turn to page 12 to learn how five trailblazing labs are seizing the opportunity to adopt new tests and treatments, paving the way to faster testing, more reliable results, and better outcomes for patients and providers.

In our Industry feature on page 16, Scott Wallask discusses the key factors driving the billion-dollar blood and clinical chemistry analyzer market, as well as how clinical labs can take full advantage of new technologies and the rising demand in testing. For more business insights, turn to page 24, where Tyler Radke, MLS(ASCP)^{CM}, explores the top threats facing the clinical lab industry in 2025 and beyond.

Looking for clarification on the changing regulatory landscape? In our Ask The Expert feature on page 28, experts Julie Ballard and Lindsay Strotman answer key questions about FDA, CLIA, and ISO regulations to help labs navigate recent changes. We also speak with LISA CEO James Gilmore about a new approach to crowdfunding regulatory costs related to lab-developed tests on page 32.

Also, don't miss our Emerging Technologies Guide on page 20.

We hope you'll join us virtually for our upcoming digital forums. Register for free access to all of our events with our All-Inclusive Pass at Events.ClinicalLab.com/Forums.

Cheers,

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December 6, 2024

Our top picks from the literature

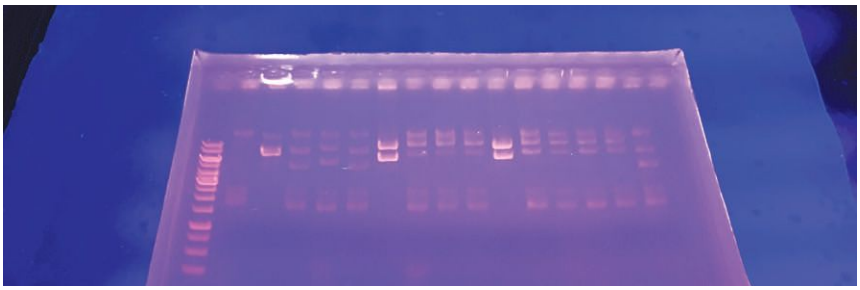
Inherited Neurological Conditions Likely Underdiagnosed

Researchers at Queen Mary University of London have unveiled significant new insights into repeat expansion disorders (REDs) through the largest study of its kind, published in the journal *Nature Medicine*. Using advanced bioinformatics techniques, the team analyzed the genetic profiles of 80,000 individuals, revealing that REDs—common causes of inherited neurological conditions—are up to three times more prevalent than current clinical estimates suggest. The study indicates that REDs like Huntington's disease "are nearly three times more common than we think, meaning we're underdiagnosing these conditions," said Arianna Tucci, PhD, clinical reader in genomic medicine at Queen Mary University London, who led the research. The findings also suggest that having certain DNA repeats may not lead to illness in some individuals, prompting a needed reevaluation of genetic testing and counseling practices. The research draws on data from the 100,000 Genomes Project, marking a significant shift from traditional research that focuses on small, family-based samples to extensive population-wide analysis. "These results are extremely important," said Sarah Tabrizi, PhD, professor of clinical neurology at the UCL Queen Square Institute of Neurology and co-author on the paper. "These data will force us as a community of researchers, academics, and doctors to evaluate whether these DNA repeats address an unmet diagnostic need in rare neurological diseases, meaning the investigation of repeat expansion disorders deserves much more close attention now." Future research will aim to study larger cohorts carrying these genetic changes, enhancing our understanding of how these disorders manifest in individuals. This study not only reshapes our perspective on REDs but also paves the way for improved genetic diagnostics and patient care.

Ibañez K et al. Increased frequency of repeat expansion mutations across different populations. *Nat Med.* 2024. doi.org/10.1038/s41591-024-03190-5.

Advances in Genetic Diagnostics for Ultrarare Diseases

A Germany-wide multicenter study has shed light on the genetic diagnostics of ultrarare diseases, emphasizing the importance of exome

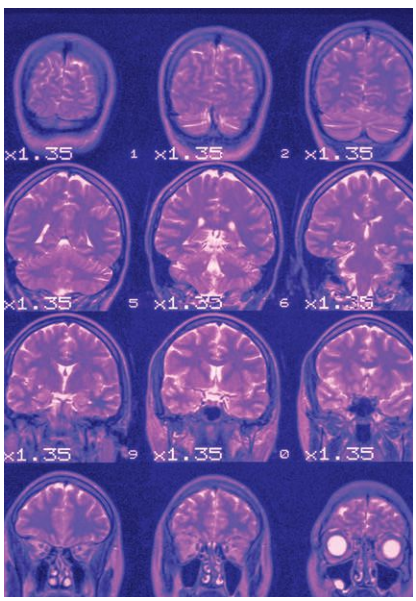


sequencing (ES) in identifying underlying genetic causes. Conducted as part of the TRANSLATE NAMSE innovation fund project, the study involved the analysis of ES data from 1,577 patients, leading to diagnoses in 499 individuals, including 34 with previously unknown genetic conditions. The findings have been published in the journal *Nature Genetics*. Theresa Brunet, MD, a lead author from the Institute of Human Genetics at the Technical University of Munich, said, "We are particularly proud of the discovery of 34 new molecular diseases, which is a great example of knowledge-generating patient care at university hospitals." The project aimed to use innovative examination methods to identify the genetic basis of rare diseases, with the research uncovering changes in 370 different genes. For the remaining unsolved cases, Tobias Haack, MD, said, "We will examine the affected patients for whom we have not yet been able to find a diagnosis as part of the model project Genome Sequencing, or MVGenomSeq for short." This initiative aims to continue the momentum of TRANSLATE NAMSE, allowing for advanced analysis through methods like long-read sequencing, which enables the detection of difficult-to-detect genetic changes. Additionally, the study evaluated the effectiveness of the GestaltMatcher, an AI system designed to analyze facial features for diagnosing congenital genetic syndromes. Professor Peter Krawitz highlighted the software's potential, stating, "GestaltMatcher is like an expert opinion that we can provide to any medical professional in a matter of seconds." This innovative tool aims to enhance early diagnosis, particularly during routine pediatric screenings. The GestaltMatcher software and app will be accessible to medical professionals through the non-profit organization Arbeitsgemeinschaft für Gen-Diagnostik e.V. (AGD).

Schmidt A et al. Next-generation phenotyping integrated in a national framework for patients with ultrarare disorders improves genetic diagnostics and yields new molecular findings. *Nature Genetics*. 2024;56:1644–1653.

Treatment Breakthrough for Aggressive Childhood Brain Cancer

A recent study led by researchers at Newcastle University has unveiled key findings regarding group 3 medulloblastomas, a highly aggressive type of brain tumor in children. This research, part of the £5 million INSTINCT program funded by multiple childhood cancer charities, has been published in the journal *NeuroOncology*. Medulloblastomas account for 5–10 percent of childhood cancer deaths, and group 3 variants are particularly difficult to treat, often proving nearly incurable with existing therapies. Professor Steve Clifford, director of the Newcastle University Centre for Cancer, emphasized the importance of identifying a specific patient subgroup that urgently requires new treatment approaches. The researchers analyzed the largest cohort of MYC-amplified tumors ever studied to date, uncovering critical variations in clinical outcomes. "New therapies are urgently required to treat these tumors, but there has been a lag in their development," Clifford said in a recent press release. The study highlights a potential target for new treatments: the serine/glycine synthesis pathway, which is crucial for the growth of MYC tumors. Experimental models have shown that PHGDH inhibitor drugs can effectively slow tumor growth by targeting this metabolic pathway. Ed Schwalbe, PhD, an associate professor in the department of applied sciences at Northumbria University, who led the initial phase of the study, noted that understanding the differing outcomes for children with MYC medulloblastomas can inform better treatment selections and "paves the way for new approaches to treat this devastating disease." The research marks a crucial step toward more effective, targeted

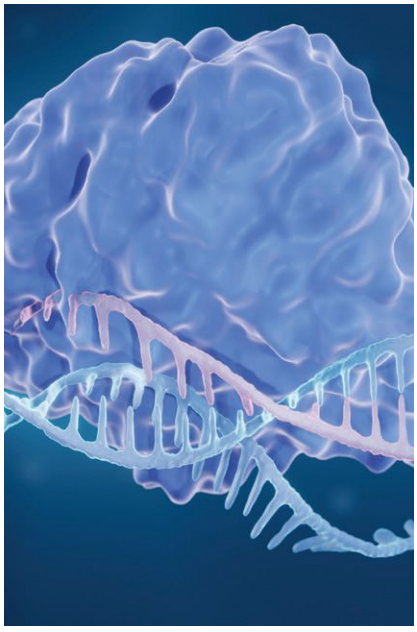


therapies that aim to improve survival rates and quality of life for young patients battling this formidable cancer.

Schwalbe et al. Molecular and clinical heterogeneity within *MYC*-family amplified medulloblastoma is associated with survival outcomes: A multicenter cohort study. *Neuro-Oncology*. 2024;noae178. doi.org/10.1093/neuonc/noae178.

Enhancing the Precision of CRISPR Gene Editing

Researchers at Lehigh University are embarking on an innovative project to enhance the safety and efficacy of CRISPR gene editing technologies. Funded by the National Science Foundation, this initiative is led by bioengineering researcher Tomas Gonzalez-Fernandez and focuses on developing predictive models using artificial intelligence and deep learning. CRISPR, a revolutionary tool for genome editing, enables precise modifications to DNA. However, as Gonzalez-Fernandez noted in a recent press release, "CRISPR is very powerful, but it comes with side effects." Altering one gene can inadvertently affect multiple others, leading to unintended outcomes, he said. To address this, Gonzalez-Fernandez has assembled an interdisciplinary team, including faculty from bioengineering and computer science, as well as Joshua Graham, a third-year bioengineering PhD student who is integrating machine learning techniques into the project. "Machine learning has been used for enhancing CRISPR's precision before, but this is the first time it's being used to create a surrogate genome model," Gonzalez-Fernandez said. This model will allow researchers to simulate the effects of gene modifications on the entire genome, facilitating the identification of



suitable genetic targets while avoiding adverse consequences. "If we have a specific therapeutic application, but we don't know what gene to modify, the model will help us identify different candidates," he explained. Their work has significant implications for various medical fields, including cancer treatment and regenerative medicine. For instance, they aim to enhance the differentiation of induced pluripotent stem cells into cancer-fighting cells and improve the development of cartilage cells for treating osteoarthritis. Additionally, the project addresses the delivery mechanism for CRISPR components through nanoparticle vehicles, which can negatively impact cell viability. The team will utilize computer modeling to predict and mitigate these effects. Gonzalez-Fernandez emphasized the collaborative nature of the research, which merges computer science, genetic engineering, and molecular biology to tackle the complex challenges posed by CRISPR technology. With this work, the team aspires to unlock new therapeutic applications, making CRISPR a safer and more reliable tool for treating a variety of diseases.

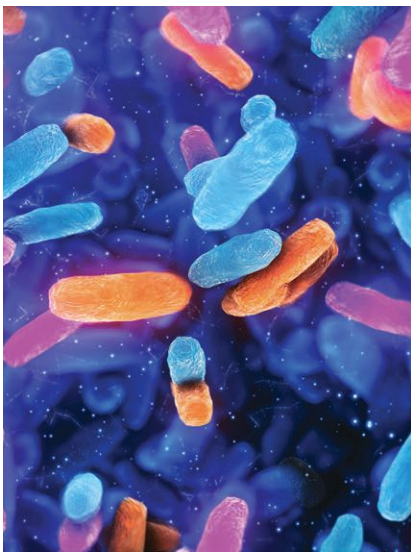
Larkin C. Advancing CRISPR: Lehigh researchers to develop predictive models for gene editing. *Lehigh University*. Published October 7, 2024. https://engineering.lehigh.edu/news/article/advancing-crispr-lehigh-researchers-develop-predictive-models-gene-editing.

Single-Cell Genomics Unlocks Bacterial Genomes

Researchers at Waseda University, led by associate professor Masahito Hosokawa, PhD, have pioneered a novel single-cell genome approach to explore the complexities of the human microbiome. Traditional metagenomics has limitations in revealing microbial diversity at the strain level and profiling antibiotic resistance genes, prompting the development of this innovative method. Their findings, published in the journal *Microbiome*, represent a significant leap in microbial research. "The limitation of metagenomics inspired us to develop a new approach to explore the human microbiome at the single-cell level," Hosokawa said in a recent press release. "This single-cell genome approach can enhance our understanding of how bacteria interact and exchange genetic material including antibiotic resistance genes, providing deeper insights into human health and disease." The research involved a large-scale analysis of microbial samples from 51 participants, who provided saliva and fecal samples. Utilizing SAG-gel technology, commercialized as bit-MAP® by bitBiome, Inc., individual bacteria were encapsulated in a gel, allowing for the amplification and analysis of their genomes. This technique resulted in the recovery of genomes from

300 bacterial species that traditional methods had missed. The study's analysis encompassed 30,000 individual genomes of oral and intestinal bacteria, creating the largest genomic dataset of its kind. The study showcases the power of single-cell genomics for elucidating microbial diversity and interactions. The implications of this research are far-reaching. In public health, the detailed profiling of antibiotic resistance genes can lead to more effective treatment strategies and disease prevention. Additionally, the technique holds potential for environmental monitoring and agricultural practices, helping manage the spread of antibiotic resistance across ecosystems. This groundbreaking work underscores the transformative potential of single-cell genomics in microbiome research, offering valuable insights that could enhance medical and public health applications in the future.

Kawano-Sugaya T et al. A single amplified genome catalog reveals the dynamics of mobilome and resistome in the human microbiome. *Microbiome.* 2024;12(1):188. doi:10.1186/s40168-024-01903-z.



Genetic Insights into COVID-19 Severity

Despite widespread vaccination, COVID-19 remains a critical health challenge, often leading to severe complications due to disrupted coagulation and heightened inflammatory responses. A key player in this process is plasminogen activator inhibitor-1 (PAI-1), which when elevated, contributes to impaired clot dissolution and increased thrombosis risk. Recent research from Juntendo University, published in the journal *Frontiers in Immunology*, investigates the impact of the PAI-1 4G/5G polymorphism on COVID-19 severity in Japanese patients. Led by associate professor Beate Heissig, MD, PhD, and associate professor Koichi Hattori, MS, PhD, the study used a case-control design, collecting blood samples from patients categorized by disease severity according to LEOSS criteria. Researchers analyzed the genetic profiles, focusing on the 4G/5G polymorphism's effects on fibrinolysis, thrombosis risk, and inflammation.The study found distinct effects associated with the two alleles of the PAI-1 promoter polymorphism. "The 4G allele is linked to fibrinolysis inhibition and thrombosis risk, whereas the 5G allele is associated with increased fibrinolysis activity and overactivation of inflammation," explained Heissig in a press release. Specifically, the 4G allele resulted in elevated PAI-1 levels, impairing clot breakdown, while the 5G allele was correlated with lower PAI-1 levels, promoting enhanced fibrinolysis and cytokine responses. Interestingly, while comorbidities like obesity and diabetes can influence PAI-1 expression and COVID-19 severity, the study found no direct link between these factors and the genotypes studied. These findings carry significant implications for

COVID-19 management, suggesting that identifying individuals with specific PAI-1 polymorphisms could inform personalized treatment approaches. "Establishing the genotype could help estimate the risk for inflammation-induced thrombosis and cytokine storms, allowing targeted therapies to manage endothelial dysfunction and reduce thrombosis risk," Heissig said. This research underscores the importance of genetic factors in influencing disease outcomes, particularly in the context of COVID-19. By integrating genetic insights like the PAI-1 4G/5G polymorphism into clinical practice, healthcare providers can better identify and manage high-risk individuals, ultimately improving patient outcomes. Future studies should further explore the potential of PAI-1 inhibitors and other therapeutic interventions to address the implications of these genetic variations.

Yatsenko T et al. The influence of 4G/5G polymorphism in the plasminogen-activator-inhibitor-1 promoter on COVID-19 severity and endothelial dysfunction. *Front Immunol.* 2024;15:1445294. doi:10.3389/fimmu.2024.1445294.

Note: These news summaries were generated by AI based on published press releases, followed by a review from human editors.

ONE IN A MILLION

A Nationwide Diagnostics Strategy for Ultrarare Diseases

LEVERAGING INTEGRATED HEALTHCARE FRAMEWORKS CAN SIGNIFICANTLY REDUCE DIAGNOSTIC DELAYS

by Zahraa Chorghay, PhD

How do you diagnose a disease that is as rare as one in a million? It often takes years. In a study published in the journal *Nature Genetics* earlier this year, Schmidt et al. report how they successfully implemented a novel diagnostic concept for ultrarare diseases in a nationwide study in Germany. The new concept uses a standardized approach that combines clinical assessments and advanced sequencing methods like exome sequencing to reduce diagnostic delays.[1] Their efforts decreased time-to-diagnosis to less than a year and established molecular genetic diagnoses for an impressive one-third of the study's cohort. The research demonstrates the power of harnessing integrated frameworks to improve the diagnosis and management of rare diseases.

What is an ultrarare disease?

An "ultrarare disease" is one that has an extremely low prevalence in the general population, e.g., less than 1 in 50,000, but for an estimated 80 percent of the 5,000+ known rare genetic diseases, this number is closer to a prevalence of one in a million.[2] As a group, ultrarare diseases occur in 3–6 percent of the global population, representing a significant global health burden. Many rare diseases are related to or caused by a single gene (i.e., monogenic), but single gene analyses or small gene panels to detect gene variants often fail to establish a diagnosis, especially for phenotypes with high genetic heterogeneity.

A nationwide strategy for reducing time-to-diagnosis

With the aim of decreasing time-to-diagnosis for rare diseases, researchers in Germany launched a three-year prospective study called TRANSLATE NAMSE. In the study, multidisciplinary teams (MDTs) across 10 university hospital-based centers for rare diseases used standardized structures and procedures to diagnose as many patients enrolled in the study as possible.

To do so, the MDTs reviewed patient records to conduct clinical assessments and select appropriate diagnostic procedures for each study participant, including exome sequencing and additional methods as needed (multi-omics sequencing and facial analysis), and evaluated all findings. Between 2018 and 2020, the researchers analyzed exosome sequencing data for 1,577 individuals with a suspected rare disorder that were enrolled in TRANSLATE NAMSE. Notably, Germany has a health care system where most people have statutory health insurance, creating the perfect conditions to carry out this type of multisite study.

Exome sequencing led to molecular diagnoses for patients

From the analyzed data, a molecular diagnosis was established for 32 percent of patients using exome sequencing. The study identified 549 disease-causing

variants in 362 different genes and structural variants in 14 genomic regions, including 34 novel and 23 candidate genotype–phenotype associations.

"We are particularly proud of the discovery of 34 new molecular diseases, which is a great example of knowledge-generating patient care at university hospitals," said Theresa Brunet, MD, one of the study authors from the Institute of Human Genetics at the Klinikum rechts der Isar of the Technical University of Munich, in a recent press release about the study.[3]

Exome sequencing revealed *de novo* mutations underlying 45 percent of the diagnosed cases. Parental mosaicism was seen in just over 1 percent of diagnosed cases, a frequency that falls within the expected range.[3] Almost 15 percent of the diagnosed cases involved autosomal recessive (AR) inheritance, which has important considerations for family planning. Schmidt et al. also identified cases with more than one phenotype, as well as medically actionable variants that were unrelated to the present phenotype.

Exome sequencing: sequencing the protein-coding regions of the genome. This method can identify variants that fully or partially explain the rare disease phenotype.
***De novo* mutations:** mutations that are not inherited as they arose spontaneously.
Mosaicism: presence of two or more populations of genetically distinct cells within an individual.

For undiagnosed cases, the researchers assessed the non-clinical exome for potentially deleterious variants and performed multi-omics assays, including methylome, proteome, and transcriptome analyses. While 13 of the cases remained unsolved, the successful diagnosis of nearly 500 rare disease patients in a single study is unprecedented.

Machine learning for phenotyping ultrarare diseases

To assess the links between phenotype and the diagnostic yield of exome sequencing, Schmidt et al. applied the YieldPred machine learning model. The model found clinical annotations of certain rare disease groups like ataxia, hematological abnormalities, and cognitive dysfunction were more predictive of exome sequencing establishing a molecular diagnosis, whereas groups like autism, anterior eye chamber anomalies, and skin abnormalities were least predictive. The model's performance improved significantly when facial image analysis was included. Therefore, rare disease diagnosis can be enhanced by supplementing case annotations and molecular diagnosis with facial analysis.

Accurate diagnoses enable targeted and effective therapy

Schmidt et al.'s integrated, national framework for diagnosis significantly enhanced the detection of ultra-rare genetic diseases, reducing time-to-diagnosis from years to less than a year. Quick and accurate diagnosis is crucial for individualized treatment plans directed against the mechanism of the disease, such as prescribing creatine supplementation for an individual with the *SLC6A8* variant. Therefore, such an improvement in rare disease diagnosis can greatly impact clinical outcomes for patients.

Importantly, the success of this novel diagnostic approach for quickly and accurately establishing a diagnosis for otherwise highly challenging cases depended upon the active participation of MDTs across Germany, a platform for systematic data collection, and the ability to perform data analysis on independent and combinatorial sources of data. Together, this study demonstrates the remarkable power of implementing integrated frameworks within healthcare systems to treat individuals with complex diseases.

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2. Wakap SN et al. Estimating cumulative point prevalence of rare diseases: analysis of the Orphanet database. *Eur J Human Genetics.* 2020;28:165–173.
3. Genetic diagnostics of ultra-rare diseases. University Hospital Bonn. Published July 22, 2024. https://www.uni-bonn.de/en/news/146-2024.
4. Lee M et al. Revealing parental mosaicism: the hidden answer to the recurrence of apparent de novo variants. *Human Genomics.* 2023:17–91.

***Zahraa Chorghay**, PhD, specialized in neuroscience during her undergraduate (University of Toronto) and doctoral studies (McGill University). She continues to explore her passion for neuroscience and for making science accessible and inclusive.*

5 Clinical Laboratories Leading the Way in Patient Care

THESE FIVE TRAILBLAZING LABS ARE AMONG THE FIRST TO ADOPT NEW TESTS AND TREATMENTS FOR LONGSTANDING CHALLENGES

by Michael Schubert, PhD

Research advancements and regulatory changes are rapidly altering the landscape of diagnostic testing and disease treatment—and clinical labs are seizing the opportunity to blaze new trails in patient care. From better brain diagnostics to easier cancer monitoring, early adopters are crucial contributors to the widespread acceptance and use of new tests, guidelines, and interventions. Here, we round up five exciting "firsts" paving the way for faster testing, more reliable results, and better outcomes for patients and providers.

First hospital performing blood tests for concussion

In April 2024, the FDA approved the first rapid blood test for traumatic brain injury (TBI), including concussion.[1] Now, Orlando Regional Medical Center (ORMC) in Florida has become the world's first hospital using that test to evaluate patients with suspected mild TBIs.

The test uses Abbott's proprietary i-STAT Alinity System with a dedicated TBI cartridge to measure circulating levels of ubiquitin C-terminal hydrolase L1 and glial fibrillary acidic protein, biomarkers commonly elevated in TBIs.[2] Because time is of the essence when diagnosing and treating these injuries, the i-STAT TBI test returns results in 15 minutes and is performed on a handheld device that can be used at the point of care or even in the field. This will allow ORMC to rapidly triage the approximately 1,500 TBI patients it sees each year—quickly identifying those who need imaging or treatment and preventing unnecessary interventions in those who don't.

"Now, doctors are finally armed with a blood test to check your brain," said Linda Papa, director of clinical research at Orlando Health, in a press release.[3] "This is a game-changer, and we are just getting started."

First use of blood-based biomarkers for dementia

Alzheimer's disease diagnosis is based primarily on clinical presentation, with imaging and laboratory testing largely reserved for ruling out other conditions with similar signs and symptoms. However, this clinical approach leaves the door open to diagnostic errors and delays, meaning that patients may miss

opportunities for lifestyle interventions or disease-modifying treatments, both of which are most effective in the early stages of the disease.[4]

To accelerate early detection and increase diagnostic accuracy, New York's Mount Sinai Health System has become the first in the northeastern United States—and one of the first in the world—to implement blood-based biomarker testing for Alzheimer's disease and related dementias. The tests will examine circulating levels of three proteins: p-tau 217, neurofilament light chain, and glial fibrillary acidic protein. The first is a known biomarker for Alzheimer's disease,[5] including at the preclinical stage; the latter two are biomarkers of neuronal inflammation and damage and are frequently elevated in early dementia.[6]

"This project is critical for providing noninvasive, low-cost testing options and improving how we diagnose and treat these disorders," Fanny Elahi, project co-leader and director of fluid biomarkers at Mount Sinai's Maurice Deane Center for Wellness and Cognitive Health, said in a statement.[7] "What we're measuring today is just a tip of the iceberg of so much more to come."

"From better brain diagnostics to easier cancer monitoring, early adopters are crucial contributors to the widespread acceptance and use of new tests, guidelines, and interventions."

First Canadian hospital offering in-house liquid biopsy for cancer

With the global cancer burden growing rapidly and survival rates frequently dependent on stage at diagnosis, short turnaround times and reliable results are vital.[8] That's why William Osler Health System in Ontario, Canada, recently became the first Canadian hospital to offer in-house liquid biopsy for cancer diagnosis, monitoring, and treatment selection.[9]

The move's value is supported by a three-year retrospective study in which Osler's lab at Brampton Civic Hospital, a full-service community teaching hospital serving more than half a million people, provided liquid biopsy testing to 124 patients on clinician request.[10] The results? A median turnaround time of three days, with 14 percent of results reported within 24 hours. Overall sensitivity was lower than that of tissue biopsy at 71 percent, suggesting that the technique requires further improvements to replace, rather than supplement, tissue testing. Nonetheless, a positive diagnosis via liquid biopsy could spare patients the costs, delays, and risks of a more invasive procedure.

First guidance on laboratory diagnosis of respiratory viruses

Since the outbreak of the COVID-19 pandemic, respiratory infections have been at the forefront of people's minds—and now, with SARS-CoV-2 joining the group of endemic viruses that cause these infections, best practices for diagnostic testing are urgently needed.

In May 2024, the Association for Diagnostics and Laboratory Medicine (ADLM) released the first-ever formal guidance on respiratory virus testing to support clinical labs in determining whom, when, and how to test.[11] The guidance covers

- patient populations most likely to need testing (those who are hospitalized, immunocompromised, or whose results will affect management),
- timing (when respiratory infections are likely and the results will change management, infection control, or epidemiological surveillance),
- specimen type (with nasopharyngeal swabs preferred where possible), methodologies used for virus detection (ideally nucleic acid amplification testing), and
- recommendations for result interpretation based on test type and clinical presentation.

First clinical trials of lung cancer vaccine

Most people diagnosed with lung cancer have non-small cell lung cancer (NSCLC), a condition whose five-year survival rate rests at just 25 percent.[12] To tackle this devastating disease, the world's first mRNA vaccine candidate against lung cancer, BioNTech SE's BNT116, has entered clinical trials in 10 countries across three continents.

The vaccine encodes six lung cancer-associated antigens common in NSCLC and is intended to spur the recipient's immune system into combating cells with those markers—

potentially offering lasting protection against recurrence. The vaccine is currently being tested alone and in combination with cemiplimab or docetaxel in two separate studies: a Phase 1 trial in patients with advanced NSCLC (stage III/IV unresectable or stage II/III resectable tumors)[13] and a Phase 2 trial in patients with advanced NSCLC whose tumors have greater than 50 percent PD-L1 expression.[14]

"We hope adding this additional treatment will stop the cancer coming back because a lot of time for lung cancer patients, even after surgery and radiation, it does come back," Siow Ming Lee, a professor of medical oncology at University College London and one of the trial investigators, recently told press.[15] "It's simple to deliver, and you can select specific antigens in the cancer cell, and then you target them. This technology is the next big phase of cancer treatment."

"This is a game-changer, and we are just getting started."

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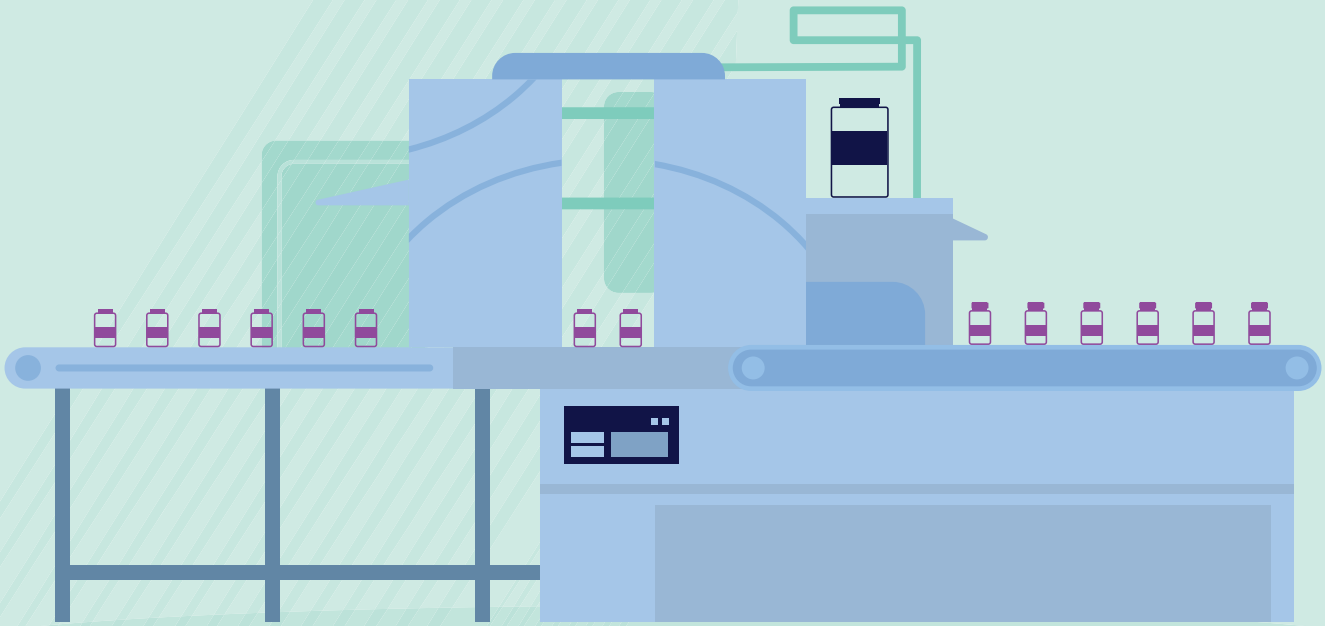


Clinical Chemistry Analyzer Market on the Rise: What's Driving Demand?

CLINICAL LABS SHOULD NOTE ADVANCING TECHNOLOGY AND RISING DISEASE MORTALITY TO CAPTURE NEW DEMAND

by Scott Wallask, BA

Smaller. More sensitive. Automation friendly.

Welcome to the current state of the blood and clinical chemistry analyzer market, where influencing factors include evolving technology, increased disease incidence, and billions of dollars at stake.

Judging by the exhibition floor at the Association for Diagnostics & Laboratory Medicine (ADLM) 2024 annual meeting and lab expo, many companies—from established giants to fledgling startups—are either already in the analyzer market or want a piece of it.

Medical laboratories that are evaluating new clinical chemistry and hematology analyzers should consider these features:

- Greater ability to integrate with automated systems
- Artificial intelligence's role in interpreting results
- Increased ease of use at the point of care

More vender-neutral automation choices are available

On the show floor, there were several examples of clinical chemistry and blood analyzers that plug into other vendors' automated systems.

A1C analyzers are largely moving toward trackless automation systems to allow labs to scale their efforts and provide more hands-off operations, said Priya Sivaraman, PhD, a senior product manager at Tosoh Bioscience.

This year at ADLM, Tosoh touted its G8 high-performance liquid chromatography analyzer's new integration with Sysmex's XN-9000 hematology automation system, which Sivaraman noted was one of several automation options for labs.

Indeed, at least 41 of the nearly 900 vendors on the ADLM expo hall floor promoted automation hardware and services.

In July, Inpeco launched a new total lab automation system called FlexLab X, which integrates with 30 different analyzer lines and 12 specialties.

Such vendor-neutral setups give labs more purchasing power because they are not locked into deals for one line of analyzers from a single seller, said Markus Gross, global marketing director at Inpeco.

This type of automation "openness" should appeal to clinical labs, said J.L. Bedini, MD, head of the core laboratory at Clinic de Barcelona and a customer of Inpeco.

"The trend will be for analyzers and automation to be more open," Bedini said. "If you are able to buy an automation system and use different analyzers that you need on that system, it's helpful."

"A lab's needs change often," he added. "With analyzers, I prefer to have the best of everything rather than buy from one vendor."

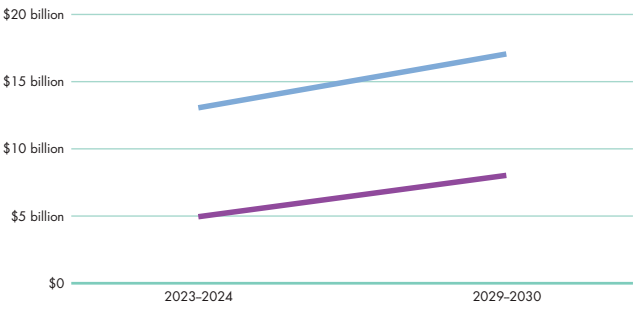
AI and point-of-care testing will steer analyzers

The core technology behind clinical chemistry analyzers isn't changing, said Stephen Harding, PhD, vice president of research and development at The Binding Site, part of Thermo Fisher Scientific. Instead, expect AI to have a growing influence on the results that analyzers produce.

"If we start thinking about where we will go in the next three to four years, the world is going to be dominated by higher sensitivity systems, such as mass spectrometry and next-generation flow cytometry and cell staining," Harding said. "The higher the sensitivity, the more reliant it will be on AI solutions to interpret."

Projected Analyzer Market Growth through 2030

	Clinical chemistry analyzer market	Hematology analyzer market
2023–2024	$13 billion	$5 billion
2029–2030	$17 billion	$8 billion



▲**Sources**: Markets and Markets, Data Bridge Market Research, and Mordor Intelligence

"Whilst clinical chemistry analyzers will be faster with higher throughput and use the same technologies … the revolution that's coming will be around sensitivity and AI interpretation," he added.

Other observers at ADLM noted the amount of startup analyzer manufacturers that have their eyes on the point-of-care market.

In some cases, new analyzers are not much bigger than a laptop computer, making them easy to locate in point-of-care locations such as clinician's offices and urgent care centers.

> "A1C analyzers are largely moving toward trackless automation systems to allow labs to scale their efforts and provide more hands-off operations."

Breaking into the blood and clinical chemistry analyzer market will take a level of finesse from startups, given the established competition. For those smaller firms, innovation may need to occur outside the technology, perhaps in the manufacturing process or in staff training, to help entry into the market.

The roots of clinical chemistry analyzer market growth

In part, growth in the analyzer market stems from public health concerns: Deaths are on the rise from chronic diseases detected by blood and clinical chemistry analyzers.

For example, the American Heart Association noted in a 2024 update that global deaths related to ischemic heart disease rose 72 percent from 1990 to 2021, while deaths associated with stroke increased 47 percent during the same period.[1]

"Whilst clinical chemistry analyzers will be faster with higher throughput and use the same technologies ... the revolution that's coming will be around sensitivity and AI interpretation."

"[Analyzer market] growth is owing to the increasing prevalence of chronic disorders, such as cardiovascular and liver disorders, which result in increasing patient admissions to healthcare facilities," *Medical Buyer* noted in a July 2024 article.[2]

While it's hard to put an exact value on the current analyzer market and where future sales are heading, information from three research firms reveals a general range:

- The clinical chemistry analyzer segment is estimated to be worth from $13 billion to $14 billion currently and expected to increase to $17 billion (and perhaps as high as $20 billion) by the end of the decade, according to analyses from Markets and Markets, Data Bridge Market Research, and Mordor Intelligence.[3,4,5]
- The hematology analyzer segment is valued from $5 billion to $6 billion now, and it will rise to $8 billion to $9 billion within six years, Markets and Markets, Data Bridge, and Mordor noted.[6,7,8]

According to these estimates, in total, blood and clinical chemistry analyzers may soon bring in close to $30 billion in annual sales revenue.

A possible shift in purchasing power

For clinical laboratory managers, two key points stand out: First, with so many analyzers available on the market and an expected push to sell more, educated lab leaders may find themselves at a buying advantage when considering these purchases.

Second, by following the money, it's clear that vendors see opportunity in rising cases of illness like cardiovascular disease. Laboratories should likewise review their own business plans to ensure they fully capture a segment of patient care that appears to be overflowing with demand.

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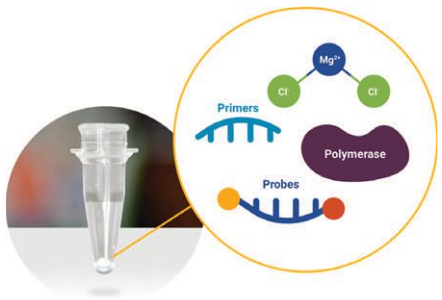
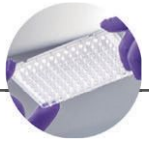
Streamline Your PCR Workflow with Lyophilized Master Mix Solutions

A lyophilized PCR is an environmentally sustainable assay format that can streamline laboratory processes and improve testing accuracy.

Lyophilized PCR is an assay format that is:



Easy to use
- Simply add sample and analyze
- Automation friendly
- Reduce contamination risk
- Minimize reagent handling



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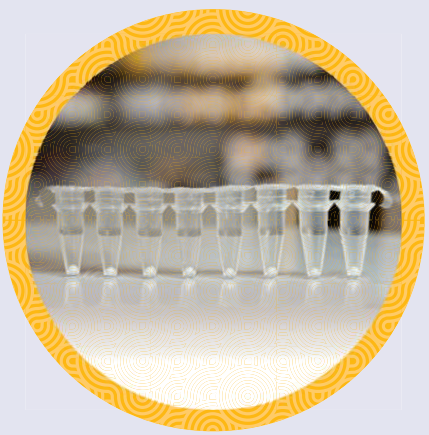
- Bead format dispensable into almost any format
- Ideal for environmental or point-of-care testing

Environmentally sustainable
- No cold-chain transport
- Shelf-stable storage
- No special storage conditions required

The set-up of a liquid-based PCR requires combining multiple reaction components prior to cycling which can increase the chances of error and poor reaction performance.



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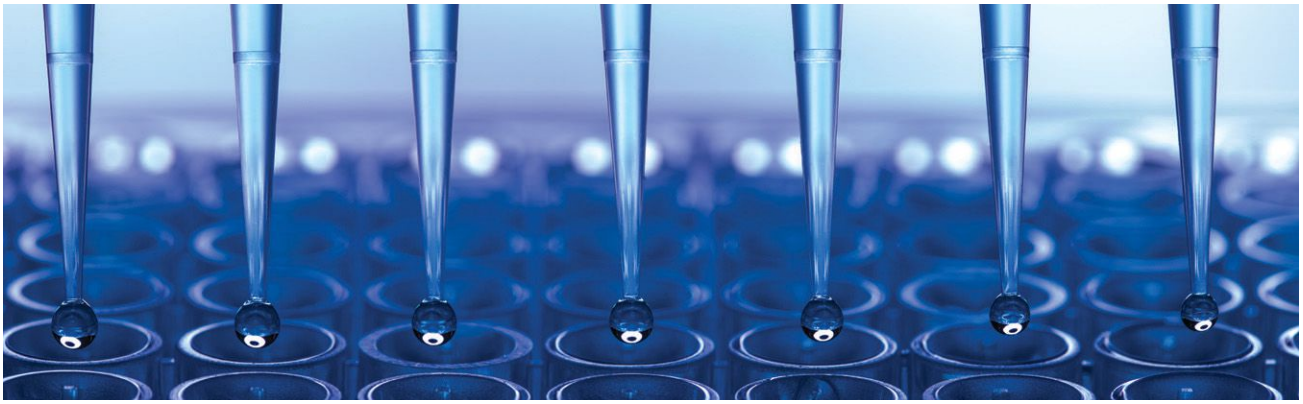
Emerging **Technologies**

YOUR GUIDE TO NAVIGATING TOMORROW'S TECH LANDSCAPE

INTEGRA's Innovative Modules Simplify Magnetic Bead Purification Workflows

INTEGRA

INTEGRA Biosciences is excited to announce the launch of its MAG and HEATMAG modules for efficient, automated magnetic bead purification. These innovative solutions allow researchers to streamline several processing steps in molecular biology and proteomics workflows for maximum lab throughput. These time-saving devices are complemented by the COLDPLATE and BIOSHAKE—for precise temperature control and orbital shaking of magnetic beads, respectively—to further streamline protocols.



Verso Dx

HAMILTON

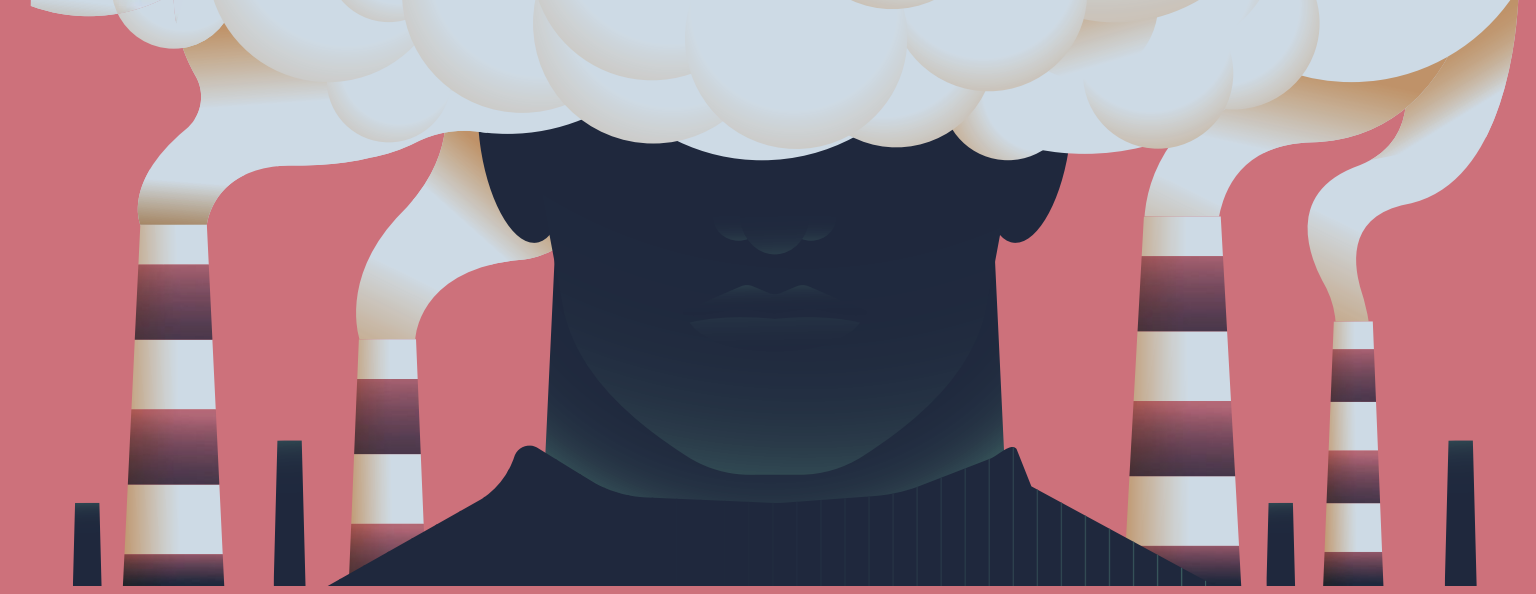
Hamilton's innovative Verso Dx is an automated postanalytical storage system that caters to different workflows thanks to its ability to load samples either manually or via lab track. This flexible system, which can be built in multiple sizes, features a storage capacity ranging from 30,000 to 1 million tubes. The platform can store tubes at ambient or the common temperature of 5°C, while also boasting the capability to store samples at -20°C for special applications.

Streamline Your Clinical PCR Workflows with QIAcuityDx

QIAGEN

QIAcuityDx is tailored for IVD applications. This fully automated digital PCR system enhances diagnostic precision and operational efficiency by reducing hands-on time and ensuring accurate detection and quantification of important genetic variations. Easily develop your own assay menu* by using QIAcuityDx utility mode and IVD medical device consumables, reagents and software.

**FDA 'Medical Devices; Laboratory Developed Tests' final rule, May 6, 2024 and European Union regulation requirements on 'In-House Assays' (Regulation (EU) 2017/746 -IVDR- Art. 5(5))*
The QIAcuityDx dPCR System is intended for in vitro diagnostic use, using automated multiplex quantification dPCR technology, for the purpose of providing diagnostic information concerning pathological states.
QIAcuity and QIAcuityDx dPCR instruments are sold under license from Bio-Rad Laboratories, Inc. and exclude rights for use with pediatric applications.



Improving Indoor Air Quality in Clinical Labs: Best Practices for Safety and Compliance

by Michael Schubert, PhD

Is your lab's air breathable? You may think so, but a surprising number of indoor air quality hazards in laboratories go unnoticed until a safety issue arises—often because they are poorly understood, difficult to detect, or the blame for physical signs and symptoms is placed elsewhere. Poor lab air quality not only presents a safety risk, but can also affect equipment function and even test results. Frequent monitoring, preventive maintenance, safety training, and awareness of potential hazards are all key aspects of ensuring clean air in the clinical lab.

Key factors affecting lab air quality

Three kinds of hazards can potentially impact your lab's air: biological, chemical, and physical.[1]

- **Biological hazards** include pathogens such as bacteria or viruses, contaminants such as mold or fungi, or even allergens like pollen that have been brought in from the outdoors.
- **Chemical hazards** include carbon monoxide, carbon dioxide, ozone, or volatile organic compounds arising from substances used in the lab. They also include radon, which exists as an invisible and odorless gas that, at high levels, poses a radiological hazard that may increase people's risk of cancer.
- **Physical hazards** typically include particulate matter, which can arise from laboratory activities, other activity (such as construction) in the area, or incidental issues such as pollution or wildfire smoke.

"All of these can contribute to lab air quality," says Ken Roy, PhD, chief science safety compliance adviser for the National Science Teaching Association. "That's why it's important to ensure that the lab's ventilation system is not only working well, but also capable of meeting the needs of the space."

Roy refers to the National Fire Protection Association standard NFPA 45,[2] which establishes requirements for all laboratories using chemicals alongside additional specifications for labs in healthcare facilities. "It prohibits the recycling of lab air," he says. "There must be fresh air coming in and used air going out." This requirement for continuous flow is a recent change from previous guidance, which—despite mandating a minimum number of air exchanges per hour—left lab occupants vulnerable to buildups of hazardous substances.

Roy also emphasizes the importance of checking air quality in separately ventilated spaces such as fume hoods. "I had a case in which the laboratorians reported feeling unwell every time they used the fume hood. The facilities department checked the equipment sensors and said everything was working fine, so I got called in to investigate. I said, 'Send one of your workers onto the roof to tell me if everything's working appropriately on the ventilation unit.' It turned out that the fan belt had broken, but because the motor was still working, the sensor was reporting no issues even though the unit actually wasn't ventilating at all."

Improving your lab's air

"The first thing I recommend is hiring a consultant firm to do indoor air quality testing in the laboratory," says Roy. "You need a specialist for this, which can be a little costly, but is well worth it." He adds that it's not only the air itself that should be tested. "You want to take samples from lab benches and other surfaces because contaminants there will be a result of your air quality." Once testing is complete, the Occupational Safety and Health Administration (OSHA) requires management to share the results with employees so that everyone in the lab is aware of potential hazards.

Roy's next priority for labs is to establish maintenance schedules to check that ventilation and filtration systems are operating within appropriate parameters. "That should happen at least once a year," he says. "Some places should do it more often—for example, quarterly—depending on the types of tasks undertaken in the lab." He highlights that some populations, such as people who are pregnant or have respiratory issues, are particularly vulnerable to air quality issues, so may need more frequent or in-depth checks.[3]

"I've been in some labs where the filters haven't been changed in five years," says Roy. "They're not filtering anything out anymore—and people wonder why they aren't feeling well." Air filters for laboratories should be rated MERV 13 or higher,[4] but Roy often encounters labs whose systems are fitted with inadequate filters. Specific areas of the lab may need additional or alternative filters. For instance, tissue workstations should include permanganate filters to remove formaldehyde vapors, chemical fume hoods may need adsorbents such as carbon filters to remove contaminants, and biosafety cabinets should be fitted with HEPA or ULPA filters to ensure protection against microscopic particles and pathogens.

For fume hoods and biosafety cabinets, Roy offers additional advice. Where possible, he recommends systems that are vented to the building's exterior rather than portable units with self-contained filtration systems. Laboratorians should be trained in the use of these systems and perform safety checks before operating them. "Before they begin, they should make sure the hood is removing air fast enough. The easiest way is to get a strip of paper, hold it between your fingers, and turn on the hood. If the paper waves into the fume hood, it's probably moving enough air—but if it just hangs down, there may be a problem. It sounds silly, but I can't tell you how often I find malfunctioning fume hoods using that little strip of paper."

Roy recommends that supervisors periodically observe the equipment in use to spot and correct potential hazards, such as inadequate ventilation settings, insufficient sash closure, or too many people using or observing the equipment at once.

Finally, he emphasizes the importance of expert installation and inspection. "I've been called into new labs where several of the fume hoods were connected backwards," he says. "Instead of removing the air, the systems were blowing it in users' faces! There are many things that can go wrong, so it's crucial to consider everything and not assume that previous steps have been done correctly."

Good air is worth the cost

A common objection Roy encounters to his recommendations is, "Do you know how much it will cost to do these things?" His response: not as much as the potential cost of not doing them. "If any health and safety issues arise in the laboratory, management has shared liability," Roy explains. "Under OSHA, they are responsible for maintaining a safe working environment for their employees."

He urges lab staff to speak up when they have concerns, follow up on queries in writing, and maintain personal copies of all correspondence.

For management, he advises meeting with employees regularly to ask about any problems or concerns in the lab—particularly with respect to health and safety. "This not only helps protect employees, but also management. It demonstrates that you're looking for, listening to, and following up on issues."

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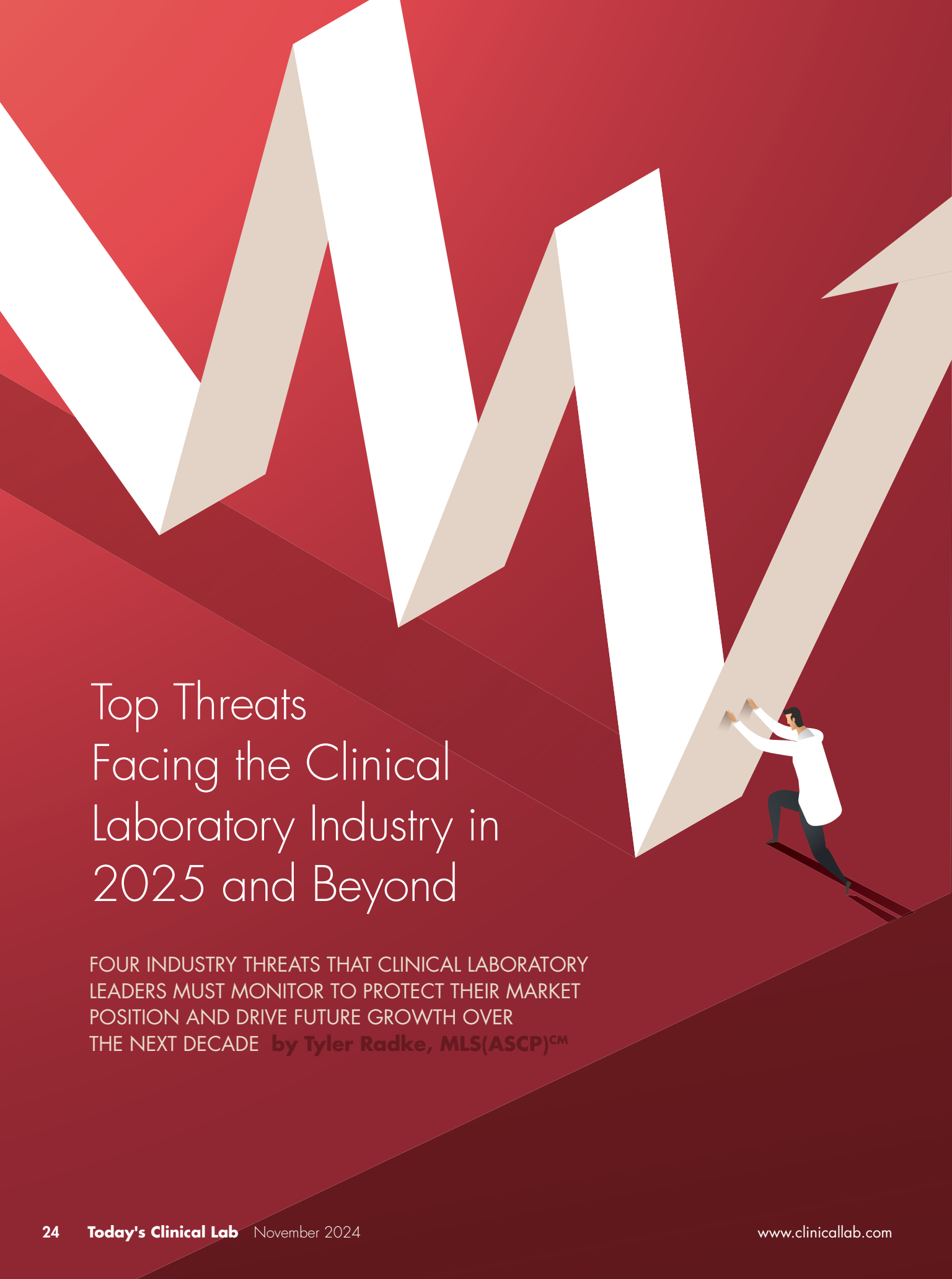
***Michael Schubert**, PhD, is a veteran science and medicine communicator. He holds graduate degrees in biochemistry and molecular biology with a research focus on chromatin structure and function and has written on subjects from subspeciality pathology to fictional science.*



Top Threats Facing the Clinical Laboratory Industry in 2025 and Beyond

FOUR INDUSTRY THREATS THAT CLINICAL LABORATORY LEADERS MUST MONITOR TO PROTECT THEIR MARKET POSITION AND DRIVE FUTURE GROWTH OVER THE NEXT DECADE **by Tyler Radke, MLS(ASCP)CM**

Market dynamics in health care are in constant flux. Many laboratory leaders closely follow the release of new tests to improve their workflows, diagnostics capabilities, and enhance patient outcomes. Others look for opportunities to expand market share. However, savvy lab leaders not only track emerging innovations but also monitor external industry trends that could threaten market share to better guide their efforts toward sustained success.

Here are four top industry threats that clinical laboratory leaders should monitor to safeguard their market position and drive future growth:

Direct-to-consumer testing

Offering patients the ability to order self-directed lab tests online from home (direct-to-consumer or DTC testing) is a growing industry trend. Consumer interest in DTC testing is growing with an estimated market of $2 billion by 2025.[1] Some vendors have even purchased ad space on social media pages. Lab testing in this space includes niche services like food sensitivity tests, wellness panels, and microbiome composition determination. Other more basic assessments like complete blood counts, thyroid function, and STI determinations can also be found.

DTC tests appeal to consumers who want more control over their healthcare decisions. Often, DTC vendors offer promotional prices to entice sales. This model works as it avoids the cost and hassle of third-party insurance, as well as avoids costs tied to filing claim forms, waiting for payment, and managing denials or prior authorizations.

Consumers' growing interest in DTC testing poses deleterious effects to an integrated healthcare delivery model for several reasons:

- Revenue is pulled away from community health care
- Test results and records are not integrated into patients' local EMR
- Ordering lacks of test clinical relevance/need
- Lack of regulation/quality can yield false results
- No specific patient history/context (no personalized medicine)
- No comparator method may exist
- Negligent follow-up on abnormal results
- Loss of health system analytics

As the DTC testing market continues to take shape, clinical labs need to create their own strategy for dealing with this trend. For example, one option could involve a partnership with primary care that discourages the fragmentation of care. Another approach would be to leverage current system labs by offering DTC testing to outpatients.

Third-party specialty lab services

Similar to the DTC market, third-party specialty laboratories that work directly with your providers to offer specialty referral testing may also pose a threat to your lab. Specialty testing is often targeted toward clinic patients and includes tests such as fetal-maternal genetic testing, toxicology services, rheumatology panels, and other laboratory-developed assays.

Many specialty lab services have a clearly defined use cases, but their expanding menu of routine labs can sometimes begin to divert business from traditional laboratories. In the case of rheumatology services, some third-party laboratories perform extensive panels that also include common laboratory tests like compliment protein, anti-citrullinated protein, and anti-nuclear antibody.

Third-party testing can also lead to fragmented and missing patient data from the electronic medical record, causing delays in care and potentially increasing follow-up costs. For labs, diagnostic stewardship is a key strategy that can help validate and manage the addition of referral services while minimizing the loss of critical lab tests.

Commoditization and acquisition of lab services

Laboratory services operate at a significantly lower cost compared to other care teams like nursing, cardiology, oncology, etc. Patients' costs are also significantly less per unit of service compared to a visit with any other department or specialty. With low operational cost and low patient cost, laboratory services tend to be viewed as a commodity in health care.

This drastic diminishment of laboratory value can lead to becoming the target of external acquisition—essentially, an asset to be sold off. This is occurring at varying degrees across the US with entities like Quest and Labcorp acquiring hospital laboratories for their outpatient and outreach businesses.[2,3]

To combat the threat of acquisition, clinical laboratory leaders must clearly demonstrate their value to executive leadership and dispel their beliefs that selling the laboratory is a reasonable transaction without significant consequences to patients. Consider highlighting how laboratory operations directly contribute to integrated patient care, participating in quality and stewardship committees, and emphasizing the net positive revenue added to the system's financials.

Preferred laboratory networks

Although laboratory networks excel at providing continuity of care for patients, helping to reduce repeat visits or sample collections, preferred laboratory networks can also sometimes be a detriment to quality care.

A preferred lab network is a listing of all laboratories that insurance companies encourage the insured patient to use. While the major insurers claim the preferred labs have met "higher standards," the criteria defining those standards is proprietary and therefore not available to the public.[4] Instead, insurance companies benefit from lower fee-for-service agreements that favor profit margins to enhance profitability. Unfortunately, the lower cost for insurance does not translate to lower out-of-pocket costs for patients, or more importantly, to better care.

Other types of laboratory networks may be designed to keep patient care and revenue within a state or local region. While that approach may seem laudable to local businesses, it can be detrimental to patients living near a boundary line who may have to drive several hours to find "in-network" care. This can cause significant patient dissatisfaction, as well as delay care.

Preferred laboratory networks can not only hurt patients but also other clinical laboratories, where labs outside of preferred networks are often left with few options. Insurers may reject laboratory claims not within their preferred network, causing labs to write off charges. That could be seen as patient inducement by providing free services to get patients to visit, a violation of federal law.[5]

"The risk of labs being viewed merely as assets to be bought and sold is rising across the US."

Alternatively, some labs may opt to collect "out-of-network" patient samples only to send them to an "in-network" laboratory at an often significant operational cost, as labor, vehicle, and IT integration is necessary.

Though preferred laboratory networks may seem like a distant or unlikely threat, lab leaders should familiarize themselves with these networks, as their popularity is likely to grow among commercial insurers. The problem with these arrangements is manifold, causing unnecessary travel, delayed care, dissatisfied patients, increased costs for specimen and report integration, etc.

Adapting to ever-changing industry challenges

Threats to the lab industry are constantly changing in response to the political landscape, technological advancements, and shareholder profitability, requiring continual vigilance. For example, although DTC testing experienced initial setbacks and legal drama, it has since gained significant popularity among consumers. Similarly, the risk of labs being viewed merely as assets to be bought and sold is rising across the US as profit margins are increasingly squeezed in the post-pandemic economy. Laboratories that can attain a preferred status with insurers will secure stable revenue while maintaining continuity of care through an integrated delivery model.

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Julie Ballard

Lindsay Strotman

The regulations and guidelines that govern clinical laboratories' operations are constantly being expanded and updated. The U.S. Food and Drug Administration (FDA) is phasing out its enforcement discretion over laboratory-developed tests (LDTs),[1] the Clinical Laboratory Improvement Amendments (CLIA) have established new quality standards for lab personnel and proficiency testing,[2,3] and even the International Organization for Standardization (ISO) updates its requirements at least once every five years.

With so many changes happening at once, how can labs ensure they stay up-to-date and in compliance? Experts **Julie Ballard**, founder and principal consultant at Carrot Clinical, and **Lindsay Strotman**, a CLIA lab director and technical consultant at Lighthouse Lab Services, untangle the complexities of today's regulatory environment for clinical labs.

FDA, CLIA, and ISO—Which Regulations Apply to Your Lab?

Experts Julie Ballard and Lindsay Strotman help you navigate the complexities of FDA, CLIA, and ISO standards for the clinical lab

Q: What are the key differences between the FDA, CLIA, and ISO?

Julie Ballard: The FDA is a US federal government regulatory agency. They regulate medical devices, including *in vitro* diagnostic (IVD) tests, which are used in clinical laboratories. They also categorize the complexity of tests (waived, moderate-complexity, high-complexity, and so on).

CLIA is a set of mandatory federal regulations that apply specifically to clinical laboratories. Laboratories must be CLIA-certified by the Centers for Medicare & Medicaid Services (CMS) before accepting human specimens for testing. CLIA requirements focus on quality standards in all aspects of laboratory operations, including specimen collection, quality control procedures, result reporting, personnel qualifications, training, and competency.

ISO is an international voluntary organization. They provide guidelines that are not legally binding unless they have been adopted by a country's regulatory framework. ISO 15189 specifies requirements for quality and competence in clinical laboratories. ISO certification is akin to College of American Pathologists (CAP) accreditation in that neither is required, but laboratories may choose to have these to demonstrate their commitment to quality and continuous improvement.

Lindsay Strotman: Each accrediting agency has its own unique role in regulating laboratories, but there is

overlap. Laboratorians in the US are most familiar with CLIA, because its certification is mandatory. CLIA regulates laboratories that perform testing on patient specimens to ensure that the tests are accurate and reliable. Its focus is mainly on day-to-day lab operations, with specific attention paid to personnel qualifications and competencies.

The CDC develops technical standards and laboratory practice guidelines, CMS issues CLIA certificates and monitors compliance with CLIA regulations, and the FDA categorizes tests based on their complexity. Of the three, CMS is the central authority for laboratories because they are the primary administrators of CLIA, including conducting lab inspections, enforcing regulatory compliance, and approving accreditation agencies. With the publication of the FDA's LDT final rule, however, the FDA will play a greater role in regulating LDTs going forward.

"Laboratories are facing a perfect storm of impending regulatory changes—and to continue meeting patients' needs, it's crucial to stay ahead of the curve."

Clinical laboratories use FDA-approved IVDs, but were not subjected to many FDA regulations—until recently, when the FDA introduced its final rule on LDT regulation.[4] Now, clinical labs that offer IVDs as LDTs are subjected to FDA regulations because they are considered "manufacturers" and are responsible for proving the safety and effectiveness of their tests.

Finally, although ISO standards are not legally required for laboratories, compliance can enhance laboratory quality and reliability and may be required for specific contracts or international work.

Q: Which labs and activities are governed by each of the three bodies?

JB: The three main bodies that regulate US medical laboratories are the Centers for Disease Control and Prevention (CDC), CMS, and the FDA.

Blood banks are a unique case in which the FDA bears a greater responsibility. CMS and CLIA play a role in testing all donated blood, but the FDA, through its Center for Biologics Evaluation and Research, regulates the blood supply by licensing and inspecting blood banks, setting quality standards and guidelines to ensure blood safety, and monitoring adverse events.

For clinical laboratories, ISO certification is optional and is "icing on the cake" for a laboratory that is already CLIA-certified.

LS: Labs should prioritize understanding the standards set by these bodies in the following order: CLIA (mandatory), FDA (mandatory if considered a manufacturer), and ISO (voluntary). Laboratorians must be well-versed in all CLIA requirements, as well as the accreditation standards of agencies like CAP, COLA, and The Joint Commission.

Regarding FDA regulations, labs must determine whether they qualify as a manufacturer of an IVD offered as an LDT without falling under any of the exceptions in the final rule. If they do, they are required to comply with FDA regulations; if not, they should be familiar with medical device reporting requirements, strictly follow approved IVD instructions for use, and use the FDA CLIA database, which is a valuable resource to determine test complexity.

ISO compliance, though voluntary, enhances a lab's quality management system. Notably, the FDA has aligned its quality guidelines with ISO 13485, creating significant overlap—if not complete equivalence—between the two.

Q: Are there any areas in which these regulations conflict—or may in future?

JB: Historically, laboratories have had to comply with CLIA and FDA requirements primarily as IVD users. For example, if a laboratory, as a user of an FDA-cleared device, becomes aware that the device may have caused a death or serious injury, they're required to report this adverse event to both the FDA and the manufacturer.

With the FDA's LDT final rule, laboratories are considered the manufacturers of their LDTs and will have to comply with requirements as the manufacturer. Going back to the

adverse event as an example, if the laboratory's LDT may have caused a death or serious injury, they're required to report the adverse event to the FDA as the manufacturer of the device. However, because the laboratory is also the user, reporting requirements as a user may also apply. I say "may" because there are still many uncertainties and unanswered questions regarding the interpretation and implementation of the final rule; in this example, requiring the laboratory to report as both the manufacturer and the user may be redundant.

"The FDA has aligned its quality guidelines with ISO 13485, creating significant overlap—if not complete equivalence—between the two"

LS: For labs that are considered manufacturers of LDTs, the regulations may be duplicative or more stringent. A key example is the quality system requirements defined under Stage 3 of the FDA's LDT final rule.[5] Though laboratories already adhere to quality regulations under CLIA, they will need to meet additional requirements and familiarize themselves with the terminology the FDA and ISO use for quality standards. For validations, the FDA may be more specific than CLIA about the required studies and methodologies; as an example, the FDA might mandate adherence to specific Clinical & Laboratory Standards Institute guidelines they recognize as consensus standards, whereas CLIA provides recommendations without explicitly mandating specific protocols.

Q: What common regulatory errors or misunderstandings have you encountered?

JB: A common misconception at the moment is the belief that CLIA regulations no longer apply to LDTs now that the FDA is regulating them. This is not the case at all. The FDA's regulations are in addition to, not instead of, CLIA requirements.

LS: In the past, there were fewer inquiries, but recently, more laboratorians are seeking clarity on navigating the various regulations. Most of the current questions revolve around understanding the LDT rule—specifically, whether individual labs are classified as manufacturers of IVDs offered as LDTs. Some of these questions concern what is considered a "modification" of a test; although the FDA somewhat defined this in the final rule, more guidance would be helpful.

Q: Where do labs struggle most with quality and compliance—and do those areas differ between FDA, CLIA, and ISO requirements?

JB: CLIA requirements focus on laboratory processes and personnel, whereas the FDA's focus on processes to ensure IVD quality, including design control and risk management. For laboratories with LDTs that will need to comply with the final rule, design control will be the most challenging. CLIA already requires some processes, such as complaint handling or acceptance activities, so labs will already be familiar with them—but no CLIA requirement resembles the FDA's design control stipulations.

LS: Labs are primarily facing challenges due to a lack of personnel and expertise to fully grasp the new FDA requirements, not to mention ISO standards. This issue is further compounded by the fact that many laboratorians are already stretched for time to ensure compliance with these standards. Additionally, because many quality regulations are duplicative—though they may use different and unfamiliar terminology—the learning curve is expected to be steep.

Q: Are there upcoming or anticipated changes to any of these sets of guidance?

JB: The FDA's LDT final rule defines the general regulation but does not explain how the final rule will be interpreted or regulated. The FDA plans to issue guidance documents to communicate their compliance expectations. Laboratories should look for these documents during the enforcement phaseout timeline over the next several years.

LS: Labs need to stay informed about recent CLIA changes, particularly those related to proficiency testing and laboratory director requirements. Regarding the FDA, many labs affected by the LDT final rule must first understand whether they need to comply with the first two stages and, if so, how. Beyond these stages, most labs are awaiting further guidance or actions.

Laboratories are facing a perfect storm of impending regulatory changes—and to continue meeting patients' needs, it's crucial to stay ahead of the curve.

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SNAPSHOT OF LDT REGULATIONS

2003 Amendments to CLIA '88 introduce new requirements for LDTs but deem them outside the FDA's purview.

2014 The FDA releases draft guidance declaring that LDTs should be held to the same standards as IVDs.

2016 The House Committee on Appropriations directs the FDA to suspend efforts to regulate LDTs.

2020 The VALID Act is introduced in Congress outlining the FDA's intent to regulate all *in vitro* clinical tests, including LDTs, but it is never passed.

2023 The FDA announces proposed rule to regulate all IVDs and phase out its discretionary approach to LDTs.

2024 The FDA publishes final rule on LDTs and two draft guidance documents: enforcement discretion in declared emergency situations and in the absence of a declared emergency.

PHASE OUT DEADLINES

2025 **Stage 1**: Requires LDTs to comply with medical device reporting requirements, including correction and removal of tests, and quality system requirements regarding complaint files.

2026 **Stage 2**: Implementation of other IVD requirements not covered in Stage 3, e.g., registration.

2027 **Stage 3** (May): Compliance with quality system requirements other than for complaints.

Stage 4 (November): Premarket review requirements for high-risk LDTs, unless a premarket submission has been received.

2028 **Stage 5**: Expands premarket review requirement compliance to low- and moderate-risk LDTs for which a premarket submission has not been received.

Thought Leadership

First Ever Effort to Crowdfund Diagnostic Assays Launches in Response to FDA LDT Final Rule

LISA CEO EXPLAINS WHY CROWDFUNDING IS A VIABLE WAY TO SHOULDER THE NEW REGULATORY COSTS BEHIND LABORATORY-DEVELOPED TESTS

James Gilmore

In this interview, we speak with LISA CEO ***James Gilmore*** *about a ground-breaking initiative to crowdfund diagnostic assays. For those not familiar with crowdfunding, it is a mechanism where groups get together to fund a project and leverage the power of social networks and online platforms.*

Q: What does "LISA" stand for and why does it matter to clinical labs accredited by the College of American Pathologists (CAP) or COLA?

A: LISA stands for "Laboratory Integration Strategic Association" and is a coalition of industry and CAP/COLA lab partners. Our goal is to provide a path for CAP/COLA labs to bring new assays to market in light of the FDA final rule on laboratory-developed tests (LDTs).

Q: Why does this need a coalition approach? Can't CAP/COLA labs just go it alone to make new assays?

A: Absolutely, but many will find it extraordinarily challenging. This is a completely different set of regulatory guidelines—ones that labs will not necessarily be familiar with—and it is very resource intense. In my experience, a relatively simple five-target assay will cost between $1.5 million and $4.2 million to develop. A broad assay with more targets could be upwards of $14 million for development. Besides the regulatory burden and costs, managing analytical validation along with the clinical verification requires a dedicated team, and you can argue this is a distraction for CAP/COLA labs.

Q: How does LISA work?

A: At its essence, in LISA we share the cost of developing an assay. But unlike other crowdfunding mechanisms, in LISA the CAP/COLA labs are backing the assay development by purchasing reagents. These are reagents the labs would likely purchase or want anyway. So, LISA is reward-based crowdfunding. And it is completely voluntary: A CAP/COLA lab member that is part of LISA is not required to back any projects, only the ones they want. Further, LISA members are encouraged to nominate assays they consider worthy of crowdfunding.

Q: LISA just launched its first crowdfund projects for urinary tract infection (UTI). Can you take us through that as an example?

A: We are really excited for this one! There are three projects that can be backed, and each project is a multiplex PCR assay with four pathogen targets plus an external extraction and amplification control. You can back just one, two, or all three projects depending on the breadth of the panel you want developed. Additionally, you can pledge at different target amounts. The higher the pledge, the higher the reagent discount. Once each project hits the minimum amount for activation, we begin the FDA clearance journey.

Q: And the pledge is by purchasing reagents?

A: Correct, and in this case, backers of the project will pledge an annual minimum purchase amount of UTI-related reagents. LISA has a number of reagents in this area that labs may find useful.

Q: What else do backers get?

A: There are material advantages. For instance, backers also get a discount on any cleared device that comes out of the project. But I think equally important, if not more, is that backers get peace of mind and a path

through the final LDT rule. LISA will provide cGMP manufactured reagents—a requirement in Phase 3 of the rule. If backers opt in, they can be listed on the regulatory submission of the assay—a requirement in Phases 4 and 5. Essentially, CAP/COLA labs can launch new assays and build a client base while staying in compliance.

Q: Some labs may believe the FDA guidelines will be struck down or altered. How does this impact LISA?

A: In my opinion, unsettled regulatory frameworks inhibit both investment and growth. But in no case are we talking about doing away with FDA regulated devices. The goal of LISA is to gain clearance on devices, and this can benefit CAP/COLA labs by making devices, such as a UTI panel, not only easier to reimburse but likely more profitable.

Q: What kind of experience do the industry partners have?

A: We went with partners that have a strong background. Our manufacturing partner is Argonaut Manufacturing Services. They are FDA inspected and have produced millions of diagnostic kits. The development and clinical trials are led by Arete Biosciences, who has helped a number of diagnostic assays gain regulatory clearance. We have also engaged the legal team of Epstein Becker & Green, and they are top notch in both the LDT space and FDA devices.

Q: It seems that any effort to crowdfund diagnostic assays needs momentum to be successful. Is that correct?

A: Yes. It is an absolute requirement since the costs are distributed by the number of backers. The more labs that join, the more assays we can get submitted before the final FDA deadline, and this benefits all backers.

If you have more questions about LISA, are interested in backing a UTI assay, or want to know more on how crowdfunding diagnostic assays can help your lab, please visit www.lisabio.com.

LISA

Thought Leadership

Supporting Biomarker-Driven Clinical Trials Through a Future-Ready Lab

by Deborah Phippard, PhD

With the rise of precision medicine, significant advancements in laboratory infrastructure and workflow are needed to support the complex requirements of biomarker-driven clinical trials. Now that biomarkers have transitioned from nice-to-have exploratory endpoints to essential tools for patient enrollment, clinical decision-making, and treatment monitoring, laboratories must evolve to meet the demands of this new era.

Creating a new paradigm for clinical labs

Biomarkers have become ubiquitous, particularly in oncology clinical programs where they are often a critical component of study designs. This shift has been amplified by the current restrictive funding environment, where there is increased pressure for phase 1 studies to give an early efficacy readout or at least provide insight into pharmacokinetic (PK)/pharmacodynamic (PD) relationships.

While labs are accustomed to fast turnaround times (TAT) for PK assays used to inform dose escalations, sponsors are now asking to review data from the first patients dosed to see if a PD effect is detectable. This demand has led to a new paradigm where PD assays must be performed in tandem with PK assessments, placing new stress on labs.

Beyond the strain associated with performing PD assays in real-time rather than in batches, PD assays are often drug-specific, requiring specialized protocols and training. If this boutique assay enriches or stratifies populations, it's likely that speed will be combined with compliance to CLIA or ISO 15189, particularly post-phase 1.

Meeting the needs of biomarker-driven trials

As clinical trials increase in complexity, here is how Precision for Medicine has prepared our laboratories to deliver a wide range of assays with fast TAT under high regulatory standards. All future-ready labs can rise to this challenge by:

- **Adopting platform-agnostic technologies** that offer the flexibility and scalability to adapt to the diverse needs of biomarker-driven studies with multiple time-sensitivities. With a platform-agnostic approach, technology selection is driven by the scientific question to be answered and which assay types can be integrated. It may also save setup time and costs if a sponsor already has a research-grade assay on a specific platform as there is no need to prove equivalence on a different platform. Adding multiplexing capability allows for monitoring of multiple biomarkers, while high-throughput next-generation sequencing is essential for genomic biomarker analysis.
- **Streamlining sample management** to reduce queries, thereby enhancing TAT and overall efficiency. The process begins at the clinical site, where accurate and complete metadata must be collected alongside the sample to enable rapid accessioning into the laboratory information management system. The use of custom collection kits and advanced biorepository systems that provide real-time visibility into sample status and availability can be invaluable. Close coordination with sponsors and sites allows labs to anticipate sample inflows and to schedule assays accordingly, reducing the time between sample collection and data reporting.
- **Standardizing workflows** to maintain consistency and quality. A key aspect of workflow standardization is cross-training of laboratory personnel. In an environment where a wide range of assays are performed within tight timelines and under varying regulatory requirements, cross-training ensures high throughput and flexibility without compromising data quality. Another important consideration is the use of targeted automation for activities such as sample preparation or data analysis.

Looking ahead to the next generation of labs

At Precision for Medicine, we are seeing drug development become ever more complex and personalized, requiring multiple tests to be performed at the same time to optimize patient treatment. As the volume of data generated increases exponentially, more labs will need to incorporate the sophisticated tools needed for data integration and analysis, including artificial intelligence (AI), in biomarker-driven clinical trials AI will play a pivotal role in identifying correlations among this data and generating insights that guide treatment and accelerate future development. To keep pace, other future-ready labs should also be prepared to validate and incorporate AI and other emerging technologies to deliver the detailed, nuanced data necessary for supporting the continued advancement of precision medicine.

Deborah Phippard, *PhD, is chief scientific officer at Precision for Medicine, a clinical research organization.*

Thought Leadership

The Quiet Brilliance of Efficient Water Purification

IMPECCABLE WATER PURIFICATION SYSTEMS POWER THE LAB WITH MINIMAL STAFF INTERACTION

by Elga

▲Antonino Di Bartolo

Since 2006 at Veolia, ***Antonino Di Bartolo*** *has led a top team of service engineers in North America's clinical diagnostic industry. Di Bartolo now manages business and commercial activities across the Americas and serves as global account manager. He holds a master's in economics from Venice University and an executive MBA from MIB Trieste School of Management.*

Q: What types of contaminants does a lab water purification system need to remove?

A: A lab water purification system must remove ions, bacteria, and organic contaminants. Ensuring purity is critical in a clinical lab. If you're looking for the presence of a specific chemical in blood or tissue, you need to be confident that you are detecting its presence in the sample, not background from contaminated water. False positives and inaccurate results can have a catastrophic impact on patients.

Q: How can labs optimize their water purification process?

A: Water purification requires teamwork through a combination of people, technologies, and processes. Where people are involved, minimizing direct interaction with systems as much as possible and having operators monitoring water purification system status updates and interpreting readout should be sufficient. With decades of experience, manufacturers like ELGA LabWater can ensure the best unit tailored to the clinical work being done is being used in the lab. Paired with service engineers and support staff, these elements all form parts of the system that works as a synergistic whole.

Q: How can labs ensure their water is high quality?

A: They must work with a manufacturer who is an expert leader in the field with an abundance of experience and accreditations such as ISO. This field is not one size fits all, and there are specific products for specific needs. Working with a trusted manufacturer ensures that if you follow the basic daily steps, your work and interactions are minimal, reducing maintenance and daily tasks required to keep your water purification system working.

Q: How do ELGA LabWater water purification systems work?

A: There is a wide range of technologies available, and the secret is the right mix, in terms of specifications. We always start with a pre-treatment, which is basically removal of large, suspended compounds. One of these is chlorine, which is ironically naturally found in water and is removed with activated carbon. Then, the lab water is run through reverse osmosis, removing up to 97 percent of water contaminants. Treating the water this way, from an organic point of view, is a combination of photooxidation. Because bacteria remaining at this stage of purification are hardy, there is a final physical filter which works like a final barrier to ensure the water is as close as pure as possible.

Q: How can manufacturers ensure pure water while adhering to sustainability goals?

A: Currently, zero environmental impact is not possible while producing lab-grade water. The priority is producing water that provides reliable results. The secondary focus is on minimizing environmental impact. ELGA LabWater facilities are close to net zero carbon footprint for our consumables, and they have minimized CO_2 released during manufacture. Our water purification systems minimize electricity usage compared to previous models, and we continue to look for ways in which materials, energy, and environmental impact can be reduced.

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