

# C L N

Clinical  
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News

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EASING UP ON  
SWEAT TESTS

**<0.3**  
**μL/min**

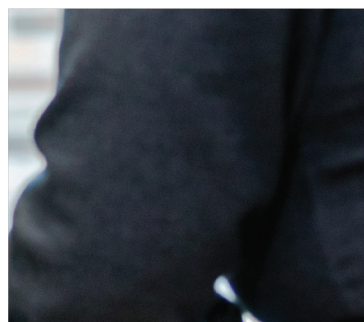
Proposed lower threshold for  
reporting chloride  
concentration

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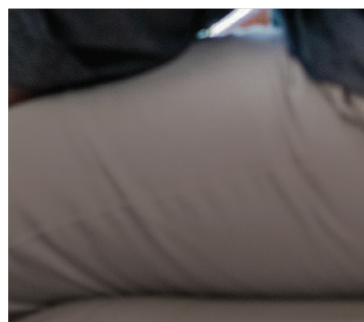
## The Search for Early Pancreatic Cancer Tests



### FDA Moves on Lab Developed Tests



### Standardizing ALT Reference Intervals



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“Labs measuring troponin in serum should strongly consider using plasma to achieve the turn-around times necessary for rapid rule in or rule out of myocardial infarction.”

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## President Biden Issues Executive Order on Artificial Intelligence

President Biden's executive order establishing new standards for artificial intelligence (AI) safety and security offers a roadmap for the implementation of AI in healthcare and clinical research.

The executive order calls for several actions to ensure emerging technology is used responsibly, such as requiring AI developers to share their safety test results with the U.S. government, calling on Congress to pass data privacy legislation, and developing principles to maximize the benefits of AI for workers.

Several provisions in the executive order seek to provide oversight for AI use in healthcare. The executive order requires the Department of Health and Human Services (HHS), in consultation with the Secretary of Defense and the Secretary of Veterans Affairs, to establish an AI Task Force by January 28 to develop a regulatory action plan around issues such as use of AI in healthcare delivery and assessing whether AI-enabled technologies in healthcare maintain appropriate levels of quality. Existing HHS programs will be leveraged to develop AI tools that can create patient immune-response profiles.

Furthermore, the executive order directs HHS to allocate the 2024 Leading Edge Acceleration Project awards, a funding opportunity offered through The Office of the National Coordinator for Health Information Technology, to initiatives that explore ways to responsibly develop AI tools for "clinical care, real-world-evidence programs, population health, public health, and related research."

### ● PAYING OUT-OF-NETWORK LABS FOR TEST SERVICES IS A POTENTIAL VIOLATION OF ANTI-KICKBACK STATUTE

On September 25, the Department of Health and Human Services Office of Inspector General (OIG) issued Advisory Opinion 23-06, which rejected an anatomic pathology laboratory's proposal to purchase technical component (TC) services, such as slide preparation, from out-of-network laboratories for insured patients. The opinion is significant because OIG analyzed the

proposed arrangement only from the laboratory's perspective and without discussing either party's intent, according to law firm Bass, Berry, & Sims.

The author of the advisory request operates commercial anatomic pathology laboratories across the U.S. that perform both TC and the professional component (PC), the pathologist's interpretation of test results. Third-party physician and nonphysician laboratories that can perform both TC and PC sought to enter into an arrangement with

the laboratory, whereby the laboratory would pay the third-party laboratories for TC services, and the laboratories would send slides to the laboratory for its pathologists to conduct PC. The laboratory would then submit a global claim for both PC and TC services.

In its unfavorable opinion, OIG wrote that the arrangement would generate prohibited remuneration under the federal anti-kickback statute, because the laboratory would pay remuneration to laboratories that could in turn

refer federal healthcare program (FHCP) business to the laboratory. Though the arrangement would not involve any pathology services reimbursable by FHCPs, OIG argued that this does not insulate the arrangement from anti-kickback liability, as payment for FHCP business can be disguised as payment for non-FHCP business.

● **HHS OFFICE FOR CIVIL RIGHTS SETTLES RANSOMWARE CYBER-ATTACK INVESTIGATION**

The Department of Health and Human Services Office for Civil Rights (OCR) announced a settlement under the Health Insurance Portability and

Accountability Act (HIPAA) with Doctors' Management Services, a Massachusetts medical management company that provides a variety of services, including medical billing and payor credentialing.

In April 2019, Doctors' Management Services filed a breach report stating that 206,695 individuals were affected when their software was infected with ransomware. OCR found evidence of potential failures by Doctors' Management Services to monitor potential risks to electronic protected health information, as well as insufficient monitoring of health information systems' activity and a lack of policies aimed at implementing the requirements of the HIPAA

Security Rule, for which Doctors' Management Services incurs a liability despite being attacked. Under the terms of the settlement agreement, Doctors' Management Services will pay \$100,000 to OCR, which will monitor the management company for 3 years to ensure HIPAA compliance.

According to OCR, ransomware and hacking are the primary cyber-threats in healthcare. In the past 4 years, there has been a 239% increase in large breaches reported to OCR involving hacking and a 278% increase in ransomware. In 2023, hacking accounted for 77% of the large breaches reported to OCR, which have affected more than 88 million individuals.

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## Practical Considerations for Endocrinology Testing: A Focus on Pheochromocytoma



Ashley R. Rackow, PhD

Pheochromocytomas are a rare type of secretory tumor that arise from chromaffin cells within the adrenal glands. In the early stages of disease, patients are often asymptomatic, but as the tumor grows, individuals may experience symptoms such as hypertension, headaches, increased sweating, and episodes of unexplained generalized anxiety or dread.

Pheochromocytomas secrete the hormone epinephrine, also known as adrenaline, and norepinephrine — collectively referred to as catecholamines. Patients with pheochromocytomas are at increased risk for experiencing a “catecholamine storm” that presents itself as a severe hypertensive crisis requiring emergency intervention.

Early identification is essential for patient care, but diagnosing a pheochromocytoma is challenging given the diffuse and sporadic nature of symptoms, a high proportion (50–60%) of asymptomatic individuals, and low population prevalence. Pheochromocytomas are diagnosed from the biochemical measurement of metanephrines, the metabolites of catecholamines, followed by imaging studies. As such, it is critically important that pheochromocytoma testing is accurate, sensitive, and specific.

To ensure high-fidelity results are released, clinical laboratorians must understand the biological role and properties of catecholamines and metanephrines and apply this knowledge to build processes that protect result integrity.

### PREANALYTICAL SPECIMEN HANDLING: THE FOUNDATION FOR ACCURATE RESULTS

Preanalytical factors such as diet, medication use, stress, collection practice, and posture all affect catecholamine secretion. Exogenous factors that increase catecholamine secretion

include caffeine, nicotine, strenuous exercise, acetaminophen, decongestants, and tricyclic antidepressants.

When placing an order, providers should discuss how these factors may alter test results and advise patients to avoid ingestion of products that stimulate catecholamine release. Catecholamines are produced in response to stress, which may even be noticeable from difficult or traumatic venipuncture. Phlebotomists should note difficult collections so that they can be viewed along with the result and clinical context. Venipuncture should be performed in the supine position, as standing and upright postures increase catecholamine secretion. Best practices state there should be a pause between needle insertion and blood collection to allow the patient time to recover from the stress of the initial puncture.

For metanephrines testing, the same collection practices should be observed. However, metanephrines are significantly less responsive to preanalytical variability compared to catecholamines. The timing of patient presentation also affects the measurement of catecholamines and metanephrines. In the setting of a secretory tumor, catecholamines are produced in a pulsatile fashion that correlates with symptomatic onset. Individuals who present in the absence of acute symptoms often have normal



concentrations of catecholamines, which limits their diagnostic utility. Metanephrines, however, are produced at a relatively constant rate that is independent of symptomatic presentation. Due to decreased variability in response to preanalytical variables and constant rate of production, measurement of metanephrines is the preferred first-line test for diagnosis of pheochromocytoma.

Following specimen collection, blood samples should be placed on ice and spun down within the hour to prevent analyte degradation. Room temperature transport or delayed processing will falsely lower catecholamine concentrations, which may result in a missed or delayed diagnosis of a new or recurring tumor. By using the laboratory information system (LIS), laboratories can layer process improvement strategies throughout the sample collection protocol.

For example, the laboratory can program popup windows to alert the phlebotomist of special collection and handling instructions. Labels also may be programmed to signal to laboratory staff that samples should arrive on ice and be processed immediately upon arrival. Building a system with multiple checkpoints educates and empowers staff across the hospital to follow best practices and rapidly identify problems that affect specimen integrity.

### **ANALYTICAL TECHNIQUES INFORM CLINICAL INTERPRETATION**

The analytical methodology is also an important consideration when following a patient with

## **Due to decreased variability in response to preanalytical variables and constant rate of production, measurement of metanephrines is the preferred first-line test for diagnosis of pheochromocytoma.**

a newly diagnosed or established pheochromocytoma. The Endocrine Society provides diagnostic guidelines for pheochromocytoma, which endorse the measurement of metanephrines and catecholamines by either high-performance liquid chromatography (HPLC) or liquid chromatography-tandem mass spectrometry (LC-MS/MS).

Compared to HPLC and LC-MS/MS, immunoassays for catecholamines suffer from reduced analytical sensitivity, higher limits of detection, and an overall negative bias. The diagnosis of pheochromocytoma requires accurate testing with a wide dynamic measuring range, because patients with pheochromocytomas can have metanephrine or catecholamine levels 1,000 times higher than the reference range. On the other hand, monitoring recurrence requires a low limit of quantitation, as even small changes in metanephrine and/or catecholamine content may suggest early recurrence.

To optimize clinical sensitivity, pheochromocytomas are diagnosed by performing plasma metanephrine testing followed by imaging. Routine monitoring of diagnosed adrenal tumors can be performed by collection of catecholamines with or without metanephrines, a decision

that should be made on a case-by-case basis and dictated by clinical history.

Laboratories can measure catecholamines and metanephrines in a single blood sample or a 24-hour urine collection. Due to the temporal variability in catecholamine secretion, spot urine tests are of little clinical value. From a practical standpoint, 24-hour urine collections may be more time intensive than plasma measurements; however, urine collections offer an alternative for patients with difficult vascular access or anxiety about venipuncture. Avoiding a difficult draw also preserves specimen integrity by eliminating stress as a source of pre-analytical variability.

As demonstrated in the case of catecholamine testing, clinical sensitivity of endocrinology testing is influenced by preanalytical variability and the analytical approach. Designing robust systems that mitigate sources of variability and encourage interdepartmental collaboration serves to further improve laboratory testing and support evidence-based medicine.

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**Ashley Rackow, PhD**, is a clinical chemistry fellow at Johns Hopkins University. Her clinical and research interests include main chemistry, endocrinology, toxicology, and therapeutic drug monitoring.

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## Researchers Propose Cystic Fibrosis Testing Changes

Preliminary data suggest that pooling bilateral collections may be a feasible way to achieve the required volume for sweat chloride testing in cystic fibrosis (CF) patients and that the minimum sweat rate for macroduct collectors may be overly stringent (J Appl Lab Med 2023; doi: 10.1093/jalm/jfad067).

Sweat chloride testing is the gold standard for CF diagnosis. Guidelines from the Clinical and Laboratory Standards Institute (CLSI) endorse a minimum sweat rate for reporting results and recommend bilateral sweat collection. If both sites fail to meet the minimum rate or quantity is insufficient, the test should be repeated.

The researchers examined the correlation between sweat rate and sweat chloride concentration, assessed the accuracy of specimens collected at suboptimal rates, and investigated use of pooled bilateral specimens for chloride measurement. They used a Pearson correlation to analyze the relationship between sweat rate and chloride concentration (Cl<sup>-</sup>) in 674 macroduct collections. The researchers weighted kappa to CF diagnostic classification concordance for 18 tests with paired arms above versus below the minimum sweat rate. They also applied Deming regression to compare Cl<sup>-</sup> from pooled bilateral specimens to neat specimens in 27 collections with residual volume available after clinical testing.

The Pearson correlation of sweat rate versus Cl<sup>-</sup> was minimal across specimens with varying rate and Cl<sup>-</sup>, the researchers found. They observed substantial agreement in CF diagnostic classification between arms for bilateral collections with discordant sweat rates. Regression analysis of Cl<sup>-</sup> in pooled versus nonpooled specimens revealed a slope of 0.984 and an intercept of 0.796.

The researchers concluded that sweat rate does not influence sweat Cl<sup>-</sup> when following the CLSI recommendations and using macroduct collectors, and that negligible correlation of sweat rate and Cl<sup>-</sup> suggests the minimum sweat rate for macroduct collectors may be overly stringent. Reporting of Cl<sup>-</sup> in specimens equal to or greater than 10 μL, or with a rate equal to or greater than 0.3 μL/minute, may reduce quantity not sufficient rates without compromising diagnostic accuracy, the researchers added.

### ● NEW ALS GUIDELINES CALL FOR MORE TESTING, BETTER LAB PRACTICES

New evidence-based, consensus guidelines for amyotrophic lateral sclerosis (ALS) genetic testing and counseling call upon clinicians to offer them to all ALS

patients in the United States, regardless of family history (Ann Clin Transl Neurol 2023; doi: 10.1002/acn3.51895).

Testing should cover mutations in the most common genes linked to the disease, the guidelines say. At a minimum, these include

*C9orf72*, *SOD1*, *FUS*, and *TARDBP* because genetic mutations can occur in both the familial and sporadic forms of the disease. The guidelines describe patient education and genetic risk assessments to be provided.



Noting labs' inconsistent methodology and clinical results reporting, the guidelines propose standards to harmonize methodologies. They suggest that testing DNA derived from tissues outside of the central nervous system is sufficient to establish the presence of a *C9orf72* repeat expansion and that *C9orf72* testing should use a method with high sensitivity and specificity for expanded alleles. The guidelines also recommend as acceptable repeat-primed PCR, performed bidirectionally for detecting expanded *C9orf72* alleles with high sensitivity and specificity in some circumstances, as well as dual-mode for detecting expanded *C9orf72* alleles with high sensitivity and specificity. Interrogation of non-*C9orf72* ALS genes should use simultaneous sequencing methods instead of sequential gene sequencing.

The guidelines call on labs to harmonize reporting. Those with *C9orf72* findings should specify the sizes of non-expanded alleles, while those alleles classified as "intermediate" or "uncertain" should include a statement outlining up-to-date data regarding uncertainty of pathogenicity of these allele sizes. *C9orf72* repeat expansion findings should include a statement clearly outlining the maximum number of repeats detectable by the assay employed. Additionally, gene panel reports should differentiate clearly between genes that are causal for ALS and those genes where the evidence is sparse, conflicting, or insufficient, based on National Human Genome Research Institute Clinical Genome Resource (ClinGen)

## Noting labs' inconsistent methodology and clinical results reporting, the guidelines propose standards to harmonize methodologies.

classifications. The guidelines also state that if testing involved targeted-capture, exome, or whole-genome methods, reports should note inadequately assessed gene regions that should be interrogated further.

These guidelines are a first step toward a uniform and equitable approach to ALS and will require periodic revision based on genetic discoveries and new genetic therapies relevant to ALS, the authors said.

The researchers concluded that their results demonstrate how large exome sequencing studies, combined with efficient burden analyses, can identify additional breast cancer susceptibility genes. They called for further studies to replicate their findings in large datasets.

### ● RISK STRATIFICATION BENEFITS YOUNGER MEN WITH EARLY PROSTATE CANCER

**P**rostate cancer (PC) patients younger than 70 with early PC and unfavorable PC risk profiles can be identified so they potentially may benefit from treatment escalation with androgen receptor signaling inhibitors or cytotoxic chemotherapy and participate in randomized treatment escalation studies, recent research suggests. (JAMA Network Open 2023; doi: 10.1001/jamanetworkopen.2023.36390).

Age under 70 years, comorbid diseases, and other likely indicators of fitness are important covariates when predicting risk of

prostate-specific antigen (PSA) failure and survival, the study adds.

A shorter time interval to PSA failure is associated with worse clinical outcomes, but specific factors defining this state are unknown. The researchers reported on unplanned post-hoc analyses from a larger trial and identified factors associated with shorter time to PSA failure among 250 patients with nonmetastatic unfavorable-risk PC. The researchers sought to measure cumulative incidence rates curves of PSA failure, defined as PSA nadir plus 2 ng/mL or initiation of salvage therapies. The researchers used Fine and Gray competing risks regression to assess prognostic association between these factors and time to PSA failure.

After a median follow-up of 10.2 years, the researchers found that baseline PSA of 10 ng/mL or greater, a Gleason score of 8–10, and being younger than 70 were associated with shorter time to PSA failure. The researchers combined these three factors to create a high-risk category associated with almost 3-fold higher risk compared to men without the three factors and a 43.8% risk of PSA failure at 3 years.

An accompanying editorial calls for risk stratification for early PC that also includes pathologic and genomic features of the PC and detailed patient assessment of fitness and comorbid disease to decide on the optimal intensity, type, and duration of treatment.

# FDA GOES ALL IN

# to Regulate Laboratory Developed Tests

By some accounts, the agency has aimed to regulate these tests for more than 30 years. Now the fight is coming to a head, with a proposal that could end up at the Supreme Court.

**BY KIMBERLY SCOTT**

**A**s the Food and Drug Administration (FDA) moves forward with its attempt to regulate laboratory developed tests (LDTs), the Association for Diagnostics & Laboratory Medicine (ADLM, formerly AACC) and many others in the lab community question whether the agency has the authority to pursue such oversight. ADLM also warns that the attempt could drastically limit patients' access to critical laboratory tests, even crippling some labs.

The FDA on October 3, 2023, issued a proposed rule that would allow the agency to regulate LDTs as medical devices, much as they do in vitro diagnostic (IVD) test kits manufactured by IVD companies. Specifically, the FDA seeks to amend its regulations to make explicit that IVDs are devices under the Food, Drug and Cosmetic Act "including when the manufacturer of these products is a laboratory." Although the proposed new regulatory text is only 10 words, the FDA devotes more than two dozen pages justifying what it sees as a need to regulate LDTs.

Historically, the FDA has exercised enforcement discretion over most LDTs because it has viewed them as lower risk because of their small volume. However, the agency states in the proposal that the LDT landscape has evolved significantly since 1976, when Congress first created a system to regulate





medical devices. At that time, LDTs were mostly manufactured in small volumes by laboratories that served their local communities and were typically intended for use in diagnosing rare diseases for which there were no other tests.

Now, many LDTs rely on high-tech or complex instrumentation and software to generate results and clinical interpretations, and laboratories often provide them in high volume for large and diverse populations, according to the FDA. “Many LDTs are manufactured by laboratory corporations that market the tests nationwide, as they accept specimens from patients across the country and run their LDTs in very large volumes in a single laboratory,” the FDA said, arguing that the risks associated with most modern LDTs are much greater than they were in 1976.

The rule proposes a 4-year phase-out of enforcement discretion, beginning 1 year after publication of the final rule. The agency said this “phaseout policy should ultimately enable IVDs offered as LDTs that are supported by sound science to remain on the market.”

The agency asked for input in a number of areas, including:

- Whether it should maintain its current enforcement discretion approach with respect to premarket review and some or all quality system requirements for LDTs already on the market;
- Public health rationales for having a longer phaseout period for LDTs offered by laboratories with annual receipts below a certain threshold;
- Whether the FDA should implement a different phaseout approach for academic medical center laboratories;

- How the FDA might leverage programs such as the New York State Department of Health Clinical Laboratory Evaluation Program or those within the Veterans Health Administration as part of the phase-out approach;
- Any implication of continued enforcement discretion for LDTs used for law-enforcement purposes and any factors that the FDA should consider — particularly as it relates to civil rights and equity — regarding the scientific validity and accuracy of such tests.

This is not the first time the FDA has threatened to regulate LDTs, but this is the first time the agency has formally issued a proposed rulemaking timeline for enforcement. The agency has been discussing the need for more oversight of LDTs formally for more than a decade. It held

a workshop on the issue in 2010, proposed draft guidance documents in 2014, issued a discussion paper in 2017, and gave input on proposed legislation in Congress several times, including in 2022.

ADLM has long opposed the FDA's efforts to regulate LDTs and argued that these tests are already regulated by the Centers for Medicare and Medicaid Services (CMS) under CLIA. ADLM President Octavia Peck Palmer, PhD, said in a statement that the FDA's proposal would create a dual, expensive, and potentially contradictory regulatory environment for clinical laboratories, eliminating most labs' ability to perform LDTs.

"We continue to advocate for a balanced, evidence-based approach

to regulating laboratory developed tests," Peck Palmer said. "We must identify what problems we are trying to fix and correct them without hindering scientific advancement or limiting patient access to these innovative, often life-saving tests. We urge the FDA to join us in working within the regulatory system to advance patient care and prioritize health equity."

#### **IS A LEGISLATIVE SOLUTION OFF THE TABLE?**

Many stakeholders had hoped that Congress itself would establish a regulatory framework for diagnostic testing, thus averting the FDA's attempts to get involved. Legislation originally introduced in 2020 and again in 2022 that would have established a new

risk-based framework for diagnostic tests at the FDA came close to passing but ultimately failed. The Verifying Accurate Leading-Edge IVCT Development (VALID) Act has been reintroduced again in the House this year, but not the Senate. ADLM and other laboratory advocates opposed VALID because it would have meant FDA regulation of LDTs, user fees for laboratories, and dual oversight under both CMS and the FDA.

Moreover, ADLM has argued that the best legislative approach would be to modernize CLIA to require that laboratories demonstrate a test's clinical validity, among other updates. "The development and utilization of a vast majority of LDTs is a shared responsibility between clinician



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DIAGNOSES  
WOULD BE MISSED  
OR DELAYED.  
— DENNIS DIETZEN**

and laboratory — it is the practice of medicine in action," said Dennis Dietzen, PhD, DABCC, FADLM, professor of pathology and immunology at Washington University School of Medicine and medical director of laboratory services at St. Louis Children's Hospital. "These lab-developed procedures are regulated by CLIA today. A refresh of CLIA regulations is the most appropriate way to fix existing regulatory gaps."

Legal observers believe it's unlikely that VALID will move forward. "I think the FDA proposed this rule because it was frustrated with the lack of action that Congress has taken to implement comprehensive diagnostics reform," said Christopher Hanson, an FDA Regulatory Partner with Nelson Mullins. "There has been a clear push for five or six years to come to a resolution about how LDTs and conventional IVD test kits can be regulated under the same framework. I think this was the FDA's last resort."

Hanson believes that the FDA has made finalizing its LDT proposal a priority, noting that the agency declined requests to extend the 60-day comment period. ADLM joined with 88 other organizations in seeking to extend the comment period to 120 days. In an Oct. 31 letter to FDA Commissioner Robert Califf, MD, the groups said they needed additional time to fully assess, research, and understand how the proposed rule would affect their constituencies. They noted that similar legislation, enacted in Europe in 2017, experienced multiple delays, which led regulators to issue grace periods for classes of devices to avoid widespread diagnostic shortages. Comments

on the FDA proposal were due Dec. 4, 2023.

"I think the FDA will push very hard to get this rule finalized in 2024 before the presidential election," said Hanson.

Joyce Gresko, a partner with Alston & Bird, agrees that the FDA appears eager to finalize the rule next year, but said she has not given up all hope of a legislative solution.

"Will this light a fire under Congress? Maybe," she said. "One possibility is that lawmakers bring up the VALID Act again. Another possibility is that Congress could pass legislation that says the FDA does not have the authority to regulate LDTs. It may spur some activity that isn't necessarily Congress taking the VALID Act over the finish line."

**PARSING A CLOUDY  
DEFINITION OF LDTs**

Part of the difficulty with LDTs lies in the fact that there is not a precise definition of what a lab

developed test actually is. Tests with mass-produced reagents that are marketed widely, such as those mentioned by the FDA in its discussion, should not be considered LDTs, said Dietzen.

"This is a loophole for mass-produced IVDs to avoid FDA regulation," he argued. "Lumping all LDTs into the same bucket is not the right solution." Dietzen, an ADLM past president, believes that FDA oversight of LDTs would have a dramatic impact on his lab as well as many others and that patient access to necessary testing would suffer.

"The LDTs we maintain in our lab are already resource-intensive," he said. "The additional regulation and user fees that this proposal promises would make it very difficult to continue testing. Diagnoses would be missed or delayed. Treatment would get delayed. Patients would suffer unnecessarily."

**OBSTACLES AHEAD  
FOR FDA'S RULE**

Even if the FDA finalizes its proposal to regulate LDTs, it is likely that the agency will face lawsuits, which could delay implementation of the rule, Hanson and Gresko both believe.

"This could very well get tied up in court if there is some type of injunction," said Gresko. Depending on the judge and the court, it could have applicability nationwide, at least for a time.

Hanson thinks a lawsuit challenging the rule, if filed, could even make its way to the Supreme Court, where it's anyone's guess as to how the high court would rule.

"To the casual observer, it might seem that the conservative nature of the court would mean it would rule against regulatory overreach

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by the FDA, but we have found that the court can surprise us," he said. "We often find interesting voting blocs on different cases, so it's hard to predict where it might come out on this."

Then there's the question of cost and resources. Many have questioned whether the FDA has sufficient staff to review the additional submissions it would receive if this proposal were finalized. The FDA estimates that its regulatory plan will cost the industry an average of about \$5 billion per year and would have annualized benefits of about \$31 billion per year.

However, diagnostic consultant Bruce Quinn, MD, PhD, said a deeper dive into FDA's calculations show that the actual cost to the industry would be \$43 billion over the first 5 years while concurrently requiring an additional \$4 billion in FDA staff resources. This compares with the FDA's total annual budget of \$8 billion for all its operations.

In a white paper published Oct. 10, 2023, Quinn of Bruce Quinn & Associates, said that FDA's estimated annualized benefits of about \$31 billion per year are based on projected life values at several million dollars per patient while the costs to the industry are actual cash costs. Any way you look at it, the costs just don't add up, he argued.

"My conclusion is that when costs are scrutinized, the FDA's LDT proposal is simply impossible to execute as proposed (in five years), and it's difficult to foresee a timetable under which it could be executed," Quinn said. 🍷

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# The QUEST

## to Standardize ALT Reference Intervals

Laboratory experts propose new clinical decision limits for ALT assays that account for the influence of factors such as body mass index and alcohol consumption.







Over the past decade, a fierce debate has been brewing over alanine aminotransferase (ALT) reference intervals, involving prominent organizations such as the American College of Gastroenterology (ACG); the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN); laboratory experts from the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC); and the Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) (1).

What sparked the debate is a set of clinical guidelines released by ACG and NASPGHAN in 2017 that included key recommendations for ALT's concentration-based upper reference limit (4, 5) and that proposed using these upper limits as action thresholds. ACG and NASPGHAN developed these guidelines in an effort to remedy longstanding problems with ALT testing. However, their recommendations ended up raising deep concerns within the laboratory medicine community.

Below, we delve into the intricacies of these concerns, while also exploring the significance of ALT testing, its underlying issues and how these affect patients, and how clinical laboratories can make the right choices regarding ALT methods and reference intervals.

#### THE PROBLEM WITH ALT: REFERENCE INTERVALS

To comprehend the significance of the ALT reference interval debate, it is essential to grasp the role of ALT and its counterpart, aspartate aminotransferase (AST), in the context of liver health. These enzymes are predominantly found in hepatocytes. While ALT and AST are also present in other tissues, such as the heart, skeletal muscles, and kidneys, tests for these enzymes often are referred to as liver function tests because of their rise in blood concentration associated with liver damage (2).

The primary issue with ALT lies in the widely varying reference intervals used by clinical laboratories worldwide (3). This diversity in reference intervals has significant implications for the development of clinical guidelines. When these guidelines are formulated, they rely on specific ALT values to determine when medical intervention is necessary. However, the variable reference intervals employed by different laboratories create a challenging landscape for setting universal clinical standards.

The practical result of this lack of standardization is evident when examining clinical guidelines. Often, instead of providing a specific universal cutoff value for ALT, guidelines use relative measures such as "Take action if ALT exceeds 2 or 3 times your upper limit of normal." This approach is problematic because it means that the threshold for medical intervention depends on what an

**BY CHRISTOPHER D. KOCH, PHD, DABCC, AND JOE M. EL-KHOURY, PHD, DABCC, FADLM**

individual laboratory considers their upper limit of normal. This lack of standardization can lead to confusion and inconsistencies in patient care and diagnosis — and it's what led ACG and NASPGHAN to release their 2017 guidelines.

These guidelines specifically recommended adopting universal cutoffs of 33 U/L for adult males, 25 U/L for adult females, 26 U/L for pediatric males, and 22 U/L for pediatric females. However, in an opinion article published in *Clinical Chemistry*, a group of laboratory medicine experts led by Mauro Panteghini, MD, expressed their reservations about the proposed ALT reference intervals (1). They not only disagreed with the suggested thresholds but also criticized the universal application of these cutoffs.

Moreover, they were rightly upset that both American guideline panels, ACG and NASPGHAN, did not include any laboratory medicine professionals in their decision-making process. This omission of laboratory experts from guideline development was a notable oversight and a significant concern for the laboratory medicine community.

So, what were the primary arguments put forward by Panteghini, et al., and why were they at odds with the American guideline panels? To understand the core of this dispute, let's explore these arguments in detail.

### THE LABORATORY EXPERTS' PERSPECTIVE: THREE KEY ISSUES

#### Lack of Standardization in ALT Methods

To appreciate the importance of this point, it is crucial to understand that clinical laboratories have various options when it comes to ALT assays. These assays differ in a significant way — the presence or absence of pyridoxal-5-phosphate (P-5-P) as a cofactor in their reagents. P-5-P is a form of vitamin B6 and plays a critical role in the ALT enzyme's activity. It is needed for the enzyme to be active and capable of catalyzing the reaction that produces the signal measured by laboratory instruments.

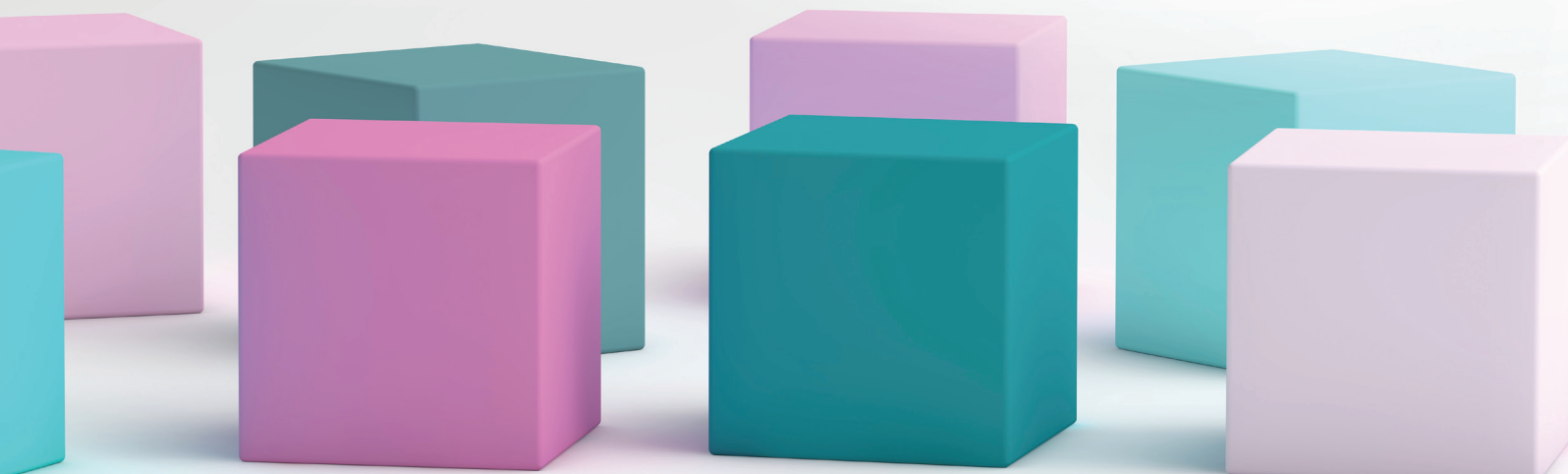
The issue is that many major manufacturers offer clinical laboratories a choice between ALT methods that include P-5-P and those that do not. While having choices is typically desirable, it is a

significant concern in this context. The reason is simple: ALT assays without P-5-P are unable to detect serious elevations in ALT levels in patients with vitamin B6 deficiency. In other words, if you have a vitamin B6 deficiency, your blood may contain a substantial amount of ALT, but the assays that lack P-5-P may not generate detectable signals (6). This is a crucial problem because these assays may fail to identify patients with potentially severe liver conditions, including alcoholic hepatitis.

Panteghini, et al., rightfully argued that ALT assays without P-5-P, which miss severe ALT elevations in patients with vitamin B6 deficiency, are still used in clinical laboratories around the world. This practice is deeply concerning, given the clear evidence in favor of assays with P-5-P, and IFCC recommending their use since 2003.

#### Lack of Traceability to IFCC Measurement

The second point raised by Panteghini, et al., pertains to the traceability of ALT results to the IFCC reference measurement procedure (1). When results from



different laboratories are aligned with the IFCC reference measurement procedure, they should be similar, with minimal variation. This traceability ensures that when a patient is tested in one lab and then in another, the reported ALT results will be consistent, even if the labs use different methods. However, the opinion article authors noted that many ALT methods lack this essential traceability to the IFCC reference measurement procedure. As a result, different ALT assays can produce different results, making it challenging to establish universal reference intervals or thresholds, as proposed by ACG and NASPGHAN.

### Inappropriate Criteria for the Selection of a Reference Population

In the realm of laboratory medicine, there is a unique power that laboratory professionals possess — the power to decide who is considered healthy. But deciding who is healthy is a complex task, as the criteria for selecting a reference population have far-reaching implications. One critical aspect of this debate revolves around the criteria used to select individuals for reference interval studies. For instance, overweight and obese individuals, those with a body mass index (BMI) over 25, are known to have higher ALT levels (7). This elevation is primarily due to the inflammatory effects that excess weight exerts on the liver.

A study performed by one of the coauthors of the opinion piece, Ferruccio Ceriotti, MD, initially included overweight individuals in its reference population, which influenced the proposed ALT reference intervals (1, 11). The opinion piece authors revisited this data, and by adjusting for the effect of overweight individuals, they lowered

the proposed reference intervals, aligning them more closely with the recommendations made by ACG and NASPGHAN. This highlights the sensitivity of reference intervals to factors like BMI.

However, when we attempted to verify these new reference intervals in our own laboratory, we encountered challenges. For instance, we recruited individuals with a healthy BMI, those not taking any medications, and with normal profiles for lipids, iron, and hepatitis, and discovered that over 10% of the participants had ALT levels above the newly proposed limits. This discrepancy led us to question what other factors might be influencing reference intervals that are not accounted for. As we delved deeper into the literature and collaborated with our clinical colleagues, we discovered another significant factor: alcohol consumption. Regular alcohol consumption, even in moderate amounts, is known to increase ALT levels, with a more pronounced effect in overweight and obese individuals (7). Studies on alcohol abstinence have also supported this theory, showing a substantial drop in ALT levels after just a few weeks of abstinence in individuals with a history of heavy drinking (8).

The problem with the study by Ceriotti, et al., is that it included individuals who reported consuming up to 30 grams of alcoholic beverages per day (1, 11). This equates to roughly 1 ounce of an alcoholic beverage, in which the quantity of alcohol can vary greatly depending on the type of alcoholic beverage consumed. The problems with the inclusion of alcohol consumers in this study are threefold: First, investigators had no way to verify the actual amount of alcohol participants consumed because

**Table 1.** Summary of Recommended ALT Thresholds by Different Groups

Organization/Guideline	Recommended ALT Upper Limit (U/L)
American College of Gastroenterology (ACG)	Adult Males: 33 Adult Females: 25
North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN)	Pediatric Males: 26 Pediatric Females: 22
International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)	Adult Males (after excluding BMI $\geq$ 25): 49 Adult Females (after excluding BMI $\geq$ 25): 33
Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER)	Pediatric Males (13–19 y): 33 U/L Pediatric Females (13–19 y): 24 U/L
2021 Updated Definition by Valenti, et al. (10)	Adult Males: 42 U/L Adult Females: 30 U/L

inclusion in the study relied on self-reported survey responses. Second, participants may not accurately recall or report their average alcohol consumption, making it challenging to ascertain the true extent of their drinking habits. Third, not all alcoholic beverages are created equal, making it difficult to equate the impact of different types of alcohol on ALT levels. As a result, we suspected that the inclusion criteria in the study, while well-intentioned, might not have effectively excluded individuals who regularly consumed high amounts of alcohol. This raised questions about the study's validity and the need to account for the influence of alcohol on ALT levels.

### NEW STUDY: ALCOHOL CONSUMPTION AND ALT REFERENCE INTERVALS

To address this issue, we aimed to determine if alcohol consumption

was indeed a significant factor affecting reference interval studies (8). However, we recognized that it would be difficult (and expensive) to recruit 120 men and 120 women who abstained from alcohol entirely, especially considering this investigation was undertaken amidst the COVID-19 pandemic, a time when alcohol consumption in the United States increased substantially. So, we resorted to what is called an "indirect sampling approach" (9). Essentially, we retrieved anonymized outpatient data from more than 7,000 individuals who had visited our institution over a 2-year period (8). These individuals had their blood tested on a Roche cobas 8000 platform using IFCC-traceable ALT and AST assays, both of which included P-5-P. The participants were carefully selected; only those with BMIs between 19 and 25 were included in the study. Additionally, individuals who had elevated AST levels and ALT levels above 80 U/L were excluded from the analysis, as these values were highly suggestive of underlying liver pathology.

This indirect sampling approach, although imperfect, aimed to investigate whether age and sex-specific

reference intervals could provide insights into the source of the reference interval variability. We stratified the data by age and sex and derived theoretical reference intervals for each group. In the case of individuals aged 13–17 years, we estimated reference intervals that closely resembled those proposed by CALIPER: 34 U/L for males and 27 U/L for females (8). We felt that this validated our approach, as alcohol is not expected to be a major factor in this age group.

However, for individuals aged 18–20 years, things took a different turn. In the United States, these individuals are considered adults, but the legal drinking age is 21. Theoretically, they should have more restricted access to alcohol compared with the rest of the adult population. While this scenario does not necessarily reflect the reality of college life in the U.S., it does present an interesting test case. So we sought to answer a crucial question: Using an ALT assay with P-5-P that was traceable to the IFCC reference measurement procedure, did reference intervals differ for adults with normal BMIs under the age of 21 compared to those above 21?

The results of this analysis provided a noteworthy insight. Men and women aged 18–20 had upper reference limits of 38 U/L and 25 U/L, respectively, while the age groups above 21 displayed higher reference ranges, varying between 40–54 U/L for men and 34–40 U/L for women. This indicated an upward and then downward trend in ALT reference intervals with increasing age, with the over-80 age group having reference intervals closest to those of the 18 to 20-year-olds.

These findings provided new insights: the prevalence of

overweight and obese individuals and the varying amounts of alcohol consumption within populations were two major factors contributing to the inability to agree on a universal ALT cutoff. The study results also hinted at a possible solution: adopting clinical decision limits, rather than relying on population-based reference intervals that vary according to each population's dietary and drinking habits.

To address the reference interval variability problem, we suggest adopting clinical decision limits and adjusting ALT reference intervals to 42 U/L for men and 30 U/L for women, based on a study that derived these limits using an IFCC standardized test with P-5-P in over 21,296 healthy individuals and over 2,000 patients with dysmetabolism and chronic liver disease (10). These decision limits are evidence-based and have the potential to provide more meaningful guidance to healthcare professionals. The focus would shift from establishing an arbitrary "normal" range to recognizing actionable thresholds for patient care. Additionally, by ensuring that ALT assays include P-5-P and are traceable to the IFCC reference measurement procedure, the accuracy of these results could be improved substantially.

### THE TAKEAWAYS: WHAT MATTERS MOST?

The ALT reference interval debate is undoubtedly a complex issue, affecting patient care and clinical laboratory practice. The perspective of laboratory experts, with its emphasis on the importance of ALT methods, traceability to IFCC measurements, and the influence of factors like BMI and alcohol consumption, offers a fresh lens through which to examine this debate.

**Table 2.** Summary of Recommendations for Laboratories Measuring ALT

Number	Recommendation
1	Ensure that your laboratory is employing ALT assays with P-5-P as a cofactor and that are traceable to the IFCC reference measurement procedure.
2	Evaluate the implementation of CALIPER-based reference intervals for your pediatric populations.
3	Evaluate the implementation of clinical-decision limits for ALT: 42 U/L for adult males and 30 U/L for adult females.

The newly proposed clinical decision limits of 42 U/L for men and 30 U/L for women hold promise as a pragmatic approach to ALT reference intervals. The adoption of these limits would ensure more consistent patient care across different laboratory settings. They would also provide a valuable opportunity to refocus on the primary goal of laboratory medicine — delivering precise and actionable results to aid clinicians in making critical healthcare decisions.

However, it is essential to recognize that this is an ongoing debate, and our recommendations are not universally accepted. Clinical practice is guided by evidence-based medicine, and as more research emerges, it may further shape and redefine the reference intervals and clinical decision limits for ALT.

In conclusion, the ALT reference interval debate serves as a compelling reminder of the dynamic nature of medical science and laboratory medicine. It underscores the importance of continuous collaboration between clinicians and laboratory professionals, as well as the need for evidence-based guidelines that can adapt to the evolving landscape of patient care and diagnostic technology.

Ultimately, what matters most is the well-being of patients and the accurate, actionable information that laboratory tests can provide to guide healthcare decisions. By addressing the issues raised in this debate, we take a step closer to ensuring that every patient receives the best possible care based on reliable laboratory data. 🍓

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### References

1. Panteghini M, Adeli K, Ceriotti F, et al. American liver guidelines and cutoffs for "normal" ALT: A potential for overdiagnosis. *Clin Chem* 2017; doi: 10.1373/clinchem.2017.274977.
2. **El-Khoury JM, Wang S.** Aspartate aminotransferase and alanine aminotransferase. In: Kazmierczak SC, Azzazy HME, editors. *Diagnostic Enzymology*. Berlin, Germany: De Gruyter, 2014:81-104.
3. Neuschwander-Tetri BA, Unalp A, Creer MH, et al. Influence of local reference populations on upper limits of normal for serum alanine aminotransferase levels. *Arch Intern Med* 2008; doi: 10.1001/archinternmed.2007.
4. Kwo PY, Cohen SM, Lim JK. ACG clinical guideline: Evaluation of abnormal liver chemistries. *Am J Gastroenterol* 2017; doi: 10.1038/ajg.2016.
5. Vos MB, Abrams SH, Barlow SE, et al. NASPGHAN clinical practice guideline for the diagnosis and treatment of nonalcoholic fatty liver disease in children: Recommendations from the expert committee on NAFLD (ECON) and the North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN). *J Pediatr Gastroenterol Nutr* 2017; doi: 10.1097/MPG.
6. Mills JR, Greene DN, Bainton J, et al. Fluctuating serum aspartate aminotransferase activity in a complicated

For an interactive presentation on this topic, check out Episode 3 of El-Khoury's YouTube channel: [www.youtube.com/@clinchemJoe](http://www.youtube.com/@clinchemJoe)

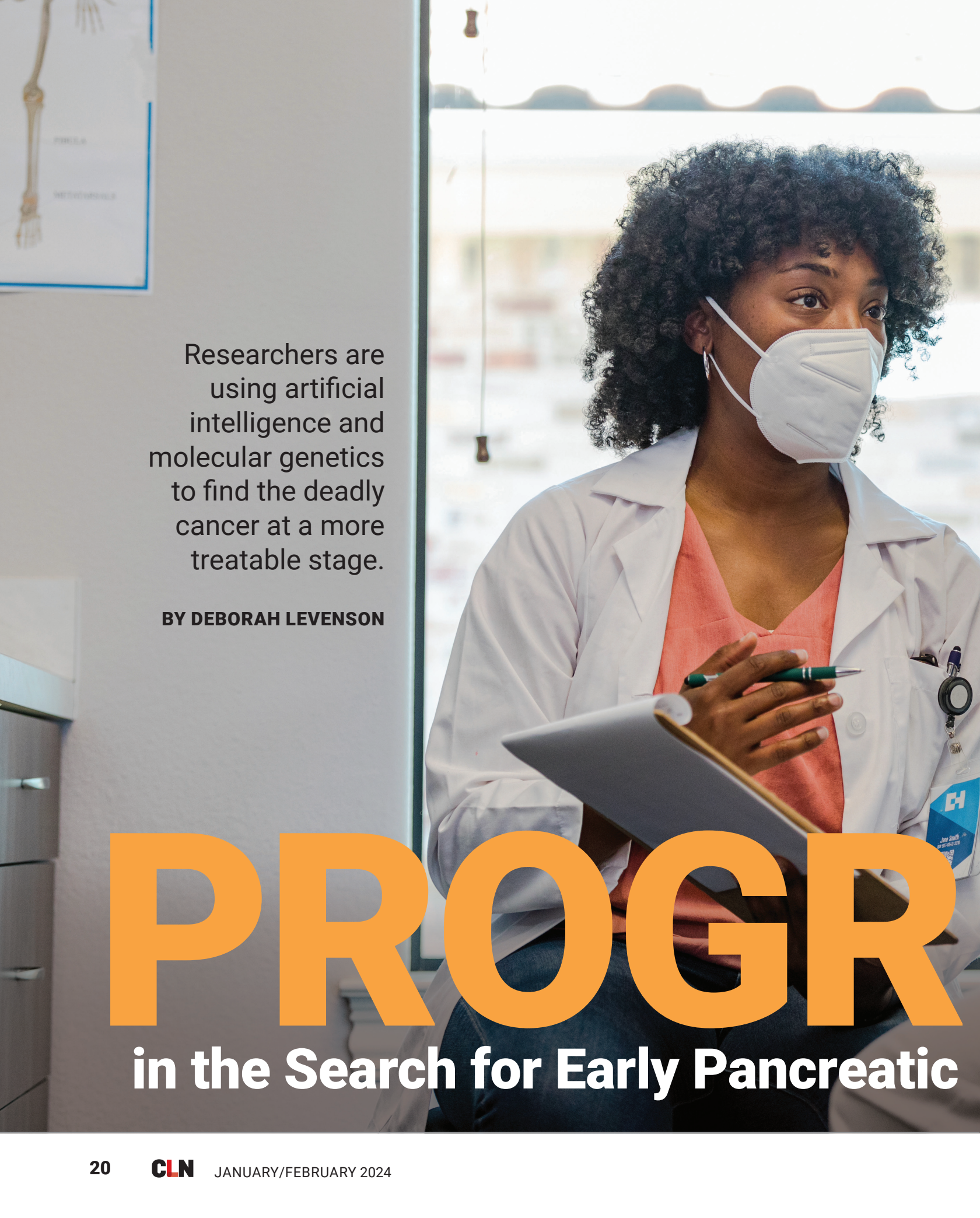
- pregnancy. *Clin Chem* 2015; doi: 10.1373/clinchem.2014.
7. Alatalo PI, Koivisto HM, Hietala JP, et al. Effect of moderate alcohol consumption on liver enzymes increases with increasing body mass index. *Am J Clin Nutr* 2008; doi: 10.1093/ajcn/88.4.
  8. Vera MA, Koch CD, Liapakis A, et al. The ALT upper reference interval debate: Blame it on the alcohol. *Clin Chim Acta* 2022; doi: 10.1016/j.cca.2021.12.
  9. Jones GRD, Haecel R, Loh TP, et al. Indirect methods for reference interval determination — review and recommendations. *Clin Chem Lab Med* 2018; doi: 10.1515/cclm-2018-
  10. Valenti L, Pelusi S, Bianco C, et al. Definition of healthy ranges for alanine aminotransferase levels: A 2021 update. *Hepatol Commun* 2021; doi: 10.1002/hep4.1794
  11. Ceriotti F, Henny J, Queralto J, et al. Common reference intervals for aspartate aminotransferase (AST), alanine aminotransferase (ALT), and  $\gamma$ -glutamyl transferase (GGT) in serum: Results from an IFCC multicenter study. *Clin Chem Lab Med* 2010; doi: 10.1515/CCLM.2010.

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Researchers are using artificial intelligence and molecular genetics to find the deadly cancer at a more treatable stage.

**BY DEBORAH LEVENSON**

# PROGR

in the Search for Early Pancreatic



# ESS

## Cancer Tests

**P**ancreatic cancer is a particularly aggressive and usually lethal malignancy. Pancreatic ductal adenocarcinoma (PDAC), the most common type, is the third largest cause of cancer death in the United States, even though it is uncommon. Early disease has very subtle or no symptoms, and pancreatic cancer is therefore often diagnosed at advanced stages. Meanwhile, clinicians lack a standard diagnostic lab tool or established method for early detection. Because the pancreas is located deep in the abdomen, hidden behind other organs, imaging is also difficult. Clinicians long for minimally invasive screening methods and accurate early diagnostic methods, especially blood tests.

Early detection efforts now focus on high-risk patients with genetic mutations known to cause pancreatic cancer, older people, and those with family history of the disease. However, about 75% of pancreatic cancer occurs in patients who are not considered high-risk. The United States Preventive Services Task Force in 2019 recommended against pancreatic cancer screening of asymptomatic adults, citing lack of data.

Two recent studies highlighted the ongoing search for early detection methods. One assessed pancreatic cancer risk using CA19-9 and bilirubin concentrations in the blood to distinguish early-stage pancreatic cancer from benign neoplasms. (JAMA Netw Open 2023; doi:10.1001/jamanetworkopen.2023.31197.) The other described an artificial intelligence (AI) model that may point to a population screening method to prompt monitoring and expedite diagnosis and treatment (Nat Med 2023; https://doi.org/10.1038/s41591-023-02332-5).

These are just two examples of research advancing early diagnosis, said Peter Allen, MD, professor of surgery and chief of the division of surgical oncology at Duke University School of Medicine. The outlook for early diagnosis is improving given “new understanding of the ability to image the pancreas, pancreatic cancer biology, and our ability to block a predominant *KRAS* mutation, which is thought to be undruggable,” he said.

### NEW RESEARCH ON DIAGNOSTICS

The JAMA paper describes a study in nearly 500 adult patients almost evenly split between development and validation cohorts at four academic hospitals in Italy, the Netherlands, and the United Kingdom. Both cohorts involved patients in their late sixties. In external validation, the prediction model showed an area under the (AUC) curve of 0.89 (95% CI, 0.84–0.93) for early-stage pancreatic cancer versus benign periampullary diseases, and outperformed CA19-9 (difference in AUC [ $\Delta$ AUC],

0.10; 95% CI, 0.06–0.14;  $P < .001$ ) and bilirubin ( $\Delta$ AUC, 0.07; 95% CI, 0.02–0.12;  $P = .004$ ). In the subset of patients without elevated tumor markers, the model showed an AUC of 0.84 (95% CI, 0.77–0.92).

At a risk threshold of 30%, decision curve analysis showed that performing biopsies based on the prediction model was equivalent to reducing the biopsy procedure rate by 6% (95% CI, 1%–11%), without missing early-stage pancreatic cancer in patients, the researchers noted. They said the model could be used to assess the added diagnostic and clinical value of novel biomarkers and prevent potentially unnecessary invasive diagnostic procedures for patients at low risk.

The method is practical and cost-effective because it relies on

readily available routine biomarkers, said corresponding author Elisa Giovannetti, MD, PhD, associate professor at Vrije Universiteit University Medical Center in Amsterdam.

The Nature Medicine paper described how researchers trained of an AI algorithm on 41 years' worth of Danish National Patient Registry records of 6.2 million patients, 23,985 of whom developed pancreatic cancer. The algorithm associated future pancreatic cancer risk based on disease trajectories and was able to detect the cancer up to 3 years early using only these records.

For example, gallstones, anemia, type 2 diabetes, and other gastrointestinal problems were associated with greater risk for pancreatic cancer within 3 years. Then the researchers tested their algorithm

on 21 years of U.S. Veterans Health Administration data. This data encompassed almost 3 million records spanning 21 years, including 3,864 individuals diagnosed with pancreatic cancer.

Training AI models on high-quality data, large representative datasets of clinical records aggregated nationally and internationally, and on local health data in the absence of globally valid models is crucial, the researchers noted.

### COULD AI BEAT TRADITIONAL BIOMARKERS?

Michael Goggins, MBBCh., MD, professor of pathology at Johns Hopkins School of Medicine, said that the blood biomarker test might be applied to high-risk patients with pancreatic imaging abnormalities. The test provides

## A PERSONALIZED Vaccine for Pancreatic Cancer?

A small trial recently found that half of pancreatic ductal adenocarcinoma (PDAC) patients who received a personalized mRNA cancer vaccine after surgery had no tumor recurrence 18 months later (Nature 2023; doi: 10.1038/s41586-023-06063-y).

The vaccine is designed to help immune cells recognize specific neoantigens on patients' pancreatic cells. Previous research has shown that pancreatic cancer survivors had a stronger response to neoantigens from T cells than those who do not survive.

Researchers at Memorial Sloan Kettering Cancer Center (MSKCC) used mRNA technology to target 19 pancreatic cancer surgery patients' own tumor neoantigens. Five had stage 1 disease, eight had stage 2, and six had stage 3 cancer. After removal of tumors, the

researchers shipped samples to BioNTech in Germany, where the company analyzed the genetic makeup of neoantigens.

BioNTech produced personalized vaccines designed to train each patient's immune system to attack the tumors using mRNA. All patients received the immune checkpoint inhibitor atezolizumab before getting the vaccine in nine doses over several months. After the eighth dose, patients also received standard chemotherapy drugs, followed by a ninth dose. Sixteen of 19 patients remained well enough to get at least some of the vaccine doses. In half these patients, the vaccines activated T cells that could recognize the pancreatic cancer specific to the patient.

Using a novel computational strategy, the researchers showed that T cells that recognized the neoantigens were not found in patients' blood before vaccination.

Among eight patients with strong immune responses, half had T cells that targeted more than one vaccine neoantigen.

After 18 months, patients who had strong T cell responses to the vaccine were cancer-free. Among patients whose immune systems didn't respond to the vaccine, the cancer recurred within an average of just over a year. In just one patient with a strong response, T cells produced by the vaccine seem to have eliminated a small tumor that had spread to the liver.

These results suggest that the T cells activated by the vaccines kept the pancreatic cancers in check, researchers noted.

In the paper, the authors say their results must be replicated in larger studies. In October, MSKCC announced a new trial to test the vaccine in 260 patients at nearly 80 sites around the world.



some useful information but would not drive changes in patient care in its current form, he predicted.

Giovannetti said that a potential process for expanding the biomarker score would involve examining other biomarkers, including mutations commonly associated with pancreatic cancer, inflammatory or metabolic markers like LDH or GLUT1, or maybe specific microRNA profiles.

Meanwhile, Goggins own research has found that genetic factors influence the levels of CA19-9 circulating in blood, a finding worth considering when using the biomarker, he said. (Clin Cancer Research 2023; doi: 10.1158/1078-0432.CCR-23-0655.)

“Even if this test catches an early cancer, it is likely lethal,” Allen said. “A better approach would be removing high-risk lesions before they become truly invasive. An ounce of prevention is worth more than a pound of cure here. That applies to pancreatic cancer more than any other disease we currently study.”

For this reason, he and Goggins were intrigued by the AI method. The Nature paper is “proof of principle that machine learning can be applied to medical records and potentially prevent some cancer,” Goggins said.

The AI method identified high-risk patients in need of monitoring, especially those with pre-neoplastic lesions that could advance to cancer, noted Brian Haab, PhD, professor of cell biology at Van Handel Institute Graduate School. A viable AI test could spur lab analysis of pancreatic fluid to determine development of high-risk lesions, he added.

## IMAGING AND BIOMARKERS WILL WORK TOGETHER

Currently, choices for detecting pancreatic seem to keep changing. Immunovia, which in 2021 received Food and Drug Administration (FDA) approval for its IMMray PanCan-d test focused on early detection of pancreatic cancer, has discontinued it. The company plans to focus on developing a next-generation pancreatic cancer detection method intended to work equally well across multiple patient risk groups, including those who do not produce CA19-9. The company says the forthcoming test will be performed on a widely used commercial platform.

Meanwhile, ClearNote Health’s Avantect Pancreatic Cancer Test has FDA Breakthrough Device designation for a method based on 5-hydroxymethylcytosine (5hmC) profiling of cell-free DNA (cfDNA). And Grail’s Galleri test uses next-generation sequencing and machine-learning algorithms to analyze methylation patterns of cfDNA to screen for multiple cancers, including pancreatic cancers.

Randall Brand, MD, professor of medicine at University of Pittsburgh, noted that a 22-gene panel developed at University of Pittsburgh, PancreaSeq, classifies pancreatic cysts as potentially cancerous or benign. Based on mutations in KRAS and GNAS, PancreaSeq diagnosed mucinous cysts accurately in 90% of cases in a recent study (Gastroenterology 2022; doi: 10.1053/j.gastro.2022.09.028).

Brand also pointed to radiomics, which involves an advanced image analysis technique to study a cyst or surrounding pancreatic tissue beyond what

# The Nature paper is proof of principle that machine learning can be applied to medical records and potentially prevent some cancer.

- Michael Goggins

is visible to the human eye. His own study integrates radiomics and genomics to characterize the biology of pancreatic cysts and improve clinical management. The goal is to determine whether a combination of radiomic and genomic biomarkers is superior to each alone for detecting mucinous cysts and advanced neoplasia.

Allen noted that Johns Hopkins University researchers are developing novel imaging techniques that are “more sensitive than what we currently have.” They rely on a suite of algorithms, called FELIX, that recognize pancreatic lesions from CT images without human input.

Lab and imaging tests combined will be key to improving pancreatic cancer treatment, Brand emphasized. “We need better early detection to improve our chance for a cure. It’s not just treatment.”

*Disclosures: Allen serves on the scientific advisory board for the Lustgarten Foundation. Brand has submitted a research proposal to Biologic Dynamics.*

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BY CARLY MAUCIONE, MD, AND NICHOLAS C. SPIES, MD

# Color Me Intrigued: Communicating Results Efficiently and Effectively With Color

Visualizing our data plays a crucial role in how we extract and convey information in laboratory medicine.

**P**ie charts? Three-dimensional graphics? Misleading axis choices? We often hear all about what not to do when visualizing our data. But what makes a good visualization good? In his classic volume, *The Visual Display of Quantitative Information*, statistician Edward R. Tufte quips that graphical excellence means “that which gives to the viewer the greatest number of ideas in the

shortest time with the least ink in the smallest space.”

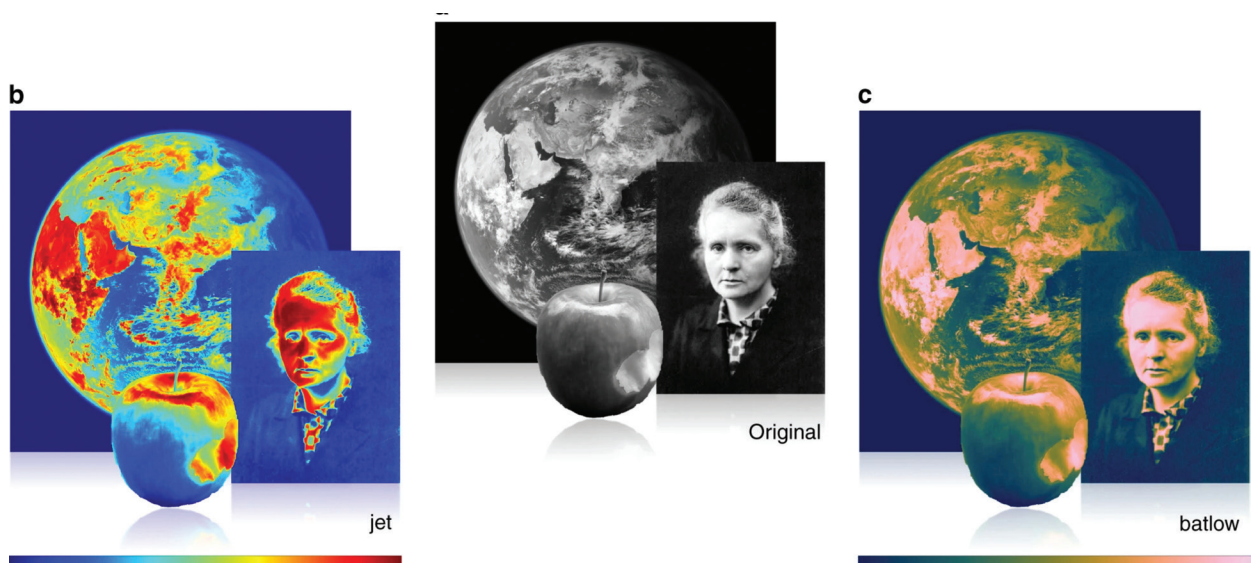
As laboratorians, communicating our findings is an integral part of our jobs. Doing so effectively means getting the most out of the budget of time and attention your reader has allocated to you. In this article, we will provide a brief overview of the tips and tricks behind some key principles in graphic design applied to laboratory medicine, with the

goal of equipping you with the tools you need to create more effective figures and visualizations.

## The Science of Design

In its essence, effective visualization catalyzes the process of turning data into information — and information into knowledge. To achieve this, we first must take a foray into the science of perception to uncover how we encode visual information.

**Figure 1.** How the rainbow color map can distort an image.



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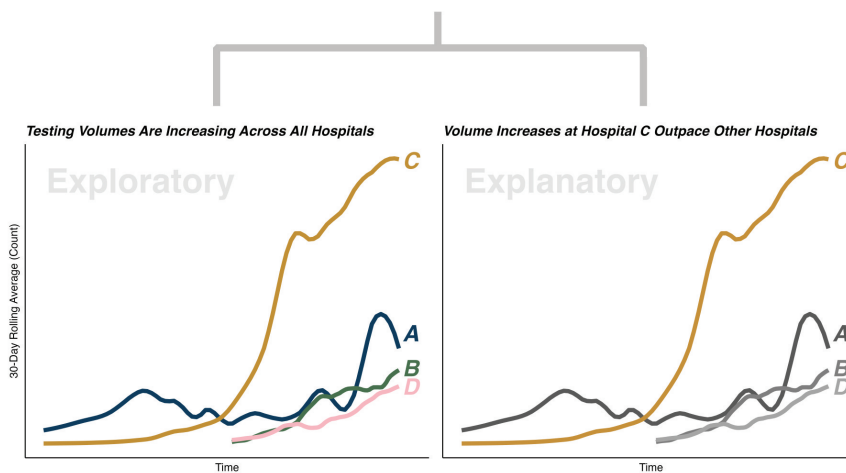
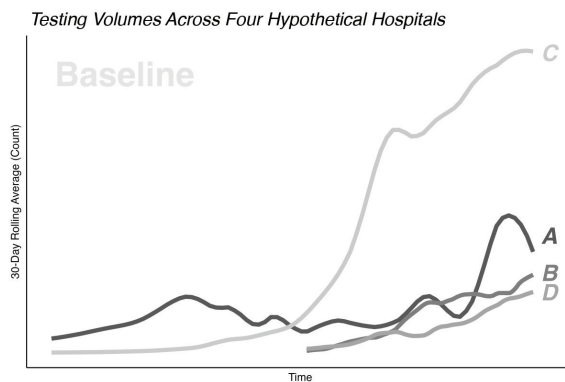
These concepts extend beyond the basic needs of adequate contrast between colored figures, or fonts large enough for deciphering from a distance. Though striving for visually pleasing color palettes and formats are also desirable elements of a presentation, a pleasing display does not always yield the most efficient results. In other words, there is a “right” and “wrong” way to display data.

### Representing Numbers as Colors With Color Maps

Color as a representation of measurement is one of the most common ways to represent a measurement. When using color, besides the oft-overlooked element of ensuring that those with color vision deficiencies (CVD) can still glean insights from our visualizations, it is also our responsibility to convey data in ways that are both efficient and free of manipulation. This requires careful consideration of how the numerical inputs in our data are being represented as colors through a color map. Figure 1 highlights just how important the selection of a color map can be (1).

Unfortunately, the most recognizable color map, called rainbow (or jet, as in the figure), distorts the underlying image because of its sharp demarcations at the transitions between blues, yellows, and reds. More scientifically, the rainbow color map is not perceptually uniform: The variation in shade and lightness is not weighted equally in our eyes, leading to distortions in the representation of our data (1).

**Figure 2. An example of start with gray, then add color.**



Beyond the aesthetic aspects of proper color map selection, there are also efficiency and effectiveness considerations. Borkin and colleagues have demonstrated the danger of the rainbow in their work evaluating color maps used for identifying vulnerable regions on angiogram visualizations in patients with coronary artery disease (2). Their results showed more errors and longer read times for the rainbow color map when compared to a more appropriate, diverging color map (2).

Fortunately for us, the same authors that highlighted the

shortcomings of the rainbow color map in Figure 1 have provided a solution. Fabio Crameri’s scientifically derived color maps ([www.fabiocrameri.ch/colourmaps](http://www.fabiocrameri.ch/colourmaps)), which are known as batlow, present data in a perceptually uniform, CVD-accessible, reproducible, and even citable manner (3). Crameri also has made it remarkably simple to start using these color maps in your own work with a straightforward user guide ([www.fabiocrameri.ch/colourmaps-userguide](http://www.fabiocrameri.ch/colourmaps-userguide)) and masterclasses through Undertone Design ([www.undertone.design](http://www.undertone.design)).

## Following the strategies outlined in this article can help you streamline the process from raw data to actionable insights, ensuring that your visualizations not only capture attention but also convey your message with clarity and precision.

### Practical Advice to Improve Your Visualizations

So, with these principles now in mind, what practical advice can we offer now that you are ready to display your data? We propose a series of four steps to get the most out of your figure-making:

1. Think about the story you're trying to tell.
2. Plot the data in gray.
3. Add color intentionally to highlight key story elements.
4. Solicit feedback often.

### Think About the Story of Your Data

First, think about the story you need your figure to convey. Are you trying to explain a key finding, or help readers explore the data on their own?

Explanatory figures should provide only the data that is necessary and sufficient to support a conclusion, such as plotting medians or distributions, while exploratory figures ought to present as much of the data as feasible for the given medium.

Explanatory figures often are best for time-bound, goal-oriented presentations to multiple audience members in person, such as lectures, quality improvement meetings, and proposals. In contrast, when readers can devote as much — or as little — time as they would like to extract information from a figure, an exploratory figure can be much more powerful. Appropriate settings may include research articles, quality assurance reports, and dashboards.

### Start With Gray, Then Add Color

Next, besides the key points to be gleaned from the data, what is it that you want your audience to notice first? Usually, there is an order in which it makes the most sense to understand a figure. We can augment that perception by using the idea of starting with gray. Figure 2 represents a hypothetical healthcare system with four hospitals, A–D, each with their own laboratories. You have been tasked with presenting data about testing volumes to a set of hospital stakeholders and business leaders. Your color choices can have a clear impact on the first, and lasting, impression that your audience takes from the data being shown.

By first plotting all the data in gray, you must make intentional color choices to highlight key points. Figure 2 shows two possible options that depend entirely on the story you aim to tell. Bottom left displays the more exploratory color choices, where each hospital is represented as its own discrete color within the batlow color map. This figure underscores the point that testing volumes across all four hospitals are increasing.

However, if you instead wanted to highlight hospital C's outlier status, perhaps in a pitch to fund more technologist positions, you could keep the other hospitals gray, while highlighting only hospital C in color (bottom right).

### Solicit Feedback

Finally, solicit feedback often:

can viewers interpret your data quickly, without extra prompting or explanation from you? Do they recognize the most important points you are attempting to highlight? If not, adjust and repeat. Making intentional design and color choices can help to get the most out of your readers' attention, resulting in quick and accurate data interpretation.

Following the strategies outlined in this article can help you streamline the process from raw data to actionable insights, ensuring that your visualizations not only capture attention but also convey your message with clarity and precision. With the right tools and approach, you can elevate the impact your visualizations have on your audience, and we look forward to seeing how they enhance your next project.

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### References

1. Crameri F, Shephard GE, and Heron PJ. The misuse of colour in science communication. *Nat Commun* 2020; doi: 10.1038/s41467-020-19160-7.
2. Borkin MA, Gajos KZ, Peters A, et al. Evaluation of artery visualizations for heart disease diagnosis. *IEEE Trans Vis Comput Graph* 2011; doi: 10.1109/TVCG.2011.192.
3. Crameri F. Scientific colour maps 8.0. <https://www.fabiocrameri.ch/colour-maps> (Accessed November 2023).

# ADLM 2024

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### CALL FOR POSTER ABSTRACTS

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BY RYAN S. NELSON, PHARM.D, GWENDOLYN A. MCMILLIN, PH.D, DABCC (CC,TC), FADLC, AND ERIK R. FORSMAN, BS CH.E

## Leveraging Blockchain to Catalyze Consensus in Precision Medicine Through Meta-Analysis

In pharmacogenetics and other areas, a new tool promises to resolve the logjam in evidence analysis and stakeholder agreement to speed advances in patient care.

**A**chieving scientific consensus has been a challenging and contentious task since the dawn of the Scientific Revolution. Even as scientists have built up the body of experimental evidence, humans still have struggled to agree about what it means and what we should (or shouldn't) do about it. Especially in the current era, stakeholders in industry, government, philanthropy, and science all have varying motives driving their scientific pursuits. These biases make it more difficult to agree on the policies and practices current evidence supports — and about which areas to investigate next. This crisis of consensus can compromise any evidence-based endeavor in medicine, including clinical and laboratory stewardship.

This problem underscores the need all stakeholder groups have for an open-access, decentralized data repository that thoroughly abstracts data from published evidence, enables streamlined peer review and voting on

inclusion/exclusion in meta-analyses, displays aggregate results, and highlights differences in interpretation of the data among stakeholders.

Now, a group of volunteer clinicians, data scientists, students, and web developers are working to develop MetaCensus: the first open-access data repository built to host data to be peer-reviewed and meta-analyzed to catalyze consensus in science.

### The Case of DPYD Genotype-Guided Chemotherapy

The serious consequences of a lack of agreement about scientific evidence was visible in the controversy over the use of DPYD genotype-guided chemotherapy for cancer patients. Fluoropyrimidines are a widely utilized chemotherapeutic in cancer care with well-known toxicity risks. Carriers of pathogenic DPYD gene variants treated with fluoropyrimidines are reported to have a 25.6 times greater risk of

treatment-related death than patients with non-pathogenic DPYD variants (1).

In North America, routine preemptive DPYD genotyping is not currently considered standard of care. For example, pretreatment DPYD testing is not promoted by the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), or U.S. Food and Drug Administration (FDA). Meanwhile, the European Medicines Agency (EMA), the French National Agency for the Safety of Medicines and Health Products, and the Medicines and Healthcare Products Regulatory Agency (United Kingdom) recommend preemptive DPYD/DPD testing for patients treated with fluoropyrimidines (2–4).

Such international discord on what actions might be considered appropriate for DPYD testing in routine patient care decisions compounds the problem in the U.S. Patient harm from fluoropyrimidine use without DPYD testing has led to lawsuits, including one against Oregon Health and Science University (OHSU), which paid a \$1 million settlement to the widow of a patient with DPD deficiency fatally affected by fluoropyrimidine toxicity. OHSU also agreed to hold seminars to educate clinicians on the risks associated with DPD deficiency, how to identify and treat

**Especially in the current era, stakeholders in industry, government, philanthropy, and science all have varying motives driving their scientific pursuits.**

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severe fluoropyrimidine toxicity, and, where appropriate, how to order DPYD testing (5,6).

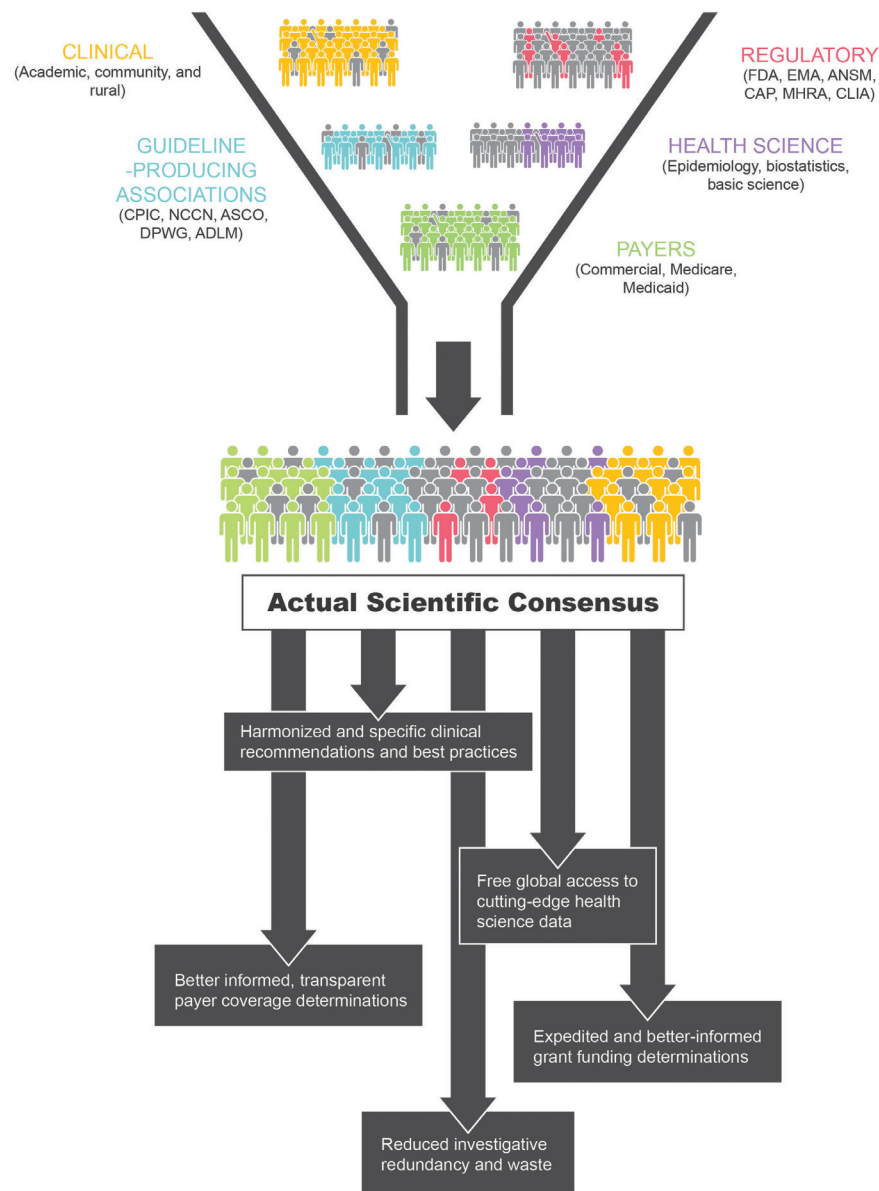
In August 2022, Dana-Farber Cancer Institute — a National Cancer Institute (NCI) - designated cancer center, the highest federal rating a cancer center can achieve — began encouraging routine DPYD testing, even though practice guideline-producing entities like the NCCN (which controls NCI-cancer center designation) and the FDA state there isn't adequate evidence to recommend pretreatment screening (7). Moffitt Cancer Center, Levine Cancer Institute, University of Chicago, Dartmouth, Cleveland Clinic, Yale, and University of Michigan have also implemented DPYD testing.

Many factors contribute to the discord on whether to implement DPYD testing. Still, one central issue is the absence of a shared data resource where all individual stakeholder groups (regulatory bodies, and basic scientists, clinicians, insurers, guideline-producing associations) provide their input on the current strengths, limitations, and conclusions drawn from available data. This limits the ability of each individual stakeholder group to compare other's data and practices to their own. Such comparisons are essential for deliberation and an attempt at consensus to be catalyzed through meta-analysis and multicriteria decision analysis (MCDA) (8).

### How The MetaCensus Network Can Help

MetaCensus is built on a distributed ledger that employs blockchain technology to render data

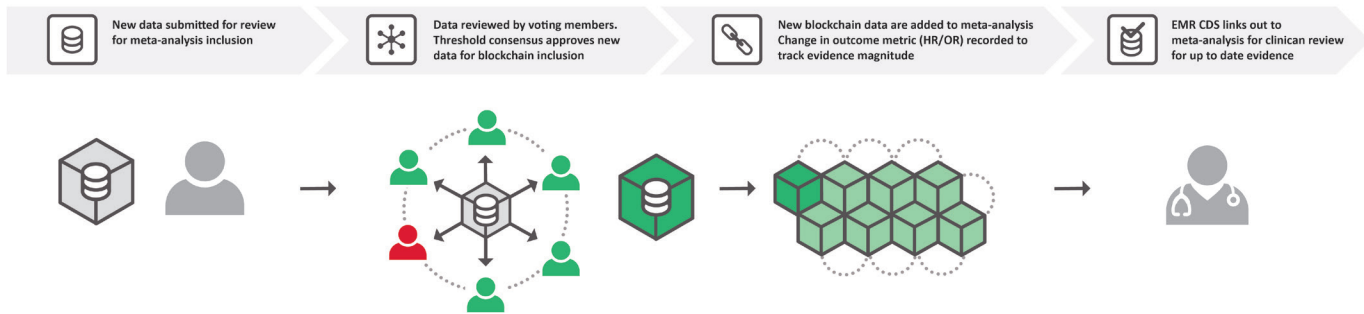
**Figure 1. Various stakeholders involved with consensus in precision medicine assisted by MetaCensus**



*The stakeholders all have access to the same data (for the most part) and aim to take as objective an approach as possible, but all come with biases inherent in their specialties. The different silos each stakeholder group resides in fail to effectively and efficiently collaborate or exchange critical analyses of the data with the other silos, thus hindering scientific progress and consensus. MetaCensus is built to support the exchange of data review and meta-analysis by varying entities, and to perform multicriteria decision analysis (MCDA) to analyze and account for varying perspectives, counterpoints, and biases (8). Abbreviations: U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), Clinical Pharmacogenetics Implementation Consortium (CPIC), National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO), French National Agency for the Safety of Medicines and Health Products (ANSM), Dutch Pharmacogenetics Working Group (DPWG), College of American Pathologists (CAP), Clinical Laboratory Improvement Amendments (CLIA), Medicines and Healthcare Products Regulatory Agency (MHRA) (United Kingdom)*



**Figure 2. Introducing the MetaCensus Network**



*MetaCensus is an open-access meta-analysis (MA) voting tool and decentralized database that stores the results of MAs. Voting members who are vetted for relevant credentials to participate in particular MA topics will execute peer review for individual papers and meta-analyze them. They will also create and execute PRISMA protocols for an MA. No single voter will hold greater ownership of or influence on MAs than any other voting member. Non-voting members are anyone who wishes to review the results of any MA on the network (that will be open access online, globally). Web applications will be able to interface with the network to develop webpages, dashboards, clinical decision support tool links, educational content, and other resources.*

open and free for the public to review. It also structures a peer review voting mechanism that encourages voters to critically analyze the data, provide feedback, and vote on its inclusion in meta-analyses hosted on the blockchain. Any interested party can build web applications that provide free access to the data they use from MetaCensus. This can help solve the challenges society faces with most scientific journals not offering open-access publishing (9).

A blockchain network based on the Ethereum platform has been created using the Proof of Authority consensus method, which removes the cryptocurrency component inherent in blockchains and ensures that only credentialed and vetted actors that are a part of the MetaCensus network can

contribute to the security and stability of the network.

Blockchain networks store the state of the network at a defined frequency, and those states are “mined” (verified) as a “block” which gets added to its canonical history. Smart contracts are immutable code that live on the network and drive the network’s purpose.

For MetaCensus, there are eight smart contracts with functions and data types that store and run the logic to maintain scientific consensus for any scientific discipline, or community, which chooses to store their standard of consensus on the network. These functions cannot be changed, only interacted with, and are used to ensure standardized logic to reach the goals, rules, and consensus needed. Additionally, the data structures built into the smart contracts store

the data abstracted from results in peer-reviewed publications, maintaining an up-to-date consensus.

All of this is driven by the community of members that are a part of a scientific discipline. Voting members of the community take part in peer review and voting for or against pending data being included in any meta-analysis. Nonvoting members can only access the data and voting results.

Pending data items include: approving a paper to be part of the standard consensus model or not, changing the way the consensus model is calculated, adding and removing members and voters, or changing the threshold consensus percent to pass a pending data item.

Inherently, the data and code in blockchain networks are available for anyone to view and use. However, in an effort to simplify and streamline access, a website is being created for users to easily interact with the network without knowing coding software required for blockchain interaction.

The smart contract structure enables the community to review

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**Voting members of the community take part in peer review and voting for or against pending data being included in any meta-analysis.**



how any member has voted longitudinally. This structure also allows the community to track how a member's votes compare with other members within their same stakeholder group's expertise versus those of others and perform MCDA on the results. Comparisons could include clinicians, biostatisticians, payers, regulators, or a guideline-producing association.

The indelible ledger inherent with blockchain ensures that a record of prior voting histories (collective and individual) is available for review and analysis as the landscape of available evidence changes. As individual papers amass peer reviews, this may hold the potential to generate a new publication score that is more informative than a journal's impact factor, number of citations, or other measures of significance.

## Conclusion

MetaCensus aims to catalyze consensus by providing an open-access repository to scientific information that is peer-reviewed by credentialed volunteer subject matter expert communities. Importantly, it makes this data free and accessible to all, empowering anyone who wishes to investigate and learn.

As consensus is cultivated, we hope that a better understanding of factions raised by various stakeholder domains will inform the community on what next steps in research should be prioritized in grant funding. We also believe it will enable guideline-producing groups to leverage data to develop their recommendations, improve how insurers efficiently review data to weigh coverage decisions, and enable clinical groups to use

the data for web applications in clinical decision support.

The MetaCensus team eagerly welcomes all feedback, considerations, and volunteer contributions of data or effort that advances our mission.

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## References

1. Sharma BB, Rai K, Blunt H, et al. Pathogenic DPYD variants and treatment-related mortality in patients receiving fluoropyrimidine chemotherapy: A systematic review and meta-analysis. *Oncologist* 2021; doi: 10.1002/onco.13967
2. NHS England. Pharmacogenomic testing for DPYD polymorphisms with fluoropyrimidine therapies. <https://www.england.nhs.uk/publication/clinical-commissioning-urgent-policy-statement-pharmacogenomic-testing-for-dpyd-polymorphisms-with-fluoropyrimidine-therapies/> (Accessed November 2023).
3. U.K. Chemotherapy Board. Personalised medicine approach for fluoropyrimidine-based therapies. <https://www.theacp.org.uk/userfiles/file/resources/dpd-testing-ukcb-july-2020-updated.pdf> (Accessed November 2023).
4. European Medicines Agency. Fluorouracil and fluorouracil related substances (capecitabine, tegafur, and flucytosine) containing medicinal products. <https://www.ema.europa.eu/en/medicines/human/referrals/fluorouracil-fluorouracil-related-substances-capecitabine-tegafur-flucytosine-containing-medicinal> (Accessed November 2023).
5. The Oregonian. OHSU to pay \$1 million, promises change to settle lawsuit from widow of cancer patient. <https://www.oregonlive.com/health/2022/05/ohsu-to-pay-1-million-promises-change-to-settle-lawsuit-from-widow-of-cancer-patient.html> (Accessed November 2023).
6. The Oregonian. OHSU chemotherapy killed cancer patient, suit claims. <https://www.oregonlive.com/news/2019/12/ohsu-chemotherapy-killed-cancer-patient-suit-claims.html> (Accessed November 2023).
7. Precision Medicine Online. Cancer centers nudge oncologists toward DPYD testing as PGx supporters push for guidelines change. <https://www.precisionmedicineonline.com/regulatory-news-fda-approvals/cancer-centers-nudge-oncologists-toward-dpyd-testing-pgx-supporters> (Accessed November 2023).
8. Gongora-Salazar P, Rocks S, Fahr P, et al. The use of multicriteria decision analysis to support decision making in healthcare: An updated systematic literature review. *Value Health* 2023; doi: 10.1016/j.jval.2022.11.007
9. The Guardian. Is the staggeringly profitable business of scientific publishing bad for science? <https://www.theguardian.com/science/2017/jun/27/profitable-business-scientific-publishing-bad-for-science> (Accessed November 2023).

# Regulatory Roundup



## Hereditary Cancers Panel Receives FDA Authorization

The Food and Drug Administration (FDA) has granted de novo marketing authorization to the Invitae Common Hereditary Cancers panel, an in vitro diagnostic test that detects hundreds of genetic variants associated with an elevated risk of developing certain cancers.

The test — the first of its kind to be granted FDA authorization — also identifies potentially oncogenic hereditary variants in 47 genes in individuals diagnosed with cancer. The FDA reviewed the test under its de novo premarket review pathway for new types of low- to moderate-risk devices.

The test covers clinically significant genes including the breast and ovarian cancer-associated *BRCA1* and *BRCA2*; Lynch syndrome-associated *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*; hereditary diffuse gastric and lobular breast cancer-associated *CDH1*; and Peutz-Jeghers Syndrome-associated *STK11*.

Invitae bases clinical interpretation of variants on evidence from published literature, public databases, prediction programs, and the company's internal curated variants database using its variant interpretation criteria, which is consistent with those established by appropriate professional organizations or accredited boards.

Along with this de novo authorization, the FDA also is establishing special controls that define requirements related to labeling and performance testing. These new requirements pertain to accuracy for reporting of substitutions, insertions and deletions, and copy number variants. These controls and requirements create a new regulatory classification, meaning subsequent devices of the same type as Invitae's panel with the same intended use may go through the FDA's 510(k) premarket process.

### ● ADENO-ASSOCIATED VIRUS TEST GETS FDA BREAKTHROUGH DESIGNATION

Quest Diagnostics has received Breakthrough Device Designation from the Food and Drug Administration for its AAVrh74 ELISA assay.

The enzyme-linked immunosorbent in vitro diagnostic assay is intended for the semiquantitative detection in human serum of IgG antibodies to the capsid of the adeno-associated virus (AAV) vector AAVrh74. The test is in-

tended to be used in conjunction with other available clinical information to help identify patients eligible for treatment with Elevidys (delandistrogene moxeparvec-rokl), a gene therapy developed by Sarepta Therapeutics for certain individuals with Duchenne muscular dystrophy.

Additionally, Quest and Sarepta announced an expanded collaboration under which Quest will develop companion or complementary diagnostics in connection with Sarepta's portfolio of investigational and on-market gene therapies.

The collaboration may encompass screening assays for antibodies to Sarepta's other AAV vector-based gene therapies for muscular dystrophies, including Duchenne muscular dystrophy and limb girdle muscular dystrophies.

### ● FDA APPROVES FOUNDATIONONE COMPANION DIAGNOSTICS FOR NEW INDICATIONS

The Food and Drug Administration (FDA) has approved FoundationOne CDx and

FoundationOne Liquid CDx as companion diagnostics for Braftovi (encorafenib) in combination with Mektovi (binimetinib) for the treatment of adult patients with metastatic non-small cell lung cancer with a *BRAF V600E* mutation.

The company also announced FDA approval for its FoundationOne CDx test as a companion diagnostic for Retevmo (selpercatinib). This drug is approved by the agency for the treatment of adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion who have either had prior systemic treatment, have no satisfactory alternative treatment options, or whose tumors have progressed on.

Using a tissue sample, FoundationOne CDx analyzes more than 300 cancer-related genes in a tumor. The test has more than 30 companion diagnostic indications. Using a blood sample, FoundationOne Liquid CDx analyzes more than 300 cancer-related genes and has several companion diagnostic indications.

#### ● NEW YORK STATE APPROVES UTI TEST

Pathnostics has earned approval from the New York State Department of Health (NYSDOH) for its urinary tract infection (UTI) test, Guidance UTI. The approval broadens patient access to the test, which enables rapid diagnosis and treatment of complicated, recurrent, and persistent UTIs.

According to Pathnostics, the test is the only NYSDOH-approved UTI test that uses molecular technology

## The test – the first of its kind to be granted FDA authorization – also identifies potentially oncogenic hereditary variants in 47 genes in individuals diagnosed with cancer.

to identify organisms and resistance genes combined with pooled antibiotic susceptibility results. It delivers results less than a day after samples are received, compared with standard urine culture testing, which can take up to 5 days to produce results. The company added that its test has higher diagnostic specificity and sensitivity than standard testing and can identify specific uropathogens even when multiple organisms are present. Multiple studies show the test significantly reduces patient hospitalizations, emergency and urgent care visits, and empiric therapy rates.

#### ● RAS MUTATION KIT APPROVED AS COMPANION DIAGNOSTIC FOR VECTIBIX

The Food and Drug Administration has granted premarket approval to EntroGen's CRCdx RAS Mutation Detection kit as a companion diagnostic for Vectibix (panitumumab), a targeted therapy used in the treatment of colorectal cancer.

According to the company, CRCdx is the first real-time PCR-based test approved in the U.S. that fully meets the biomarker identification requirement for Vectibix.

The kit detects *KRAS* and *NRAS* exon 2, 3, and 4 mutations

with high sensitivity and specificity in colorectal cancer patients. This enables clinicians to identify patients most likely to benefit from Vectibix therapy and avoid unnecessary side effects and costs from treatment.

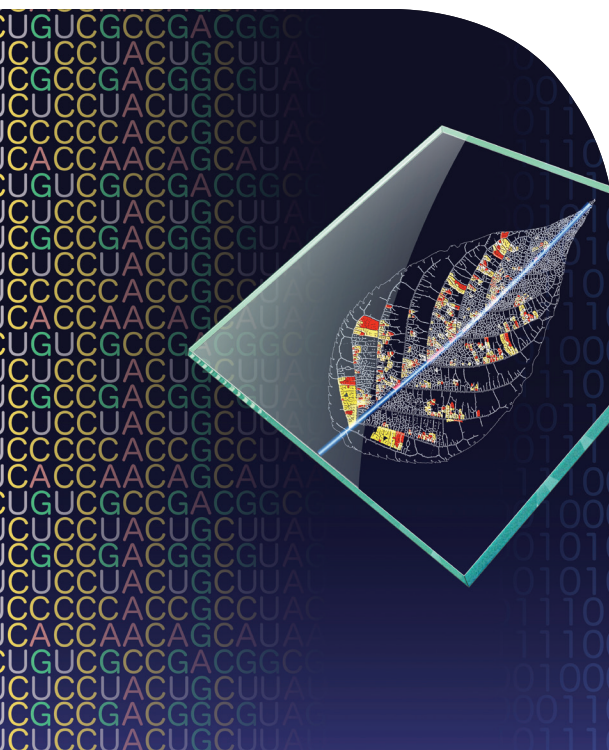
Company officials added that they hope the test will improve small and mid-size laboratories' access to *RAS* testing by simplifying the process and lowering costs.

#### ● LUNG CANCER MUTATIONAL BURDEN TEST GETS CHINESE APPROVAL

Geneseeq Technology has announced that its Non-Small Cell Lung Cancer (NSCLC) Tumor Mutational Burden (TMB) test kit has gained approval from the Chinese National Medical Products Administration (NMPA) as a breakthrough medical device.

NMPA's approval allows use of the kit for qualitative detection of TMB in formalin-fixed paraffin-embedded tissue samples from patients with EGFR/ALK-negative non-squamous NSCLC. The test covers 425 cancer-associated genes.

Company officials said the approval will "benefit the clinical implementation of immunotherapy in China with a standardized TMB assessment assay."



## Partnership Aims to Build AI Platform for Biological Engineering and Biosecurity

Ginkgo Bioworks and Google Cloud recently announced a 5-year strategic partnership to enable Ginkgo to develop and deploy artificial intelligence (AI) tools for biology and biosecurity.

Under the partnership, Ginkgo will work to develop new large language models that run on Google Cloud's Vertex AI platform across genomics, protein function, and synthetic biology. These models and the platform will help Ginkgo's customers in fields as diverse as drug discovery, agriculture, industrial manufacturing, and biosecurity, the companies said.

Ginkgo intends to make Google Cloud its primary cloud services provider to increase its next-generation cloud computing resources. Google Cloud will provide funding to help Ginkgo achieve certain milestones over the next 3 years.

The companies anticipate that their collaboration will result in new Ginkgo offerings and initiatives. In addition to including large language models, the companies envision developing new advanced infrastructure, generative AI enterprise search, development of improved central data repositories, and public data aggregation and exchange.

### ● VELA DIAGNOSTICS AND SRL COLLABORATE ON PRODUCT DISTRIBUTION IN JAPAN

Vela Diagnostics has established a collaboration with the Japanese healthcare services company SRL to facilitate the distribution of Vela Diagnostics' molecular diagnostic solutions in Japan.

Vela Diagnostics aims to capitalize on SRL's comprehensive distribution network and market understanding, enabling the company to introduce its Sentosa SQ HIV-1 Genotyping Assay Kit to Japanese healthcare and diagnostic institutions.

SRL officials said that their company has begun feasibility studies for the Sentosa SQ HIV-1 Genotyping Assay Kit. The Sentosa SQ HIV-1 Genotyping Assay is Vela's solution for automated next-generation sequencing (NGS)

of HIV-1, which received Food and Drug Administration de novo designation in 2019, the officials said. They added that the assay has relatively low hands-on and turnaround time, offers sensitivity to mutations in three key drug targets, and provides critical insights into the virus's drug resistance profile.

Vela Diagnostics officials said that SRL's extensive network and expertise would augment their company's ability to deliver innovative products to patients and healthcare providers in Japan.

### ● DEAL AIMS TO ADVANCE CLINICAL AND BIOLOGICAL INSIGHT FROM NGS DATA

United Kingdom-based OGT recently announced a new partnership with Intelliseq to provide customers with a thorough and comprehensive

next-generation sequencing (NGS) workflow.

The partnership will enhance lab productivity by automating the interpretation of NGS data and delivering actionable insights about cancer, OGT officials said.

In addition, Intelliseq's biological and clinical interpretation will allow its SureSeq users to examine any genomic content they want while receiving insight from a wide variety of clinical and biological databases.

Intelliseq officials said that partnering with OGT is an opportunity for their company to expand the reach of its advanced NGS reporting solutions.

### ● PARTNERSHIP TARGETS SYNDROMIC DISEASES AND DRUG-RESISTANT PATHOGENS

A partnership between Seegene and Springer Nature is intended

to better diagnose syndromic and infectious diseases, as well as detect drug-resistant pathogens, Seegene announced recently.

Seegene said that its “Open Innovation Program” is part of its Seegene OneSystem business, which develops diagnostic products and early diagnosis methods in all fields, including cancer and infectious diseases. To achieve this goal, the Seegene OneSystem business will share Seegene’s technology and expertise.

The inaugural Open Innovation Program consists of 15 projects to develop 15 syndromic quantitative PCR (qPCR) diagnostics assay reagents across infectious and vector-borne diseases and for detection of drug-resistant pathogens. The 15 projects encompass categories including urinary tract infection, dermatophytes, sexually transmitted infection, vaginitis screening, respiratory panel, nontuberculous mycobacteria typing, tick-borne disease, tropical fever virus, methicillin-resistant *Staphylococcus aureus*, and multidrug-resistant organisms.

A PCR molecular diagnostics company typically can develop only a few syndromic assays annually. However, with the Open Innovation Program, Seegene aims to significantly increase the number of assays that can be developed to hundreds and thousands a year, Seegene said.

The program has already sought applications for research grants. Awardees, which Seegene plans to announce in March 2024, will get research grants of up to \$600,000 per project, plus Seegene’s syndromic qPCR reagents, extraction reagents, consumables, education on clinical study methods, instruments,

## A PCR molecular diagnostics company typically can develop only a few syndromic assays annually. With the Open Innovation Program, Seegene aims to increase that number to hundreds and thousands a year.

and software for automated experimentation at no cost to use and perform preclinical and clinical studies for defined target pathogens during the study period.

Seegene officials said that their company will initially lead the Open Innovation Program’s product design, product development planning, and feasibility studies without clinical specimens so the awardees can focus on conducting preclinical and clinical studies with clinical specimens. “In the next phase, awardees will utilize the Seegene Digitalized Development System to conduct the entire development program from product designs to clinical validations.”

Springer Nature officials urged scientists from different fields to collaborate with Seegene in the development of PCR assays that can have a real impact on global health.

### ● BIOFIRE DEFENSE SECURES \$18.8M U.S. DEFENSE CONTRACT FOR INFECTIOUS DISEASE TESTING

The U.S. Department of Defense (DoD) recently awarded BioMérieux subsidiary BioFire Defense an \$18,815,630 order-dependent contract for maintenance and support of the DoD’s Next Generation Diagnostic System.

Under the contract, BioFire Defense will provide support for a military-use version of the firm’s multiplex PCR instrument for infectious disease testing through January 31, 2029. Work locations

and funding will be determined with each order, according to DoD.

Genome Web has reported that the company is also providing the Department of Defense custom BioFire FilmArray test panels developed under the Next Generation Diagnostic System (NGDS) program.

The newly awarded contract comes 10 years after the DoD awarded BioFire Defense’s parent company and two other companies \$23.1 million to develop the NGDS platform, according to Genome Web.

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## Switching From Serum to Heparinized Plasma for Troponin Testing

### What are acceptable specimen matrices for troponin testing?

**A:** Serum and/or plasma are appropriate for contemporary and high-sensitivity cardiac troponin (hs-cTn) T and I assays. However, variation in analytical performance between sample types precludes the interchangeable use of serum and plasma in the clinical management of a patient. This is especially true for hs-cTn assays, with certain vendors reporting different 99th percentile upper reference limits based on sample type. The International Federation of Clinical Chemistry and Laboratory Medicine provides a comprehensive summary of acceptable collection containers and sample types for contemporary and hs-cTn assays.

A review of test menus from clinical labs across the United States shows that most labs are using lithium heparin plasma for hs-cTn T and I assays.

### What are the benefits of using plasma versus serum?

Plasma offers several advantages over serum. Plasma specimens can improve turnaround times from time of collection to time of result upload to a patient's medical record since they can be immediately processed and tested expeditiously upon receipt. This is because collection of anticoagulated blood eliminates the 30-60 minutes required for clot formation for isolation of serum. Rapid turnaround times for troponin assays are key for effective and efficient assessment, management, and triage of patients with acute chest pain in the emergency department or critical care settings.

Clotting time in serum may be prolonged in patients on anticoagulation therapy, leading to delayed clotting

and downstream analytical issues. Additionally, incomplete clot formation may occur in serum, resulting in the presence of microclots, which can obstruct analytical probes used in automated testing platforms.

### What do labs need to consider when switching to plasma-based troponin testing?

There are several operational and clinical considerations when changing from serum to plasma for troponin assays. Changing sample type or introducing a new collection tube for troponin, such as a lithium heparin gel separator tube, can alter preanalytical workflows and laboratory practice. Laboratory workflows developed for troponin testing using plasma may also differ from those previously used for serum and from pre-existing workflows for analytes already measured in plasma, including blood gases, ammonia, and hemoglobin A1c.

Laboratory personnel will need to discuss automated versus manual processing, hand delivery versus automated routing, and aliquot versus primary container analysis to determine the most efficient sample workflow within the laboratory. Laboratories with automation capabilities may opt for an automated workflow, but this may result in longer turnaround times compared to a manual approach, depending on the instrument configuration and specimen volume. A manual approach, on the other hand, requires effective communication between the preanalytical and analytical areas and sufficient staffing to ensure proper handling and transport of specimens. When deciding between these two options, the laboratory should perform internal laboratory



**Kyana Garza, PhD, DABCC**

timing studies to develop streamlined workflows that expedite result reporting. Staffing, lab automation, specimen volume, turnaround time, and patient care goals should all be considered and ultimately guide these decisions.

In general, individual labs within a large health system with standardized processes, documents, and test menus will need to consult with stakeholders from other sites prior to changing the specimen type. Lack of harmonization for troponin is not uncommon across a healthcare system, but labs should aim for standardization of assay and sample type to mitigate interpretive challenges and maintain continuity of care. These considerations are particularly important if patients are transferred or seen at multiple clinics or locations within a healthcare system.

Lastly, with the expected turnaround time improvements, quality assurance practices should include monitoring the troponin turnaround time before and after switching sample types. As more hospitals implement the European Society of Cardiology algorithms, labs measuring troponin in serum should strongly consider using plasma to achieve the turnaround times necessary for rapid rule in or rule out of myocardial infarction.

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# Plasma Volume: One of the Most Important Critical Care Assays

## Recent Published Studies Highlight Clinical Importance

1. Calculated Plasma Volume Status is Associated with Poor Outcomes in Acute Ischemic Stroke Treated with Endovascular Treatment. *Frontiers in Neurology* 2023
2. Estimated Plasma Volume Status in COVID-19 Patients and Its Relation to Comorbidities and Clinical Outcomes. *J Thromb Thrombolysis* 2023
3. Prognostic Value of Estimated Plasma Volume Status in Patients with Sepsis. *J Korea Med Sci* 2022
4. Estimated Plasma Volume Status (ePVS) is a Predictor for Acute Myocardial Infarction In-Hospital Mortality: Analysis Based On MIMC-III Database. *BMC Cardiovasc Discord* 2021
5. Calculated Plasma Volume Status is Associated with Mortality in Acute Respiratory Distress Syndrome. *Crit Care Explorations* 2021
6. Prognostic Value of Estimated Plasma Volume in Patients with Chronic Systolic Heart Failure. *J Investig Med* 2021
7. Estimated Plasma Volume Status (ePVS) Could Be an Easy-To-Use Clinical Tool to Determine the Risk of or Death in Patients With Fever. *J Of Crit Care* 2020
8. Prognostic Value of Estimated Plasma Volume in Acute Heart Failure in Three Cohort Studies. *Clinical Research In Cardiology* 2019

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Request a summary of recent clinical studies of the importance of estimated plasma volume assessment in critical illness

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\*Balasubramanian P et al. Association of plasma volume outcomes in hospitalized patients COVID-19 ARDS patients: a retrospective multicenter observational study." *Journal of Critical Care*, August, 2023.

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