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New Trends, Applications, and IVD Industry Analysis

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## Diagnostics Lagging for Tickborne Infections

The incidence of tickborne infections is on the rise in the United States. Yet, prevention and management of these infections are hampered by inadequate diagnostics, according to a perspective published in the Aug. 23 issue of the *New England Journal of Medicine* by the leadership at the National Institute of Allergy and Infectious Diseases.

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## Rapid Molecular Testing Saves Hospitals Time, Money Ruling Out TB

Molecular testing facilitates faster discontinuation of respiratory isolation for individuals undergoing evaluation for active tuberculosis (TB) in U.S. hospitals, according to a study published Aug. 27 in *JAMA Internal Medicine*. Incorporation of sputum molecular testing is not only safe and feasible in real-world clinical care, but it yields substantial patient, clinical, and economic benefits.

"These measures of impact place rapid molecular testing for TB among a select group of interventions that have been shown to advance the 'quadruple aim': improved population health, a better patient experience, a better clinician experience, and lower costs," write the authors led by Lelia Chaisson, from Johns Hopkins University in Baltimore, Md.

Infection control measures are intended to prevent in-hospital transmission of TB, but can lead to prolonged stays in isolation rooms due to the time it takes to run conventional rapid diagnostic testing for TB, with serial sputum collection for microscopic examination taking two or more days. Despite this considerable burden on patients, clinicians, and hospitals, and national recommendations, molecular testing has not been widely adopted as a replacement to sputum-smear microscopy to guide discontinuation of respiratory isolation.

The current study evaluated implementation of rapid, molecular testing at Zuckerberg San Francisco General Hospital and Trauma Center. Prior to the 2015 introduction of molecular testing, the hospitals TB

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## Diagnostics Lagging for Tickborne Infections, *from page 1*

The number of reported cases of tickborne disease has more than doubled over the past 13 years, according to the Centers for Disease Control and Prevention (CDC).

Even still, experts believe the public health burden of tickborne pathogens is considerably underestimated. For example, the CDC reports approximately 30,000 cases of Lyme disease per year but some estimate that the true incidence may be 10 times higher.

> *"The burden of tickborne diseases seems likely to continue to grow substantially."*
> — Catharine Paules, M.D.

This discrepancy in understanding the incidence of tickborne infections results partially from limitations in surveillance and reporting systems, but it also arises from the constraints of available diagnostics.

The authors say that diagnostic utility is affected by a number of factors, including variability among laboratories, timing of specimen collection, suboptimal sensitivity during early infection, imperfect use of diagnostics (particularly in persons with low probability of disease), inability of a single test to identify coinfections in patients with acute infection, and the cumbersome nature of some assays, which require specialized laboratories.

Current diagnostics, which rely heavily on serologic assays, have difficulty distinguishing acute from past infection. Additionally, there is a lag in being able to identify novel, emerging tickborne pathogens.

Yet, there are several new developments that may improve detection of tickborne infections. First, multiplex technology is now capable of detecting antibodies to thousands of epitopes, enabling distinction between eight tickborne pathogens. Additionally, nonserologic platform technologies, like next-generation sequencing, can help identify emerging pathogens.

"The burden of tickborne diseases seems likely to continue to grow substantially," write the authors led by Catharine Paules, M.D., from the Office of the Director, National Institute of Allergy and Infectious Diseases in Bethesda, Md. "Prevention and management are hampered by suboptimal diagnostics, lack of treatment options for emerging viruses, and a paucity of vaccines. If public health and biomedical research professionals accelerate their efforts to address this threat, we may be able to fill these gaps."

*Takeaway: Development of new diagnostics is needed to help combat the rise in tickborne pathogens and infections in the United States.*

# AI Using Laboratory Data to Inform Clinical Decisions

Artificial intelligence- (AI-) based technology is beginning to penetrate health care. Like most other clinical decision-making, several early AI applications rely upon laboratory data.

While personalized medicine is often thought of in tandem with genomic medicine, genomics is not the only data source to inform AI-based algorithms. Other biological high throughput data (transcriptomics, epigenomics, proteomics, metabolomics) can impact clinical decision-making, but so can imaging, electronic health records (EHRs), health claims data, and data from wearable sensors or mobile health apps.

While there are cases where a single marker can stratify patient populations (e.g., Herceptin and HER2), most diseases are complex—either impacting multiple biological pathways or with a unique interplay between biological and environmental or lifestyle factors. Understanding of these multifactoral signatures requires processing of complex, high-throughput data, which is increasingly done with AI.

Several new studies show that laboratory test results, including genetic sequencing data, can be successfully incorporated into AI algorithms to predict disease risk and treatment response.

## AI Predicts Aneurysm Risk With Genomic Data

A new algorithm that incorporates genome-sequence data and electronic health records can predict an individual's risk of abdominal aortic aneurysm (AAA) based on the interaction of genetic susceptibility and lifestyle factors, according to a proof-of-principle study published Sept. 6 in *Cell*. This platform can potentially be used to develop clinical tests for other complex diseases, as well as personalized health management and disease intervention.

AAA affects an estimated 3 million people each year, the authors say, and is the 10th leading cause of death in the United States. It often develops asymptomatically, with the aorta silently enlarging, until it bursts, with often deadly consequences. There is currently no early screening test.

The authors say AAA was an ideal condition to target using the AI technology because it has a strong genetic component (an estimated heritability of 70 percent), yet its genetic underpinnings are not understood and there are "robust" associations between clinical outcomes and lifestyles.

The Stanford University researchers performed high-coverage, whole-genome sequencing (WGS; average genome coverage of 50×) for 268 AAA patients and 133 controls seen at the Veterans Affairs Palo Alto Healthcare System, Stanford University, and Kaiser Permanente. They devised a novel machine-learning framework with a cloud-based analytical pipeline that was able to process large amounts of personal genomes and electronic health record data.

At the individual variant level, the algorithm, called Hierarchical Estimate From Agnostic Learning (HEAL), examined the potential clinical relevance of each individual mutation by annotating its functional consequences, population frequency, and the predicted pathogenicity. In total, 66,047 rare, nonsynonymous mutations (missense, nonsense, and those affecting splice

sites) that were not present in the European populations analyzed in the 1000 Genomes Project were identified.

The machine-learning framework agnostically identified a subset of 60 genes showing distinct mutational patterns capable of distinguishing cases from controls and used this pattern to predict clinical outcomes from personal genomes. The mutations implicated 40 distinct functional pathways that played roles in blood-vessel function and aneurysm development, as well as some more surprising functions, such as regulation of immune function. In validation analysis, these AAA-related mutational patterns were not seen among healthy individuals.

Using genetic sequence data only, HEAL could accurately predict with about 70 percent accuracy who is at high risk for AAA. But, with the addition of EHR information from their last clinical visit (e.g., sex, age, status as a regular smoker, heart rate, waist-to-hip ratio, insulin level, fasting glucose level, lipid profiles), HEAL's predictive abilities improved to nearly 80 percent, a level similar to or better than many existing clinical screening tests like those used for gestational diabetes, significant coronary stenosis, and cytology-based cervical cancer screening, the authors say.

"Our study suggests that HEAL could be potentially developed into a clinically actionable test for early screening of AAA," writes senior author Michael Snyder, Ph.D., from Stanford University. "By simultaneously modeling individual genomes and personal EHRs, HEAL revealed the interplay between the personal genome baseline and individual lifestyles underlying AAA predisposition, demonstrating its potential as a highly personalized health management tool."

The authors acknowledge that the genome-based model has a "low" false-negative rate, but a "relatively higher" false-positive rate. They add, though, that early assessment for disease risk is "critical," given the disease's irreversible progression and that inexpensive and noninvasive ultrasound can be used as follow-ups for positive results.

In their next phase of work, the research group is looking to apply HEAL to detect the genetic underpinnings of preterm birth and autism.

*Takeaway: AI is enabling better understanding of disease pathology through examination of complex data sources. The HEAL platform has been successfully applied to AAA risk and may become a screening test or personalized health management tool for other complex conditions.*

## Metabolite Panel May ID Kids With Autism Spectrum Disorder

A group of blood metabolites help detect some children with autism spectrum disorder (ASD), according to a study published Sept. 6 in *Biological Psychiatry*. This panel may indicate alterations in amino acid (AA) metabolism and can detect about 17 percent of kids with ASD.

"It is unlikely that a single marker will detect all autism," said senior author David Amaral, Ph.D., from University of California, Davis, in a statement. "The long-term vision is, once we've been able to analyze all the data from

[the] Children's Autism Metabolome Project, we would have a series of panels. Each of these would be able to detect a subset of kids with autism. Ultimately, metabolomics may be able to identify most children with autism."

ASD presents heterogeneously both behaviorally and biologically. Experts believe it may arise from a complex interplay of environmental, metabolic, and genetic factors. Currently, there is no reliable biomarker that can identify children at risk for ASD or definitively diagnose children. Diagnosis is based on behavioral evaluation.

Plasma metabolites were analyzed for 516 children with ASD (aged 18 to 48 months) and 164 age-matched, typically developing (TYP) children using liquid chromatography mass spectrometry. The training set included 338 (ASD, 253 and TYP, 85) and the test set included 342 (ASD, 263; TYP, 79). In the training set, diagnostic thresholds were established to identify a subpopulation with at least 10 percent of the ASD population.

The researchers found that a simple analysis of the mean concentrations of free plasma amines did not reveal meaningful differences between the ASD and TYP populations of children. However, they identified three ASD-associated amino acid dysregulation metabotypes (AADM). The combination of glutamine, glycine, and ornithine AADMs identified a dysregulation in AA metabolism that is present in 16.7 percent of the study's ASD subjects, with a specificity of 96.3 percent and a positive predictive value (PPVs) of 93.5 percent.

While there is substantial overlap of children identified by each of the metabotypes, each of the metabotypes also identifies a unique group of subjects. The AADMglutamine identified 7.9 percent of the ASD subjects in the total CAMP population, AADMglycine 9.7 percent, and the AADMornithine 9.1 percent, with PPVs of 97.6 percent, 94.3 percent, and 92.2 percent, respectively. However, taken together, the three AADM subtypes identified 16.7 percent of all ASD subjects with a specificity of 96.3 percent and a PPV of 93.5 percent.

"Metabotypes of ASD can be useful in stratifying the broad autism spectrum into more biochemically homogeneous and clinically significant subtypes," writes Amaral. "Stratifying ASD based on metabotypes offers an opportunity to identify efficacious interventions within metabotypes that can lead to more precise and individualized treatment. The hope is that by combining the established metabotypes into a more comprehensive diagnostic system, that a substantial percentage of children at risk for ASD will be identifiable at a very early age."

*Takeaway: Blood-based metabolite analysis may offer a way to meaningfully identify subpopulations of children with ASD and can inform more personalized intervention.*

## Point-of-Care Test Can Increase Access to Toxoplasma Testing

A novel fingerstick test may improve access to Toxoplasma gondii testing for pregnant women, according to a study published Aug. 16 in *PLoS Neglected Tropical Diseases*. The study demonstrates that the point-of-care test has comparable performance to whole-blood and reference testing and may have other potential, multiplex applications.

Toxoplasmosis is a parasitic infection transmitted from eating undercooked meat, from infected mothers to fetuses, or from exposure from soil or cat feces. While the majority who are exposed are asymptomatic, newborns and those with compromised immune systems are at risk for death, brain damage, and vision problems. However, with timely detection and intervention, the infection is treatable, even before birth.

Pregnant women who are at risk of infection should be tested once a month during pregnancy. Current practice involves serological testing. But, point-of-care testing may improve access to testing, both domestically and internationally in developing nations, where infection is more prevalent.

The lateral flow immunochromatography Toxoplasma ICT IgG-IgM point-of-care test was developed by LDBIO Diagnostic (France). Researchers compared its performance to serum-based testing and reference testing in obstetrical patients in Chicago, Ill. and in Morocco (with genetically distinct patients and parasites). The point-of-care test takes less than two minutes of operator time with results available for visual interpretation within 20 to 30 minutes. The test costs $4 to $5 per test.

There was 100 percent concordance between fingerstick and venipuncture point-of-care testing and reference testing. For the fingerstick, point-of-care testing, sensitivity was 100 percent and specificity was 100 percent. Point-of-care testing was even able to diagnose individuals with lower levels of anti-Toxoplasma antibodies in the range detected by gold-standard tests.

While point-of-care testing is less invasive and can be conducted at a clinical site without laboratory equipment, it cannot distinguish seropositivity for IgG and IgM and, therefore, cannot differentiate between acute from chronic infection. A positive point-of-care test prior to 12 weeks of gestation, the authors say, requires further confirmatory testing.

"Our demonstration of the high performance of this whole-blood point-of-care test and the test's strong functionality at the point of care, which has not been previously demonstrated, provide the proof of principle of its potential utility and widespread applicability in clinical settings" write the authors led by Joseph Lykins, from University of Chicago in Illinois. "This new test also fulfills the World Health Organization criteria for the ideal point-of-care test (affordable, sensitive, specific, user friendly, rapid/robust, equipment-free, and deliverable to users)."

*Takeaway: This point-of-care test has high reliability for toxoplasmosis screening and has the potential to improve access to testing for pregnant women globally.*

## Blood Test Can Cut Unnecessary Ultrasounds to Rule Out Blood Clots

D-dimer (DD) testing is still underutilized for the assessment of deep venous thrombosis (DVT), according to a study published in the July issue of the *Annals of Vascular Surgery*. Further, DD testing in conjunction with a clinical assessment to attest the likelihood of disease can significantly

*"With current constraints of health resources, better utilization of DD as an integral part of diagnostic workup for VTE is imperative."*

— Albeir Mousa, M.D.

reduce the number of unnecessary, immediate venous duplex ultrasounds (VDUs) performed to rule out DVT.

DD is part of a degraded protein produced during the clotting process. While not specific for location, etiology, or pathology, DD can serve as a clinically sensitive marker of acute thrombotic events, including DVT, with results available in under 30 minutes. Yet, many clinicians still proceed directly to VDU, regardless of the pretest likelihood of disease or DD results to inform decision making.

The researchers retrospectively analyzed data from 1,670 patients who presented to a high-volume tertiary care center with lower limb swelling with or without associated pain during June and July of four consecutive years (2012 to 2015). Electronic health records were analyzed to collect the necessary data elements (e.g., calf or leg swelling, paralysis or bedridden, localized tenderness, previous DVT) in order to calculate the Wells criteria probability (WCP) score, assessing the pretest likelihood of DVT. Based on the WCP, patients were divided into low-, moderate-, and high-risk categories. Similarly, DD values (Siemens Innovance DD assay) categorized patients into low (0.1 to 0.59), moderate (0.60 to 1.2), and high (more than 1.3 mg/L fibrinogen equivalent units). VDU diagnosis of DVT was noted to be either proximal (above popliteal vein) or distal (below popliteal vein).

DD testing was ordered in 202 patients and correlated with all positive and negative DVT patients (100 percent sensitivity and negative predictive value, with 14.9 percent specificity and 15.9 percent positive predictive value). For the 22 patients with DD in the normal range, all were negative for DVT. However, the DVT rate was significantly increased in patients with DD levels in the moderate and high ranges.

For the 51 patients with mid-level DD results, only 3 DVTs were recorded, all of which were distal DVTs.

"There is little doubt that using a combination of WCP and DD, along with establishing new thresholds or cut points for DD levels by receiver operator characteristic curve analysis, WCP, or age adjustment, can help compensate for the low specificity of DD alone," write the authors led by Albeir Mousa, M.D., from West Virginia University in Charleston. Unnecessary VDUs were conducted on the 685 patients with low WCP probability and no DD testing, plus the 77 patients with low or intermediate DD, yielding a total of 762 patients that had an unnecessary immediate VDU study, the authors say.

The authors estimate that at $1,557 per imaging study (minus the cost of DD testing at $182/test), there was a total of $1,047,75 in potential charge savings.

"With current constraints of health resources, better utilization of DD as an integral part of diagnostic workup for VTE is imperative," the authors conclude.

*Takeaway: Higher utilization of DD testing in the workup of patients with suspected DVT can limit unnecessary VDU imaging and yield substantial health care savings.*

# Drug Testing Remains Low Among Patients on Long-Term Opioids

A more universal approach to administering and responding to urine drug testing is needed, according to a study published in *Drug and Alcohol Dependence*. Only one in five patients receiving long-term opioid therapy (LTOT) for chronic pain in the Veterans Affairs (VA) system undergoes urine drug testing. Further, there are racial differences in initiation of testing and discontinuation of opioids for among those that test positive for illicit drugs while taking LTOT.

*"Our findings are in keeping with previous studies showing that clinicians have been slow to integrate urine drug testing into patient care, even for patients at high risk for opioid misuse and abuse."*

— Julie Gaither

Multifaceted approaches are needed to combat misuse of prescription opioids. According to the U.S. Centers for Disease Control and Prevention (CDC), more than 40 percent of all opioid overdose deaths in the United States are due to prescription opioids. While there has been increasing attention on prescribing practices, there has been less attention paid to assessing how well clinicians monitor patients for signs of misuse once opioids are initiated.

"There is a general consensus among experts in the field of pain management that urine drug testing is one of the best tools clinicians have for identifying opioid misuse, illicit drug use, and the concomitant use of sedatives or other substances that may increase the risk of overdose," write the authors led by Julie Gaither, from Yale University in New Haven, Conn.

The CDC's opioid prescribing guidelines call for clinicians test for illicit drug use in all patients with chronic pain receiving LTOT, including a urine drug testing before initiating opioid therapy and at least annual urine drug testing after that. For those with a positive test for illicit drug use or other behavior suggestive of addiction, more frequent monitoring is appropriate, experts say.

The present study examined drug testing patterns and how clinicians respond to evidence of illicit drug use among 15,366 patients (48.1 percent black and 51.9 percent white; 97.5 percent male) initiating LTOT through the VA between 2000 and 2010. The researchers used electronic health records to examine administrative, clinical, laboratory, and pharmacy data for participants of the Veterans Aging Cohort Study. Patients with a palliative or end-of-life care code were excluded. This analysis looked at the first urine drug test received by patients during the initial 6 months of LTOT. LTOT was defined as receipt of at least a three-month supply of opioids prescribed for chronic pain.

The researchers found that only 21 percent of patients received a urine drug test within the first 6 months of treatment. Black patients were significantly more likely to receive a urine drug test overall (25.5 percent versus 15.8 percent for whites). They were also significantly more likely to be tested within 1 month, 3 months, and 6 months of initiating opioid therapy, compared to whites.

"Our findings are in keeping with previous studies showing that clinicians have been slow to integrate urine drug testing into patient care, even for patients at high risk for opioid misuse and abuse," writes Gaither and colleagues. "Why some clinicians have failed to adopt this universal approach to urine drug testing and how patients are selected for testing remains unclear."

The vast majority of patients who tested positive for cannabis or cocaine (90 percent) refilled an opioid prescription within the next 60 days. Overall, LTOT was discontinued in 11.4 percent of patients who tested positive for cannabis and in 13.1 percent of those who tested positive for cocaine. However, blacks were twice as likely to have opioids discontinued after testing positive for cannabis and three times more likely after testing positive for cocaine.

"The magnitude of the discrepancy we found in discontinuation rates for blacks compared to whites suggests that in the absence of clearer urine drug testing guidelines, extraneous factors unrelated to the risks and benefits of LTOT— including racial stereotypes— may enter into the decision-making," write the authors. "In light of this potential, we believe that the safest and most judicious way forward is for clinicians to adhere to the latest guidelines from the CDC.

The authors add that clinicians need clearer guidance for how to respond to aberrant toxicology results.

*Takeaway: Adherence to CDC guidelines calling for regular illicit drug testing among patients taking LTOT for chronic pain is low. Further, racial disparities exist in testing initiation and response to positive test results.*

## 2017 Opioid Positivity Rates Decline, Overall Drug Positivity Up in U.S. Workforce

Drug use by U.S. workers remains at its highest rate in more than a decade, according to a report released by Quest Diagnostics (Secaucus, N.J.).

Using data from the 30th annual Quest Diagnostics Drug Testing Index, an analysis of national workplace drug positivity trends based on the company's de-identified laboratory data, the company found that the positivity rate for the combined U.S. workforce remained steady at 4.2 percent in 2017.

"It's unfortunate that we mark 30 years of the Drug-Free Workplace Act with clear evidence that drugs continue to invade the country's workplaces," said Barry Sample, Ph.D., Quest's senior director, science and technology, in a statement. "Not only have declines appeared to have bottomed out, but also in some drug classes and areas of the country drug positivity rates are increasing."

For opiates, the positivity rate of urine drug testing for the general U.S. workforce declined 17 percent between 2016 and 2017 (0.47 percent to 0.39 percent). Quest's workforce drug testing looks for prescription opiates, semi-synthetic opiates, and related metabolites, but does not include synthetic opioids, such as fentanyl and its synthetic analogs, the company says.

"The depth of our large-scale analysis supports the possibility that efforts by policymakers, employers, and the medical community to decrease the availability of opioid prescriptions and curtail the opioid crisis is working to reduce their use, at least among the working public," said Kim Samano, Ph.D., Quest's scientific director, in a statement.

The 2017 data suggests shifting patterns of drug use. Despite progress with opioids,

- The positivity rate for cocaine increased for the fifth consecutive year in the general U.S. workforce across every specimen type.
- For methamphetamine positivity rates, four geographic areas—East North Central division of the Midwest, East South Central division of the South, Middle Atlantic division of the Northeast, and the South Atlantic division of the South—saw increases between nine percent and 25 percent.
- Marijuana positivity in urine testing continued its five-year surge, with the largest increases in states that have enacted recreational use statues.

# Guidelines at a Glance

## ASCO Endorses CAP's Guidelines for HPV Testing in Head and Neck Carcinomas

The American Society of Clinical Oncology has endorsed the clinical guidelines developed by the College of American Pathologists for human papillomavirus (HPV) testing with head and neck cancers.

HPV tumor status should be determined for newly diagnosed oropharyngeal squamous cell carcinomas, with testing performed by surrogate marker p16 immunohistochemistry either on the primary tumor or from cervical nodal metastases if an oropharyngeal primary tumor is present. Results are positive with at least 70 percent nuclear and cytoplasmic expression at least moderate to strong intensity. Confirmatory testing should be at the discretion of the pathologist and/or treating clinician.

HPV tumor status is not necessary in nonsquamous carcinomas of the oropharynx or non–oropharyngeal squamous cell carcinomas of the head and neck. If there is uncertainty of histologic type or a poorly differentiated oropharyngeal tumor is nonsquamous, HPV tumor status testing should be at the discretion of the pathologist and/or treating clinician.

## USPSTF Reaffirms Syphilis Screening in All Pregnant Women

The U.S. Preventive Service Task Force reaffirms its 2009 recommendation for syphilis screening early in pregnancy, concluding that there is convincing evidence that screening for syphilis infection in pregnant women provides substantial benefit. If a woman has not received prenatal care prior to delivery, she should be tested at delivery.

Untreated syphilis infection in pregnant women can be transmitted to the fetus (congenital syphilis) causing significant mortality and morbidity in infants (e.g., bone deformities and neurologic impairment). According to the U.S. Centers for Disease Control and Prevention, syphilis increased from 2012 to 2106 by 87 percent.

## USPSTF Updates Cervical Cancer Screening Strategies

The U.S. Preventive Service Task Force (USPSTF) recently updated its cervical cancer screening recommendations. The USPSTF maintains its guidance that women aged 21 to 29 years should still receive cervical cytology screening—a Pap test—every three years. However, the task force now gives women aged 30 to 65 years a choice in screening strategy: a Pap every 3 years, a high-risk human papillomavirus (hrHPV) test every five years, or a Pap plus HPV test every five years.

The USPSTF recommends against screening for cervical cancer in women younger than 21 years or in women older than 65 years who are not at high risk for cervical cancer or who have had adequate prior screening. Similarly, the task force recommends against screening for cervical cancer in women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion or cervical cancer.

## AMP Defines Genes For Chronic Myeloid Neoplasm Panels

The Association for Molecular Pathology (AMP) has identified critical genes for inclusion in high-throughput sequencing testing panels for chronic myeloid neoplasms (CMNs). In response to the "recent explosion of literature" regarding the clinical relevance of small DNA variants in CMNs, the AMP CMN Working Group conducted a thorough review of the literature to identify evidence of clinical utility for gene inclusion. This list of minimum recommended genes includes: ASXL1, BCOR, BCORL1, CALR, CBL, CEBPA, CSF3R, DNMT3A, ETV6, EZH2, FLT3, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NF1, NPM1, NRAS, PHF6, PPM1D, PTPN11, RAD21, RUNX1, SETBP1, SF3B1, SMC3, SRSF2, STAG2, TET2, TP53, U2AF1, and ZRSR2.

With the increasing use of targeted therapies, high-throughput sequencing remains critical for patient management. But the work group acknowledges new evidence is being rapidly produced. So, this list will evolve with new insights into the effects of combinations of biomarkers on specific clinicopathologic characteristics of CMNs.

## Genetic Testing Should Be Standard of Care for Familial Hypercholesterolemia

The American College of Cardiology scientific expert panel, convened by the Familial Hypercholesterolemia Foundation, recommends that genetic testing become the standard of care for patients with definite or probable familial hypercholesterolemia (FH), as well as for their at-risk relatives.

FH is common, potentially fatal, but treatable. Yet, it remains underdiagnosed. The panel recommends that testing should include the genes encoding the low-density lipoprotein receptor, apolipoprotein B, and proprotein convertase subtilisin/kexin 9, as well as any other genes may also need to be considered based on patient phenotype. The panel expects that such testing will result in greater diagnoses, more effective cascade testing, initiation of therapies at earlier ages, and more accurate risk stratification.

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infection-control policies required all possible TB patients to stay in isolation for collection of two or more sputa over two separate days for concentrated acid-fast bacilli smear microscopy and mycobacterial culture. Testing was carried out in a single batch once daily. Patients with a high clinical probability of TB were placed in airborne infection isolation, while patients at low clinical probability of TB could be placed in respiratory isolation in conventional private rooms without negative-pressure ventilation systems, if no airborne infection isolation rooms were available. Isolation could be discontinued for TB-negative patients when two or more sputa tested negative.

The researchers found that the median time from hospital admission until initial sputum collection was similar pre- and post-implementation (19.1 versus 18.0 hours, respectively).

The 2015 update for discontinuing respiratory isolation incorporated molecular testing. The updated algorithm allowed discontinuation of isolation after negative smear and/or molecular assay examination results of two sputa for patients with low probability of infection or for three negative sputa results for patients with a high probability of infection, based on clinical presentation.

From January 2014 to January 2016, which includes before and after implementation, 621 underwent sputum examination for evaluation for active pulmonary TB. Molecular sputum testing was conducted using GeneXpert MTB/RIF (Cepheid; Sunnyvale, Calif.), which provides testing results in less than two hours.

The researchers found that the median time from hospital admission until initial sputum collection was similar pre- and post-implementation (19.1 versus 18.0 hours, respectively). Clinicians completed the TB testing evaluation process at similar rates pre- and post-implementation (77 versus 81 percent, respectively).

Among the 320 patients evaluated in the post-implementation period, clinicians ordered molecular testing 73 percent of patients and received results for 98 percent of tests ordered. For patients with assay testing ordered, 74 percent had one test ordered, 24 percent had two tests ordered, and 3 percent had three tests ordered (totaling 302 molecular tests ordered).

Ten patients pre-implementation (4.3 percent) and nine patients post- implementation (2.7 percent) after had positive rapid TB test results, including six assay-positive and eight smear-positive results after implementation. The molecular testing algorithm accurately diagnosed all seven patients with culture-confirmed TB and excluded TB in all 251 patients with culture-negative results, yielding one false-negative assay result, which was safely diagnosed based on an additional sputum sample sent for molecular testing, per the risk-stratified algorithm. The algorithm also detected one patient with TB who had a negative smear evaluation, who would have otherwise gone undetected.

Post-implementation, median time to first test result after sputum collection significantly decreased from 18.4 hours to 4.6 hours, as did median time to final test result after sputum collection (a decrease from 39.1 hours to 22.4

> *"The diffusion into clinical and public health microbiology laboratories has been slow owing to budget constraints in the laboratories, physicians wary to act on molecular results, and general reluctance to implement change for such a new technology."*
>
> — Max Salfinger, M.D.

hours). Mean time in isolation for patients with negative test results significantly decreased 29 percent (from 3.9 days per patient pre-implementation to 2.8 days post-implementation. Similarly, median hospital length of stay decreased (6.0 to 4.9 days) and mean hospital costs per patient with negative rapid TB test results decreased from $46,921 to $33,574 post-implementation, yielding an average savings of $13,347 per patient.

"The diffusion into clinical and public health microbiology laboratories has been slow owing to budget constraints in the laboratories, physicians wary to act on molecular results, and general reluctance to implement change for such a new technology," writes Max Salfinger, M.D., from National Jewish Health in Denver, Co., in an accompanying editorial. "The evidence showed that clinicians and infection preventionists, as well as hospital administrators should work with all stakeholders to identify barriers at their institution (e.g., outdated electronic ordering algorithms, not acknowledging system-wide savings when only focused on laboratory expense) preventing a wider implementation of nucleic acid amplification test testing.

*Takeaway: A molecular testing strategy to rule out active TB infection in the hospital setting is feasible; reduces turnaround time for testing, isolation, and hospital length of stay; and substantially cuts hospital costs, compared to a conventional microscopy-based testing strategy.*