G2 INTELLIGENCE
A DIVISION OF PLAIN LANGUAGE MEDIA

DIAGNOSTIC TESTING & Emerging Technologies

New Trends, Applications, and IVD Industry Analysis

APRIL 2019

INSIDE THIS ISSUE

New Federal Taskforce to Speed Implementation of Emergency Use Diagnostics

Three federal agencies announced the creation of a new taskforce to provide timely recommendations to laboratories for rapid implementation of in vitro diagnostic (IVD) assays during public health emergencies.

The U.S. Food and Drug Administration, Centers for Disease Control and Prevention (CDC) and the Centers for Medicare and Medicaid Services (CMS) announced the launch of the Tri-Agency Task Force for Emergency Diagnostics. The taskforce's charter calls for coordination of the implementation of IVD assays authorized for use under FDA's Emergency Use Authorization (EUA) in laboratories within the U.S.

Continued on page 2

Laboratory Initiation of Cascade Genetic Testing Spurs Uptake

A laboratory-initiated, online effort to reach cancer patients' relatives coupled with discounted genetic tests can increase rates of cascade testing, according to a study published in the January issue of the *Journal of the National Cancer Institute*. Almost half of patients' first-degree relatives followed through with genetic testing when contacted by a laboratory.

"The results have been very striking, as traditional approaches to cascade testing result in only about 30 percent of relatives undergoing testing," said coauthor **Allison Kurian**, M.D., from Stanford University (California), in a statement.

While cascade testing is recommended for Lynch Syndrome and Hereditary Breast and Ovarian Cancer Syndrome, in practice, there are barriers to its implementation, including cost (with tests costing more than $500), insurance restrictions (e.g., Medicare does not cover preventive genetic testing of cancer-free relatives), and confidentiality laws that prevent doctors or genetic counselors from directly contacting a patient's relatives.

Continued on page 8

New Federal Taskforce to Speed Implementation of Emergency Use Diagnostics, *from page 1*

healthcare system—both public health and clinical laboratories—with the ultimate goal of improving responses to public health emergencies.

"Time and time again, we're reminded that disease knows no borders," said **Chesley Richards**, CDC's Deputy Director for Public Health Science and Surveillance, in a statement. "During public health emergencies, it is critical for diagnostic tests to be made available and adopted quickly into clinical and public health laboratories for rapid patient care."

The taskforce will provide a forum to streamline interagency approaches for the implementation of EUA diagnostic tests through better federal communication and leveraging of each agency's expertise to assist in public health preparedness and improve the availability of these diagnostic tests in times of emergencies.

The FDA has authority to issue an EUA for appropriately developed diagnostic tests during public health emergencies. The CDC is responsible for providing agent-specific subject matter expertise in epidemiology, laboratory expertise, and guidance to clinicians and laboratories responding to the emergency. The CDC and other federal laboratories often also develop new tests in response to emergency needs. CMS has authority to ensure quality testing at laboratories through the Clinical Laboratory Improvement Amendments (CLIA).

"Timely implementation of EUA diagnostic assays in the U.S. health care system is dependent upon laboratories understanding the instructions for use and applying them to the patient samples received for testing," said CMS' chief medical officer and director of the Center for Clinical Standards and Quality **Kate Goodrich**, in a statement. "As part of this taskforce, it is our goal to provide clear and consistent guidance to laboratories on the application of CLIA requirements for these emergency assays."

According to public feedback received by the agencies, the clinical laboratory community had concerns about how to implement EUA diagnostic tests in a CLIA environment.

Takeaway: Ultimately, the taskforce is expected to provide a more efficient federal government response to speed implementation of available diagnostic tests during public health emergencies.

DTET

Lori Solomon, Editor
Glenn S. Demby, Executive Editor
Elayne Demby, Contributing Editor
Paula Santonocito, Contributing Editor
Catherine Jones, Contributing Editor and Social Media Manager
Barbara Manning Grimm, Managing Editor
Jim Pearmain, Layout & Design
Myra Langsam, Business Development
Michael Sherman, Director of Marketing
Pete Stowe, Managing Partner
Mark T. Ziebarth, Publisher

Diagnostic Testing and Emerging Technologies (ISSN 2330-5177) is published by G2 Intelligence, Plain Language Media, LLLP, 15 Shaw Street, New London, CT, 06320.
Phone: 888-729-2315
Fax: 855-649-1623
Web site: www.G2Intelligence.com.

Preventive Genomic Screening In Young Adults Highly Cost Effective

A new model shows that universal preventive genomic screening for multiple conditions in early adulthood could be highly cost-effective in a single-payer health care system, according to a study published Feb. 18 in *Genetics in Medicine*. Population screening could significantly reduce the incidence of and mortality from hereditary cancers, as well as the burden of severe childhood-onset genetic disease, compared with targeted testing, but ethical issues remain, the authors say.

Up until now, most modeling of adult genetic screening has been limited to single genetic conditions in targeted, high-risk populations, rather than the general population. However, there is increasing evidence that the current model of family history- or clinical criteria–based gene testing for hereditary cancer is failing to reach many at-risk individuals.

The present study combined modeling for familial cancer and preconception carrier screening for conditions that have clinical guidelines and reimbursed health services available in Australia for identified individuals or couples. The model included screening of 2,688,192 individuals (all adults aged 18 to 25 years in Australia) for pathogenic variants in BRCA1/BRCA2/MLH1/MSH2 genes, and carrier screening for cystic fibrosis (CF), spinal muscular atrophy (SMA), and fragile X syndrome (FXS), all of which have an evidence base demonstrating that early identification of risk has high clinical impact.

The model assumed 71 percent testing uptake (substantially higher than the current estimated rates of targeted testing of 15 percent for cancer gene testing and 5 percent for preconception carrier screening, the authors say). Per-test costs included in the model ranged from AUD$200 to $1,200 (~USD$140 to $850) and are based upon current government-reimbursed price for hereditary breast and ovarian cancer testing (AUD$1200) and the prepair™ carrier screen (AUD$385). Total costs included genetic counseling, surveillance, and interventions (reimbursed only) for at-risk individuals and couples. Cost-effectiveness was defined by the willingness-to-pay threshold of AUD$50,000 per disability-adjusted life year (DALY) prevented.

The researchers found compared to targeting testing, that population screening would reduce variant-attributable cancers by 28.8 percent, cancer deaths by 31.2 percent, and the three severe childhood-onset genetic diseases by 24.8 percent.

In isolation, only population screening for breast cancer was cost-effective. However, combined testing for hereditary breast and ovarian cancer, combined testing for Lynch syndrome, and combined carrier screening were all cost-effective, demonstrating the efficiency of combined screening. Population testing for all four cancers combined was highly cost-effective, independently of carrier screening (AUD$10,656/DALY prevented). Combined screening for all seven conditions together was cost-effective up to and including AUD$1,200 per test.

Continued on page 4

Preventive Genomic Screening In Young Adults Highly Cost Effective, *from page 3*

"Screening at a cost of AUD$400 was found to be highly cost-effective," write the authors led by **Lei Zhang**, Ph.D., from Monash University in Australia. "However, if AUD$200 per-test could be achieved, screening could become cost-saving for the health system, providing a significant platform for the consideration of health system–funded screening."

The authors say that for the benefits of population-based genomic screening to be achieved, screening would require scalability, public education to drive informed consent, and ethical oversight.

"Funding decisions based on imputed cost-savings must not result in implicit pressure on individuals to violate personal ethics to reduce financial burden on society," write the authors. "We strongly believe that any decision regarding individual health interventions should be grounded in informed consent and personal autonomy, without presumed obligation or implicit pressure."

Takeaway: Combining hereditary cancer and carrier screening for preventive population genomic screening in young adults appears to be highly cost-effective for single payer systems.

Zika Blood Screening Not Cost-Effective, Study Finds

Screening blood donors for Zika virus is not cost-effective in the United States or Puerto Rico, according to a study published Jan. 8 in the Annals of Internal Medicine. Despite U.S. Food and Drug Administration (FDA) requirements, analysis shows that universal screening of donated blood would only be cost-effective in the high mosquito season in Puerto Rico and never in the 50 states.

"To reduce the vulnerability of the blood supply to emerging and reemerging pathogens, public officials have responded to newly discovered transfusion-transmitted infections (TTIs) with recommendations for donor deferrals, antibody and NAT screening, and use of approved pathogen reduction technology," writes **Katherine Ellingson**, Ph.D., from University of Arizona, Tucson, and **Matthew Kuehnert**, M.D., from MTF Biologics in Edison, N.J., in an accompanying editorial. "Successes and failures in the implementation of these strategies have led the public to expect near-zero acceptable risk for TTIs. Maintaining such low levels of risk comes at a substantial cost."

In August 2016, the FDA began requiring universal individual donor nucleic acid test (ID-NAT) screening for Zika virus in the United States and territories. In July 2018, the FDA issued revised guidance recommending universal mini-pool NAT (MP-NAT; 6 to 16 pooled sample donations) with triggers to ID-NAT during outbreaks.

The study used microsimulation to evaluate the effectiveness and cost-effectiveness of universal ID-NAT, universal MP-NAT, and alternative

screening strategies, including a separate-inventory policy where donations were screened with ID-NAT or MP-NAT for components intended to be transfused to women of childbearing age and others were not screened. Other screening strategies targeted donors who resided in or had recently traveled to areas of known local transmission. For Puerto Rico, the researchers also considered seasonal strategies: either ID-NAT or MP-NAT in high mosquito season and no screening in low season and ID-NAT in high mosquito season and MP-NAT in low season.

The models aggregated costs associated with the blood centers, adverse events, and lifetime health economic consequences of adverse events due to Zika virus transfusion transmission during 1 year under each policy.

The researchers found that with no screening, an estimated 242.2 cases of transfusion transmission would have occurred during the first year of screening in Puerto Rico. Analysis found that in Puerto Rico, MP-NAT exclusively during high mosquito season was cost-effective at $81,123 per QALY.

With no intervention, an estimated 44.7 cases of transfusion transmission would have occurred during the first year of screening in the 50 states. However, no screening policy was cost-effective. The authors found that ID-NAT screening of the U.S. blood supply cost an unbelievable $341 million per quality-adjusted life-year (QALY) saved versus no screening. By comparison, MP-NAT for HIV and hepatitis B and C viruses costs about $1.3 million per QALY gained, the authors say.

"Although Zika virus has life-threatening sequelae, they were unlikely to manifest because of transfusion transmission during the period of analysis even without screening," write the authors led by **W. Alton Russell**, from Stanford University in California. "If the Zika virus rate among donors remained unchanged, we would expect transfusion transmission of Zika virus to result in one case of Guillain–Barre syndrome every 16 years in Puerto Rico (every 84 years in the 50 states) and 1 case of congenital Zika syndrome every 33 years in Puerto Rico (every 176 years in the 50 states) without screening."

Overall, the authors estimate that MP-NAT is cost-effective only in donor populations with rates above 1.2 in 1,000 donations and that escalation to ID-NAT is cost-effective only in populations with rates above 9.8 in 1,000 donations.

"Since the introduction of HIV antibody testing in 1985, the FDA has never discontinued screening for a TTI once required," writes Russell and colleagues. "Because the infectious donation rate drives the expected benefit and cost-effectiveness of disease marker screening, the FDA might consider identifying infectious rate thresholds for all TTIs, below which screening requirements are downgraded or eliminated. This could help ensure that blood centers allocate resources effectively, cost-efficiently, and in a prioritized manner.

Takeaway: The authors bring highlight the staggering lack of cost-

New Lab-Based, ER Protocol Cuts Invasive Procedures in Febrile Infants

A prediction rule can identify febrile infants at low risk for serious blood infections (SBIs) using urinalysis, absolute neutrophil count (ANC), and procalcitonin levels, according to a study published Feb. 18 in *JAMA Pediatrics*. The authors say the protocol can both standardize care and potentially cut the need for lumbar punctures, unnecessary antibiotics, and hospitalizations, which have traditionally been included in diagnostic workups due to the serious consequences of a missed SBI (e.g., bacteremia and meningitis) in infants.

The researchers from the Pediatric Emergency Care Applied Research Network developed and validated the prediction rule to identify febrile infants (60 days and younger) at low risk for SBIs presenting at 26 emergency departments (between March 2011 and May 2013). All infants had blood and urine cultures, while cerebrospinal fluid testing was performed at the discretion of the treating clinician.

A urinary tract infection (UTI) was defined as the growth of a single urine pathogen with at least 1,000 cfu/mL for cultures obtained by suprapubic aspiration, at least 50,000 cfu/mL from catheterized specimens, or 10,000 to 50,000 cfu/mL from catheterized specimens in association with an abnormal urinalysis. From the 1,821 infants, 908 were randomized to the development cohort and 913 to the validation cohort (mean age, 36 days; 42 percent girls; 43 percent white; 20 percent black; and 29 percent Hispanic).

The researchers found that SBIs were present in 9.3 percent of all infants, including 1.4 percent with bacteremia, 8.3 percent with UTIs, 0.5 percent with bacterial meningitis; and 0.9 percent with concurrent SBIs. In the development cohort, the prediction rule identified infants at low risk of SBI using a negative urinalysis result, an ANC of 4090/µL or less, and serum procalcitonin of 1.71 ng/mL or less. When applied to the validation cohort, the rule had sensitivity of 97.7 percent, specificity of 60.0 percent, negative predictive value of 99.6 percent, and negative likelihood ratio of 0.04. Across both cohorts, one infant with bacteremia and two infants with UTIs were misclassified, but no patients with bacterial meningitis were missed by the rule.

The rule's performance was nearly identical when only bacteremia and/or bacterial meningitis was included. Neither the addition of clinician suspicion nor the Yale Observation Scale score significantly improved the rule. Rounding the numerical thresholds of the ANC (4000/µL) and serum procalcitonin (0.5 ng/mL) to easier-to-apply numbers also resulted in nearly identical model test characteristics.

Takeaway: With further validation, use of prediction rule based on standard laboratory tests can potentially decrease the use of lumbar punctures, broad-spectrum antibiotics, and hospitalization for many febrile infants 60 days and younger.

With Focus on Cost Cutting, Post-Op Labs Not Needed After Knee Replacement

Routine postoperative laboratory testing is not necessary for low-risk patients having elective total knee arthroplasty (TKA), according to a study published Jan. 18 in the *Journal of Clinical Orthopaedics and Trauma*. The authors say targeted postoperative testing should be guided by patient risk factors.

"With joint replacement procedures already making up the largest proportion of inpatient surgical procedures for Medicare beneficiaries and with the demand expected to increase several folds by 2030, it is of vital importance to look for opportunities to curb unnecessary costs and resource utilization," write the authors led by **Mohamad Halawi**, from University of Connecticut Health Center in Farmington. "With expansion of the bundled payment models, there may exist an opportunity to cut overall costs while maintaining quality of care by eliminating unnecessary interventions."

The researchers retrospectively reviewed charts for 319 patients who underwent TKAs at a single institution (Jan. 1, 2015, through and July 15, 2017). Pre- and post-operative laboratory values for hemoglobin, hematocrit, sodium, potassium, and creatinine were available for all patients and outcomes were assessed for rates of acute blood loss anemia requiring transfusion, acute kidney injury (AKI), electrolyte abnormalities, and 90-day emergency department visits and readmissions. Additionally, the researchers sought to identify risk factors among patients with abnormal postoperative laboratory values.

Analysis showed that just over one-fourth of patients (27.9 percent) had abnormal postoperative laboratory results. However, the vast majority of patients with abnormal results (78 percent) were due to electrolyte (sodium or potassium) abnormalities. The rate of AKI was 3.8 percent and 1 percent for blood transfusion.

Abnormal baseline electrolyte levels and preoperative anemia were significantly associated with postoperative electrolyte abnormalities. Need for blood transfusion was associated with were American Society of Anesthesiologist Physical Status Classification (ASA) score, preoperative anemia, and no tranexamic acid use during surgery, while AKI was associated with chronic kidney disease, as well as a combination of older age, higher body mass index, ASA score, diabetes, heart disease and/or anemia.

There was no increased risk for 90-days emergency department visits or readmissions associated with abnormal laboratory values and for most patients (95.6 percent) laboratory results did not change the course of care.

"With increasing pressure for cost containment in an era of bundled payment models, the very low rate of laboratory associated interventions suggest that routine postoperative laboratory tests is not justified," write the authors. "A strategy aimed at preventing complications combined with good patient history and clinical examination cannot be overemphasized and it should be used to guide laboratory testing."

Takeaway: In an era of cost containment, routine postoperative laboratory testing provides little clinical value for low-risk patients undergoing TKA.

Laboratory Initiation of Cascade Genetic Testing Spurs Uptake, *from page 1*

This study evaluated an online initiative in which carriers of one of 30 cancer-associated genes, or their first-degree relatives, could offer low-cost testing to other at-risk, first-degree relatives. The known carrier or their first-degree relative, could apply to the family testing program by creating an online account and uploading their previous test results. In addition to those applicants with a qualifying pathogenic result, the laboratory distributed information about the program through online advertisements, at clinics, and at events for families with hereditary cancer. After initial application, the testing laboratory sent emails to first-degree relatives, identified by the applicant, inviting them to undergo multiplex sequencing of these 30 genes at an out-of-pocket cost of $50 through a CLIA-certified laboratory. The protocol required first-degree relatives with positive results to speak by phone with a genetic counselor to obtain test results and receive counseling about cancer risk.

The researchers found that over the program's first year (September 2016 through September 2017), there were 1,101 applicants (741 carriers and 360 first-degree relatives), who invited 2,280 first-degree relatives to undergo genetic testing. Most applicants were female (78.1 percent). Just under half of invited relatives (47.5 percent) underwent genetic testing over a median of 216 days of follow-up. Of first-degree relatives who tested positive, 12.0 percent continued the cascade by inviting additional relatives to test.

"While the cascade rate might be expected to decrease with each successive invitation of relatives, the observed drop-off to 12.0 percent is likely suboptimal," the authors write. "This drop-off could reflect limited understanding of test results, which is the major potential weakness of an online approach without in-person counseling."

Invited female relatives were significantly more likely to follow through with testing than males (52.6 percent versus 42.0 percent). However, follow through was similar whether the carrier who invited them had a variant associated with a well-characterized syndrome or in a less well-characterized gene.

As might be expected, the authors say, 48.1 percent of tested relatives carried the identified familial pathogenic variant. However, 4.9 percent of tested relatives had a pathogenic variant in a different gene from the known familial one and 16.8 percent had a variant of uncertain significance.

"These pathogenic mutations were totally unexpected and suggest that this may reflect the prevalence in the general population of known cancer-associated mutations," said Kurian in a statement. "It addresses a long-standing question in the field about what we might find if we routinely tested everyone."

The genetic testing firm Color Genomics (San Francisco) partially funded the study.

Takeaway: Laboratory initiation of cascade testing may be an effective, low-cost way to overcome some of the barriers traditionally associated with adoption.

INSIDE THE DIAGNOSTICS INDUSTRY

The Practice of Early Gestational Diabetes Screening Evaluated

The U.S. Centers for Disease Control and Prevention estimates that each year, gestational diabetes mellitus (GDM) affects between 2 percent and 10 percent of pregnancies. Experts say there has been a steady rise in the prevalence of gestational diabetes as risk factors for the disease are also increasing (e.g., rates of obesity and increasing age of women at the time of pregnancy).

Despite American College of Obstetricians and Gynecologists recommendations for GDM screening, questions remain, particularly about early screening in practice, including concerns about diagnostic thresholds and the utility of early screening in obese women.

Several studies presented at the Society for Maternal-Fetal Medicine's annual Pregnancy Meeting (Las Vegas; Feb. 11-16) by a group of researchers from University of Alabama at Birmingham sought to answer these practice-based questions related to GDM screening.

Diagnostic Thresholds for Early GDM Screening

Early screening (14 to 20 weeks) for GDM may require using lower diagnostic cutoffs than are used for regular GDM screening at 24 to 28 weeks, according to a study presented at the conference.

The researchers randomized 912 obese women to either early GDM screening (14 to 20 weeks) or to routine screening (24 to 28 weeks). GDM screening used a 50-g, 1-hour glucose challenge test followed by a 100-g, 3-hour glucose tolerance test if test results were ≥135 mg/dL. Test characteristics were assessed, comparing early and regular screening, as well as the ideal cutoff. Lastly, the incidence of a composite of adverse perinatal outcomes was evaluated above and below these cutoffs.

Analysis showed that just over one-third of women (35 percent) had a glucose challenge test available at both time points and 9.4 percent were diagnosed with GDM after 24 wks.. The mean gestational age at first screen was 17.3 weeks and 26.2 weeks at second screen. Results from glucose challenge tests performed at 14 to 20 weeks were closely associated with GDM at 24 to 28 weeks (area under the curve, 0.80), with an optimal cutoff of 130 mg/dL. Lowering the threshold from 135 mg/dL to 130 mg/dL increased the sensitivity from 63 percent to 70 percent and increased the number of glucose tolerance tests performed by four per 100 patients.

Early glucose challenge test results of 130 mg/dL or above were associated with a significantly higher incidence of adverse perinatal outcome. Using the Liu method, ideal cutoffs for early diagnosis of GDM using the glucose tolerance test were 97 (fasting), 155 (1-hour), 127 (2-hour), and 95 (3-hour). Applying these cutoffs yielded an additional 37 women with an early diagnosis of GDM, 43 percent of whom were diagnosed with GDM at 24-28 weeks and 75 percent of whom had the adverse composite outcome.

The authors say that while evidence suggests lower diagnostic cutoffs may be needed for early GDM screening, outcomes with these lower levels should be assessed before implementation.

Continued on page 10

INSIDE THE DIAGNOSTICS INDUSTRY

The Practice of Early Gestational Diabetes Screening Evaluated, *from page 9*

HbA1C Should Not Be Used for Early Screening

The University of Alabama researchers used data from the same randomized controlled to identify 501 women who had both a normal HbA1c in early pregnancy and screening for GDM at 24-28 weeks. The relationship between HbA1c and GDM was assessed, as well as ideal test characteristics for HbA1c.

The researchers found that the average gestational age at HbA1c measurement was 17.5 weeks and the average HbA1c level was 5.3 percent. The gestational age at repeat testing was 26.3 weeks, and 51 women (10.2 percent) were diagnosed with GDM at 24 to 28 weeks. The receiver operator characteristics curve had an area under the curve of 0.63, indicating only a moderate association between early HbA1c and a diagnosis of GDM, the authors say.

At the selected cutoff of 5.4 percent, sensitivity and specificity were both poor (60.8 percent and 60 percent, respectively). Further, HbA1c measurements greater than the cutoff point were not associated with the primary adverse perinatal composite outcome.

"HbA1c for early screening for GDM in obese women performs poorly and should not be used for this purpose," conclude the authors led by **Elizabeth Ausbeck**.

Rationale for Early GDM Screening Questioned

Early screening for gestational diabetes may not be linked with better perinatal outcomes in obese women, according to a large study presented at the conference.

Researchers used data from the same randomized controlled to assess the benefits of early screening in terms of a composite of perinatal outcomes. In addition to the glucose challenge test, HbA1c was also measured for all patients. Women negative for GDM at early screening were rescreened at 24 to 28 weeks.

The researchers found that of the 454 women randomized to early screening, 15.2 percent were diagnosed with GDM—6.4 percent before 20 weeks and 8.8 percent after 24 weeks. Approximately 12 percent of the 458 women randomized to routine screening had GDM.

However, early screening did not reduce the incidence of the composite of adverse perinatal outcomes, which was actually nominally higher in the early screening group (59.0 percent versus 53.3 percent). Further, hypertensive disease of pregnancy trended higher in the early screening group (13.5 percent versus 9.6 percent in the routine screening group) and use of insulin was significantly increased in the early screening group (2.6 percent versus 0.7 percent in the routine screening group).

"Recommendations for early GDM screening need to be reassessed in light of these findings," conclude the authors, led by **Lorie Harper**, who also call for additional large studies in diverse populations to validate these findings.

Takeaway: New evidence may clarify some unanswered questions about the practice of early GDM screening, particularly in obese women.

Can a Blood Test Quantify Pain?

A new test could help clinicians objectively measure pain. According to a study published Feb. 12 in *Molecular Psychiatry*, the identified biomarkers can predict pain severity and future emergency department visits for pain, as well as targeted, non-addictive therapy. The authors say that the test holds the potential to help improve diagnosis of pain and offer more treatment options that could alleviate the current opioid epidemic.

It's very important to have an objective measure of pain, as pain is a subjective sensation," said lead author **Alexander Niculescu**, M.D., Ph.D., in a statement. "The rationale for identifying validated and reproducible blood biomarkers is precisely because you cannot directly biopsy brain and spinal centers of pain perception. Blood biomarkers are easily accessible, and constitute a surrogate."

The study used three independent cohorts of patients with major psychiatric disorders from the Indianapolis VA Medical Center: a discovery cohort, validation cohort, and testing cohort. The discovery cohort longitudinally assessed 28 participants that had at least one diametric change in pain from low pain to high pain using a visual analog scale. Over multiple visits, a total of 79 blood samples were collected for subsequent gene expression microarray analysis. Researchers prioritized candidate biomarkers, including from the literature, and analyzed the patient data from the discovery cohort, using both an absent-present approach, as well as a differential expression. Top candidates were evaluated in the validation cohort (n = 23) yielding 65 candidate biomarkers and a short list of five markers (MFAP3, PIK3CD, SVEP1, TNFRSF11B, ELAC2) with the best evidence. All of the markers were then evaluated in the test cohort (n = 162).

The researchers found that predictive pain-related gene expression biomarkers were more effective when personalized by gender and diagnosis. For instance, overall CNTN1 was the best predictor for pain state, GBP1 for first year emergency department visits, and GNG7 for all future visits. However, in females, DNAJC18 was the best predictor for state, GBP1 for trait first year emergency department visits, and ASTN2 for tall future visits. But in males, the three most predictive markers were CNTN1, Hs.554262, and MFAP3, respectively. Predictors also varied by diagnosis (e.g., bipolar, post-traumatic stress disorder, and depression). Some of the individual biomarkers are targets of existing drugs, while nearly all have been tied to other psychiatric disorders.

"Our work opens the door for precision medicine for pain, with objective diagnostics and targeted novel therapeutics," write the authors led by Niculescu, from Indiana University in Indianapolis. "Given the massive negative impact of untreated pain on quality of life, the current lack of objective measures to determine appropriateness of treatment, and the severe addiction gateway potential of existing opioid-based pain medications, the importance of approaches such as ours cannot be overstated."

Takeaway: Researchers are optimistic that a blood-based test for gene expression will be able to objectively diagnose and improve treatment for pain.

Guidelines at a Glance

CAP Releases Recommendations for AI-Informed, Digital Pathology Analysis

The College of American Pathologists published the first-ever evidence-based clinical practice guideline to help laboratories use artificial-intelligence based analysis, called quantitative image analysis (QIA), in HER2 immunohistochemistry testing for breast cancer. In total, the expert panel developed 11 recommendations.

The guidelines say that laboratories should validate their QIA results for clinical use by comparing them to an alternative, validated method(s) such as HER2 fluorescence in situ hybridization or consensus images for HER2 immunohistochemistry. The recommendations also say that pathology reports should document that results were obtained using QIA. The American Society for Clinical Pathology has endorsed the guideline.

ASCO Endorses CAP's Practice Guidelines for HPV Testing in Head, Neck Cancers

The American Society of Clinical Oncology endorsed the American Pathologists' practice guidelines for human papillomavirus (HPV) testing in head and neck cancers.

The guidelines recommend that HPV tumor status should be evaluated for newly diagnosed oropharyngeal squamous cell carcinomas. Testing can be performed by surrogate marker p16 immunohistochemistry on the primary tumor or from cervical nodal metastases. The threshold for positivity is at least 70% nuclear and cytoplasmic expression with at least moderate to strong intensity. Additional confirmatory testing is at the discretion of the pathologist and/or treating clinician. HPV tumor status testing is not routinely needed in nonsquamous carcinomas of the oropharynx or non–oropharyngeal squamous cell carcinomas of the head and neck.

Condition: Quantitative image analysis
Source: College of American Pathologists
Date of Issue: Jan. 17, 2019
https://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2018-0378-CP

American Society of Breast Surgeons Issues Guideline on Genetic Testing

American Society of Breast Surgeons recently issued a consensus guideline on genetic testing for hereditary breast cancer. Notably, the society recommends that genetic testing should be made available to all patients with a personal history of breast cancer. Testing should include BRCA1/BRCA2 and PALB2, plus other genes dependent on clinical details and family history. The recommendations also suggest re-evaluation is necessary for patients who had genetic testing in in the past.