G2 INTELLIGENCE
A DIVISION OF PLAIN LANGUAGE MEDIA

DIAGNOSTIC TESTING & Emerging Technologies

New Trends, Applications, and IVD Industry Analysis

September 2016

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Laboratory Review of Genetic Test Orders Cuts Errors, Costs

Three percent of genetic test orders are cancelled or modified due to an order error found during a utilization management (UM) review of higher risk orders, according to a study published in the August issue of the *American Journal of Clinical Pathology*. Furthermore, clinicians without specialty training in genetics make genetic test order errors at a significantly higher rate than geneticists. Ensuring the laboratory is actively involved in the diagnostic workup through UM review is important to minimize diagnostic errors and unnecessary costs to patients.

Previous studies identified diagnostic errors tied to mistakes in test selection and ordering. Additionally, send-out test orders, particularly, for genetic tests remain a costly issue for laboratories. However, results show that lab UM programs can address both of these issues—effectively decreasing send-out testing costs and minimizing errors associated with genetic test orders.

The researchers retrospectively analyzed a UM case database at a pediatric, tertiary care medical center consisting of 1,393 genetic test orders (September 2012 to February 2015). Reviewers categorized order modifications and cancellations, quantified positive results and order errors, and compared errors by provider (genetics with nongenetics) for both inpatient and outpatient orders. Cancellations were characterized as resulting from cost, redundancy, inappropriateness, lack of insurance preauthorization, deferral of testing (e.g., waiting for other testing results), or new information making the test no longer necessary.

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RNA Profiling May Aid in Fever Differentiation in Infants, Children

Treating fevers in young children has been a longstanding challenge for clinicians. Rapid differentiation between viral and bacterial infections can alter the course of clinical care and use of antibiotics. Two new studies published in the Aug. 23/30 issue of the *Journal of the American Medical Association (JAMA)* show that RNA signatures of host response may represent an important advance in determining the pathogenic source of infection in febrile children.

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The UM system required reviews by doctoral-level faculty or genetic counselors for laboratory orders with costs (to the laboratory) above a defined threshold (lowered from $1,000 to $700 during the course of this study), multiple genetic tests on one order, orders requested to be sent to a non-preferred or international laboratory, orders requested for send outs for tests performed in-house, and orders for tests associated with predefined conditions known to be associated with errors or other ordering problems (e.g., familial mutation testing).

The researchers found that overall 67 percent of test orders were approved (n=936), while the UM affected one-third of all genetic test orders. Specifically, the review led to 15 percent of orders being performed sequentially (n=205), 9.4 percent were modified (n=131), and 8.6 percent were cancelled (n=121). The most common reason for modifications was high cost, while problems with preauthorization were the most common reasons for cancellation. The overall error rate (derived from incorrect orders that were corrected during review or cancelled because they were deemed inappropriate) was 3.0 percent.

"Of the orders with errors, we found that approximately one-fourth (or about 1 percent of all orders) could have had diagnostic implications for the patient if the order was not corrected, demonstrating that the UM program not only decreases waste but also helps prevent diagnostic errors," write the authors led by Patrick C. Mathias, M.D., Ph.D., from University of Washington, Seattle. Additionally, the authors say "more than half of modifications or cancellations decreased costs by selection of an alternate reference laboratory or were prompted by the institution's insurance preauthorization policies (which were instituted to prevent patients from receiving unexpected large bills due to rejection of claims by insurance carriers)."

Errors, Cancellations by Provider Type

The cancellation rate for nongenetics providers was three times the rate for geneticists, although rates of abnormal results were similar between the two groups. However, the authors suspect the influence of the UM program on test cancellation may have contributed to the similar positive result rates between the groups. Geneticists were more likely to order sequential testing than nongeneticists.

Approval rates and abnormal result rates were similar for inpatient and outpatient orders. Tests ordered or recommended by nongeneticists had error rates near 5 percent in both inpatient and outpatient settings. However, order error rates reached approximately 8 percent among tests recommended by genetics providers in the inpatient setting, which the authors say, "reflects the fact that inpatient orders are entered by residents who have less experience ordering genetic tests."

"The findings of this study reinforce past work suggesting that send-out testing presents a high risk for order entry error," writes Mathias and colleagues. "These findings emphasize that developing system solutions to handle the total genetic testing process should be a priority for laboratories and health systems. … Even orders from genetics providers had an error rate of nearly 2 percent, which emphasizes the utility of a structured UM program that relies on expert review by laboratory professionals."

Takeaway: UM review of higher risk genetic test orders can cut costs for laboratories and patients, as well as catch order errors that potentially hold diagnostic implications for patients.

Periodic Exome Reanalysis Yields New Diagnoses

Reanalysis of clinical exome data at a two- to three-year interval could result in an incremental 10 percent diagnostic yield, according to a study published online July 21 in *Genetics in Medicine*. The authors offer some practical suggestions for laboratories evaluating the cost-benefit of the time, labor, and expense associated with reanalysis versus the incremental gain in understanding of variant-disease associations reported each year.

"Frequent reevaluation of exomes is challenging in practice because of the required labor."

— Aaron Wenger, Ph.D.

A 25 percent diagnostic yield for clinical exome sequencing of patients with presumed Mendelian disorders has been previously reported. However, approximately 250 new, gene-disease and 9,200 variant-disease associations are reported annually, the authors say.

In the present study raw exome (pro-band only) and phenotypic data of 40 individuals with previously nondiagnostic clinical exomes were reanalyzed with current software (ANNOVAR, version 527, to annotate variants) and literature for each candidate causative variant. Overall, the majority of participants were female (n=25), 10 years of age or younger at the time of initial sample collection (n=31), and had a neurologic or neurodevelopmental condition (n=28). On average, the initial clinical exome reports were issued 20 months before reanalysis.

The researchers made a definitive diagnosis for 4 of the 40 participants—a causative, de novo variant in a relevant autosomal-dominant disease gene. At the time of the initial clinical exome reports, the literature to tie the causative genes to the participants' phenotypes was weak, nonexistent, or not readily located and the variant was not listed in the report. But at the time of diagnosis by reanalysis, the supporting literature was 1 to 3 years old.

The authors say that the growth in the literature is exemplified by case 1, who was issued a nondiagnostic exome report on July 25, 2012. However, the first paper linking the de novo mutation to the condition was published two weeks after the report—in August that year. The data was added to the Human Genome Mutation Database the same day as publication.

"Yet, nearly three years later, the patient remained undiagnosed," write the authors, led by Aaron Wenger, Ph.D., from Stanford University in California. "This illustrates the great need to regularly reevaluate nondiagnostic exomes in light of updated knowledge to maximize diagnostic yield."

Some clinical laboratories do reanalyze exomes upon a provider's request, the authors acknowledge, but may limit reanalysis requests to one per year or require a fee for reanalysis. The cost-benefit calculation for more frequent reanalysis could be shifted with increased automation; the ordering of trio exomes; and requests for providers for reanalysis that include an update on the patient phenotype.

"Frequent reevaluation of exomes is challenging in practice because of the required labor," writes Wenger and colleagues. "Larger studies may be helpful to define a standard practice for the timing of reanalysis, taking into account the cost of reanalysis and the evolving rate of discovery of gene-disease relationships."

Takeaway: Periodic, systematic reanalysis of clinical exome data may yield relevant additional diagnoses based on improvements in variant understanding in the interim time. Ideal time for reanalysis requires further study.

Expanded, Panethnic Carrier Screening May Be More Effective

Expanded carrier screening may significantly increase the detection of carrier status for severe genetic conditions, compared to current screening guidelines, according to a study published in the Aug. 16 issue of the *Journal of the American Medical Association*. Additionally, universal expanded carrier screening can help narrow the discrepancy in detection rates among different ethnicities, the authors say.

> *"Just because these variants can now be detected, there needs to be convincing evidence before they all are tested for and possibly acted upon."*
>
> — Wayne Grody, M.D., Ph.D.

"Expanded carrier screening revealed that many non-European racial/ethnic categories have a risk of profound or severe genetic disease that may not be detected by the guidelines in place at this time of analysis," write the authors led by Imran Haque, Ph.D., vice president of scientific affairs at molecular testing firm Counsyl (South San Francisco, Calif.).

Currently, carrier status is screened for a limited number of single-gene conditions, partially based on the patient's ethnicity. Experts say that for a disorder to be included in recommended population-based carrier screening guidelines the condition must be relatively frequent, associated with well-characterized, predictive mutations, and uniformly severe clinically. Even still, there is a lack of consistency in national organizations' recommendations—the American Congress of Obstetricians and Gynecologists (ACOG) only recommends universal screening for cystic fibrosis, while the American College of Medical Genetics and Genomics (ACMG) recommends both cystic fibrosis and spinal muscular atrophy testing for all.

Counsyl conducted retrospective modeling analysis of results from expanded carrier screening conducted on 346,790 reproductive-aged individuals (Jan. 1, 2012 to July 15, 2015) without a known indication for genetic testing. Testing used Counsyl's Family Prep Screen on either a targeted genotyping or next-generation sequencing platform. The test screens for status of 110 genes causing 94 autosomal or X-linked recessive conditions, including rare and ultra-rare disorders. The laboratory reported only known and likely pathogenic variants. Results were based on 11 self-reported racial/ethnic categories with a minimum of 5,000 samples.

The researchers found that the frequency of fetuses potentially affected by a profound or severe condition ranged from 94.5 per 100,000 for Hispanic couples to 392.2 per 100,000 for Ashkenazi Jewish couples. In all racial/ethnic categories, except African or African American and Southeast Asian, the expanded carrier panel would detect at least twice as many hypothetical fetuses with severe and profound diseases versus testing using the ACOG and ACMG panel recommendations.

"Just because these variants can now be detected, there needs to be convincing evidence before they all are tested for and possibly acted upon," cautions Wayne Grody, M.D., Ph.D., from University of California, Los Angeles, in an accompanying editorial. "Every additional disease screened requires additional genetic counseling resources to convey the results and risks of the test. … In the emotionally charged prenatal setting, a cautious approach to prenatal carrier screening … is the most prudent course of action."

Takeaway: Despite the optimism that expanded, panethnic carrier screening can identify more potential risk of severe and profound diseases, there needs to be some caution in how to practically counsel clients on a potentially large number of variants. G2

Inside The Diagnostics Industry

Laboratories Play Key Role in Combatting Hospital-Acquired Infections

Hospital-acquired infections (HAIs) are one of the most frequent complications for hospitalized patients. External pressures, including value-based reimbursement and national efforts to improve antibiotic stewardship, are causing hospitals to refocus their efforts on combatting HAIs. Evidence shows that a combination of infection control methods is most effective in bringing down HAI rates. But, increasingly laboratories have a central role to play in the investigation of cases of HAI.

A Sizable Issue

The U.S. Centers for Disease Control and Prevention (CDC) estimates there are about 722,000 HAIs in U.S. acute care hospitals annually and HAIs contribute to 75,000 patient deaths during their hospitalizations. HAIs not only can be life threatening, but they are also costly—nearly $10 billion annually in HAI. CDC data shows HAIs are declining, but they remain a pervasive problem given that on any given day, approximately one in 25 U.S. patients contracts at least one infection during their hospital care. Stubbornly high HAI rates demonstrate the need for improved infection control in U.S. hospitals.

It is widely recognized that no one strategy can prevent all HAIs. Active surveillance—the systematic collection of samples from either all or high-risk asymptomatic patients—is thought to be an effective tool in hospitals' arsenal to combat HAIs. A landmark study published in the *Journal of the American Medical Association* in June 2015 showed that a "bundle" of pre-surgical interventions can significantly reduce the incidence of surgical site infections due to Staphylococcus aureus. Central to this strategy was early nasal screening of patients undergoing total hip or knee replacements and cardiac operations. Yet, active surveillance is not as widely adopted as some in infection control would hope, in part because of mixed results of studies assessing the strategy's clinical and cost effectiveness.

HAIs are Declining

CDC's 2016 HAI Progress Report is based on data from 2014. For the top five HAIs, CDC found:

- 50 percent decrease in central line–associated bloodstream infections between 2008 and 2014
- 17 percent decrease in surgical site infections from 2008 to 2014, although rates varied by procedure
- 13 percent decrease in methicillin-resistant Staphylococcus aureus bacteremia between 2011 and 2014
- 8 percent decrease in Clostridium difficile infections between 2011 and 2014
- No change in catheter-associated urinary tract infections between 2009 and 2014

"There is not universal agreement about the impact active surveillance makes on infection rates," Michael Pfaller, M.D., chief medical officer at T2 Biosystems, tells *DTET*. "Beyond that, if you are doing active surveillance, there is no standard approach. You must understand what your local problem is. Then you must decide who to screen, how often, and what to do with the results."

Currently, though, hospitals are feeling increased pressure to combat HAIs due to increasing concern over multidrug-resistant organisms, as well as financial incentives created by quality-based reimbursement. For U.S. fiscal year 2017, the Centers for Medicare & Medicaid Services is adopting new outcome measures for the safety domain in its Hospital Value-Based Purchasing Program, which intends to tie Medicare payments to the quality of inpatient care. There will be penalties for hospitals with too high rates of hospital-onset methicillin-resistant Staphylococcus aureus (MRSA) bacteremia and Clostridium difficile (C. diff) infection. Additionally, this safety domain will carry increased weight in determining payments.

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Role of Laboratories

This increasing pressure on hospitals provides an opportunity for clinical microbiology laboratories to play an important and strategic role in cutting HAIs. To do this, laboratories need to provide high-quality testing to identify pathogens and drug susceptibility. Aside from testing, though, John Daly, M.D., chief medical officer at the non-profit accreditor COLA, says microbiology labs can support infection control and surveillance efforts in a number of important ways.

- The microbiology laboratory should serve as a consultant to the infection control program and designate a high-level person to serve on the infection control committee.
- Laboratories should monitor and report results of unusual findings suggestive of an outbreak or emergence of multi drug-resistant organisms.
- Make laboratory test data accessible, including for support of epidemiologic analysis.
- Store isolates that may require further testing for outbreak investigations.

In a recent review published June 7 in *Frontiers in Microbiology* experts from Universidade Nova de Lisboa in Portugal offer additional suggestions.

- The director of the microbiology laboratory should be a clinician or a laboratory scientist with expertise in both infectious diseases and microbiology.
- Laboratory information systems are critical for aiding communication within the hospitals between clinicians and laboratories. These information systems need to be designed collaboratively to ensure effective communication and a positive impact on decision-making.
- Off-site location of laboratories can delay communication and can weaken infection prevention and antibiotic stewardship infrastructures.

Economics of Active Surveillance

The literature remains conflicted regarding the most effective way to screen for HAIs and what portion of infection control efforts should be devoted to screening in vertical infection control efforts versus activities like hand hygiene, environmental cleaning, and other horizontal approaches.

Economic analyses can aid in evaluating the real-world feasibility of competing strategies. Two recent studies published in *PLOS One* examined cost of screening and demonstrate the complexity of trying to optimize active surveillance efforts.

Given that the majority of MRSA carriers are asymptomatic, a Canadian hospital compared risk-based screening for MRSA upon admission to universal MRSA screening. Patients with a positive polymerase chain reaction (PCR) test result were placed on contact precautions until hospital discharge or documented MRSA eradication. Costs for laboratory testing, contact precautions and infection control, private room costs, housekeeping, and length of hospital stay were compared.

The researchers found that risk factor-based MRSA screening assessed approximately 30 percent of admitted patients and cost the hospital over $780,000 annually. The universal screening program screened approximately 83 percent of admitted patients and

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cost over $1.94 million dollars, with an estimated additional cost per patient screened of $17.76. Costs for newly identified patients ranged from $599 for MRSA colonization to $1,834 for MRSA bacteremia. The cost associated with a false positive screening test was $526 per patient. As expected, the greatest increase in costs attributed to universal screening was from laboratory costs ($397,750/year).

Other costs resulting from universal screening and the increased number of identified patients with MRSA colonization included revenue loss due to private room use, increased length of stay ($183,989/year), contact precautions ($125,067/year), and housekeeping ($17,391/year).

The study, published July 27, showed that while the universal MRSA screening program was costly from a hospital perspective, it was not more clinically effective at reducing MRSA transmission than risk-based screening.

A separate study, published March 31, conducted a dynamic cost-effectiveness evaluation of strategies to combat C. diff. Interventions were assessed alone and "bundled" together. The interventions included aggressive C. diff testing; empiric isolation and treatment of suspected patients; improved adherence to hand hygiene and contact precautions; improved use of soap and water for hand hygiene; and improved environmental cleaning. Patients were tested for the presence of C. diff using a PCR test ($7.66 per test). Incidence of CDI ranged from 1.8 to 19.6 per 10,000 patient-days, depending on the level of importation and transmissibility of C. diff modeled.

The University of Utah researchers found that when analyzed separately, hand hygiene compliance, environmental decontamination, and empiric isolation and treatment were the interventions that had the greatest impact on both cost and effectiveness. However, when assessing the series of bundled interventions, at intermediate levels of transmission, the bundle can reduce both inpatient costs and infections. At high levels of transmission, the bundle of interventions yielded a net cost savings. Optimal levels of each intervention did not provide an added benefit that outweighed the increased cost compared with intermediate levels.

Examination of Some Real-Life Surveillance Strategies

Health care organizations with total MRSA clinical infections or blood-stream infections greater than .3 per 1,000 patient days should implement a MRSA control plan, according to a review study published June 15 in the *Journal of Clinical Microbiology*. The authors say that very low rates of clinical disease can be achieved with active surveillance testing and follow-up contact precautions or universal decolonization based on a review of studies involving more than 5 million patients.

Culture versus Molecular Identification of Pathogens

The gold standard for clinical microbiology includes culturing for isolation of pathogens followed by identification procedures (e.g., biochemical, molecular, serologic). However, molecular methods (including multiplex polymerase chain reaction [PCR], real-time PCR, and Matrix-assisted laser desorption/ionization time of flight mass spectrometry) are encouraging clinically because they speed time to results and appropriate therapy, have high specificity and sensitivity, but are more expensive and require specialized equipment and training.

Additionally, whole-genome sequencing (WGS) holds promise in infection control for its ability to efficiently generate all the genetic information needed for epidemiological studies—pathogen identification and resistance markers—and outbreak investigation. However, the translation of the large amount of data generated by WGS into clinically useful information is still evolving.

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In implementing an active surveillance testing program, the University of Chicago (Illinois) researchers say the laboratory must structure their MRSA surveillance testing based on a combination of factors. These factors include test performance (sufficient sensitivity and specificity); test cost (expense to the laboratory); and result reporting time (that enable placing patients in contact precautions for 80 percent of the time they are in the hospital).

"For example, a test with high cost and high specificity may actually be less expensive overall than one with low cost and low specificity since low specificity leads to unnecessary patient isolation, which can add as much as $30,000 of unnecessary isolation cost for every 10,000 tests done for each 1 percent loss of test specificity," explains co-author Lance Peterson, M.D., from University of Chicago.

C. Diff

Active surveillance testing for toxigenic C. diff may not be cost efficient in settings with low prevalence of colonization, according to a study published July 20 in *BMC Infectious Diseases*. Additionally, the Chinese researchers found that ICU-acquired toxigenic C. diff infections were not linked to detection at the time of admission.

Rectal swabs were collected from 360 adult patients on admission to and at discharge from a 50-bed medical ICU of a major referral hospital in western China, (Aug. 2014 to Nov. 2014). Stools were collected from patients who developed ICU-onset diarrhea. Both swabs and stools were screened for toxin B gene (tcdB) by PCR. tcdB-positive samples were cultured for C. diff.

The researchers found that the prevalence of toxigenic C. diff colonization was 1.7 percent on admission and 4.3 percent at discharge. None of these patients developed diarrhea during their hospitalization in ICU, so all were classified as carriers. Only 1.1 percent of 360 patients had C. diff infection (10.7 cases per 10,000 ICU days) and none of these cases had toxigenic C. diff either on admission or at discharge, suggesting C. diff was acquired during their ICU stay.

Takeaway: Active surveillance testing is expected to become a more integral part of comprehensive hospital infection control plans, given mounting pressure to cut HAI rates. However, evidence suggests there may not be a one-size-fits-all approach to designing these strategies.

CDC's Prevention Epicenters Program 2016 Awardees

In June 2016, CDC awarded $26 million to five academic medical centers, through 2020, as part of the Prevention Epicenters Program. These centers develop and test innovative approaches to preventing infections and improving patient safety in health care settings. Below is a sampling of laboratory-related initiatives.

Chicago Prevention & Intervention Epicenter (Illinois)

- Monitoring the regional transmission of Carbapenem-resistant enterobacteriaceae (CRE) using whole genome sequencing and phylogenetic analysis
- Building a the web-based multidrug-resistant organism registry as an informatics tool to monitor state-wide CRE trends and to improve health care facility-level and regional awareness of CRE carriage and spread

Washington University (St. Louis)

- Detecting novel biomarkers and using metabolic profiles to predict and diagnose urinary tract infections
- Studying the benefits of active surveillance to prevent and control MRSA, along with the role of colonization pressure in MRSA and C. diff acquisition

University of Pennsylvania (Philadelphia)

- Using biomarkers to inform antimicrobial prescribing
- Understanding the role of biomarkers in predicting clinical outcomes, as well as the utility of markers to distinguish specific anatomic sites of infection

RNA Profiling May Aid in Fever Differentiation in Infants, Children, *Continued from bottom of p.1*

Currently, seriously ill, febrile children are admitted to the hospital and given antibiotics until culture results can rule out bacterial infection. This poses a major burden on health care resources and a challenge for antibiotic stewardship, but is considered acceptable given the substantial risk of serious bacterial infections (estimated to be approximately eight percent) in febrile infants less than 60 days of age. Researchers are hopeful that a genomic approach, based on analysis of the host response to infection through RNA biosignatures, can more quickly and effectively differentiate bacterial and viral infection sources.

"These two preliminary studies represent promissory notes," writes Howard Bauchner, M.D., editor in chief of *JAMA*, in an accompanying editorial. "If the promises of findings reported in the studies … are fulfilled by replication and refinement in other rigorous investigations, it may be possible that such advances will further reduce morbidity, mortality, and costs associated with caring for febrile children. The day when a parent of a febrile child may do a laboratory test at home, call a physician, and mutually decide if that child should be seen for evaluation may soon be here."

RNA Biosignatures in Febrile Infants

Researchers from the Pediatric Emergency Care Applied Research Network used a convenience sample of 883 febrile infants (median age, 37 days) evaluated for fever (over 38 degrees C) in 22 emergency departments from 2008 to 2010. RNA biosignatures were assessed in 279 infants (89 with bacterial infections—including 32 with bacteremia and 15 with urinary tract infections—and 190 without bacterial infections), along with an additional 19 healthy infants.

The researchers found that 66 classifier genes were identified initially that distinguished infants with and without bacterial infections in the test set with 87 percent sensitivity and 89 percent specificity. A narrowed set of 10 classifier genes could distinguish infants with bacteremia from those without bacterial infections in the test set with 94 percent sensitivity and 95 percent specificity.

"Despite the young age of the febrile infants evaluated, they carried robust RNA biosignatures and demonstrated that regardless of the etiology of the infections, their immune systems are programmed to respond not only with shared elements induced by common microbes but also with specific patterns that allow discrimination by class of pathogen," writes lead author Prashant Mahajan, M.D.

Genetic Signatures Useful in Older Children, Too

Differentiating pathogen source in febrile children is also clinically important in older children.

Researchers from the IRIS Consortium retrospectively assessed samples from febrile children presenting to hospitals internationally between 2009 and 2013. The discovery group included 240 children (median age, 19 months) with 52 cases of definite bacterial infection (of whom 36 required intensive care) and 92 cases of definite viral infection (of whom 32 required intensive care). Ninety-six children had indeterminate infection. RNA expression signatures identified in the discovery group were assessed for diagnostic performance in the validation group. Additional validation occurred in children with meningococcal and inflammatory diseases.

The researchers found that RNA expression data identified a 38-transcript signature that distinguished bacterial from viral infection. A smaller (two-transcript) signature was implemented as a disease risk score in the validation group (130 children, including 23 children with definite bacterial, 28 definite viral, and 79 indeterminate infections; median age, 17 months). The two-transcript signature correctly confirmed definite bacterial infection in all 23 patients with microbiologically confirmed infection (sensitivity, 100 percent) while 27 of 28 patients with definite viral infection were classified correctly (specificity, 96.4 percent). High sensitivity and specificity was seen also in children with meningococcal and inflammatory diseases.

"The DRS signature, distinguishing viral from bacterial infections with only two transcripts, has potential to be translated into a clinically applicable test using current technology such as polymerase chain reaction," write the authors led by Jethro Herberg, Ph.D. "A major challenge in using transcriptomic signatures for diagnosis is the translation of multitranscript signatures into clinical tests suitable for use in hospital laboratories or at the bedside. … New methods for rapid detection of nucleic acids, including nanoparticles and electrical impedance, have potential for low-cost, rapid analysis of multitranscript signatures."

Takeaway: RNA-based tests that correctly distinguish febrile infants and children with bacterial infection from those with viral sources are emerging as a viable test that could cut time to diagnosis and reduce inappropriate antibiotic prescription.

New Strategies Increase HCV Testing in Primary Care, ER and Linkages to Care

Given how common the viral infection is, routine Hepatitis C virus (HCV) testing is not performed often enough. The majority of those infected are unaware of their status and many infected patients are diagnosed late—after decades of infection when HCV-related complications have set in.

Previous surveys identified barriers providers cite for not implementing testing, like the one-time, universal testing of baby boomers recommended by the U.S. Centers for Disease Control and Prevention (CDC). These barriers include the time required to identify risk factors from a patient history; the need to discuss sensitive or stigmatized behaviors; uncertainty that insurance would not cover HCV testing or treatment; and concern that identified patients could access HCV care.

But new models to increase routine testing and improve linkages to follow-up care may be scalable. Two new studies published in the June special supplement issue of *Public Health Reports* show that HCV testing can be expanded in both primary care and the hospital and effectively linked to follow-up care.

Testing in Federally Qualified Health Centers

As part of CDC's Hepatitis Testing and Linkage to Care initiative, the National Nursing Centers Consortium (Philadelphia, Penn.) integrated routine, opt-out HCV testing and linkage-to-care model at five Federally Qualified Health Centers (FQHCs) in Philadelphia (Oct. 1, 2012, to June 30, 2014). The model included medical assistant-initiated testing, reflex laboratory-based HCV tests, and electronic health record alerts. Two centers serving patients at high risk for HCV conducted

universal testing, while three health centers serving patients at low risk for HCV conducted risk-based testing.

The researchers found that 4,207 unique patients received HCV antibody (anti-HCV) testing, with 11.6 percent testing positive. Of those testing anti-HCV positive, 88.7 percent received a confirmatory HCV RNA polymerase chain reaction (PCR) test, with 72.3 percent of these patients (n=313) diagnosed with current infection (overall prevalence, 7.4 percent). Ultimately, 77.6 percent of HCV RNA-positive received their test results and 38.7%) were linked to care.

The authors cite several lessons learned that led to adjustments to further promote testing and improve clinic protocols.

- Bundling HCV and HIV tests resulted in a 52.7 percent increase in HCV tests performed between the 11 months before (1,786 tests performed) and after (2,728 tests performed) dual HCV/HIV testing started.
- As of June 2014, all health centers adopted universal testing. To do this, an EHR query runs each evening to identify adult patients with next-day appointments who have no HCV diagnosis or HCV test result in their chart.
- To combat testing fatigue and to accommodate new staff, a project manager visits each clinic weekly to report the total numbers of tests performed and address any training issues. An average of 211 more anti-HCV tests were performed monthly—a 63.9 percent increase—between the five months before and the five months after this adjustment.

Hospital-Based Testing

In December 2012, a South Texas safety-net hospital launched an HCV screening program for patients born between 1945 and 1965 with no HCV diagnosis or prior HCV test. An HCV screening laboratory order was automatically added upon admission for anti-HCV tests combined with reflex HCV RNA PCR confirmatory testing for identified age-eligible patients.

The researchers found that over the program's first 10 months, 2,327 patients were screened for HCV, with an anti-HCV positive prevalence of 8 percent. Of the 167 (out of 192) anti-HCV-positive patients who received follow-up HCV RNA PCR testing nearly two-thirds had detectable HCV RNA indicating chronic HCV infection, yielding an overall prevalence of detected chronic HCV infection of 5 percent.

A program review revealed that more than 60 percent of screening-eligible patients did not have the test performed because nurses were not engaging in the informed-consent process with patients for testing. The informed-consent process was deemed too onerous for nurses during intake evaluations. So, the screening protocol was adjusted to opt-out consent, with patients learning about the program from hung posters and flyers in admission packets. Following this change, monthly program evaluations demonstrated three-quarters of eligible patients had the HCV screening added to their admission orders and fewer than 5 percent of patients opted out of testing.

Diagnosing HCV Infection

Two tests are used to diagnose HCV infection. The HCV antibody test determines if someone has been exposed to the virus, while the confirmatory test detects the presence of HCV RNA to definitively identify people with current, active disease.

Takeaway: Scaling HCV testing in FQHCs and safety net hospitals is an important way to identify large numbers of people with previously undiagnosed HCV and link infected patients to follow-up care.

G2 INSIDER

Labs Must Rapidly Implement Zika Blood Supply Testing

The U.S. Food and Drug Administration (FDA) recently classified the Zika virus as a transfusion-transmitted infection and called on all U.S. blood centers to start universal screening of donated whole blood and blood components for the virus. While a necessary step to protect the nation's blood supply, experts say that immediate implementation is likely to pose a challenge for some blood banks and for the third-party laboratories.

According to the American Red Cross nearly 14 million units of whole blood and red blood cells are collected each year from about seven million donors. While the number of confirmed U.S. cases of Zika is still small in comparison, Zika has been detected in blood donated from asymptomatic individuals in Puerto Rico and there are reports of probable transfusion-transmission of Zika in Brazil.

As "precautionary measures" the FDA called for immediate implementation of nucleic acid testing of all donations and use of an approved pathogen reduction technology for platelets and plasma donations. Currently there are no approved Zika tests, however two tests are available under an investigational new drug application—Roche's cobas Zika assay and Hologic's Procleix Zika virus blood screening assay. The cost of adding Zika testing to the blood screening process is less than $10, according to the South Texas Blood and Tissue Center.

Implementation of the guidance is to be immediate for blood centers in states and territories with local transmission—Florida and Puerto Rico, which has already been screening since March. Blood centers in Alabama, Arizona, California, Georgia, Hawaii, Louisiana, Mississippi, New Mexico, New York, South Carolina and Texas have four weeks to comply, while all other states and territories have 12 weeks. Several blood centers began voluntary testing ahead of the FDA's Aug. 26 guidance.

- In late August the American Red Cross said it is conducting blood donor tests for Zika virus under an investigational study in five southeastern states at greatest risk of local mosquito transmission of Zika virus. However in September the organization will expand this testing to four additional states in the south central and southwestern United States.
- As of Aug. 1, OneBlood began using an investigational donor screening test throughout the company's service area in Florida, Georgia, Alabama and South Carolina, although the FDA had asked for testing in just the two affected Florida counties of Miami-Dade and Broward. The company says it has capacity to test 3,000 samples per day at its facility in St. Petersburg, Fla.
- In mid-July the South Texas Blood and Tissue Center became one of the first centers to begin testing blood donations for the Zika virus. Zika testing is being performed in the QualTex labs in Georgia, because of space and capacity requirements for the Roche testing equipment.

Company References

American Red Cross
800-733-2767

Counsyl 888-268-6795

Hologic 781-999-7300

National Nursing Centers Consortium
215-731-7140

OneBlood
888-936-6283

Pediatric Laboratory Utilization Guidance Services
206-987-336

Roche Diagnostics
800-428-5074

South Texas Blood & Tissue Center
210-731-5555

U.S. Centers for Disease Control and Prevention
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 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: 1-888-729-2315 • Fax: 1-855-649-1623. Web site: www.G2Intelligence.com.

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