G2 INTELLIGENCE

Diagnostic Testing & Technology Report

Competitive Intelligence & Analysis for an Expanding Global Market

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Gains Being Made Integrating IT, Genomic Data

The Mount Sinai Biobank Program (New York) announced in May that it reached the milestone of enrolling 25,000 participants in its BioME program, representing one of the most diverse patient populations in the world of individuals who have consented to DNA sequencing, ongoing contact from researchers, and longitudinal studies related to data embedded in the electronic medical record (EMR).

The program is a large repository of DNA and plasma samples enabling molecular research. On the clinical side, clinicians and information technology experts at Mount Sinai developed and are gradually implementing a program called CLIPMERGE (Clinical Implementation of Personalized Medicine through Electronic Health Records and Genomics), which unites emerging genetic understanding with EMR-based clinical information, giving doctors real-time therapeutic guidance based on a patient's genetic profile. Currently this guidance is clinically available for three conditions related to cardiovascular disease, blood clots, and high cholesterol. But Mount Sinai says that as greater genotype-phenotypic relationships are unveiled, BioMe and CLIPMERGE will be updated accordingly.

"With its interoperable BioMe and CLIPMERGE platforms as flagship institutional infrastructures, Mount Sinai has the unique capability to close the loop between genomic discovery and the implementation of genomic medicine in clinical care," says the organization in a statement.

For more information on how the integration of information technology and genomics data will affect the adoption of personalized medicine, please see *Inside the Diagnostics Industry* on page 5.

Medicare Panel's Rejection Shows Deficient Evidence Base With Emerging Molecular Tests

A Medicare advisory panel in May expressed little support for two types of genetic testing—those to determine cancer of unknown primary site (CUP) with metastatic tumors and those to identify patients at higher risk of cervical cancer. The vote of low confidence, experts say, has to do more with the lack of evidence demonstrating impact on clinical outcomes than the validity of the tests. Test developers throughout the diagnostics industry need to work to plug this evidence gap in order gain recognition by professional societies in clinical practice guidelines and by payers with reimbursement and coverage.

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▲ **Rejection of Genomic Tests,** *from page 1*

"This [process] basically establishes what evidence exists behind a test and shows there is a big hole in clinical utility. Does having information from this test make patient outcomes better? No one made that leap," says Diane Allingham-Hawkins, Ph.D., senior director, genetic test evaluation program at the consulting firm Hayes (Lansdale, Pa.). "Evidence is very much at the front and center of the discussion right now. There is awareness that this is the barometer tests will be judged by and companies must realize that. . . . Given the fact that organizations like CMS now know what they are being asked to pay for, there will be an increasing use of evidence."

As part of the review process, the Centers for Medicare and Medicaid Services (CMS) commissioned technology assessments on the two types of genetic tests. The 12-member Medicare Evidence Development and Coverage Advisory Committee voted with an average score of 2.08 (using a 1 to 5 scale of low to high confidence) for the clinical utility of DNA- or RNA-based testing to predict the origin of CUP. The panel had higher confidence (average 3.25 score) that the test results were reliable (clinical validity). Commercially available tests in this category include CancerTypeID (bioTheranostics), miRview (Rosetta Genomics), and PathworkDx (Pathwork Dx). The panel had even less confidence in the tests aimed at identifying high-risk patients for cervical cancer based on uncertain Pap smear findings. The panel voted 1.67 for the test's reliability to detect cancer.

"Manufacturers need to look critically at trial results. They say it shows clinical utility, but really it shows clinical validity. It detects what it is supposed to, but it is not showing a difference in patient outcomes. They need to go one step further," Allingham-Hawkins tells *DTTR*. "There is the 'it should make a difference' argument, but you cannot infer it will make a difference in actual practice. This is especially important for very, very expensive tests. A $100 test is not going to receive the same scrutiny as a $5,000 test. With that expense, you can understand why CMS wants to see evidence."

Acknowledgement of this evidence void is growing more widespread, and in May the Center for Medical Technology Policy (CMTP; Baltimore) released an effectiveness guidance document (EGD) aiming to close the gap between the pre-

Clinical Validity, Utility Recommendations

The Center for Medical Technology Policy has issued a set of recommendations covering how to best assess the clinical validity and utility of molecular cancer diagnostic tests. The multiyear project involving a broad spectrum of key stakeholders sets out specific evidence goals and study design recommendations to improve the quality of these studies to ensure their relevance to reimbursement, policy, and clinical decisions. The recommendations include these:

- The potential therapeutic actions or decisions based on test results must be specified in advance.
- Both beneficial and harmful outcomes of testing must be measured, including validated patient-reported outcomes and robust end points such as survival and downstream health care utilization. Insufficient end points for demonstrating clinical utility include changes in physician behavior and intended care plans, which do not necessarily link clinical management decisions with outcomes.
- Clinical utility of a molecular biomarker should be assessed with randomized controlled trials. Randomizing patients to genomics-guided treatment versus usual care reduces statistical power and is not optimal because it requires larger sample sizes to demonstrate an effect of the test.
- Prospective-retrospective study is adequate to generate evidence of clinical utility if a clinical trial with banked biospecimens exists.
- A molecular diagnostics test's clinical utility can be established with single-arms studies if it is Food and Drug Administration-approved based on pivotal trials, adequate archived biospecimens are not available, complete or overall response is a feasible end point, and comparable response data in a noncontemporaneous comparative cohort exists.
- Longitudinal observational study designs (prospective cohort studies, patient registries that explicitly include comparators, and multiple group, pretest/posttest designs) can be acceptable, but not retrospective observational studies.
- Decision-analytic models are useful if there is no direct evidence of clinical utility, if clinical validity is established.

sumed benefits of tests undergoing technology assessments and the actual evidence needs of payers, clinicians, and professional societies.

"Although the calls for better evidence are frequent, there is considerable debate about how much evidence is needed and how it can be generated in an efficient and timely way," wrote Patricia Deverka, M.D., senior research director at CMTP and lead author of the EGD. "The purpose of this initiative was to close the gap between the presumed benefits of tests undergoing technology assessments and the information needs of payers, clinicians, and patients. Our overarching goal is to bring greater clarity and predictability regarding the evidence requirements of all interested stakeholders."

With the increased reimbursement transparency that came with the initiation of 114 new molecular pathology Current Procedural Terminology codes this year and the threat of increased regulation of laboratory-developed tests looming, the need to build consensus on evidence requirements is great as future coverage and reimbursement of molecular tests is at stake for test developers.

Tethys Bioscience Set to Launch PreDx Finger Stick Test

Tethys Bioscience (Emeryville, Calif.) is commercially launching a fingerstick version of its PreDx diabetes risk stratification test. Validation results demonstrating both comparable accuracy to the whole blood version of the test as well as superior accuracy to fasting glucose tests were presented at the American Association of Clinical Endocrinologists (AACE) annual scientific congress in Phoenix in early May.

The PreDx test is a fasting blood test that estimates the five-year likelihood of developing type 2 diabetes in adults with prediabetes. The assay utilizes an algorithm that incorporates seven proteomic biomarkers (blood glucose, glycated hemoglobin, insulin, adiponectin, c-reactive protein, IL-2Rα, and ferritin) as well as age and gender to stratify patients by diabetes risk. Results are presented on a 1 to 10 scale corresponding to an individual's five-year risk of developing type 2 diabetes, with a higher score indicating a higher risk of progression. Approximately 175,000 venous blood samples have been processed since the PreDx test's launch in 2009.

In the abstract presented at the AACE meeting, the company demonstrated that after calibration, PreDx Finger Stick (FS) values from a set of 80 matched samples showed excellent one-to-one agreement across the PreDx range with no significant differences in area under the curve, positive predictive value, or sensitivity. As with the original PreDx venous blood test, performance of PreDx Finger Stick was significantly better at predicting development of diabetes than fasting glucose.

Drops of blood are collected on an AdvanceDx100 serum separator collection card, enabling the PreDx FS test to be used in primary care and wellness center settings not equipped with phlebotomy. The test is currently run in the company's CLIA-certified lab. The company says the test allows for more efficient allocation of health care resources toward those at highest risk of progressing to diabetes as well as an effective tool for monitoring the impact of lifestyle interventions in reducing the likelihood of progression.

Pamela Parkes, senior manager, marketing and communications at Tethys, tells *DTTR* that the test is reimbursed as an out-of-network test by most private payers but that discussions are ongoing to attain in-network status, as well as Medicare reimbursement. Current reimbursement is about $300 per test.

The privately held, venture-backed company is also developing tests to determine risk for first-time heart attack, osteoporotic fracture, and other cardiometabolic diseases.

Calls Increasing to Expand Drug, Alcohol Testing Programs for Physicians

While drug and alcohol testing as a condition of employment is common among physicians applying for hospital-based positions, there are increasing calls for expanding hospital quality-control programs to include screening for substance abuse impairment through random testing and following sentinel events leading to a patient's death.

Expanding substance abuse testing of physicians will bring the medical profession better in line with other high-risk industries like the airlines, railways, and nuclear power, according to an article published online ahead of print April 29 in the *Journal of the American Medical Association* (*JAMA*). Data do not exist showing impaired physicians are actually harming patients. But there is recognition that alcohol, narcotic, and sedative addiction is as common among physicians as the general population and that medical errors are common in hospitals.

California Voters May Decide on Drug Testing for Physicians

A California state ballot measure that would require doctors to be randomly subjected to drug and alcohol testing is being proposed by Bob Pack, a technology executive. The *San Francisco Chronicle* reports the campaign already has $2 million as supporters ramp up efforts this summer for a potential November 2014 ballot initiative. The California Medical Association calls the effort an "ill-fated publicity stunt" as the measure may also call for lifting the cap on damages in medical malpractice cases.

"In states without proactive [physician health] programs, it seems, by default, that patient harm has to occur before a review process occurs," write the authors, led by Julius Pham, M.D., Ph.D., from Johns Hopkins University in Baltimore.

Self-monitoring, rather than external regulation, has been the norm in ensuring physician professionalism. But the authors of the *JAMA* article say that expansion of physician health program oversight coupled with hospital-level implementation might provide a foundation for physician impairment regulation. Components of such a model, they say, might include mandatory physical examination or drug testing or both before a hospital medical staff appointment, random alcohol and drug testing as is done for federal employees and the military, routine drug and alcohol testing for all physicians involved with a sentinel event leading to patient death, and potential expansion of the Joint Commission's current physician health standards so that a national regulatory or accrediting body could maintain consistent standards across states including protections such as confirmatory testing and confidentiality, as implemented by the Federal Aviation Administration program, which may aid in protecting professional reputations in the case of false negatives.

"The need to detect and prevent physician impairment must be balanced with the rights of privacy and autonomy," writes Pham. "In other high-risk industries, this right [to be protected from impairment] is supported by regulations and surveillance. Shouldn't medicine be the same?"

G2 INTELLIGENCE
Inside the Diagnostics Industry

Emerging Technologies Present Huge Challenges In Data Collection, Utilization

Health care is being inundated with data—biologic data derived from advances in technology, namely next-generation sequencing and individual patient-level data found in electronic health records (EHRs) including imaging and laboratory test results, medical and prescription claims, and even monitoring information originating in remote, personal health devices. While the health care system is moving toward data-driven medicine to improve care and contain costs, clinicians can't keep up with emerging genomic information in the literature and even data derived from individual patients.

"We are trying to improve the speed and accuracy of diagnosis by using health information technology," says Robert El-Kareh, M.D., an assistant professor of bioinformatics at the University of California, San Diego. "Physicians are under enormous time pressure, especially for outpatients, and there is an information overload with alerts." He adds that adding genotypic information may add to that information overload so "some thought needs to be put into integrating information that has evidence so it can make a real clinical impact."

The realization of personalized medicine is dependent upon a technology-based transformation of the health care system. The technological challenge of sequencing an individual's genome has been achieved. Now, the challenge migrates to analyzing raw genomic data for actionable clinical use. Health information technology (IT) will drive the adoption of genomic-based medicine if it can surmount the big data challenge of processing, storing, and accessing relevant genomic data.

"When a doctor talks to a patient, they typically make their differential diagnosis and order the minimum number of tests that will allow them to pick the right diagnosis," says Justin Starren, M.D., Ph.D., chief of health and biomedical informatics at Northwestern University (Chicago). "They already know how they are going to interpret that test, and the way that test is interpreted does not change over time. Whereas with whole-genome sequencing there is a huge amount of data and [clinicians] are interested right now in only one tiny piece of it. The question becomes what to do with everything else. There is a need for ancillary systems."

Big data is big. Sequencing a single genome creates terabytes of raw data. Secondary analysis of data from assembled genome can cut the size

NIH Seeking Associate Director for Data Science

As a sign of its commitment to embracing big data as a programmatic goal, the National Institutes of Health (NIH) is hiring an associate director for data science who will be the overall organizational leader in the broad areas of bioinformatics, computational biology, biomedical informatics, biostatistics, information science, and quantitative biology. Among the listed responsibilities will be to coordinate all NIH data-related science activities, partner with other agencies, as well as oversee the new NIGH Big Data to Knowledge (BD2K) initiative.

The position and BD2K both emerged from recommendations made by the Data and Informatics Working Group of the Advisory Committee. The BD2K initiative seeks to improve policies for sharing data and software and for cataloging data in part through the development of standards. Additionally, the NIH will launch the InfrastructurePLUS program to advance high-performance computing, hosting, and storage approaches and to modernize the NIH network.

According to a McKinsey & Co. study, the NIH is not alone in looking for data experts. In the United States there will be a shortage of 140,000 to 190,000 people with analytical expertise in the coming years.

by a thousandfold to gigabytes. Tertiary analysis then matches patient genotype with clinical relevance. Complicating current efforts is a lack of standardization at all steps along the way, making the process of whittling down big data to clinically manageable and accessible EHR data plain daunting—from the expense of maintaining servers, privacy concerns of cloud storage, and finding staff with bioinformatics expertise to analyze the data.

Emerging Prototypes

There are a variety of emerging scenarios of how to pair actionable genomic knowledge and patient data—whether EHRs incorporate and update clinical rules or whether patient data is uploaded to ancillary systems that are queried for relevant clinical information.

The Mayo Clinic is prospectively collecting DNA and sequencing roughly 85 genes used in pharmacogenomics for 1,000 patients predicted to need a common drug (statin, anti-coagulant) over the next five years. Christopher Chute, M.D., section head for medical informatics at Mayo, says this project serves two goals. First, it is a real-world trial for how a handful of four to five genotype variants validated with clinical measures can function in EHRs with decision support. When a prescription for one of the targeted drugs is made, decision support makes a recommendation to increase, decrease, or avoid a drug altogether, informed by genetic information. Second, though, the program is sequencing significantly more genes than are currently clinically utilized, which will provide a much richer data resource to investigate not yet recognized pharmacogenomics interactions.

Several experts point out the many parallels between genomic data and the evolution that occurred with digital radiology. Radiology had to develop a system with standard formatting and medical education for the reporting and storage of imaging results in the digital age. Imaging tools have advanced to produce "image slices" greater than an individual physician is able to comprehend, requiring visualization tools to aid in clinical diagnosis. Systematizing and storing the data is still evolving as EHRs are meaningfully used and connected in a systemwide fashion. Chute predicts similar types of data repositories that are connected to EHRs will emerge for genomic data, but only a subset of that data becomes part of the patient record. Consortiums, rather than individual provider systems, are working on deciding what is clinically actionable—a task that is rapidly evolving.

Starren predicts that prototype systems will emerge, many based on those being developed in clinical research settings, over the next two to five years, but it will likely be several years after the implementation of meaningful use 3.0 before

Ingenuity Systems Bought by Qiagen

Recognizing that more rapid analysis and interpretation of genomic data derived from next-generation sequencing will be a differentiating factor, at the end of April, Qiagen (Germany) acquired Ingenuity Systems (Redwood City, Calif.) for $105 million, using existing cash reserves. In 2012 Ingenuity had net sales of $12 million. The cornerstone of Ingenuity's Web-based offerings is its Knowledge Base, a 14-year effort to curate, model, and computationally structure vast amounts of biomedical literature, including genomic variations. These data are leveraged to more quickly analyze and interpret data in research and clinical diagnostics.

"The interpretation of biological information is becoming a cornerstone of QIAGEN's ecosystem of Sample & Assay Technologies for molecular testing—both in life sciences research and in diagnostics," said Peer Schatz, Qiagen's CEO, in a statement at the time of the acquisition. "We are looking forward to expanding the seamless integration of leading biomedical information solutions into our full range of molecular testing solutions, thereby providing our customers a unique experience from sample to interpreted result and recommendations for next steps."

there is widespread adoption, as few are willing to take on more than required IT workload right now.

How these big data solutions will interface with EHRs and practice-management tools on a larger scale remains unclear. But experts agree that for genomic-based personalized medicine to become a full-fledged reality, decision-support systems must converge multiple sources of clinically meaningful data.

El-Kareh adds that one of the biggest challenges of incorporating genomics into medicine is to make it accessible, and there are a lot of barriers to doing that. "EHRs are not suited to large data sets and it will require a fair amount of work on the technical side, but also with consideration of ethics and policies," he says. "If genomic information is only available in one EHR system, what use is that if the sequence isn't available everywhere. But, building systems to exchange health information have barriers—financial, ethical, and privacy issues. It is very complex."

"Inertia and culture are not necessarily aligned with the needs of health care and society, but the genomic world has an opportunity to get our act together and agree on some aspects to make data consistent and comparable, while still allowing the research field to maintain flexibility to innovate," Chute tells *DTTR*. "Sharing data is a way for society to benefit and improve health quality."

Commercial Analysis Companies Abound

Commercial applications for genome analysis are proliferating with many able to raise venture capital financing. According to a report from Mercom Capital Group there were 104 health IT-related venture capital funding deals during the first quarter of 2013, compared with 30 during the same quarter in 2012.

Experts do not expect a dominant player or consolidation to occur in this segment any time soon as the companies attempt to differentiate their offerings and justify that their proprietary software is better than freely available options. Below is a sampling of some of the commercial genome analysis companies.

Bina Technologies (Redwood City, Calif.) in March closed a $6.25 million Series B round of financing. The Bina Genomic Analysis Platform is an end-to-end service platform that combines high-performance computing with informatics algorithms enabling more rapid analysis of a whole genome. The company says a whole human genome can be analyzed in about four hours. The server can sit in a customer's own data center.

DNAnexus (Mountain View, Calif.) offers a solution that combines a cloud computing infrastructure with scalable systems designs in which users can run their own algorithms. The company raised more than $15 million in October 2011 from investors including from Google Ventures.

GNS Healthcare (Cambridge, Mass.) applies industrial-scale data analytics to allow stakeholders across the health care industry to solve complex care, treatment, and cost challenges. The core of its approach is the REFS platform (Reverse Engineering and Forward Simulation), a scalable, supercomputer-enabled framework that automates the extraction of causal network models directly from observational data and uses high-throughput simulations to generate new knowledge.

NextBio (Santa Clara, Calif.) uses big data solutions to improve molecular data interpretation for clinical and research applications by integrating and interpreting public and proprietary molecular data with clinical patient information, population studies, and model organisms.

Personalis (Menlo Park, Calif.) offers sequencing services and interpretation for clinicians and pharmaceutical and biotechnology companies. The company was recently awarded a $1.53 million contract with the U.S. Department of Veterans Affairs to look for genetic variants in samples from as many as 1 million military veterans to explore the variants' roles in disease. The sequencing will be performed by Illumina (San Diego).

RealTime Genomics (San Francisco) offers complete analytical platforms for genomics and metagenomics either installed in users' computing environment or through cloud computing. In May the company secured $5 million to expand commercial operations. The company's platform is used at the Stanford Center for Genomics and Personalized Medicine.

Seven Bridges Genomics (Cambridge, Mass.) is a Web-based platform that offers both validated and custom design pipelines, including from curated public data sources. It aims to be accessible to people with no expertise in bioinformatics.

Half of Reported HCV Cases Not Tested for Infection, Prompting Changes to CDC Testing Recommendations

Only half of patients reported to have hepatitis C virus (HCV) infection undergo HCV RNA testing to identify current infection, according to a Vital Signs report published in the May 10 issue of *Morbidity and Mortality Weekly Report*. This current lack of identification of patients who could benefit from treatment is prompting the U.S. Centers for Disease Control and Prevention (CDC) to update its testing guidelines to include HCV RNA reflex testing in patients with a reactive HCV antibody test.

Previous CDC guidelines for HCV laboratory testing and reporting (2003) focused on identifying HCV antibody-positive persons and, therefore, reports to state and local surveillance programs have included persons with a past HCV infection that has resolved. Only HCV RNA testing can identify patients with current infection who could benefit from treatment. But according to the latest CDC data, only half of patients reported for reactive HCV antibody tests receive HCV RNA testing.

Researchers analyzed surveillance data from eight U.S. reporting sites (2005 to 2011). For the sake of analysis a positive HCV RNA result could be determined from either HCV nucleic acid testing or HCV genotyping. The researchers found that of 217,755 persons with newly reported positive test results, 49.2 percent were HCV antibody-positive only and 50.8 percent were reported with a positive HCV RNA result, indicating current HCV infection. The percentage reporting positive HCV antibody results varied only by reporting site, ranging from 76 percent in New Mexico to 23 percent in Minnesota.

As is consistent with the heavy burden of HCV infection among persons born from 1945 to 1965, the majority of patients reported in both groups were born in this range—58.5 percent of the HCV antibody-positive-only and 67.2 percent of the HCV RNA-positive. The CDC had amended testing recommendations in 2012 to include one-time HCV testing for all persons born between 1945 and 1965, regardless of other risk factors, because of the high prevalence of HCV infection in this group.

Acknowledging that testing strategies must ensure the identification of those persons with current HCV infection, in May, the CDC issued an update to its HCV testing recommendations. For primary care and public health providers, initial HCV testing begins with either a rapid or a laboratory-conducted assay for HCV antibody in blood and for reactive results HCV RNA testing using either serum- or plasma-reactive result should follow.

"CDC is issuing this update in guidance because of 1) changes in the availability of certain commercial HCV antibody tests, 2) evidence that many persons who are identified as reactive by an HCV antibody test might not subsequently be evaluated to determine if they have current HCV infection, and 3) significant advances in the development of antiviral agents with improved efficacy against HCV," wrote the CDC Association of Public Health Laboratories workgroup responsible for the amendment.

Among the changes in the commercial HCV testing market since 2003 are the availability of OraSure Technologies' rapid HCV antibody test and the discontinuation of previously recommended RIBA HCV test (Novartis Vaccines and Diagnostics).

STI Screening in Adolescents Remains Low Despite Research Into Optimizing Approaches

Despite U.S. Centers for Disease Control and Prevention recommendations calling for gonorrhea and chlamydia testing each year in sexually active women younger than age 25 years and universal HIV screening, regardless of sexual risk, beginning at age 13 years, screening rates for adolescents remain abysmally low, according to a study presented at the Pediatric Academic Societies annual meeting (Washington, D.C.; May 4-7).

Researchers from University of Pennsylvania School of Medicine (Philadelphia) randomly selected 1,000 routine visits by adolescents treated at a diverse array of 29 primary care practices and analyzed data regarding sexual history documentation and performance of sexually transmitted infection (STI) testing (gonorrhea, chlamydia, and HIV). Overall just over one-fifth (21.2 percent) had a documented sexual history, of which 21.2 percent were currently sexually active. STI and HIV testing was performed in 37.8 percent and 22.2 percent, respectively, of documented sexually active patients.

"I didn't expect the rates to be 100 percent, but it was surprising just how low they were," author Monika Goyal, M.D., now an assistant professor of pediatrics at Children's National Medical Center in Washington, D.C., tells *DTTR*. "The two messages to take away from this study are that sexual risk assessments and screening are not being done as well as they could be in a primary care provider's office and that we are still practicing risk-based screening."

Sexual history documentation was more likely to occur in patients who were older than 15 years, compared to 13- to 14-year-olds, black, and those with nonprivate insurance. STI testing was more likely to be performed in patients who were male, black, or had nonprivate insurance.

Goyal believes that getting these data out to primary care providers as well as the advent of electronic health record-based alerts may improve adolescent screening.

Screening Strategies

Two other presentations at the meeting assessed the effectiveness of alternative gonorrhea and chlamydia screening strategies—one among high-risk adolescents in a clinic and one among asymptomatic adolescents treated in an urban pediatric emergency department (ED).

> ***"The two messages to take away from this study are that sexual risk assessments and screening are not being done as well as they could be in a primary care provider's office and that we are still practicing risk-based screening."***
>
> ***—Monika Goyal, M.D.***

Researchers at the University of Louisville School of Medicine in Kentucky studied the impact of targeted screening for gonorrhea and chlamydia versus the screen-all policy implemented in 2010 at their urban clinic. A retrospective review of medical records of 879 adolescents (67 percent female; 91 percent African American) that were tested showed that 12 percent tested positive for either or both chlamydia and gonorrhea. Among 598 high-risk teens 17 percent were positive, while 1.4 percent of non-high-risk teens were positive.

Targeted screening would have detected 96.2 percent of positive teens. Based on the cost of one test ($140.80) the estimated cost of screening non-high-risk teens per ad-

ditional positive test was $9,856 overall and $13,376 in females, causing the authors to conclude that data support targeted STI screening recommendations in high-risk adolescent populations.

In an additional study, researchers from Newark Beth Israel Medical Center prospectively enrolled asymptomatic patients (aged 14 to 24 years) treated in the ED between January 2011 and September 2012. Included patients were medically stable and did not have genitourinary or abdominal symptoms. Patients reporting recent testing or treatment were excluded.

Out of the 313 patients screened (70.7 percent female) for gonorrhea and chlamydia, 16 percent tested positive for either or both STI. Patients were given specific written follow-up instructions to obtain test results and, if needed, receive free treatment and partner notification and treatment. This follow-up treatment was received by 89 percent of patients with chlamydia and 83 percent with gonorrhea.

"In populations with increased risk for gonorrhea and/or chlamydia infection and high rates of symptomatic disease, ED screening of asymptomatic patients reveals a concomitantly high rate of asymptomatic disease," write the authors, led by Devra Gutfreund, M.D. "Routine urine screening for asymptomatic gonorrhea and/or chlamydia infection within the ED should be considered and high follow-up rates support this screening."

Risk Factors Can Form Basis of Targeted Hospital Screening Program for C. diff

Asymptomatic C. difficile (C. diff) colonization is present at hospital admission in nearly one of 10 patients, according to a study published in the May issue of the *American Journal of Infection Control*. Initiating screening based on three independent risk factors for colonization can be used as the basis for a targeted surveillance program to identify asymptomatic patients with colonization at admission, thereby potentially cutting in-hospital transmission.

"While more research needs to be conducted on the transmission of C. difficile infection from colonized patients, this study may help institutions with persistently high rates of transmission develop an expanded strategy for targeted C. difficile surveillance," said Patti Grant, RN, president of the Association for Professionals in Infection Control and Epidemiology, in a statement.

Due to the steady climb (2004 to 2008) in health care-associated C. diff at Mayo Clinic-affiliated hospitals (in spite of the use of private rooms and contact precautions for patients with suspected or confirmed C. diff infection), researchers assessed data from 320 consenting adults, without symptoms of C. diff infection, admitted to a tertiary care hospital on 20 predetermined study days (March 1 through April 30, 2009). The first stool sample after admission was tested for toxigenic C. diff using polymerase chain reaction (PCR). Eighty percent of samples were received within 48 hours.

Positive results for toxigenic C. diff were found in 9.7 percent of participants. Recent hospitalization, chronic dialysis, and corticosteroid use were independent predictors of C. diff colonization. Forty-eight percent of participants had one of the three risk factors, and screening these patients at admission would identify 74 percent of C. diff carriers, which the authors say is in the range of previously published screening efficiency rates for methicillin-resistant staphylococcus aureus (MRSA).

"The risk of transmission from asymptomatic reservoirs is the rationale behind recommendations for active surveillance for health care-associated pathogens such as MRSA and vancomycin-resistant enterococci but identification of asymptomatic C. diff carriers is not currently recommended," write the authors, led by Surbhi Leekha, MBBS. "Although the extent of contamination of health care workers and the environment from asymptomatically C. diff colonized individuals is less compared with patients with diarrhea, these asymptomatic C. diff carriers could be an important source of C. diff transmission."

The authors additionally note that a "significant practical limitation" to C. diff surveillance, anaerobic cultures, was overcome in this study with use of real-time PCR.

Lack of C. Diff Testing, Improper Diagnosis Plagues European Hospitals

There are wide discrepancies across hospitals in Europe as to the percentage of diarrheal samples being tested for C. diff, and more than 6 percent of hospitalized diarrheal patients were diagnosed incorrectly, according to a study presented at the 23rd European Congress of Clinical Microbiology and Infectious Diseases or EUCLID (Berlin; April 27-30).

The first wave of results from the multicenter EUCLID study involved samples from 482 hospitals in 20 European countries. Just under 4,000 fecal samples were tested at the EUCLID national coordinating laboratory (NCL), where it was determined the average incidence rate of C. diff infection across Europe is 6.6 per 10,000 patient bed days, "substantially" higher than previously estimated.

Alarmingly, 24.6 percent of samples positive for C. diff at the NCL had not been tested at the local hospital level, and 47 patients (2.3 percent) positive for C. diff at the NCL were tested but diagnosed incorrectly (false negative) at the local hospital. Only 10.6 percent of hospitals tested all diarrheal inpatient samples. There was a wide range across hospitals with respect to the percentage of samples tested for C. diff—97 percent at a Czech hospital to 0 percent in a Bulgarian hospital. Despite national guidelines to test all inpatient diarrheal samples, only 75 percent of U.K. samples had been tested.

"These results show that there is still more to be done to improve the way C. diff infection is currently being tested in hospitals across Europe," said Mark Wilcox, M.D., a professor at the University of Leeds (United Kingdom) and coordinator for the EUCLID study. "It is important that optimal methods of diagnosis are in place, as errors may lead to inappropriate or inadequate treatment of patients and inadequate infection control measures."

A second sampling and testing wave will occur this summer with the full results and analysis expected in 2014. The study is funded by Astellas Pharma Europe.

G2 Insider

Lactoferrin, Inter-Alpha Inhibitor Protein May Differentiate Bacterial Infections in Kids . . . Lactoferrin (LF) and inter-alpha inhibitor protein (IaIp) are being investigated as potential biomarkers for differentiating serious bacterial infections in hospitalized pediatric populations, according to abstracts from two related pilot studies presented at the Pediatric Academic Societies annual meeting (Washington, D.C.; May 4-7). LF and IaIp are known to play a role in infection-related inflammation and its modulation, but they are not well studied in pediatric patients.

In the first study the Brown University researchers prospectively collected data from 40 children admitted to a tertiary children's hospital for infectious illnesses. Cases (n=28; mean age 6.7 years) had positive cultures or imaging or a discharge diagnoses consistent with bacterial disease, whereas controls (n=12; mean age 2.4 years) were negative for all three. Values of white blood count (WBC), absolute neutrophil count (ANC), procalcitonin (PCT), and LF were all significantly higher in the cases versus the controls. IaIp values approached, but did not reach, significance. IaIp values for both groups were lower than literature-based healthy control values.

In the second study, the same group of researchers sought to determine whether children with pathology-confirmed appendicitis (16 cases with mean age 10 years) had significant changes to LF or IaIp compared to children presenting with abdominal pain without appendicitis or any other surgical emergency (eight controls with mean ages 11.3 years). Values for WBC, ANC, and PCT were significantly higher in kids with pathology-confirmed appendicitis compared to controls. Values for LF and IaIp approached significance.

"There are increasingly good diagnostics for the detection of viruses, but they don't assure us that it is not a concomitant bacterial infection," co-author Russell J. McCulloh, M.D., an infectious disease fellow at Brown University in Providence, R.I., tells *DTTR*. His group will continue to pursue these biomarkers to identify the proper diagnostic mix. Future studies will be conducted in a research network of emergency departments, rather than with admitted patients, and will differentiate bacterial disease states (pneumonia, nephritis, cellulitis, etc.).

Company References

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