G2 INTELLIGENCE

Diagnostic Testing & Emerging Technologies

New Trends, Applications, and IVD Industry Analysis

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Faster Tests Needed to Diagnose Infectious Diseases

While advances in nucleic acid–based amplification technologies have contributed to improved pathogen detection, infectious disease diagnostics are still failing to return results fast enough to meet clinical need. Quicker, more meaningful results have the potential to significantly enhance outcomes in terms of improved antibiotic stewardship, more personalized patient care, and lower health care costs.

"With the current state of diagnostic testing, we are handicapped, making decisions based on limited or nonspecific information—in situations ranging from helping individual patients to identifying broader public health threats," said Angela M. Caliendo, M.D., Ph.D., from Brown University in Providence, R.I., and lead author of the Infectious Diseases Society of America's (IDSA) November 2013 report *Better Tests, Better Care: Improved Diagnostics for Infectious Diseases*. "It is critical," she says in a statement "that we not only invest in the development of new diagnostic tests, but that we also work to ensure these new tests are fully integrated into patient care."

The report calls for enhanced fiscal incentives and streamlined regulatory pathways to make diagnostics research and development more viable for companies, particularly for priority tests aimed at meeting the greatest unmet clinical needs. Specifically, IDSA calls for loosened regulation to access critically needed specimens for test validation, funding for outcomes research to demonstrate the clinical value of diagnostic tests, appropriate reimbursement, and education for providers.

For more information on emerging technologies for the diagnosis of infections, please see *Inside the Diagnostics Industry* on page 5.

G2 Index Up Nearly 50% for 2013; Half of Diagnostics Companies Surpass Broader Market

The G2 Diagnostic Stock Index gained about 14 percent for the second half of the year (July 26 to Dec. 27) and was up nearly 50 percent for the full year 2013 (Jan. 2 to Dec. 27). Thirteen stocks gained for the period, while two stocks lost ground. The G2 Diagnostic Stock Index outperformed the broader stock markets for the year even though the Nasdaq and Standard & Poor's (S&P) both gained widely over the period. The Nasdaq was up 34 percent during 2013, while the S&P increased 26 percent.

The G2 Diagnostic Stock Index's outperformance of the S&P was carried by half of the stocks, with eight companies individually outperforming the S&P. Five stocks had gains for the year but did not perform as well as the S&P.

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▲ **G2 Index Up Nearly 50% for 2013,** *from page 1*

Three of the diagnostic stocks with the largest gains had gains nearing or in excess of 100 percent. Microarray maker Affymetrix (Santa Clara, Calif.) gained 164 percent in 2013, followed by Illumina (San Diego) at 99 percent and Alere (Waltham, Mass.) at 89 percent.

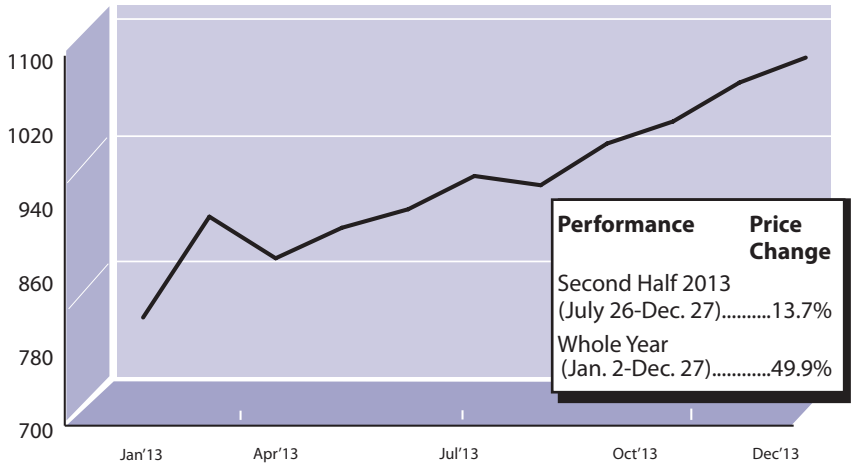
Affymetrix's gains were in part driven by positive results from the company's corporate restructuring program. Additionally, this fall the company released the Minimal Signature E. coli Array, a foodborne pathogen monitoring tool developed in conjunction with the U.S. Food and Drug Administration's (FDA's) Center for Food Safety, as well as the OncoScan FFPE assay kit, which enables whole-genome copy number analysis in highly degraded fixed-paraffin embedded solid tumor samples.

Illumina maintained its dominance in the sequencing market in 2013 and remains a much-talked-about potential takeover target. The company this fall became the first to receive FDA approval for its MiSeqDx system high-throughput sequencing analyzer. Despite the slower than hoped adoption of clinical sequencing, Illumina has begun to establish itself in testing markets through acquisitions as well as through development of its own assays including its cystic fibrosis assay.

The biggest loser for the year was **Sequenom**, whose stock lost 53 percent of its value over the year. The company's stock slid dramatically in the fall on news that a U.S. District Court overturned Sequenom's patent covering its MaterniT21 PLUS noninvasive prenatal test, although appeals are pending. Despite large growth in testing numbers and revenue that beat analysts' expectations in the third quarter, the company, like many molecular companies, is still struggling to capture reimbursement under the new molecular pathology diagnostic codes.

Despite beating analysts' quarterly estimates for the past two quarters, the stock of **OraSure** (Bethleham, Pa.) has slid. The stock was hurt by the FDA's stern warning requiring OraSure customer 23and Me to stop marketing its direct-to-consumer personal genetic test, despite the fact that sales of the oral collection kit to 23andMe represent less than 5 percent of OraSure's revenue. A bounce back is expected in 2014 as OraSure plans on launching its Intercept substance abuse detection device to domestic criminal justice and forensics markets, which holds tremendous revenue potential.

G2 Diagnostic Stock Index



Source: The G2 Diagnostic Stock Index is tabulated by *DTET* from the average percentage change in the stock price of 15 IVD companies.

Up	Price	% Chg
Abaxis	39.61	5%
Abbott Labs	38.37	21
Affymetrix	8.67	164
Alere	35.97	89
Becton Dickinson	110.35	40
Bio-Rad	124.35	16
Cepheid	46.46	31
Illumina	110.38	99
Johnson & Johnson	92.35	32
Luminex	19.17	12
Meridian	26.35	28
Qiagen	23.24	24
Quidel	27.44	38
Down		
OraSure	6.08	-16%
Sequenom	2.30	-53

Novel Maternal Blood Test Can Detect Fetal Oxygen Levels

Measuring the amount of hypoxia-induced mRNA in maternal blood is clinically correlated with the degree of fetal hypoxia in utero, according to a study published Dec. 9 in *BMC Medicine*. Using such a biochemical or molecular marker could be a new, direct strategy to monitor fetal hypoxia in utero, and researchers say the novel noninvasive maternal blood test represents a great advance in quantitatively measuring fetal danger from hypoxia both during labor or resulting from severe, chronic fetal growth restriction.

Current tests (cardiotocograph, ultrasound, Doppler waveform velocimetry analysis) can indirectly identify hypoxic fetuses but not the severity of fetal acidemia (fetal blood pH/lactate concentrations), which can have detrimental birth outcomes including stillborn and severe perinatal injury and disability.

Serial samples of maternal blood were collected prior to induction and commencement of uterine contractions, at commencement of the second stage of labor including full dilatation, and at delivery. The researchers correlated hypoxia-induced mRNA in the samples with the degree of fetal umbilical artery blood samples and placental biopsies collected immediately after delivery. Two cohorts were evaluated—one group with acute fetal hypoxia caused by induction of labor (n=30) and one group with chronic fetal hypoxia due to severe, preterm growth restriction (n=20 cases plus 30 controls), with fetuses delivered by cesarean section. Microarray and real-time reverse-transcription polymerase chain reaction (PCR) were used to quantify mRNAs.

The researchers found that hypoxia-induced mRNAs in maternal blood rose across labor with a "precipitous increase" during the second stage of induced labor. In the second cohort, hypoxia-induced mRNAs were elevated in the blood of women carrying severely growth-restricted preterm fetuses. The hypoxia gene score (sum of the relative expression of four hypoxia-induced genes, Hif1α, Hif2α, LdhA, and Adm) was strongly correlated with fetal acidemia at birth in both cohorts, as well as with the severity of ultrasound Doppler velocimetry abnormalities in fetal vessels.

"Ours may be the first 'theoretical' noninvasive test for women in labor that can determine the degree of in utero fetal acidemia," write the authors, led by Clare Whitehead, M.B.Ch.B., from the University of Melbourne in Australia. "The speed of current PCR technologies means such a test is not feasible as a clinical tool to make decisions during labor but improvements in nucleic acid detection technologies might make such a test possible in the future."

However, the test may have more immediate potential in the case of chronic hypoxia from severe fetal growth restriction, although larger validation would still be necessary for that indication.

"It is conceivable that day-to-day clinical decisions regarding timing of a fetal growth restriction fetus can await the results of a PCR result performed using machines available today. Therefore, our test may have a role in situations where current tests of fetal well-being are equivocal and the clinician is left unsure whether the fetus should be delivered," writes Whitehead. Other future iterations of the test may include expansion with identification of other hypoxia-induced genes and development of a clinical test that expresses mRNA abundance by copy number versus relative expression.

Takeaway: A future test that can quantify the severity of fetal hypoxia has the potential to improve fetal and birth outcomes. G2

Lab-on-a-Chip Development Expanding To Include At-Home Anti-Convulsant Monitoring

Researchers report the successful development of a prototype lab-on-a-chip for measuring anti-epileptic drug levels from saliva samples. Initial results show the promise of the immunoassay for two commonly used anti-epileptic drugs, but the researchers say they hope to expand the noninvasive testing system to include validation of up to 15 marketed anti-epileptic drugs, potentially replacing the need for serial, outpatient serum monitoring in optimally dosing millions of patients with epilepsy.

The researchers developed a multiplexed nanochip-based immunoassay that incorporated drug-specific sensitized beads for the anti-epileptics phenytoin and phenobarbital, according to the proof-of-concept study presented at the American Epilepsy Society annual meeting (Washington, D.C.; Dec. 6-10). Epilepsy patients taking one or both of the drugs were recruited to provide a single serum sample and multiple salivary samples (collected either by passive drool or an oral swab that was diluted). Saliva results were compared to gold-standard serum testing conducted using a particle-enhanced turbidimetric immunoassay in a clinical chemistry laboratory, as well as salivary samples assayed with gas chromatography-mass spectrometry at a commercial toxicology laboratory. Limits of detection and the useful range of the assay were computed.

The bio-nanochip calibration signals were "robust" and provided low, reliable limits of detection. The assay also compared favorably to the gold-standard serum tests and gas chromatography-mass spectrometry testing. Future work will increase the number of samples tested, expand the assay to include additional drugs, and adapt the electronic reader to a practical point-of-care diagnostic size, eventually a handheld, credit card-sized device, that will make monitoring drug levels outside of medical settings feasible.

"Labs add time, cost, inconvenience, and another problem is needlephobia and difficulties with vascular access, especially in small children," Giridhar Kalamangalam, M.D., an associate professor of neurology at University of Texas, Houston, tells *DTET*. "These bio-nanochips are a new generation of compact, programmable chemical processors that will satisfy the urgent need for a noninvasive, adaptable, and cost-effective alternative to a blood test. They have already been successfully piloted in other contexts and their advantages of portability and easy accessibility with alternate fluid samples make adaptability to the epilepsy world sensible."

While it will likely take several years before the at-home monitoring system is commercially available, Kalamangalam says making the system as user friendly as possible is the goal and that includes not just the user interface, but the cost. The disposable chips will likely cost just cents to run a test and the researchers are trying to get the electronic reader to be similar in cost to a cellphone.

Takeaway: Lab-on-a-chip test development will continue to expand the opportunity to utilize at-home monitoring for chronic conditions, including epilepsy.

G2 INTELLIGENCE
Inside the Diagnostics Industry

Labs Move Toward Rapid Diagnoses of Infections

The downstream effects of infectious disease diagnostics are significant. The appropriate test can optimize anti-microbial use, decrease hospital lengths of stay and unnecessary isolation, reduce health care costs, and most importantly improve patient outcomes by cutting time to proper therapy. At a broader level, diagnostics enable public health surveillance and can aid in detecting and responding to outbreaks to known or emerging infections. Unfortunately, current tests integrated into routine care do not yet optimally meet clinical needs for either individual patients or the public's health.

A report released by the Infectious Diseases Society of America (IDSA) in November, *Better Tests, Better Care: Improved Diagnostics for Infectious Diseases*, is designed to "raise the red flag about the paucity of new and rapid tests," according to IDSA President Barbara Murray, M.D. In addition, the report makes a number of recommendations to address unmet needs in diagnostics, including the need for rapid results.

Clinical signs of common but serious infections, including those in the bloodstream and gastrointestinal tract, present with nonspecific symptoms. While waiting for test results, many patients with suspected infections are treated with broad, empiric antimicrobial therapy, rather than appropriate therapy dictated by the rapid identification of the infectious agent. "The result," IDSA says, "is overuse of our small inventory of effective antimicrobials, whose numbers continue to dwindle due to increasing levels of antimicrobial resistance."

Priorities For Infectious Agent Diagnostics Development

To address the highest priority, unmet diagnostic needs, IDSA says that federal incentives are needed to stimulate diagnostics research and development, particularly for tests that:

- Are performed directly from accessible, minimally invasive clinical specimens (blood, respiratory samples, urine, and stool);
- Have strong test accuracy and performance characteristics (at least a 98 percent negative predictive value);
- Incorporate biomarkers (either pathogen- or host-derived) that are capable of classifying clinically significant infections (bacterial, fungal, viral, or parasitic) and demonstrating host response to a pathogen (drug resistance information);
- Are grouped as panels targeting the most important clinical syndromes (central nervous system, sepsis and bloodstream, respiratory tract, and gastrointestinal tract infections);
- Are for pediatric use;
- Are rapid and have substantially better "time to result" than currently approved tests;
- Are available at the point of care to allow for wider usage in outpatient settings; and
- Improve outbreak detection and maintain public health surveillance capability.

Despite the focus on new diagnostic technologies, including molecular platforms that have improved infectious disease identification and quantification, there is still profound reliance upon traditional diagnostic methods, concludes the report. Standard microscopy and culture methods have not changed dramatically in more than a century and remain time-consuming endeavors.

"The field of clinical microbiology is currently in transition and standard-of-care testing is now a hybrid of old and new methodologies," says IDSA. While nucleic acid–based amplification technologies have improved sensitivity and specificity, improvements are still needed in upping multiplex capabilities, decreasing turnaround time, simplifying ease of use, minimizing batch sizes while increasing workflow efficiency, and lowering test cost.

"We are at the beginning of a significant transformation in diagnostics and it is critical to capitalize on the current opportunity to invest in the most needed diagnostics and enable the

utilization of improved diagnostics for both clinical management and public health surveillance," writes IDSA.

DTET examined some of the breakthroughs in infectious disease detection in 2013, including platforms that have recently won regulatory approval as well as emerging technologies that will contribute to the continued revolution in infectious disease diagnosis in the coming years.

MALDI

While the term *game-changer* is often overused, most experts agree that the use of mass spectrometry for bacterial identification has the potential to truly alter laboratory workflow and profoundly enhance timely clinical care by cutting the time needed for identification of microbial infectious agents from days to hours.

Bruker (Billerica, Mass.) in late November received U.S. Food and Drug Administration (FDA) 510(k) clearance for its MALDI (matrix-assisted laser desorption/ionization) Biotyper CA System for the identification of gram-negative bacterial colonies cultured from human specimens. This becomes the second MALDI system approved for use in the United States. The VITEK MS from bioMerieux (Durham, N.C., and France) was approved in August 2013. Bruker plans to commercially launch the system in U.S. hospitals and reference laboratories in the first quarter of 2014.

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—IDSA

The MALDI Biotyper CA System uses proteomic fingerprinting with high-throughput MALDI-TOF (time-of-flight) mass spectrometry to identify microorganisms including bacteria, yeasts, and fungi. The company says that in the past five years, since the system received its CE mark, many European and other international laboratories have replaced classical biochemical testing for bacterial identification with MALDI due to the accuracy, speed, extensive species coverage, ease of use, and cost-effectiveness of the system. More than 1,000 systems have been sold or leased to date, the company says.

"The ability to identify organisms directly from plates—saving at minimum a day over conventional phenotypic tests for many organisms—has impacted therapy, timely infection control, and contributed to decrease in health care expenditures," says Robert Jerris, Ph.D., the director of clinical microbiology at Children´s Healthcare of Atlanta, whose center was involved in Bruker's trials. "Outcome studies have shown such significant positive results that it is predictable to say that this technology will eventually be a staple in clinical microbiology."

Other Technologies

As *DTET* has previously reported, advancing point-of-care technologies are now capable of testing human and animal samples in the field and tracking infectious disease outbreaks with a mobile phone connected to a cloud-based network. Globally this technology continues to garner interest because of its wide applicability to a variety of infectious agents, noninvasive sampling, and cheap cost. According to researchers from the University College London (UCL; United Kingdom) there are an estimated 6.8 billion mobile phone subscriptions and 1 billion social network users, representing a "massive opportunity" to widen access to tests and track emerging disease outbreaks.

"The revolution in mobile communication, nanotechnology, genomics, and 'big data' analysis offers tremendous opportunities to actively manage outbreaks and ultimately prevent infectious diseases," says Rachel McKendry, Ph.D., who leads the Interdisciplinary Research Collaboration at UCL, which works with industry to develop mobile health technologies for the early diagnosis and tracking of diseases.

Further expanding the ability to take rapid, infectious disease diagnostics into underserved areas is the development of an artificial nose. Bacteria's unique smell can be harnessed to speed the diagnosis of sepsis, according to a study presented at the American Chemical Society national meeting (Indianapolis; Sept. 8-12, 2013).

The point-of-care test combines amplification of bacteria with detection and identification in a single sealed bottle. Attached to the inside of the small, plastic bottle is a chemical sensing array (CSA), the "artificial nose," with 36 pigment dots that change color in response to signature odor chemicals released by bacteria. A blood sample is injected into the bottle and any bacteria present will grow and release a signature odor sensed by the pigment dots. The test is complete within a day, compared to the 72 hours with current technology. According to researcher James Carey, Ph.D., from National University of Kaohsiung in Taiwan, the new device can identify nine of the most common disease-causing bacteria, including two strains of E. coli, with almost 99 percent accuracy under clinically relevant conditions.

"Our CSA blood culture bottle can be used almost anywhere in the world for a very low cost and minimal training," said Carey in a statement. "All you need is someone to draw a blood sample, an ordinary shaker, incubator, a desktop scanner, and a computer."

Recent FDA Approvals of Rapid, HIA, Respiratory Infectious Disease Assays

- BD MAX StaphSR Assay with eXTended Detection Technology: Detects Staphylococcus aureus (SA) and methicillin-resistant Staphylococcus aureus (MRSA) DNA directly from nasal swabs; BD Diagnostics (Sparks, Md.); approved November 2013.
- ICEPlex C. diff Assay Kit and the ICEPlex System: Employs a quantitative multiplex polymerase chain reaction system to detect C. diff; PrimeraDx (Mansfield, Mass.); approved November 2013.
- Quidel Molecular RSV+hMPV assay: Detects the presence of respiratory syncytial virus and/or human metapneumovirus; Quidel (San Diego); approved September 2013.
- Quidel Molecular Influenza A+B assay: Detects influenza A and/or B virus; Quidel, approved August 2013.
- PRODESSE Influenza A Influenza B RSV; Gen-Probe (San Diego); approved August 2013.
- XPERT MRSA/SA Blood Culture Assay: Automated real-time PCR for SA and MRSA DNA from positive blood cultures on the GeneExpert system; Cepheid (Sunnyvale, Calif.); approved June 2013.

Economic Case for Rapid Infectious Disease Testing

While the clinical need for rapid infectious disease tests is clear from a medical practice perspective, IDSA says that increased research efforts are needed to demonstrate the outcomes benefits from such tests, including the economic benefits, as measured by decreased resource utilization resulting from earlier diagnosis.

Earlier infectious disease detection could have a huge financial impact. The Agency for Healthcare Research and Quality says that each year in the United States there are more than 836,000 hospital stays due to septicemia, the sixth most common principal reason for hospitalization in the United States in 2009, costing more than $15 billion. Additionally, the alarming increase in drug-resistant organisms leads to more complicated and lengthier care. With changes to reimbursement that do not allow for additional Medicare payments for conditions that were not present at the time of admission, hospitals are interested in rapidly determining such infections to minimize costs.

Emerging research is quantifying the economic benefit of new infectious disease assays. For example, in a study published Sept. 30, 2013, in the *Journal of Clinical Microbiology*, Nanosphere (Northbrook, Ill.) reported an average 21.7-day reduction in hospital length of stay per patient and an average savings of $60,729 in hospital costs related to use of the FDA-approved molecular assay Verigene Gram-Positive Blood Culture for the rapid detection of bacteria and antibiotic resistance in bloodstream infections caused by Enterococcus. In addition, there was a significant decrease in the average time it took for patients to receive appropriate treatment (23.4 hours), and an even greater reduction in time (31.1 hours) for patients with vancomycin-resistant Enterococcus bacteremia. Finally, there was complete agreement between conventional culture and susceptibility methods and the Verigene test results, but with a significant reduction in time to reporting of test results (47.5 hours).

Surgical-site infections (SSIs) are the most frequent health care-associated infection in the United States, occurring in about one out of every 50 operations, and contribute to the greatest portion of health care-associated infection-related costs nationally. Subsequent infection in surgical patients is heightened in surgical patients with nasal carriage of Staphylococcus aureus (SA), including methicillin-resistant SA (MRSA). According to a study published in *JAMA Internal Medicine,* SSIs due to MRSA increase hospital length of stay for patients by an average of 23 days and cost more than $40,000 per case to treat, but rapid screening and targeted decolonization decrease SSIs and have been demonstrated to improve clinical and economic outcomes for surgical patients.

"Increased accuracy in determining patient colonization with either S. aureus or MRSA can enable clinicians to implement appropriate presurgical prophylaxis and direct appropriate utilization of isolation and decolonization," said Tobi Karchmer, M.D., vice president for medical affairs at BD Diagnostics, the maker of BD MAX StaphSR Assay, the first commercially available molecular assay in the United States that detects recently discovered MRSA strains with the mecC gene.

It is hoped that such economic data will not only increase hospitals' interest in such emerging tests, but that payers will increasingly cover these new tests at reasonable rates. Yet the IDSA says there are significant challenges to the development, regulatory approval, and clinical integration of diagnostic tests that use these new technologies. In addition to increased funding for research and development efforts for critical infectious diagnostic tools, IDSA says easing regulatory requirements regarding the storage and research use of deidentified specimens and clinical use of investigational devices will aid commercialization efforts. Additionally, adoption of emerging technologies and assays will be encouraged with better adherence to guidelines, increased provider education efforts, and more rapid assignment of reimbursement codes at reasonable rates.

Takeaway: It is critically important that new tests are developed that can more rapidly diagnose infectious agents and improve treatment management.

Better Utilization of Diagnostic Testing Needed to Confirm C. Diff

Less than 15 percent of hospitalized patients treated for Clostridium difficile (C. diff) actually have laboratory-confirmed infections, according to a study presented at the midyear meeting of the American Society of Health-System Pharmacists (Orlando; Dec. 8-12).

The researchers analyzed data from the 1,971 patients treated for C. diff infections at a 240-bed hospital (February 2012 through November 2013). All of the patients had been hospitalized for at least three days and were treated with either vancomycin or metronidazole (intravenous or oral). Of the 1,971 patients, only 292 had confirmed C. diff infections via stool culture testing, meaning that 1,679 patients did not have C. diff infections.

As a result of these findings, Mercy Medical Center-North Iowa (Mason City) is developing a pharmacist-led quality improvement project, including an educational program to improve the use of appropriate diagnostic tests.

Broad Guidance Needed to Aid Biobank Sample Stewardship

Results of a recently released survey found that most biobanks do not maintain ongoing relationships with specimen contributors, but they do practice good stewardship over storage and sharing of specimens for research. The authors of the paper, published Dec. 11, 2013, in *Science Translational Medicine*, say that biobanks need better guidance emphasizing stewardship practices throughout the life cycle of specimens in order to achieve the delicate balance of respecting contributors while advancing research.

"Within the context of rapidly expanding genomic and bioinformatic capacities and the rise of next-generation biorepository research, challenges remain in obtaining consent, protecting participant privacy, and maintaining public trust," writes lead author Gail Henderson, Ph.D., from the University of North Carolina, Chapel Hill. "One response to these challenges is greater emphasis on the stewardship model of governance."

The Stewardship Model

The emerging stewardship model, which incorporates obligations on the part of the biobank throughout the life of the specimen, include:

- Community engagement—Forms may include joint governance and return of aggregate level results to participants.
- Improved research design—This includes ensuring that specimens and data are used for agreed-upon purposes, consistent with the terms of consent.
- Proper internal care and oversight of the stored specimens—Professional societies and oversight agencies often maintain these standards and policies.

Source: "Stewardship Practices of U.S. Biobanks" by Gail E. Henderson et al., published in Science Translational Medicine online Dec. 11.

Emerging models indicate that going forward there will be broader responsibilities for biobanks and more complex research relationships than previously experienced. But despite talk of the need for a stewardship model that encompasses the lifespan of biological specimens – from donation through research use – empirical evidence is scarce for how voluntary stewardship is executed in actual practice. In order to identify trends in implementation of stewardship practices, the University of North Carolina researchers conducted a national survey to examine biobank practices pertaining to contributors, within the biobank, and in relationship to researchers.

"Guidance documents do not specifically discuss stewardship as a model of governance, they do address standards for trustworthy acquisition, storage, management, and transfer of specimens and related data," write the authors. "However, implementing these various forms of guidance recommendations is voluntary, and there is no required registration of biobanks that might facilitate adoption of certain standards. Thus, there are almost no data on the extent to which biobanks are following these recommendations. Our study provides such empirical data."

Practices Related to Contributors

The overwhelming majority (96 percent) of respondents (n=404) say that contributors are informed about storage of their specimens. Of these respondents, 79 percent utilize an opt-in approach, while 12 percent utilize an opt-out method. More than three-quarters of those that have an opt-in policy use a broad consent for future research uses, which is consistent with the trend toward unrestricted use. Sixteen percent of those with opt-in policies report a limited consent for certain kinds of research uses.

Half of surveyed biobanks are in a position to create and sustain a relationship with direct, living contributors over time. Just under three-quarters (72 percent) of biobanks maintain individual contact information necessary to return results, but only 19 percent offer individual contributors results from research using their specimens. Aggregate

results are returned to contributors by 38 percent of biobanks. The majority of biobanks do not offer financial compensation to contributors, but 18 percent do. Those biobanks offering financial compensation are significantly more likely to engage in relationship-building practices, including returning aggregate results.

Practices Within the Biobank

The vast majority (94 percent) of biobank respondents have standard operating procedures for processing specimens, with 85 percent using a computerized laboratory information management system that incorporates a computerized inventory system that tracks the location and status of every specimen in the biobank.

Two business practices previously cited in literature as best practices were explored by the survey and found to be lacking in practice. Only one-third of biobanks (34 percent) have a formal business plan and just over one-quarter (26 percent) have a written plan for specimens upon closure of the biobank.

Practices Involving Researchers

Requests for use of specimens and biobank data is relatively common, with 70 percent of biobanks receiving 50 requests or less annually, though, more than one-quarter (27 percent) of biobanks only receive one to five requests. Higher-volume biobanks do exist, with 2 percent reporting between 501 and 1,000 requests annually and 3 percent reporting more than 1,000 requests annually.

Regarding oversight for research uses of stored specimens, 90 percent of biobanks require institutional review board approval, 26 percent have a community advisory board, and 81 percent reported having other oversight boards (scientific review committee or internal advisory board). The majority of biobanks (82 percent) have application forms for researchers requesting specimen or data use. Approval rates for research use vary substantially, with 41 percent of biobanks approving all requests and 58 percent saying they approve some requests. The two most common reasons for denial of requests were because of the scientific merit of the proposed research (57 percent of denials) and lack of specimen availability (43 percent of denials). On the flip side, priority access is given to some researchers based on scientific merit of the proposed study (66 percent) and the feasibility of the study (56 percent).

Researchers are charged for use above shipping and handling fees by 41 percent of biobanks. More than three-quarters (78 percent) of respondents have standardized material transfer agreements. One-third of biobanks require researchers to return remaining specimens, while 21 percent require remaining specimens to be destroyed. Just under one-fifth of biobanks that maintain identifying information (18 percent) report

Biobanks, Researchers Must Broaden Engagement Efforts

All genetic research establishments, including biobanks, must engage ethnic minorities to foster transparency and build trust to broaden research participation, writes Aaron Buseh, Ph.D., an associate professor of nursing at the University of Wisconsin–Milwaukee, in the Dec. 1, 2013, issue of *The Scientist*.

In light of past deception and abuse involving minorities (Henrietta Lacks and Tuskegee syphilis experiments), Buseh proposes use of a community-based participatory research framework that relies upon collaboration between academic and community partners to build inclusivity, education, and discourse.

"When geneticists take off their lab coats, leave the confines of their classrooms and workspaces, and venture into ethnic minority communities to share their work, they are fostering open discourse," writes Buseh. "While ethnic minorities may rightfully wish to focus the discussion on issues of medical mistrust, unethical protocols, and potential deception, genetics researchers can make use of this setting to share technological and scientific advances, and to explain how the participation of minority groups in genetics research proffers potential medical benefits and positive social impacts."

ever providing the identifiers to researchers. Finally, just over half of biobanks (54 percent) require researchers to share aggregate research results with the biobank.

"In viewing biobank practices, did we glimpse stewardship in action? We think so," conclude Henderson and colleagues. "However, what is now needed is a full articulation of the range of best practices for biobanks that address the ethics of stewardship."

Takeaway: Comprehensive guidelines encompassing best practices of specimen stewardship, across the lifespan of a sample from donation through research, are needed so that biobanks can meet increasingly complex challenges surrounding specimen handling and privacy protection.

Routine CBC Could Provide Added Mortality Risk Information

A risk score based on age and the components of a complete blood count (CBC) is strongly associated with all-cause mortality risk and cardiovascular-specific outcomes in an apparently healthy population, according to a study presented at the American Heart Association Scientific Sessions (Dallas; Nov. 16-20). The researchers say the commonly used blood test could be inexpensively incorporated into laboratory results, electronic medical records, and physician workflow to better identify previously unidentified high-risk individuals who would benefit from costly workups or preventive therapies.

The value of the CBC risk score was previously validated in general medical, hospitalized patients, but now researchers have shown the score to be generalizable to a larger, healthier population. They prospectively validated the score for use in individuals initially free of cardiovascular disease participating in a clinical trial, "Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER)" (females, n=6,568 and males, n=10,629).

The researchers found that even after adjusting for age, all-cause mortality was significantly higher in middle-risk and high-risk participants, compared to the lowest-risk participants. Risk of death was 50 percent higher in those with middle risk and nearly twice as high in the highest-risk participants, compared to the lowest-risk. For cardiovascular mortality the CBC risk score was also significantly predictive.

Risk scores have been underutilized in actual practice, often because they add complexity and time to a physicians' workload, lead author Benjamin Horne, Ph.D., says. In the case of the CBC risk score, he tells *DTET* that the CBC risk score is inexpensive both financially, because most individuals get the CBC panel as part of routine care anyway, and because it doesn't add complexity in time or effort for physicians in medical practice.

"Physicians can tell you high cholesterol and high blood pressure and smoking are risk factors, but they don't put it into a calculator to figure out the 10-year risk," says Horne, director of cardiovascular and genetic epidemiology at Intermountain Medical Center Heart Institute in Salt Lake City. "We now have a standardized, quantifiable way of assessing the risk of mortality for all individuals."

Horne says that Intermountain is now reporting the risk score electronically, both in lab reports and in electronic medical records based on lab results reported in the past 30 days. While the evidence is not yet there to start ordering CBC tests when not already utilized in practice, Horne says that in patients where CBC panels are routinely ordered including in hospital patients, the risk score can be easily implemented and can aid in identifying apparently healthy individuals at increased risk of mortality who may benefit from additional testing or standard prevention therapies.

Takeaway: Incorporating a risk score into CBC results is a way that laboratories can inexpensively provide additional value to ordering physicians and the broader health care system by aiding in better management of individual care and stewardship of health care resources.

G2 Insider

New Method Improves Accuracy of LDL-C Estimation . . . Researchers have developed and validated a novel method to estimate low-density lipoprotein cholesterol (LDL-C) that offers accuracy advantages over traditional estimation methods, according to a study published Nov. 20 in the *Journal of the American Medical Association* (*JAMA*). If validated, the authors say, this method could be implemented into practice through "most laboratory reporting systems at virtually no cost."

"It is remarkable how well the [Friedewald] equation has withstood the test of time. Nevertheless, Friedewald et al recognized that inaccuracies in very LDL-C (VLDL-C) estimation could become more important at lower cholesterol concentrations and higher triglyceride concentrations," write the authors, led by Seth Martin, M.D., from Johns Hopkins in Baltimore.

LDL-C estimates eliminate the need for ultracentrifugation needed with direct LDL-C measures and are widely used in international recommendations to guide treatment. The most common estimation method is the Friedewald equation, which assumes a fixed ratio of 5-to-1 for triglycerides to VLDL-C (TG:VLDL-C). However, the authors say, this fixed ratio is "problematic" given the actual TG:VLDL-C ratio varies significantly across the range of triglyceride and cholesterol levels. Additionally, the currently used 70 mg/dL secondary prevention target is well below the LDL values seen in the data set used to derive the equation.

In the *JAMA* study the researchers used a convenience sample of consecutive clinical lipid profiles obtained from 1,350,908 children, teens, and adults in the United States (2009 to 2011) as part of the Very Large Database of Lipids (Atherotech Diagnostics Laboratory). Atherotech's Vertical Auto Profile ultracentrifugation technique separates lipoprotein subfractions to measure cholesterol, including LDL-C, VLDL-C, and HDL-C. Clinical practice guideline LDL-C risk classification was compared using estimated and directly measured LDL-C.

The researchers found using the derivation data set (n=900,605) that the median TG:VLDL-C was 5.2 with 65 percent of the variance in this ratio explained by the triglyceride and non–high-density lipoprotein cholesterol (HDL-C) levels. Using the strata of triglyceride and non–HDL-C values, a 180-cell table of median TG:VLDL-C values was developed and applied to the validation data set (n=450,303) to estimate the novel LDL-C (LDL-CN). There were significant differences in overall agreement in guideline risk classification using standard direct LDL-C (91.7 percent), LDL-CN (85.4 percent), compared to Friedewald-derived LDL-C. Using LDL-CN, the greatest improvement in concordance occurred in classifying LDL-C lower than 70 mg/dL, especially in patients with high triglyceride levels. While still requiring additional validation, this LDL-CN estimation method could be coded into an online calculator, smartphone application, or automated laboratory reporting system, suggest the authors, making clinical adoption easy.

Company References

Affymetrix 408-731-5000	Bruker 877-442-2231	Nanosphere 888-837-4436
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