G2 INTELLIGENCE

Diagnostic Testing & Technology Report

Competitive Intelligence & Analysis for an Expanding Global Market

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CONTENTS

Circulating Tumor DNA Could Provide Noninvasive, Personalized Cancer Management

Applying targeted, deep sequencing to noninvasive blood-based biopsies of circulating tumor DNA can yield information on tumor mutations and tumor burden for personalized cancer management. Using tagged-amplicon deep sequencing (TAm-Seq) researchers have demonstrated the feasibility of detecting rare mutations for personalized monitoring of tumor dynamics, according to a study published in the May 30 issue of *Science Translational Medicine*.

The researchers, from Cancer Research UK (Cambridge), showed that TAm-Seq is capable of noninvasive identification of mutant alleles in plasma, at allele frequencies as low as 2 percent with greater than 97 percent sensitivity and specificity. The TAm-Seq method uses a combination of short amplicons, two-step amplification, sample barcodes, and high-throughput polymerase chain reaction. The technology was able to identify mutations throughout the tumor suppressor gene TP53 in circulating DNA from plasma samples of advanced ovarian cancer patients, determine the origin of metastatic relapse in a patient with multiple primary tumors, and in another case recognize an EGFR mutation not found in an initial ovarian biopsy.

"With further developments," the authors write "this and derivative methods may be applied in molecular screening for earlier detection or for differential diagnosis of cancer from benign masses."

For more information on developments in rare cell capture technology, please see *Inside the Diagnostics Industry* on page 5.

Strategy Shift in Prostate Cancer Testing Necessary in Light of Recommendations

While the U.S. Preventive Services Task Force's (USPSTF) final prostate cancer screening recommendation issued May 21 did not come as a surprise, it still ignited a firestorm of protest at the American Urological Association's (AUA) annual meeting (May 19-24; Atlanta). Few in the field believe the new recommendation will significantly change the use of the prostate-specific antigen (PSA) test in clinical practice, but the raging debate does draw attention to the need for identification of better biomarkers and development of diagnostic tests more capable of differentiating a man's risk of developing low-grade versus high-grade prostate cancer.

Continued on p. 2

▲ **Strategy Shift in Prostate Cancer Testing,** *from page 1*

The USPSTF gave the PSA test a grade D recommendation, the lowest possible, indicating that the screening test does more harm than good as a result of overdiagnosis and overtreatment of benign conditions or slow-growing cancers. The recommendation to use PSA applies to asymptomatic men of any age but does not apply to monitoring after diagnosis or treatment of prostate cancer.

"Our primary problem is that in our quest for the detection of potentially lethal disease for which we know that treatment can affect mortality, we frequently stumble on low-risk disease," write Robin Leach, Ph.D., and Ian Thompson, M.D., in the May issue of the *Archives of Internal Medicine*. "It is the detection of low-risk disease that is problematic; oftentimes, we would be far better off if we did not perform biopsies on men with this cancer phenotype."

While few would disagree that PSA, by itself, is an imperfect test for prostate cancer, those that oppose the task force's recommendations emphasize that PSA screening does save lives.

"The [European Randomized Study of Screening for Prostate Cancer] study shows reduced risk of dying from prostate cancer with PSA screening. Yes it is a small difference, but it is a difference," says Richard Hoffman, M.D., professor of medicine at the University of New Mexico. "Given that screening is often started at age 50, when life expectancy could exceed 30 years—even the most recent 11-year European follow-up data might be insufficient to gauge the ultimate benefit of PSA screening."

The recommendations are not expected to significantly impact clinical practice.

"You can't put the genie back in the bottle," says Hoffman. "PSA won't go away, but other tests can be combined with PSA for better predictive value."

"What the guidelines do do is provide a shot across the bow that the current practice is a naive approach. Prostate screening is treated almost monolithically—biopsy values above 4 and no biopsy for less than 4," Thompson, from the University of Texas Health Science Center at San Antonio tells *DTTR*. "We know this is a naive approach to PSA testing and we can increase the sophistication by incorporating other markers to assess not just a man's risk of cancer, but the risk of high-grade cancer."

PCA3, TMPRSS2-ERG, as well as methylation markers, look "promising," Thompson says. But the "fractured" nature of test development is leading to uncoordinated adoption of emerging tests.

"The trick is how to integrate markers in an intelligent fashion. You don't want to collectively test three dozen markers at a cost of $5,000 to identify a man with prostate cancer. That's a nonstarter," Thompson explains. "A pragmatic approach is needed. [Now] it is based on serendipity discovery leading to home brews and sporadic FDA registration. If I were in charge I think the right way to go about this would be for a major diagnostic company to realize there is enormous market potential. Smaller companies would do the initial leg work and license assays to larger diagnostics companies and bundle up the best of the diagnostic tests."

Additionally, an automated, "machine-driven decisionmaking" app that incorporates risk factors is in development to guide physicians in the most appropriate test selection, Thompson disclosed.

New Prostate Diagnostics Entering the Commercial Market; Emphasis on Differentiating Risk, Reducing Treatment

Despite the ongoing debate over the best clinical practices for detection and monitoring of prostate cancer, many new products aimed at differentiating risk are emerging in the commercial market. Among the companies presenting data or launching products at the American Urological Association's (AUA) annual meeting (May 19-24; Atlanta) were IRIS International (Chatsworth, Calif.), DiagnoCure (Quebec), and MDxHealth (Irvine, Calif.).

IRIS's U.S. Food and Drug Administration (FDA)-approved NADiA (Nucleic Acid Detection Immunoassay) ProsVue officially launched at the AUA meeting. The prognostic test, an in vitro diagnostic assay run at the company's CLIA-lab, identifies men at reduced risk of prostate cancer recurrence by measuring the rate of change of serum total prostate-specific antigen over a period of time following radical prostatectomy.

In a retrospective study of 304 patients, three successive ProsVue tests over a period of 10 months correctly identified 92.7 percent of men as stable and positively predicted 78 percent of patients as having a recurrence. The company says 95,000 prostatectomies are performed annually in the United States and they have already initiated conversations with surgeons responsible for 10 percent of the procedures regarding use of the test, which lists for approximately $3,500. IRIS also recently initiated the Field Experience Trial to show how NADiA ProsVue impacts clinical decisionmaking while reducing health care costs and patient morbidity from unnecessary adjuvant treatment following a prostatectomy. The trial will enroll 600 patients through 20 to 30 physician groups and is expected to be completed in 2013.

"The current test is based on three samples six weeks to 10 months. We are exploring the possibility of adding an additional study to shorten the time frame to eight months," says Thomas Adams, Ph.D., the chief technology officer at IRIS. "Additionally, there are 2 million men walking around out there that had prostate surgery and we think they would like to determine if they are at high risk for recurrence."

DiagnoCure says its FDA-approved PCA3 urine test aligns well with the U.S. Preventive Services Task Force recommendations by reducing the harm associated with PSA screening through shrinking the number of unnecessary biopsies. While the test, marketed by Gen-Probe (San Diego) is approved to assess the risk of prostate cancer in men following a negative biopsy, data presented at AUA shows that the PROGENSA PCA3 Assay holds promise in the first biopsy setting as well.

In a study conducted by the National Cancer Institute's Early Detection Research Network of 880 men, including 305 who had a prior negative prostate biopsy, a PCA3 score higher than 60 was associated with an 80 percent probability of a positive biopsy while a PCA3 score of less than 20 was associated with an 88 percent probability of having a negative biopsy. PCA3 performance was superior to all other diagnostic tools tested in the study for the detection of any cancer and high-grade cancers.

Yves Fradet, chief medical officer of DiagnoCure, says that while "there is an opportunity out there," trials for an additional FDA approval for use of PCA3 for first biopsies would need to be conducted by Gen-Probe, which has held the exclusive worldwide license to the PROGENSA PCA3 technology since 2003. As part of the

licensing agreement, DiagnoCure receives 8 percent of royalties on cumulative sales up to $62.5 million and 16 percent thereafter. As of May, half of the $62.5 million sales goal has been reached for the test, which lists for approximately $300.

MDxHealth launched its Confirm MDx for Prostate Cancer test, which analyzes DNA methylation status in negative biopsy samples at the company's CLIA lab, aids in identifying which patients can avoid a repeat prostate biopsy by distinguishing patients with a true-negative prostate biopsy from the 25 percent of men with false negatives resulting from sampling errors.

At the AUA meeting, data from the Methylation Analysis To Locate Occult Cancer (MATLOC) study showed that using patients' initial negative biopsy sample, the ConfirmMDx test accurately identified two-thirds of patients whose subsequent biopsies showed cancer while correctly confirming negative findings in approximately two-thirds of men who were cancer-free in a subsequent prostate biopsy.

"For men with a negative biopsy, there is still fear from an elevated PSA or abnormal digital rectal exam," says Chris Thibodeau, vice president of commercial operations for MDxHealth. "Given the greater than one-in-four chance the needle missed the cancer, how do you manage them? A large percent are rebiopsied, but how do you help reduce the number unnecessarily rebiopsied? Of the approximately 700,000 men with negative biopsies each year, most results are accurate so the test can immediately give them peace of mind. For the remaining 175,000 of these men who may have a false-negative biopsy result, approximately 33 percent of these men potentially harboring 'clinically significant' cancer, the test can help the urologist to locate occult cancer."

Urine Dipstick Can Detect Early Marker of Kidney Injury

A simple, inexpensive, and readily available urine dipstick test can detect protein and identify sepsis patients at risk for developing renal failure, according to a study presented at the National Kidney Foundation's annual meeting (May 9-13; Washington, D.C.).

Researchers retrospectively analyzed data from patients with severe sepsis admitted to the intensive care units at Henry Ford Hospital (Detroit). Of the 328 patients that underwent dipstick proteinuria (DP) testing at admission, serum creatinine (SCr) increased ≥ 0.3 mg/dL in 210 patients (64 percent) within the first 72 hours of admission. In this group with rising SCr levels new onset DP was found in a total of 114 patients (54 percent) and in 91 of 166 patients with acute kidney injury (AKI) (positive predictive value 60 percent). Analysis showed that de novo DP at time of admission more than doubled the odds of a patient developing AKI.

"In ICU sepsis patients 30 percent go on to develop AKI and there is not really a good biomarker for early detection. The challenge is to identify patients at higher risk that will end up on dialysis or with significantly decreased kidney function," Javier Neyra, M.D., the study's lead author, tells *DTTR*. "We haven't found a biomarker with high enough sensitivity yet, but if you combine it with urine microscopy that is more sensitive, you might have a good predictive tool that can impact practice."

Neyra says that further studies are needed to better understand the significance of new onset DP in AKI.

Rare Cell Capture Technology Gaining Acceptance

The need for more accessible, less invasive blood-based "liquid biopsies" that have the potential to provide up-to-date monitoring of disease progression and response to treatment is driving interest in cell capture technology. Recognized for its ability to capture circulating tumor cells (CTCs) in the field of oncology, the technology is now being applied to other medical disciplines, including for the early detection of cardiovascular disease.

"Usually when you develop technology, you know the end point—there is an unmet need so you develop technology to fill that need. This is different. We don't know much about the biology of these cells because we haven't had access to them," says Mehmet Toner, Ph.D., the Helen Andrus Benedict professor of bioengineering at the Massachusetts General Hospital and Harvard Medical School. "Targeted therapies are more mainstream and you need a companion diagnostic to know who you are going to give them to. For a companion diagnostic, what could be better than a liquid biopsy."

Enumeration of epithelial cells, which account for the majority of all adult tumors, is used for current clinical tests using CTC technology. Epithelial cells are antibodies targeting EPCAM on the cell's surface.

"The current definition of a CTC is an EPCAM-positive cell, which defines cells as epithelial, nucleus positive (therefore not a red blood cell), CD45 negative (therefore not a white cell), and cytokeratin positive (indicator of epithelial malignancies)," says George Bers, vice president and general manager of the expression business unit at Affymetrix. "Current approaches to CTCs are inadequate as they are based on enumeration of EPCAM-positive cells and investigators are looking for new and better approaches—looking for a better mousetrap."

"Current approaches to CTCs are inadequate as they are based on enumeration of EPCAM-positive cells and investigators are looking for new and better approaches—looking for a better mousetrap."
—George Bers, Affymetrix

CellSearch by Veridex (a Johnson & Johnson company; Raritan, N.J.) is the first and only U.S. Food and Drug Administration-cleared in vitro diagnostic (IVD) test to capture and count CTCs, the company says. CellSearch is indicated to determine the prognosis of patients with metastatic breast, colorectal, or prostate cancer and can be utilized at any time during the course of therapy as a routine blood test.

"Since 2004 we have continued exploring additional applications of the technology to CTC," says Robert McCormack, Ph.D., head of technology innovation at Veridex. "It started off to enumerate tumor cells, but we are now interested in characterizing cells. The cells of interest are sitting in a chamber and we can ask any question of them. Eight to 10 years ago this would have been unachievable, but molecular technology has advanced so quickly. Matching rare cell and molecular technology is presently where people are heading."

McCormack envisions a broadening clinical role for CTC within oncology.

"We have been long interested in moving CTC to the primary setting for cancer and we have had some accomplishments, but we are many years away from that.

The vast majority of the activity is currently in the metastatic setting," explains McCormack. "A woman that might have been diagnosed with primary breast cancer whose status was determined to be ER, or progesterone, or HER2-positive might go about her life. Many are cured, but unfortunately some will have a recurrence 10 or 12 years down the road. If there is metastatic recurrence, they are treated on the phenotype of the original tumor and it is not treated with contemporary information. But a simple blood stick can give a contemporary look at the cancer as it is about to be treated, and that is clinically relevant, as phenotype can drift. A tumor that was HER2-negative at diagnosis might now be HER2-positive, and she may now be a candidate for therapy not considered with her initial treatment."

"Our vision is that every patient with metastasized cancer will have therapy directed and managed by CTC."
—Robert McCormack, Ph.D., Veridex

The highly anticipated SO500 trial, being conducted with Veridex and the Southwest Oncology Group, may provide crucial evidence that could potentially move the value of CTC-based information earlier into treatment decisions. The study aims to show the value of changing chemotherapy three weeks after initiation of treatment for metastatic breast cancer based upon CTC counts as indicators of early response to therapy. The prospective randomized clinical trial closed to accrual in March with results expected in two years.

"Our vision is that every patient with metastasized cancer will have therapy directed and managed by CTC [technology]," says McCormack.

Growing Acceptance of the Value of the Technology

"The in vitro diagnostics arena is changing as we speak and adoption of CTC technology is caught up in that," explains McCormack. "Five years ago the standard the FDA used was analytical validity and clinical validity. But now clinical utility [is needed] and it equates device trials with drug trials. It is very challenging for IVD companies, which traditionally aren't prepared to do those kinds of trials. We now have 125 papers out on the three indicated conditions [for CellSearch]. Clinical adoption started slow but is progressing nicely as more papers come out."

CTC technology is routinely making its way into drug development and pharmaceutical trials. This spring Veridex announced a collaboration with Novarits Pharmaceuticals in which CellSearch technology will be employed to assess the clinical effectiveness of zoledronic acid (Zometa) on metastatic castration-resistant prostate cancer.

As researchers increasingly see an emerging case for the use of cell capture technology, more companies are beginning to validate additional cell capture technologies, including microfluidic devices and ICE-COLD PCR.

Affymetrix (Santa Clara, Calif.) signed a worldwide distribution agreement and commercially launched a new CTC platform in June that combines ScreenCell's (Paris) isolation devices with Affymetrix's in situ hybridization assays, microarray assays, and other non-PCR based nucleic acid assays including Affymetrix's QuantiGene ViewRNA assays, and GeneChip Microarray assays.

"We are offering a solution package . . . to the global pharmaceutical and biotech drug discovery and drug development community as well as the pathology,

surgery, oncology, and translational research community," says Bers. "Researchers can purchase QuantiGene ViewRNA coupled to two separate devices: one which captures CTCs, which are fixed and killed, for in situ cyto staining and one for capturing live cells, which can be expanded in culture and subsequently 'genomically' characterized using NGS, microarrays, etc. or screened against compound libraries."

The advantage of ScreenCell devices, Affymetrix says, is that they do not require high-complexity skills and they are relatively low-cost and easily accessible.

Future Applications of Rare Cell Technology

"I would categorize [this area] as a little like the Wild West. Everyone is running to claim territory. It's frantic now but good things will come out of it. We're still in the early stage," says Toner. "Right now there are 40 to 50 different ideas [for CTC technology]. My prediction is that in 10 years there will be a handful of different technologies with preferential use for different applications. There won't just be one technology to do everything. Different companies will have different applications."

"From a philosophical perspective you could probably diagnose and monitor every human disease in blood, as long as you know how to read it."
—Mehmet Toner, Ph.D.

"No longer is it CTC technology. Rare cell, I would say, is a more appropriate term for the technology," says McCormack. The broadening applicability of the technology is expected to penetrate clinical disciplines outside of oncology including the capture, enumeration, and characterization of circulating fetal cells for noninvasive prenatal diagnosis and circulating endothelial cells for early diagnosis or prediction prior to cardiovascular events.

Veridex collaborated on the publication of a study demonstrating that CellSearch was capable of capturing circulating endothelial cells (CECs) in 50 myocardial infarction (MI) patients. These cells were further investigated for protein markers to confirm their endothelial origin by researchers at Ortho Clinical Diagnostics Inc. The results of the study, published in late March in *Science Translational Medicine*, showed that MI patients had 400 percent more CECs in blood samples compared to healthy volunteers. Additionally, CECs in the MI patient group had distinct physical abnormalities. The research could lay the foundation for a potential blood test that could determine imminent risk of heart attack in high-risk populations.

"The difference in the shape and high incidence of multiple nuclei in these cells suggest they may possess a unique gene expression profile," said study co-author Mark C. Connelly, Ph.D., director, Cellular Research, Veridex, in a statement. "The next phase of our research will test this hypothesis and, if it is true, attempt to determine its suitability to detect early warning signs such as subclinical plaque rupture in high-risk patients."

"From a philosophical perspective you could probably diagnose and monitor every human disease in blood, as long as you know how to read it," explains Toner. "After a blood test, the next test prescribed is very expensive imaging—putting someone in a box and radiating them. Rare cells will bridge that. It won't eliminate imaging, but you will send the right people for imaging."

AHA Calls for Stricter Oversight of Genetic Tests, Ban on Gene Patents

While acknowledging the potential power to improve cardiovascular health, the American Heart Association (AHA; Dallas) has issued a policy statement calling for stricter oversight of genetic tests and most controversially, a ban on patents for gene discoveries. The policy statement, which was published in the journal *Circulation*, was comprehensive and addressed all aspects of genetic testing from regulation and reimbursement to clinical utility concerns. Among the issues addressed by the writing committee were:

- **Ban of Gene Patents:** The AHA fundamentally disagrees with the argument that isolated or purified genes are different from their naturally occurring counterparts and believes that such patents affect both the affordability of and access to medical care.
- **Expansion of the Genetic Information Nondiscrimination Act (GINA):** Believing patients should be free from discrimination based on both genetics and family history, the AHA calls for an expansion of the federal GINA law to protect patients from discrimination in the areas of life, long-term care, and disability insurance.
- **Stricter Regulation of Genetic Tests:** The committee writes, "We believe that all genetic tests, including laboratory-developed genetic tests, should be required to undergo independent review to confirm their analytic and clinical validity." The AHA believes with additional resources the U.S. Food and Drug Administration is "ideally suited" for this role.
- **Pharmacogenomic Testing:** The AHA recognizes the potential of pharmacogenomics testing in the future, particularly if preemptive, electronic medical record-linked genotyping can guide initial therapy decisions, but the group warns that randomized clinical trials to inform how a physician should use genotypic information in drug dosing might be needed.
- **Transparent Coverage Decision:** The AHA endorses the view that the Centers for Medicare and Medicaid Services should adopt a transparent, consistent, and evidence-based process for coverage, coding, billing, and payment of genetic tests under established benefits for testing.

23andMe Defends Its First Patent

Personal genomics company 23andMe (Mountain View, Calif.) announced receiving its first patent on the company's Spittoon blog May 28 and nearly immediately had to defend its position in response to concern and criticism from customers. While the patent is viewed by the company as validation of its ability to successfully leverage customer data for research purposes, it throws the company into the raging debate over the patentability of isolated genes.

The patent, (U.S. Patent 8,187,811) Polymorphisms Associated With Parkinson's Disease, is a method patent related to screening for the susceptibility of Parkinson's disease. The company had discovered that a variant in the SGK1 gene that may protect against Parkinson's disease in individuals who carry the rare risk-associated LRRK2 G2019S mutation.

While acknowledging the patent debate Anne Wojcicki, CEO of 23andMe, says "the patent will be important for a biotech or pharmaceutical company to pursue drug

A New Entrant in the DTC Testing Arena

Ancestry.com (Provo, Utah) announced in May the launch of the AncestryDNA service, a $99 test that enables subscribers to examine their geographic and ethnic origins through genetic testing. At launch the test examines 20 worldwide geographical and ethnic categories, including six regions in Europe, five regions in Africa, and Native American and relies upon populational genetic research and DNA samples assembled by the Sorenson Molecular Genealogy Foundation.

"Our competitive advantage is our ability to study allele frequency distribution and their evolutionary changes in the context of extensive and well-documented pedigrees," Senior Vice President and General Manager of DNA Ken Chahine tells *DTTR* in an e-mail. "Additionally, AncestryDNA leverages Ancestry.com's 34 million family trees and 10 billion records. . . . Together, these data comprise a unique and invaluable resource for understanding recent human evolution and migration."

development. . . . Patents give organizations researching and developing new drugs confidence that their significant investments will be commercially viable." However, in a "clarifying addendum" to the original blog post Wojcicki adds that while the company is "firm in our belief that individuals should have access to their own genetic data, . . . other entities can present . . . genetic information about the genetic associations covered in our patents without licensing fees."

While the future commercial value of the patent remains unknown, Dan Vorhaus, editor of the *Genomics Law Report,* says that it is a "relatively pedestrian diagnostic method patent that, if it ever becomes valuable enough to be challenged, might not survive the challenge."

Despite the reassurances from Wojcicki concerning customer access to their own genetic information, some customers expressed dissatisfaction of the company's continued pursuit of patents and profitability through the use of customer data. The company has 125,000 genotyped customers, of which nearly 90 percent have agreed to participate in the company's institutional review board-approved research. 23andMe says it has amassed the single largest Parkinson's research cohort in the world, comprising more than 6,000 participants including one of the largest cohorts of individuals carrying the pathogenic mutations in the LRRK2 gene.

Rapid, Whole-Genome Sequencing for MRSA Outbreak

Whole-genome sequencing can provide clinically relevant data regarding antigen characterization and transmission pathways during infectious disease outbreaks within a clinically relevant time frame, according to a study published in the June 14 issue of the *New England Journal of Medicine*.

Researchers used rapid whole-genome sequencing to retrospectively investigate a methicillin-resistant Staphylococcus aureus (MRSA) outbreak in a neonatal intensive care unit (NICU). They sequenced the MRSA bacteremia isolates from seven patients believed to be part of the NICU outbreak as well as MRSA isolates from seven patients from the institution not thought to be associated with the outbreak. Sample preparation and DNA sequencing were performed by Illumina (San Diego).

The researchers constructed a phylogenetic tree that distinguished between isolates in the outbreak and nonoutbreak groups. Anti-microbial phenotypes and genotypes showed concordance, providing proof of principle that whole-genome sequencing could guide therapy decision. But the identification of a hypermutator strain demonstrates a simple cutoff of SNPs between isolates to determine involvement in trans-

mission chain is not feasible and that "this information must be determined from the topologic characteristics of the phylogenetic tree," write the authors.

The research team, led by Sharon J. Peacock, Ph.D., from Cambridge University Hospital in the United Kingdom, said it took one and a half days to prepare the DNA libraries and sequence the isolates, which could have been reduced to less than one day through utilization of shorter sequence-read lengths. The cost of materials was about $150 per isolate, including sample preparation, library quality control, and sequencing, which is equivalent to the cost of two polymerase chain reaction tests currently used to screen for MRSA carriage.

"Once data interpretation is fully automated, we predict that whole-genome sequencing will become a standard tool for infection control and will provide the capability to monitor the spread and evolution of major pathogens both within and outside of hospitals in real time," write the authors.

Growing Interest in Applying Sequencing to Public Health Outbreaks

Bringing together the technologies from genome analysis company OpGen (Gaithersburg, Md.) and sequencing capabilities from Life Technologies (Carlsbad, Calif.), the two companies announced plans to collaborate to develop applications for use in analyzing public health food and infectious disease outbreaks. The partnership demonstrates the increasing interest in applying evolving technologies to real-world disease surveillance.

Public health officials and health care organizations hope that utilization of improved first responder technologies to rapidly identify culprit infectious agents will better allow for control and management of outbreaks. The Whole Genome Mapping and Ion Torrent sequencing technologies are available for use by the public health community, company officials say, as the partners work on commercialization plans aimed at hospital surveillance.

"The current collaboration activities are focused on demonstration of capabilities and development of whole genome guided sequence reference database, software tools and applications that enable automated assembly and analysis by combing the two technologies," OpGen CEO Doug White tells *DTTR* in an e-mail.

Whole Genome Mapping technology from OpGen is an enhanced genetic analysis technology that provides a rapid, comprehensive structural analysis of microbial genomes that, when combined with sequencing data, more accurately detects important novel genetic components associated with toxicity, virulence, and drug resistance, the company says.

The partnership provides OpGen with an opportunity to expand its business reach with Life Technologies' international footprint and increases Life Technologies' role in the public health market. As part of the agreement Life Technologies will join the public health consortium created in mid-May to evaluate Whole Genome Mapping technology with the Association of Public Health Laboratories, the Centers for Disease Control and Prevention, the University of Maryland Institute for Genome Sciences, and 11 state public health laboratories.

Future Private Equity Investment Hopeful but Uncertain

The future level of private equity investment in diagnostics companies remains unclear given continued legal, regulatory, and reimbursement uncertainties that will continue to plague the industry over the next several years. But despite concerns over long-term financing fallout from the Supreme Court's ruling against Prometheus's methods patents, venture capitalists tell *DTTR* there is both reason to be optimistic and cautionary.

"It has been extraordinary the last five years because of new technologies, new biologies," said Mark Levin, founder of the venture capital firm Third Rock Ventures (Boston), speaking to the Personalized Medicine Coalition in May. "The other side of this is it is a struggle. It is not the science, it's not the biology. It is all of us working together—the FDA, and reimbursement, pharma, biotech, and venture capitalists. There are huge opportunities right now that we are slowing down because we are not all working together."

While systematic hindrances exist, the investor community understands that personalized medicine is here to stay.

"Investors' willingness to put money up will be an enduring phenomenon," says William J. Kridel Jr., managing partner at Ferghana Partners (New York). "There is awareness in the investor community that diagnostics will improve margins, reduce the risk profile, and improve the speed to market. Fundamentally, personalized medicine and targeted therapeutics are not going away."

Kridel says that the wave of private equity financing announcements in late spring was simultaneously both a coincidence and a sign of continuing investment.

Agendia (Irvine, Calif.) closed a $65 million round of private financing at the end of May. The company said the funds will be used to expand commercialization of the Symphony suite of breast cancer tests and the ColoPrint recurrence test for stage II colon cancer prognosis, which launched June 1. The microarray test reads an 18-gene expression signature to determine which patients are at greatest risk of distant recurrence and are most likely to benefit from adjuvant treatment.

AssureRx Health (Mason, Ohio), which specializes in neuropsychiatric pharmacogenomic testing announced at the end of May that it had closed on a $12.5 million Series C round of financing. The funds will be used for commercialization of the GeneSightRx Psychotropic and GeneSightRx ADHD tests including expanded sales efforts and funding of multiple clinical trials, as well as next-generation product-development activities, the company said. The round was led by Four Rivers Group and included existing investors.

At the beginning of May, Oxford Nanopore (United Kingdom), a maker of real-time nanopore-based sequencing instruments, announced it had raised £31.4 million ($50.8 million), bringing the company's total funds raised since 2005 to approximately £105.4 million ($170.5 million). The round, which was funded by existing investors, will be used for development of commercial infrastructure, expansion of manufacturing, and additional research and development for DNA/RNA sequencing and protein/miRNA analysis applications, Gordon Sanghera, Ph.D., CEO of Oxford Nanopore, said in a statement.

G2 Insider

Lack of Meaningful Interpretation of Aluminum Testing . . . Clinically used aluminum reference ranges are widely divergent and may not represent "normal" ranges of a healthy population, especially in children, finds a study published in *Pediatrics.* In light of increased requests for aluminum testing by parents of children with developmental disorders, further studies of normal levels in children are needed.

While extreme workplace exposure and exposure to aluminum through kidney dialysis can be toxic, the consequences of routine exposure are unknown. But some parents suspect aluminum, like mercury, may have contributed to their child's autism. As the number of parents requesting aluminum testing for their children with developmental issues rises, there is little agreement about the appropriate reference range or normal level for healthy children.

Contributing to the wide variation in aluminum reference ranges used in clinical practice is the variety of testing methods used. For laboratories using the atomic absorption spectrometry method, aluminum reference ranges varied from less than 5.41 mg/L to less than 20 mg/L in serum, less than 7 mg/L to 0 to 10 mg/L in plasma, and 5 to 30 mg/L in urine. For laboratories using inductively coupled plasma mass spectroscopy, ranges varied from 0 to 6 mg/L to less than 42 mg/L for serum, 0 to 10 mg/L to 0 to 15 mg/L in plasma, and 0 to 7 mg/L to 5 to 30 mg/L in urine. These reference ranges were all established using small studies on adult populations or sick children on aluminum-containing parenteral therapy. Based on information from seven clinical laboratories that perform aluminum testing, Michelle Zeager, D.O., from Harvard University (Boston) found that none of the reference ranges were established from data on healthy children. Zeager notes that population-based studies of background aluminum levels in the United States are not readily available.

"There is currently a lack of data to support a correlation between aluminum exposure doses, aluminum levels measured in biological samples, and adverse clinical outcomes," write the authors. "As a result, it is difficult to provide meaningful interpretation to aluminum urine or blood monitoring results and to make clinical decisions based on the results."

Company References

23andMe 650-938-6300
Affymetrix 408-731-5000
Agendia 888-321-2732
American Heart Association 800-242-8721
Ancestry.com 800-262-3787
AssureRx Health 513-234-0510
DiagnoCure 418-527-6100
IRIS International 818-527-7000
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