G2 INTELLIGENCE

Diagnostic Testing & Emerging Technologies

New Trends, Applications, and IVD Industry Analysis

Editor's Note

Effective with the October issue, *Diagnostic Testing & Technology Report* is now *Diagnostic Testing & Emerging Technologies*. Our new name reflects an increasing emphasis on emerging technologies and trends in in vitro diagnostics. We will continue to bring you the latest on new tests, analysis of critical developments affecting test manufacturers, and details on mergers, acquisitions, and alliances impacting the diagnostics industry. Please send comments to Kimberly Scott, managing editor of G2 Intelligence, at kscott@G2Intelligence.com.

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Country's First Free, Public STD Home Testing Program Expands Coverage

The first public health department program to utilize free, home testing as part of its overall sexually transmitted disease (STD) control strategy is expanding to now reach a combined population of over 16 million people. The service, which began in Los Angeles County in 2009, is now available in San Francisco, Sacramento, Calif., San Diego, and Alameda, Calif., counties.

The "I Know" campaign was designed to address the barriers that prevent young adults from seeking health care services. It is particularly aimed at young, minority females in high-morbidity communities, allowing them the ability to take chlamydia and gonorrhea tests in the privacy of their own home. Self-collected, vaginal swab kits are either picked up or mailed to the user and then mailed back to a designated public health laboratory for processing. Results will be available securely online or by phone one week later with text and/or e-mail reminders to alert participants that results are available.

The first published evaluation of the program was printed in the August issue of the *American Journal of Public Health*. Researchers from the Los Angeles County Department of Public Health say that in the program's first year, promotion with a social marketing campaign targeting Hispanics and African Americans enabled 2,927 women to order home collection kits with 1,543 testable specimens returned. A total of 131 women (8.5 percent) had a positive test result, leading the authors to conclude that "the strong response, high morbidity, and program scalability indicated strong potential as a new tool for STD control." For more on the increasing interest in at-home testing, please see *Inside the Diagnostics Industry* on page 5.

Mass Spec Technology to Transform Pathogen Identification, Improve Clinical Care

With the U.S. Food and Drug Administration's August clearance, VITEK MS from bioMerieux (Durham, N.C., and France) became the first mass spectrometry-based system approved for rapid clinical identification of 193 microorganisms. The technology enables significantly more rapid bacterial and fungal identification and quicker drug susceptibility testing, which can improve anti-microbial management and decrease associated health care expenditures.

While the term "game-changer" is often overused, 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

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▲ **Mass Spec Technology to Transform Pathogen Identification,** *from page 1*

the time needed for identification of microbial infectious agents from days to hours. "MALDI-TOF [matrix-assisted laser desorption/ionization-time of flight] will have one of the greatest impacts on clinical microbiology since the use of molecular amplification methods for the identification of pathogens," said Christine C. Ginocchio, Ph.D., the senior medical director at North Shore-LIJ Health System Laboratories, whose lab has been investigationally using the system for a year.

The system is based on Nobel prize-winning MALDI technology. The soft ionization technique uses a special matrix solution that prevents fragmentation of large molecules. The travel time of the charged molecules is measured with TOF directly proportional to the molecules' mass. This is charted as a mass-to-charge ratio and compared to reference standards.

In practice, a small sample from a culture plate is applied to a slide, covered with a drop of matrix solution, and inserted into the automated system. Microbial identification can be generated within minutes of ionization with comparable accuracy to nucleic acid sequencing.

In addition to critical time savings to the patient and clinical team resulting from significantly faster pathogen identification, the MALDI system saves the laboratory significant time. Within a matter of a few minutes from the time of a positive culture, a tech can set up for identification and susceptibility testing, and with up to four slides able to run at a time and results in a little over an hour, throughput is not a rate-limiting step, says Ginocchio, whose laboratory services 11 hospitals and can run nearly 250,000 to 300,000 microbial identification tests annually. Her lab will be using two MALDI systems, with one dedicated to stat testing.

While bioMerieux estimates that there may be 800 U.S. labs with the volume to justify the VITEK MS system, laboratories that have tried the system see a financial case for adoption. In a small study based on investigational use of the system for limited volumes of testing, North Shore estimates that the system can save $150,000 in reagent costs and $130,000 in technologist savings annually.

In addition to cost savings for the laboratory from improved workflow and the larger health system resulting from improved diagnosis and patient management, Bert Top, Ph.D., from bioMerieux USA, tells *DTET* that a number of factors are likely to drive adoption of MALDI-TOF systems—the increasing number of hospitalized patients with underlying conditions making them extremely vulnerable to hospital-acquired

MALDI-TOF Saves Health Care Dollars

Rapid organism identification allows clinicians to prescribe the most appropriate treatment sooner and de-escalate empiric therapy from broad-spectrum agents that drive anti-microbial resistance. In an article published in the September issue of *Archives of Pathology & Laboratory Medicine*, researchers from the Methodist Hospital Research Institute (Houston) demonstrate that integration of rapid identification and susceptibility techniques with anti-microbial stewardship significantly improved time to optimal therapy and significantly decreased health care total costs.

The researchers compared conventional microbiology laboratory methods to MALDI-TOF technology (Bruker Daltonics, Fremont, Calif.) in consecutive adult patients hospitalized with gram-negative blood cultures between Aug. 15, 2011, and Nov. 30, 2011 (preintervention period; 112 patients) and between Feb. 1, 2012, and May 25, 2012 (intervention period; 107 patients). Differences in hospital outcomes were assessed in survivors. Appropriateness of antibiotic therapy was evaluated by an infectious diseases–trained pharmacist and the index culture time-to-positivity (TTP) was assessed.

The urinary tract was the most common infection source (42.9 percent in the preintervention group and 34.6 percent in the intervention group) and Escherichia coli was most frequently isolated (50 percent in preintervention and 43 percent in intervention group).

Average time from the blood culture TTP to final species identification and anti-microbial susceptibility occurred nearly a full day quicker with MALDI-TOF (47.1 hours for the preintervention study group versus 24.4 hours for the intervention group). Overall, adjustments to antibiotic interventions occurred, on average, 75 hours from TTP in 80 percent of patients preintervention. The time dropped to 29 hours, on average, in 94 percent of patients during use of MALDI-TOF. Mean hospital length of stay was significantly longer in the preintervention group survivors (11.9 days versus 9.3 days in the intervention group). Mean hospital costs per patient were $45,709 in the preintervention group compared to $26,162 in the intervention group.

infections, the simultaneous increase in drug-resistant organisms, and the changing reimbursement landscape requiring laboratories and hospitals to provide higher-quality care for lower total costs. The first step in bioMerieux's rollout strategy is to convert all of the company's research and investigation sites into fully operational clinical sites, which is expected to be completed in the next couple of months.

Takeaway: 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.

Corporate Venture Funding Expected to Play Larger Role in Supporting Diagnostics Innovation

With healthy balance sheets and cash to deploy to expand access to innovation, corporate venture arms are becoming an increasingly sizable portion of the venture capital world. While the technology sector has been highly visible with active venture arms such as Google Ventures and Intel Capital, health-related corporate venture has been stepping up its presence in biotech over the past several years and is expected to increasingly invest in diagnostic startups in the coming years.

Corporate venture capital stepped into the life sciences to fill a void left a few years ago as traditional venture capital firms began to shy away from early-stage startups. In a report titled "Strong Momentum in Healthcare: Trends in Mergers and Acquisitions Dollars," Silicon Valley Bank (SVB) highlights this void. Dating back to 2002, venture-backed device and biotech companies represent about a quarter of all venture dollars invested on a yearly basis. However, the report explains that that pace of investment (roughly $6.6 billion a year) is not sustainable given both the decline in venture capital fund-raising overall and a potential decline in the percentage of total venture dollars allocated to the health care sector.

"We believe that dollars invested into health care venture-backed companies will come down to the $5 billion to $5.5 billion level in the next few years, leading to a smaller percentage of overall venture investment into health care—likely 18 percent to 20 percent of total venture investment," writes Jonathan Norris, managing director of SVB, in the report.

Over the past few years, investment in health care-related companies has mostly been "follow-on activity" from older funds supporting existing portfolio companies, often in later stages of development with the need for additional time and capital to achieve clinical or commercial milestones. According to the SVB report, for biotech companies there was a decline in the number of companies raising at least $2 million in Series A funding—from 66 companies raising a total of $915 million in 2005 to 47 companies raising $605 million in 2012. Device companies (which includes diagnostics companies in the report) similarly experienced a decline in Series A financing from 60 companies raising $403 million in 2005 to 25 companies raising $155 million in 2012.

This decline in venture firms' funding of early-stage companies has been partially offset by corporate venture. According to CB Insights, over one-third of the most active corporate venture capital arms are health care-focused, including the venture arms of Novartis, GlaxoSmithKline, Merck, Johnson & Johnson, and Kaiser Permanente. SVB estimates that corporate venture capital accounts for 15 percent to 20 percent of all

investments in health care venture-backed companies, although the funds have not invested equally across the biotech and device industries.

"If you look at big biotech companies, the Street wants a pipeline of products from preclinical to phase 2. For a strong pipeline they turn to partnerships and early-stage acquisitions," Norris tells *DTET*. "In biotech 40 percent to 45 percent of V.C.-backed company exits are in preclinical or phase 1."

So three years ago, as venture capital firms began to focus on later-stage companies, corporate venture arms began to step in—filling the funding void and ensuring continued access to early biotech innovation, thereby plugging the "innovation gap." One in three venture-backed biotech companies has a corporate investor, some of which are strategically focused while some are strictly financially driven, SVB found.

"We believe that device acquirers are aware of the innovation gap that has been created in their world, and we predict over the next few years that the big players will step up their activity in the innovation economy through early investment, earlier mergers and acquisitions (M&A), and unique licensing/option deals that will look similar to corporate pharma and biotech activity today."
—Jonathan Norris, Silicon Valley Bank

But on the device side of the business, the picture is very different. Because device company exits aren't occurring until after U.S. Food and Drug Administration approval, companies have figured out the reimbursement strategy and really have traction, Norris says. Big device companies have "dragged their feet a bit and held back on early-stage acquisitions," thus propagating a cycle in which early-stage device companies are finding it even more challenging to raise early-round funding since their exits are deferred longer than their biotech counterparts'. From 2005 to 2013 there was an increase in corporate investments in venture-backed biotech companies from 9 percent to 30 percent, while device companies saw a decrease over the same period of time.

"This is really a little shortsighted [on the part of big device companies] because they can only grow so much through geographical expansion. At some point they need new products . . . and if nobody fills the [funding] gap, new companies will never get there," says Norris.

"We believe that device acquirers are aware of the innovation gap that has been created in their world, and we predict over the next few years that the big players will step up their activity in the innovation economy through early investment, earlier mergers and acquisitions (M&A), and unique licensing/option deals that will look similar to corporate pharma and biotech activity today," concludes Norris in the report. While the news of declining investments may be construed as negative news, Norris says in the long run the trend may be in the best interest of the industry.

"Companies receiving Series A investment today are poised to be a very attractive crop of companies . . . as these companies will have overcome a very high hurdle for investment," Norris says. "Fewer overall early-stage, venture-backed device companies will create a scarcity of innovative technologies for big markets that should drive better and hopefully earlier M&A, as acquirers continue to reduce research and development and look to venture-backed companies to fill the Street's requirement for innovation."

Takeaway: With a growing scarcity of investment funds for early-stage diagnostic companies, corporate venture arms are expected to step in and partially fill the gap, as has been the case in the biotech industry over the past several years. However, with limited capital, a smaller number of companies will be created in the coming years, possibly driving higher valuations. G2

At-Home Testing Has Potential To Cut Costs, Increase Screening

From the frequency of Internet searches to the advent of patient-centered care, it is undeniable that patients are more involved in their own health care than ever before. At the heart of the patient-empowerment movement are tools for information sharing and easy-to-use medical devices, including point-of-care (POC) diagnostic testing.

Aside from patient preference, policy experts are looking at POC testing, including at-home sampling and testing strategies, as a means of broadening screening efforts for a variety of diseases while containing costs. As a result, in addition to ensuring test accuracy, laboratories and diagnostics manufacturers are now increasingly considering lay user interfaces in sample collection and test design efforts.

Patients Willing and Able

Researchers are exploring rapid, at-home tests for common conditions such as strep throat, sexually transmitted diseases (STDs), and even cancer screenings. Since the 1970s with the commercial availability of at-home pregnancy tests and glucose monitoring kits, patients have demonstrated a willingness to participate in self-testing. These POC tests give immediate results in nontraditional settings and, in addition to encouraging patient responsibility in their own care, they also address patient preferences such as convenience, logistic and travel issues, and privacy concerns.

"There is a whole group of people who don't like at-home testing. If we can use fluidics and nanotechnology, we can get more sensitive tests faster and eliminate the barrier of having to send it off to skilled people, [so] why hold the technology hostage?"
—Catherine Klapperich, Ph.D.

However, over the years, critics have raised many questions about at-home testing. These concerns include questioning the reliability of the tests, particularly with inexperienced users.

With the recent commercial release of the OraQuick In-Home HIV test by Orasure (Bethlehem, Pa.), these concerns again came to the forefront in discussions about whether patients were equipped to handle receiving sensitive results on their own and if they would act upon those results. As is the case with the OraQuick HIV test, it has traditionally been incumbent upon the patient to relay at-home results to the appropriate physician and follow up for any needed treatment. While empiric data is still forthcoming from Orasure, traditionally patients do a pretty good job of conducting tests and following up, say experts. Still, there are skeptics.

"There is a whole group of people who don't like at-home testing," says Catherine Klapperich, Ph.D., director of the Center for Future Technologies in Cancer Care at Boston University. "If we can use fluidics and nanotechnology, we can get more sensitive tests faster and eliminate the barrier of having to send it off to skilled people, [so] why hold the technology hostage?"

Experts tell *DTET* that the technology to open up at-home testing options for a wider spectrum of diseases is rapidly developing and will begin to be available in commercial markets over the next three to 10 years. In the meantime, POC advocates are still addressing quality concerns.

"The problem with POC is that it is less sensitive, but if a patient doesn't come

back to get their results, the sensitivity is zero and then you have to pay to find them and get them treated," says Charlotte Gaydos, Dr.P.H., professor of infectious diseases at Johns Hopkins University Center for STD Point of Care Tests. "A little less sensitive is OK if you can get them treatment before they leave the clinic. It still saves money and prevents more disease."

Gaydos expects POC tests for STDs to continue to emerge in clinics before they are available for at-home testing, although continued research shows that patients are capable of self-collecting samples.

"Patients do a really good job [self-sampling] and the data supports that. Self-vaginal swabs do just as well as [from] a clinician; with good instructions, it is not a concern," says Klapperich. "With simple devices that are very intuitive it is very difficult to mess up. If people really want to know, if they are motivated, and it is not that expensive—it's the perfect storm [to drive at-home testing]. . . . It has to be actionable information to empower people to use it at home."

Design will also play a role in driving an increase in at-home testing.

"You have to focus on user interface simplicity and reliability because you are putting this technology in untrained hands," explains Mick Withers, managing director at the global product development advisory firm Sagentia. "Users expect to be treated like consumers, as compared to traditional medical devices that have boring user interfaces. But it is a strong case if you can get medical devices to behave like consumer devices with an intuitive user interface. It is a race to see if consumer products can up the quality to be medical products fast enough."

Models Evolving

A variety of models are emerging to better understand how at-home testing fits into the greater health care system. Some foresee broader access for middle- and upper-income patients who have the education and resources to purchase do-it-yourself tests for themselves at the local pharmacy.

"A pediatrician colleague buys for all his patients a box of lateral flow strep tests," says Klapperich. "It becomes 'run a strep test and call me in the morning' and then he can prescribe antibiotics. It is a time sink for him to see viral patients. It is an amazing model. Young, middle-class parents will test their own kid for strep—that will be routine."

For others, though, access to these tests is lacking and self-pay drugstore tests remain cost prohibitive. So policymakers are looking toward other models, especially in light of the Affordable Care Act, in which health care providers or payers facilitate at-home testing, ensuring greater integration

Mailed FIT Tests Significantly Improve Screening

Kaiser Permanente of Northern California sends every member due for colorectal cancer screening an in-home fecal immunochemical test (FIT) kit accompanied by a letter from the individual's primary care physician explaining the importance of regular screening, as well as directions on how to complete and send in the kit to a central laboratory for processing. Phone, mail, and e-mail reminders are sent to those who fail to return a sample.

Between 2004 and 2009 the program nearly doubled screening rates (an increase from 35 percent to 69 percent), allowing Kaiser to almost reach the 90th percentile of performance among commercial health plans and achieve an internal target five years ahead of schedule. Kits are batch mailed by an outside vendor and returned by the patient via mail to a centralized laboratory for analysis.

According to Theodore R. Levin, M.D., the gastroenterologist who oversees Kaiser's colorectal cancer screening program, 3,000 samples arrive daily at the lab. If a test is positive, patients are called back for a colonoscopy. When the project started, Kaiser had 60 gastroenterologists performing 25,000 colonoscopies a year. It now has 105 doctors doing 90,000 colonoscopies annually.

After an initial increase in cancers detected, there has been a decline in the number of patients diagnosed with colon cancer, but there is more early detection of cancer. Kaiser's internal analysis has found that performing annual FIT on members aged 50 years to 75 years represents the least costly approach to screening within U.S. guidelines.

of testing and results into the continuum of care. In many of these models the patient collects at-home samples and mails samples to laboratories for results. Kaiser Permanente's colorectal cancer screening program utilizes at-home sampling for mailed fecal immunochemical test kits and provides a large evidence base that a health care system-facilitated screening strategy works to improve population-based screening.

All agree that coordination of at-home sampling and testing between patients and health care providers is essential.

"You just need to get this connected to the health system to ensure the ability to get treatment," says Withers. "It requires a great amount of infrastructure for information to flow continuously, but you have to be connected, otherwise there is not much point to doing it."

What Does At-Home Testing Mean for Laboratories?

With technological advances in microfluidics and nanotechnology, development of miniaturized devices is increasingly possible. Wireless communication is already infiltrating home glucose monitoring, ensuring that results are properly reported to health care providers, thereby improving timely communication and disease management. It is a model like this, in which care quality is transformed through cost-effective means, that will drive expansion of at-home testing.

"From a policy point of view this is not going away. The Affordable Care Act mandates preventive testing and cost cutting," says Klapperich. "The only way to do that is POC—in the doctor's office, at home, or in the minute clinic. . . . We know what powerful forces it could be if a major payer pushes it."

As the Kaiser example shows, at-home sample collection may actually facilitate higher overall testing volumes, as more people who might not otherwise have been screened are brought into health care system. Many scenarios are being pondered as to how the rise of at-home testing will affect laboratories' work.

"There could be a separate stream of business flowing directly from patients. In that scenario the laboratory plays more of a quality control role. Is the sample good? Was it done properly? Did it get here on time?" says Klapperich. "Simultaneously, the demand for personalized medicine will support the clinical lab's more highly specialized tests. Are we using the right drug combination for optimized therapy? We'll never do personalized medicine at home. That's a laboratory function with highly trained staff and highly specialized tests."

Takeaway: As policymakers look for strategies to address the need to enhance quality of care while cutting health care costs, there is growing interest in at-home sampling and testing models. Advances in microfluidics and nanotechnology are nearing a tipping point where broader availability of commercially available of at-home testing products will be feasible. Preliminary research indicates that these at-home testing strategies drive increases in screening volumes for laboratories.

Allergen Testing for the Home Market

This spring the U.S. Food and Drug Administration cleared the MyAllergyTest (ImmuneTech; Foster City, Calif.), the first at-home allergy test. Individuals collect a few blood drops from a finger stick that is mailed to a lab for analysis of 10 common allergens (including food, environmental, inhalants, and animal). The test is available for a list price of $49.95 at chain pharmacy stores, as well as in wellness centers. Results are available within days of sample receipt via a secure Web site or mail.

"There are less and less allergists practicing each year. But the number of people with allergies is increasing, so there are lots of parts in the country where allergists are not so available," explains Lisa Elkins, CEO of ImmuneTech. "Allergies are the number-one self-managed conditions with most medications available over the counter, but allergies are largely addressed by avoidance, so they are conducive to patient testing."

Elkins says the company encourages communicating results with physicians but believes overall "we are definitely moving in the direction of more at-home testing. People want it. Laws are working in its favor, and more and more the FDA is allowing it."

Amidst Reimbursement Challenges, Companies Turn to Layoffs; Prenatal, Newborn Screening Segments Hit

Ongoing economic forces continued to mount pressure culminating in late-summer layoff announcements across diagnostics companies both large and small. Bryan Brokmeier, senior equity analyst for life science tools and diagnostics at Maxim Group, tells *DTET* that these layoffs are driven mostly by industrywide forces, as opposed to company-specific situations.

Many companies are turning to restructuring to address macroeconomic concerns, including continued slower global economic growth and the ripple effects of sequestration's impact, Brokmeier says. Additionally, lagging molecular reimbursement is hitting company revenues. As a result, companies are focused on cutting costs and "driving margin expansion." The latest announcements follow combined head count reductions of close to 1,000 employees made earlier in the year by Affymetrix, Agilent, Bruker Biosciences, and others.

- **Sequenom** (San Diego) is reducing its workforce by 75 employees as part of a reorganization, according to an August regulatory filing. The move will cut compensation-related and future operating expenses by $10 million on an annualized basis, although it will record $1.2 million in severance-related expenses during the third quarter.

  For the quarter ending June 30, the company reported a 91 percent increase in revenues ($34.9 million versus $18.3 million a year ago), which fell way below analyst estimates of $44.1 million. The positive rise in tests accessioned (38,000 of the patient samples tested during the quarter were MaterniT21 PLUS test, up from 35,000 during previous quarter) only exacerbated payment delays and coverage denials resulting from the new 2013 molecular pathology coding and payment system. As a result, Sequenom Chief Financial Officer Paul Maier said in a statement that, "going forward, we plan to implement expense reduction initiatives to reduce our net operating loss as we work to improve reimbursement."

  In a late July research note, Brokmeier expressed concerns that although "the company plans to curtail service in order to focus on covered patients and accelerate its profitability . . . if competitors don't follow Sequenom's lead, we expect the service curtailment to negatively impact the strength of its leadership position, but not eliminate it." Additionally Brokmeier says that expense-reduction initiatives won't "be sufficient to offset our reduced revenue outlook" and now believes the company won't turn a profit until 2016.

- **GeneNews** (Toronto, Canada) in mid-August announced a restructuring to sharpen its focus on the commercialization of ColonSentry while reducing the company's cost structure, including reducing staffing levels by 60 percent. The company said the staffing cuts will concentrate on reducing internal research, while maintaining its business development, commercialization, and regulatory functions, particularly around its expected third- or fourth-quarter launch of the ColonSentry test through a joint venture with Innovative Diagnostic Laboratory. The company saw second-

quarter revenues fall year over year while losses for the six months ending June 30 grew to $3.4 million, compared to a net loss of approximately $2.5 million for the same six-month period in 2012.

- At the beginning of August, **Luminex** (Austin, Texas) began a restructuring effort focused on its newborn screening group within its Assay and Related Products segment. Luminex will spin off its NeoPlex business, including assays nearing regulatory submission for congenital hypothyroidism, congenital hyperplasia, and cystic fibrosis. The company expects to reduce its 700 person workforce by approximately 5 percent and close its Brisbane, Australia, office, which will result in annualized cost savings of $5 million to $6 million. The reallocation of resources will allow the company to focus on its molecular diagnostics business, while improving profitability and providing additional financial flexibility, the company said in a statement.
- **PerkinElmer** (Waltham, Mass.) laid off 265 employees during the second quarter, according to regulatory filings, as part of a restructuring plan to consolidate and realign operations and research and development resources as a result of previous acquisitions. The nearly $19 million in charges will be split by its Human Health segment and its Environmental Health segment.

  Noting PerkinElmer's joint venture with noninvasive prenatal screening firm Verinata, Brokmeier wrote in an August research note that, "PerkinElmer stated that they feel good about the reimbursement for the Verifi and that it didn't experience the same reimbursement problems that Sequenom reported. However, we wouldn't expect it to be much of an issue for PerkinElmer given their focus on profitable testing volume and not market penetration."
- **Thermo Fisher Scientific** also in early August announced it had reduced head counts by approximately 655 employees during the first half of the year, according to regulatory filings. The charges were split by the Analytical Technologies segment, which saw 250 layoffs in the first half of the year, and Specialty Diagnostics, with a reduction in staff by 185 employees. Laboratory Products and Services additionally cut 220 employees through the first six months of the year. The company still has nearly 39,000 employees globally.

Takeaway: Companies throughout the diagnostics industry are feeling the effects of a slow global economic recovery, which has been exacerbated by the 2013 changes to molecular reimbursement. As a result, companies both large and small are turning to layoffs to contain costs and drive profitability.

New Pharmacogenomic Panel May Improve Addiction Treatment

Initial evidence suggests that a five-marker genotype panel can effectively predict which patients will have a more favorable treatment response with an experimental drug for alcohol addiction, according to a study published in the *American Journal of Psychiatry*. While additional validation is needed, the authors say that the identification of these genetic variants represents a step forward toward personalized pharmacogenomic treatment of addiction.

The researchers had previously identified that the SLC6A4-LL/TT genotypes in the 5-HTT serotonin transporter gene predicted a significantly greater effectiveness of the experimental drug ondansetron. Without patient stratification by genotype, there was

no difference between treatment effect in the ondansetron and placebo groups. Since the drug works by blocking certain serotonin receptors (as opposed to binding with the transporter molecules regulated by the 5-HTT gene), the scientists speculated that additional genetic variations affecting the binding receptor might further determine the effectiveness of ondansetron.

In the current study, genotyping was performed on one rare and 18 common single-nucleotide polymorphisms in HTR3A, HTR3B, and SLC6A4 genes utilizing samples from the same cohort previously studied. The 283 patients were participating in a randomized, double-blind, 11-week clinical trial in which they received oral ondansetron or placebo along with weekly counseling.

The researchers found that individuals carrying one or more of genotypes rs1150226-AG and rs1176713-GG in HTR3A and rs17614942-AC in HTR3B showed significant overall mean differences (comparing ondansetron and placebo) in drinks per drinking day, percentage of heavy drinking days, and percentage of days abstinent. When the HTR3A/HTR3B variants were combined with the previously identified SLC6A4-LL/TT genotypes, the target cohort of patients likely to benefit from the drug increased from 20 percent (identified in the previous study) to 34 percent. A subset of these carriers (totaling approximately 25 percent of the cohort) may constitue a group of "super-responders" as they had more than a fivefold increase in percentage of participants with no heavy drinking days when taking the drug.

"These initial statistical trends generally [support] a molecular basis for the use of ondansetron as a treatment for a particular cohort of alcohol-dependent individuals," write the authors, led by Bankole Johnson, D.Sc., M.D., from the University of Virginia (Charlottesville). "Perhaps because of [alcoholism's] heterogeneity, the therapeutic effect sizes of the approved medications for the treatment of alcohol dependence have been relatively small. A personalized approach based on the patient's genetic makeup is increasingly being investigated for delivering optimum treatment to suitable patients."

Johnson reports financial ties to the pharmaceutical industry, including ADial Pharmaceutical, which is developing and testing an ondansetron product for addiction.

Takeaway: The identification of genetic variants that predict the success of drug treatment for alcohol dependence is another step toward the clinical practice of personalized medicine. Ondansetron provides another example of how patient stratification, based on genetics, can play a crucial role in drug trials.

CA125 May Be Useful Ovarian Cancer Screening

A screening strategy that evaluates change of carbohydrate antigen 125 (CA125) levels over time may be able to identify early-stage ovarian cancer, according to a study published online Aug. 26 in *Cancer*. To date, no strategy has proven effective for the early detection for ovarian cancer. CA125 marker, which has been used to predict ovarian cancer recurrence, is imperfect as it can be elevated for other reasons potentially leading to false positives as a screening tool.

"Ovarian cancer screening requires invasive surgery and removal of the ovaries in order to make a definitive diagnosis. Therefore, any screening strategy for ovarian cancer must minimize false positives in order to decrease the number of unnecessary operations," write the authors, led by Karen Lu, M.D., from M. D. Anderson Cancer Center in Houston.

Complicating screening efforts is the low prevalence of the disease in the general population. To achieve a positive predictive value (PPV) of 10 percent, a generally accepted limit for balancing risk with benefit, the authors say the screening strategy must exhibit a sensitivity greater than 75 percent for asymptomatic disease and a specificity of more than 99.6 percent.

In the current study, postmenopausal women (aged 50 to 74 years) had annual CA125 blood tests. The Risk of Ovarian Cancer Algorithm (ROCA), based on the patient's age and CA125 score, stratified women into one of three risks groups, which dictated their follow-up protocol: annual CA125 test (low risk), repeat CA125 test in three months (intermediate risk), or transvaginal ultrasound (TVS) and referral to a gynecologic oncologist (high risk).

The researchers found that based on 4,051 women participating over 11 years at seven sites (4.2 average screen years per woman), the average annual rate for triage to the normal-risk group was 93.3 percent, whereas the rate of three-month follow-up was 5.8 percent and the average annual referral rate to TVS 0.9 percent. Of the 117 women classified as high-risk, 82 women had a normal TVS and 11 had benign ovarian findings. Of the 10 women with suspicious TVS findings, all underwent surgery, with four invasive ovarian cancers (all stage I and II), two ovarian tumors of low malignant potential (both stage I), one endometrial cancer (stage I), and three benign ovarian tumors. All four women with invasive ovarian cancer were enrolled in the study for at least three years with low-risk classification prior to rising CA125 levels.

The specificity for the two-stage screening strategy was 99.9 percent with a PPV for identifying invasive ovarian cancer of 40 percent. This U.S. trial had similar findings to the United Kingdom Collaborative Trial of Ovarian Cancer Screening, both of which "greatly exceed" the minimum clinical benchmark of 10 percent PPV.

"Data from our study suggests that incident cases detected through ROCA are likely to be early-stage cancers. This contrasts with the current presentation of ovarian cancer in which more than 75 percent of women are diagnosed with stage III or IV disease," write the authors. Lu added in a statement, "I've become an admitted skeptic of ovarian cancer screening. Now . . . I'm cautiously optimistic that in the not too distant future, we may be able to offer a screening method that can detect the disease in its earliest, curable stage."

Lu says the next steps in the project include assessing the strategy's effect on decreasing ovarian cancer mortality. Additionally, her group will assess if combining other biomarkers (such as HE4, CA72.4, and MMP7) with CA125 improve sensitivity without decreasing specificity.

Several study authors report financial ties to the diagnostics industry, including Robert Bast, M.D., who discovered CA-125 and receives royalties.

Takeaway: Risk stratifying women based on assessments of changes in CA125 markers over time may constitute an effective strategy to begin population-based screenings for ovarian cancer, which while not perfectly sensitive, will aid in identifying more earlier-stage cancers than are presently detected.

G2 Insider

AHRQ Identifies 178 Available Genetic Tests for Common Cancers . . . The Agency for Healthcare Research and Quality (AHRQ; Rockville, Md.) recently released an updated technology assessment that identifies 178 commercially available genetic tests for common cancers.

The report, "Update on Emerging Genetic Tests Currently Available for Clinical Use in Common Cancers," was conducted at the request of the Coverage and Analysis Group at the Centers for Medicare and Medicaid Services and is intended to aid both payers and providers in making informed decisions about emerging molecular tests.

The assessment, conducted by the Tufts Medical Center Evidence-Based Practice Center, covers a range of genetic tests (genetic variations, panels of genetic markers, measurements of gene expression and transcription products, and biochemical biomarkers) that are already available in clinical practice, particularly for the management of Medicare-aged adults. The tests are used in patients with 10 common solid tumors and hematologic cancers (including breast, lung, colorectal, pancreas, leukemia, and lymphoma) for diagnosing, treating, predicting, prognosticating, monitoring, and detecting cancer recurrence.

The report covers tests that are U.S. Food and Drug Administration-cleared (or pending clearance), conducted in CLIA-certified labs and require a physician order, or are offered by Internet sites that specifically require a physician order. The authors caution that the included tests are based on a review of "grey sources," including Internet news searches, commercial and manufacturers' Web sites, and the National Institutes of Health's Genetic Testing Registry, and should not be construed as definitive clinical evidence or as recommendations endorsing their routine clinical use.

In total, the horizon scan reports have identified 178 different genetic tests including 66 new genetic tests since 2011 with the largest number of these tests being utilized for breast cancer. The most frequent indication for use of all of the identified tests was for therapeutic management.

A total of 21 of the 104 tests "in development" in the 2006 report matured to clinical use, with 76 tests currently being identified as tests in development or in research. Several tests listed in a previous report were removed: Three tests (PyloriProbe, PreGen Plus, and OvaSure) have been withdrawn from the market, two tests are used in the context of aspiration of cervical or breast specimens, and one test evaluates genetic material of infectious agent. AHRQ will continue with horizon scans as it is anticipated that the number of clinically available genetic tests will continue to increase in the coming years.

Company References

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