G2 INTELLIGENCE

Diagnostic Testing & Technology Report

Competitive Intelligence & Analysis for an Expanding Global Market

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New Efforts Under Way to Increase Early HIV Detection

Recent Food and Drug Administration approval of an over-the-counter rapid HIV testing kit highlights the need for and benefit from improved screening to detect HIV as early as possible.

More than 40 percent of adults and adolescents diagnosed with HIV are diagnosed with the infection during their first HIV test, according to a study published in the June 22 issue of *Morbidity and Mortality Weekly Report*. Researchers from the U.S. Centers for Disease Control and Prevention (CDC), who conducted the study, say that these findings demonstrate that enhanced efforts are needed to increase annual HIV testing to improve early HIV detection.

Researchers from the CDC analyzed data from 18 jurisdictions participating in surveillance through the CDC's National HIV Surveillance System (2006 to 2009). Of the 125,104 persons aged 13 years and older diagnosed with HIV from 2006 to 2009, 41 percent were diagnosed with HIV infection at their first HIV test, while 59 percent had a previous negative test at some point before their diagnosis. Of these, 24 percent had a negative test 12 months or less before their diagnosis. Younger people (ages 13 years to 29 years), men who have sex with men, and whites were more likely to have had a previous negative test, whereas those most likely to be diagnosed at their first test were more likely to be over the age of 50 years, intravenous drug users, blacks, and heterosexual men and women.

For more information on efforts to increase HIV testing, please see *Inside the Diagnostics Industry* on page 5.

Venture Capital Report Shows Rosier Picture Than Expected for Investment, M&A in Diagnostics Industry

Life science companies saw seven-year highs in the number of "big exits" and total mergers and acquisitions (M&A) dollar value in 2011, according to a report titled *Continued Rebound: Trends in Life Science M&A*, published in July by Silicon Valley Bank (Santa Clara, Calif.). Diagnostics companies contributed to this positive trend data, topping the device sector.

"Questions surround the life science industry's ability to provide substantial venture returns, the decline in fundraising, the difficulty of navigating the regulatory environment, and establishing reimbursement," writes Jonathan Norris, managing director of Silicon Valley Bank. "However, if we examine the underlying life science data and recent M&A activity, a different, decidedly positive perspective emerges."

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▲ **Venture Capital Report Shows Rosier Picture Than Expected for Investment,** *from page 1*

Calling 2011 the best year for venture-backed exits in life science and the largest generator of liquidity since 2005, the bank's research shows there were 35 "big exits" among private, venture-backed companies worth $12.5 billion. Total value of deals in life sciences has been increasing for the past three years creating "substantial returns to the venture community," the report says. Diagnostics accounted for top dollars in the device sector (along with orthopedics and cardiovascular), which together accounted for 18 of the big exits.

"Eighteen device big exits in 2011 is a strong indicator of acquirer interest," writes Norris in the report.

In the device sector big exits were defined as acquisitions where the up-front payment, not including any future milestone payments, totaled $50 million or more. The average device big exit in 2011 was $225 million, which Silicon Bank called "solid exit values overall."

Despite the positive trend data in the number of exits and dollar volume, the report acknowledges that up-front deal size and overall total deal value in diagnostics has not recovered to highs reached in 2009 and 2010. Additionally, the time to exit has increased. Device deals averaged close to eight-and-a-half years to exit as acquirers are looking for private companies to be near "significant commercialization" prior to exit. The majority of the 2011 device exits studied occurred with derisked, post-Food and Drug Administration-approved devices (70 percent). Only four device big exits were acquired in five years or less from the close of their Series A.

"While we had observed increased investment in diagnostics over the last seven years, we believed it was concentrated among a small set of investors. However, this data shows pervasive investment in diagnostics—including many personalized medicine companies among a broad number of investors."
—Jonathan Norris, Silicon Valley Bank

"Despite the general perception of gloom and doom around early-stage device investing, in the last three years we observed some buying signals from acquirers willing to buy still unproven medical device companies," the report found. "Getting to exit without raising a large commercialization round is often critical in order to obtain a higher exit multiple."

Will this generally upward trend continue for the diagnostics sector? The report points to some positive indicators that suggest that M&A activity in the diagnostics industry is likely to remain strong.

Silicon Valley Bank defined venture-backed companies as those that raised at least $500,000 in Series A dollars. Series A funding of life sciences companies has remained relatively stable, representing about 12 percent to 15 percent of all life sciences funds deployed since 2009. Series A investment had been "substantially" higher in 2005 to 2008 investment patterns, both in dollars deployed and companies created.

Diagnostics was the second-largest life science sector in terms of investment, receiving more than $1.65 billion from 2005 to 2011. For diagnostic device companies the average raised was $17 million with average Series A financing of $5 million. Diagnostics was also the life sciences sector with the most number of companies started—106—over the seven-year period.

"While we had observed increased investment in diagnostics over the last seven years, we believed it was concentrated among a small set of investors," writes Nor-

ris. "However, this data shows pervasive investment in diagnostics—including many personalized medicine companies among a broad number of investors."

Given these investments are just reaching the eight-year window from close of Series A, many of these diagnostics companies are entering the time frame when big exits would be most likely to occur.

An additional optimistic indicator for the future pipeline of diagnostics companies is that Silicon Valley Bank's Entrepreneur Services Group has seen a resurgence in Q1 2012 in the number of preventure backed medical device companies. It remains to be seen, though, if there is enough early-stage life science venture capital to invest in these companies.

Life Technologies' Acquisitions to Speed Company's Diversification Efforts

In July, Life Technologies (Carlsbad, Calif.) announced the acquisitions of Pinpoint Genomics, (Mountain View, Calif.) and Navigenics (San Francisco). Taken together the acquisitions further Life Technology's strategy of diversifying outside of tools and aggressively accelerating growth in molecular diagnostics, analysts say.

With the purchase of Pinpoint Genomics, Life Technologies gained access to its early-stage non-small cell lung cancer test that can help predict those early-stage patients at high risk for disease progression and death. Identification of patients at greatest risk for recurrence can improve upon conventional staging techniques and steer higher-risk, early-stage patients to chemotherapy. The lab-developed test uses quantitative polymerase chain reaction (PCR) to measure expression levels in a proprietary 14-gene panel.

"Since the test was developed and will be run in the Pinpoint laboratory on Life's qPCR platform, in addition to offering an LDT in the United States, we will be able to leverage our existing global installed qPCR platforms, which are currently being utilized in a significant number of clinical labs outside of this country," said Ronnie Andrews, president of medical sciences at Life Technologies. "Life Technologies intends to pursue in vitro diagnostic certification outside of the United States, so the test can be broadly deployed on the company's regulated platforms including the 7500 Fast Dx for qPCR."

Life Technologies said in a statement it is actively working to develop diagnostic tests across its multiple platforms, including next-generation sequencing. It is expected that Life Technologies will use the CLIA lab, gained in the Navigenics acquisition, for the design and validation of new diagnostic assays, which is a "long-term strategic positive," Bryan Brokmeier, a senior equity analyst at Maxim Group (New York), wrote in a research note at the time of the acquisition.

While financial terms of the deals were not disclosed, the company expects the combination of the two acquisitions to be 2 cents dilutive to earnings in 2012, 5 cents dilutive in 2013, and accretive thereafter. Life Technologies is coming off of a "decent" second quarter, while the tools sector as a whole was "mixed," characterizes Brokmeier. "The

financial crisis in Europe has been a headwind for the entire industry," he says. "Some are feeling the difficulty of selling larger systems. For Life Technologies, 80 percent of their revenue comes from consumables, which will help them get through this. They are not as dependent on one-time large-ticket orders."

Life has been slower than some other tools companies to enter applied markets, with an estimated 10 percent of its total revenue coming from molecular diagnostics, Brokmeier noted. But through the combination of partnerships announced in the past year, these acquisitions, and the hiring of Ronnie Andrews to commercialize the company's diagnostic applications, the company is well positioned for "accelerated growth in the diagnostics market," Brokmeier believes.

Activity in Transplant Sector: Thermo Fisher Acquires One Lambda, Roche Launches First FDA-Approved CMV Test

Thermo Fisher Scientific (Waltham, Mass.) agreed in July to pay $925 million in cash for transplant diagnostics company One Lambda (Canoga Park, Calif.). One Lambda, whose products include HLA typing and antibody detection to determine the compatibility of donors and recipients pretransplant, achieved revenue of $182 million in 2011.

"One Lambda gives us access to the attractive transplant diagnostics market and complements our existing immunosuppressant monitoring assays," said Marc N. Casper, CEO of Thermo Fisher, in a statement. "With its strong technology platform, high margin profile and good growth prospects, the business is perfectly aligned with our specialty in vitro diagnostics strategy. . . . It also offers the opportunity to leverage our global commercial infrastructure to serve growing transplant needs in emerging markets."

The deal, which is expected to close in the fourth quarter of this year, includes a one-year earn-out provision based on the achievement of certain financial targets. Thermo Fisher said Lambda One will merge with its specialty diagnostics segment and it expects the acquisition to be immediately accretive and is estimated to add 9 cents to 11 cents to the company's 2013 adjusted earnings per share (EPS).

Roche to Launch CMV Test

In mid-September Roche (Basel, Switzerland) plans on launching its COBAS AmpliPrep/COBAS TaqMan CMV test for testing a patient's viral load of cytomegalovirus (CMV). The test, approved in July, is the first CMV test approved by the U.S. Food and Drug Administration (FDA) and is intended to aid in the clinical management of solid organ transplant patients who have the viral CMV disease.

The fully automated, polymerase chain reaction-based test runs on the COBAS AmpliPrep/COBAS TaqMan system with a turnaround time of 5.5 hours, the company says. Based on CPT code data, Roche estimates that there were approximately 900,000 reimbursed CMV tests (all lab-developed tests) in 2011 in the United States. Of course, this is based on LDTs, as the Roche test is the first FDA-approved IVD test. There are not yet clinical guidelines for CMV monitoring, so there is not a fixed number of tests performed per patient, the company notes.

G2 INTELLIGENCE
Inside the Diagnostics Industry

Recent Shifts in HIV Testing Strategy and Market; Rapid In-Home Assay Approved, Testing Expands

Following AIDS 2012, the international AIDS conference held in Washington, D.C., July 22-27, there is renewed vigor in the fight to end the AIDS epidemic. In response to the 2011 Treatment as Prevention study, which demonstrated that a 96 percent reduction in transmission occurred when an HIV-positive partner began treatment early, conference organizers and AIDS experts worldwide are calling for big increases in HIV testing and treatment.

While the United States is far from achieving the Centers for Disease Control and Prevention's (CDC) 2006 calls for universal testing, there are distinct efforts under way to dramatically increase the number of people tested both in medical and nontraditional community settings. Experts hope that more widespread testing efforts will reach the 240,000 unknowingly infected people in the United States, who are disproportionately responsible for the 50,000 new HIV infections that occur nationally each year.

Home HIV Testing Approved

Beginning in October the first approved over-the-counter rapid HIV test will be commercially available. In what has been heralded as a "landmark decision," the U.S. Food and Drug Administration in July approved the OraQuick In-Home HIV Test from OraSure Technologies (Bethlehem, Pa.). The test is the only rapid HIV test approved in the United States for sale directly to consumers. The over-the-counter test is a version of the company's OraQuick ADVANCE HIV 1/2 Antibody Test that has been used by medical professionals for eight years. Using an oral swab, the test can detect antibodies to both HIV-1 and HIV-2 in 20 minutes.

"We set out with a clear purpose—to dramatically impact the number of people getting tested for HIV nationwide," said Douglas Michels, CEO of OraSure, at the time of the approval. "For the first time ever, individuals will have access to an in-home oral test that will empower them to learn their HIV status in the comfort of their home and obtain referral to care if needed. This new in-home rapid test—the same test doctors have used for years—will help individuals at risk for HIV who otherwise may not test in a professional or clinical setting."

Michels tells *DTTR* that the OraQuick In-Home HIV test will be "broadly" available in the United States at launch in more than 30,000 retail pharmacies, mass retailers like Wal-Mart, and large food chains. The anticipated retail price, he says, is $39, but retailers will set the final price. OraSure has stated that it believes the U.S. retail market for the test to be greater than $500 million or 12.8 million tests. The company is also launching a comprehensive education and support effort with the test including a toll-free customer support center and a consumer Web site to answer questions about HIV/AIDS and how to use the test, to interpret the results, and to provide direct referral to care if needed.

Outside experts are optimistic and believe the home test has value in testing some who may not otherwise be screened, but how widespread the impact will be remains to be seen.

"In general I'm a supporter of the home HIV test. I think people should have easy access knowing their HIV status – it's important for their sexual health," says Rochelle Walensky, M.D., from Massachusetts General Hospital and Harvard Medical School in Boston. "My suspicion is that it will likely not make a large impact on the U.S. epidemic, however. As enthusiastic about the test as I am, I suspect the price point will be too high. There will be a demographic willing to pay, but those who cannot afford the $40 price tag can likely can get tested elsewhere for free."

Decentralized Testing in the Community

The home HIV kit follows a trend toward decentralization of HIV testing in non-traditional or nonmedical settings.

"We are still finding people late in the disease," says Lisa Fitzpatrick, M.D., from Howard University in Washington, D.C. "We have to get out in the community, in the workplaces and churches."

This summer the CDC announced a two-year pilot program to train pharmacists and retail store clinic staff to deliver confidential rapid HIV testing at 12 rural and 12 urban sites in areas with high HIV prevalence or unmet HIV testing needs. CDC staff will use the results of the pilot effort to develop a model toolkit for implementation of HIV testing in similar settings across the country. The CDC said their goal is to make HIV routine, just as a blood pressure check.

"We know that getting people tested, diagnosed, and linked to care are critical steps in reducing new HIV infections," said Kevin Fenton, M.D., director of CDC's National Center for HIV/AIDS, Viral Hepatitis, STD and TB Prevention, in a statement. "By bringing HIV testing into pharmacies, we believe we can reach more people by making testing more accessible and also reduce the stigma associated with HIV."

The Department of Health (DOH) in Washington, D.C., is taking the trend of testing in the community one step further, instituting free HIV testing at the Department of Motor Vehicles (DMV), just as you can register to vote or sign up to be an organ donor. The program is a public-private partnership between the District government and Family and Medical Counseling Service. The program is supported in part by Gilead Sciences.

The rapid, oral test is administered in a confidential space at the DMV. Gilead Sciences has provided funding to Family and Medical Counseling Services for the project to provide an incentive, a $15 discount on DMV services for those who get tested. DOH provides the HIV test kits and informational materials. At initiation, the project targeted testing of a minimum of 15 percent of customers. Since its initiation in October 2010 the program has tested 9,000 people and a similar

program was established in a facility in a food stamp office, testing 3,500 since November 2011.

Testing Expansion in Medical Settings

Expansion efforts are taking a two-pronged approach. While experts wait for evidence of success in decentralized testing, including testing at home and in nontraditional settings, there is a concerted effort to simultaneously expand testing in medical settings, making HIV screening a standard of care in routine medical practice.

In 2006, CDC expanded its guidelines to recommend HIV screening for adults, adolescents, and pregnant women over the age of 13 years in health care settings and HIV testing at least annually for persons at high risk for HIV infection. The CDC's strategic plan calls for earlier detection thereby increasing the percentage of HIV-positive people who know their serostatus and are diagnosed at earlier stages of disease, as well as improving linkage to care and ultimately, health outcomes.

"Family practice doctors who have never screened must screen just like cholesterol or diabetes," says Fitzpatrick. "The biggest challenge is with the health care providers who don't believe it is their issue. They need incentives to routinely screen. There are issues with reimbursement, and they believe they can discern who needs testing, which patients are at potential risk, and which are not at risk. We are finding, though, that all are at risk if they are sexually active."

"The theme of the recent [AIDS] conference was turning the tide. You can't get there if you don't identify who has HIV. All road maps begin with identification, so in the short term there will be big efforts to increase screening."
—Lisa Fitzpatrick, M.D.

The CDC's recommendations apply to patients seen in hospital emergency departments, inpatient services, correctional health care facilities, clinics including substance abuse treatment facilities, public health centers, and primary care settings. Recognizing that they may be barriers to testing, separate informed consent for testing and pretest counseling are no longer required.

"In health care settings the number of platforms available that can deliver test results in 30 minutes to 60 minutes is driving more testing to laboratories versus point of care—like emergency room patients," says Bernard Branson, M.D., associate director at CDC's Laboratory Diagnostics Division of HIV/AIDS Prevention CDC. "The trend of using automated platforms in the laboratory will help with high-volume screening. But in nonclinical settings the trend is to decentralized, point-of-care testing, and we need to take advantage of all opportunities to expand testing. A lot of people at risk, especially youth, don't have many encounters with health care settings."

"The theme of the recent [AIDS] conference was turning the tide," says Fitzpatrick. "You can't get there if you don't identify who has HIV. All road maps begin with identification, so in the short term there will be big efforts to increase screening."

Neogen Launches New, Rapid Listeria Test for Food Industry

Neogen (Lansing, Mich.) has launched a listeria assay for its ANSR (Amplified Nucleic Single Temperature Reaction) platform. The August launch is the second rapid test for the food industry available on the system, following the April launch of ANSR for salmonella.

ANSR's single enrichment step reduces enrichment time from 24 hours to 16 hours for testing of environmental surfaces. The listeria assay runs in 20 minutes. The ANSR system, which has a benchtop footprint, utilizes an isothermal amplification method that exponentially amplifies bacteria DNA to levels detectable by fluorescence. The ANSR system was designed to combine accuracy of molecular testing with a scalable, low-cost instrument for in-plant testing. The assay is run in a 16-well instrument, ideal for batch-processing workflows, and the list price for 96 tests is about $1,000, says Gerry Broski, Neogen's senior marketing director of food safety.

The ANSR instrument is reasonably priced to facilitate adoption of the technique—making DNA-definitive technology affordable, says Broski. There are over 60 million listeria tests conducted annually and ANSR should be able to address the requirements for a substantial portion of this market.

This test targets environmental surface testing for food processors and producers. Neogen says it is awaiting the Association of Official Analytical Chemists Research Institute Performance Tested Methods approval. The company is additionally finalizing a listeria assay for food matrices as well. The launch of this test comes in an extremely productive period for Neogen's food safety research and development group. Since March 1, the company says, it has launched nine new food safety and quality testing products, including three new mycotoxin tests, two food allergen tests, two indicator organism tests for sterility testing, and now two innovative foodborne pathogen tests. Additional tests for the ANSR platform are expected to be launched in the coming months, including tests for E. coli.

Validation for Pronota's Pre-Eclampsia Screening Test; Commercial Launch, Regulatory Submission Expected

Pronota (Ghent, Belgium) has announced the successful validation of its midgestation pre-eclampsia screening test. The test, which combines an assay of five protein biomarkers and blood pressure, can correctly identify 80 percent of women at risk for the development of preterm pre-eclampsia (pre-eclampsia that results in birth of a premature baby), according to an abstract presented at the International Society for the Study of Hypertension in Pregnancy meeting (Geneva; July 9-12).

The company says between 4 percent and 7 percent of healthy women develop pre-eclampsia during their first pregnancy with no prior predisposition or warning signs and that there is currently no test that accurately predicts pre-eclampsia among these women. Biomarker discovery and validation studies were conducted using samples from participants in the international Screening for Pregnancy Endpoints (SCOPE) study. Initial identification of 30 plasma proteome profiles was completed in predisease plasma samples (22 weeks to 26 weeks) from women who subsequently developed pre-eclampsia and

those with uncomplicated pregnancies. An insulinlike growth factor binding protein, acid labile subunit (IGFALS), was identified and found to have predictive value for term as well as preterm disease. Validation of the prediction panels was performed in an independent subcohort of SCOPE that included 50 samples from women who developed pre-eclampsia and 150 without. IGFALS mass spectrometry quantitation data could be interchanged with IGFALS ELISA data without affecting the predictive algorithms.

Katleen Verleysen, Ph.D., CEO of Pronota, tells *DTTR* that the company plans on launching the test in the United States as a lab-developed test by the end of 2013 while pursuing U.S. regulatory approval. The company will be having its first discussion with the U.S. Food and Drug Administration in September and will commence prospective sampling for a clinical study for regulatory submission in both the United States in Europe beginning in November. While exact pricing has not been worked out yet, Verleysen says this will be a very affordable test with a straightforward reimbursement case.

MDx Penetration Positive in Europe, Survey Finds; Growth Expected to Be Positive for MRSA, HPV

A new survey by investment firm Leerink Swann shows better than expected trends for the diagnostics industry in Europe. Despite the economic challenges throughout the continent, the company uncovered some positive news for diagnostics firms including stable European laboratory budgets and positive growth forecasts for some specific molecular diagnostics product categories.

The survey, conducted from mid-June to mid-July, included 21 European diagnostics labs, all of which perform some molecular testing. Dan Leonard, an analyst at Leerink Swann, found that while overall volume growth was modest at best, several molecular product categories appear to be faring better, with more positive adoption trends.

- Methicillin resistant staphylococcus aureus (MRSA)—Of the 14 laboratories currently performing MRSA testing, both testing volume and number of labs using molecular technologies are expected to grow over the next two years. The responding laboratories plan to increase the percentage of patients admitted to hospitals that are being tested (estimated to be 10 percent cumulative annual growth, Leonard says). Additionally, three of the six laboratories performing culture testing plan on converting to molecular testing within two years.
- Human papillomavirus (HPV)—Of the 10 responding laboratories that currently perform HPV testing, test volume is expected to grow 2.3 percent over the next year. While this growth is seemingly modest, Leonard says, it outpaces growth in other women's health testing categories including C. trachomatis/N. gonorrhea and Trichomonas testing.

New Evidence for NGS's Clinical Emergence: Transgenomic Launches NGS Mitochondrial Function Test at MCW

A late-summer announcement provides evidence that tests utilizing next-generation sequencing technology are continuing their slow immersion in clinics. The Medical College of Wisconsin (Milwaukee) and Transgenomic (Omaha, Neb.) said in July they will partner to offer next-generation genetic testing services for patients in a high-value commercial collaboration.

Under the terms of the agreement announced at the end of July, the Medical College of Wisconsin laboratory will become the first laboratory to offer Transgenomic's NuclearMitome Test, which can identify mutations in 448 genes that are considered important for mitochondrial function. Clinical deployment of this next-gen test will shorten patients' diagnostic odysseys, says Howard Jacob, Ph.D., the director of the Medical College of Wisconsin's Human and Molecular Genetics Center.

Not only will the collaboration enhance patient care, but Transgenomic hopes such commercial next-generation sequencing collaborations will contribute to the continued growth of its business units. In the beginning of August Transgenomic reported its second-quarter financial results, which included 41 percent growth in its laboratory services segment and 17 percent growth in its diagnostic tools segment.

"This collaboration allows Transgenomic to rapidly expand the commercial use of our NuclearMitome Test in addition to building out our offerings in whole genome and exome testing," said Craig Tuttle, CEO of Transgenomic, in a statement at the time of the announcement. "The Medical College of Wisconsin . . . [has] a robust presence in genomics and genetic testing. . . . We look forward to working with MCW, and to building rapid value through these products."

Specific Signature of Monocytes May Be Marker for ALS

The profile of monocytes in patients with the degenerative disease amyotrophic lateral sclerosis (ALS, also known as Lou Gehrig's Disease) may serve as a biomarker for disease progression, even from the earliest, presymptomatic stages of the disease. Researchers are hopeful that with further validation the monocytes, which have been identified in both a mouse model and human ALS patients, might be useful as a blood test to monitor the disease, according to a study published in August in the *Journal of Clinical Investigation*.

Although immune abnormalities have been reported before in ALS, it is not generally considered an inflammatory disease. But the researchers found that recruitment of inflammatory monocytes in the spinal cord plays an important role in disease progression with their progressive recruitment correlating with neuronal loss.

Expression of a specific monocyte signature—Ly6C and CD39—distinguished peripheral inflammatory monocytes from resident microglia in mice, which were found to decrease in the spinal cord with disease progression. Using miRNA and gene expression profiling, altered expression profiles were detectable even prior to disease onset. The Ly6Chi monocyte profile was present in the spleen a month prior to disease onset, while CD39+ resident microglia expressed Ccl2 and other chemotaxis-associated mol-

ecules in the spinal cord, but not the brain, prior to ALS onset. In testing of patients diagnosed with ALS, the analogous monocytes (CD14+CD16–) exhibited an ALS-specific microRNA inflammatory signature similar to that observed in the ALS mouse model.

Currently the only way to track ALS progression is through clinical measurements, including the ALS Functional Rating Scale and measures of muscle strength that are known to fluctuate over the short term. Study author Howard L. Weiner, M.D., from Brigham and Women's Hospital in Boston, tells *DTTR* that the next step is to test the monocyte signature longitudinally in ALS patients to see if it correlates with disease progression and with different subtypes of MS. He says that a test that could be used in clinical practice will likely take at least five years to complete the necessary validation studies.

Combo of Urinary Markers May Test for Active, Chronic Lupus

New research has found that the combination of urinary biomarkers and select established markers of renal function are associated with tissue changes observed in conjunction with lupus nephritis activity and chronicity. Renal involvement is one of the main determinants of poor prognosis in the autoimmune disease systemic lupus erythematosus. With future validation, accurate longitudinal noninvasive assessment of lupus nephritis disease status is feasible allowing for more effective and personalized monitoring, say the authors of the study published in the August issue of *Arthritis & Rheumatism*.

Currently, histologic characterization of kidney biopsy samples is used to diagnose and guide lupus nephritis treatment as traditional measures of lupus nephritis—including blood pressure, proteinuria, urine sediment, complement components C3 and C4, and glomerular filtration rate—are considered too inaccurate to reliably discriminate between the acute inflammatory changes that will benefit from immunosuppressive therapy and chronic degenerative changes that will not improve.

The researchers analyzed urine samples from 76 patients that were collected within two months of kidney biopsy. They found a specific increase in levels of multiple urinary biomarkers that formed a pattern reflective of histologic features seen in different states of lupus nephritis. The combination of monocyte chemotactic protein 1 (MCP-1), 1-acid glycoprotein (AAG), and ceruloplasmin (CP) levels plus protein-to-creatinine ratio was excellent in predicting lupus nephritis activity. Neutrophil gelatinase–associated lipocalin in combination with creatinine clearance plus MCP-1 was an excellent diagnostic test for lupus nephritis chronicity, while the combination of MCP-1, AAG, transferrin (TF), and creatinine clearance plus C4 was a good diagnostic test for membranous lupus nephritis.

Combinations of the biomarkers included in this study yielded excellent diagnostic abilities for lupus nephritis activity and chronicity, writes Hermine I. Brunner, M.D., from the Cincinnati Children's Hospital Medical Center in Ohio. However, the presented analyses also suggest that additional markers are needed to provide the highly accurate (AUC >0.9) diagnostic tests that are urgently needed by clinicians to help guide lupus nephritis LN therapy.

Brunner tells *DTTR* that validation of these measures is in progress and once completed she anticipates it would be one to two years until the markers could be used for clinical care.

G2 Insider

Should HbA1c Cutoffs Vary by Race? . . . Evidence that hemoglobin A1c (HbA1c) levels differ by race at any given glycemic level raises questions of whether race-based HbA1c cutoff points should be established. But new research published in the August issue of the *Annals of Internal Medicine* demonstrating that the frequency of retinopathy, an early clinical complication of diabetes, actually occurs at lower HbA1c levels in blacks than in whites is causing some to call for further research on the benefit of using lower, not higher, HbA1c thresholds for diagnosing diabetes in black people.

The 6.5 percent HbA1c threshold for diagnosing diabetes, established in 2010 by the International Expert Committee, the American Diabetes Association, and the World Health Organization, was selected based on the prevalence of diabetic retinopathy at that level.

"Although there is evidence that HbA1c levels are consistently higher in black persons than in white persons for any given glycemic level, we found that the HbA1c level at which the prevalence of retinopathy begins to increase is paradoxically lower in black than in white U.S. adults," write the authors led by Yusuke Tsugawa, M.D., from Harvard Medical School.

The researchers analyzed data from 2,804 white persons and 1,008 black persons participating in the National Health and Nutrition Examination Survey (2005 to 2008). In white persons, the adjusted prevalence of retinopathy was significantly higher at HbA1c levels 6 percent to 6.4 percent or higher. But among black adults HbA1c levels of 5.5 percent to 5.9 percent had significantly higher risk for prevalent retinopathy.

"Our findings argue against increasing the HbA1c diagnostic threshold for blacks," conclude the authors. "[But] longitudinal studies with larger samples are warranted to determine whether a lower threshold of HbA1c should be considered for the diagnosis of diabetes in this population."

If the diagnostic threshold of HbA1c were lowered from 6.5 percent to 6 percent, an estimated additional 1.8 million black and 7.6 million white U.S. adults over the age of 40 years would be diagnosed with diabetes, of whom 0.2 million and 0.8 million, respectively would be expected to manifest diabetic retinopathy at the time of examination.

Company References

Leerink Swann 800-778-1653
Life Technologies 760-603-7200
Medical College of Wisconsin 414-456-8296
Neogen 517-372-9200
OraSure Technologies 610-882-1820
Pronota +32 (0)9 241 11 64
Roche +41-61-688 1111
Silicon Bank 408-654-5555
ThermoFisher Scientific 781-622-1000
Transgenomic 402-452-5400
U.S. Centers for Disease Control and Prevention 404-639-3311

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Kimberly Scott, Managing Editor, kscott@G2Intelligence.com; Lori Solomon, Editor; Heather Lancey, Designer; Beth Butler, Marketing Director; Dan Houder, COO and Publisher

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