Diagnostic Testing and Technology Report

Competitive Intelligence & Analysis for an Expanding Global Market

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WASHINGTON G-2 REPORTS

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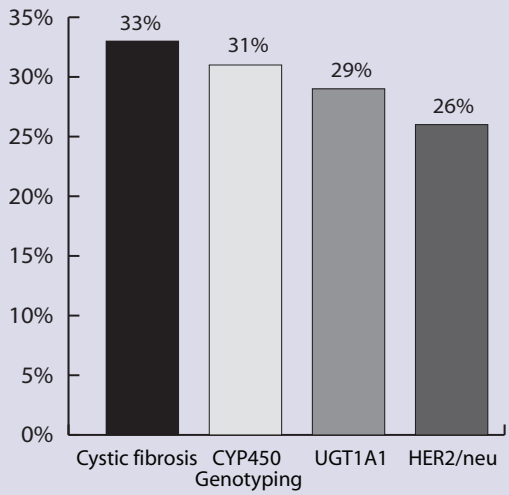
In Planning Menu Additions, Labs Prioritize Genetic Testing

In a recent survey, Washington G-2 Reports found that nearly two-thirds (65 percent) of 117 U.S. laboratories surveyed currently offer molecular diagnostic tests. While the current molecular offerings of these labs are dominated by infectious disease testing, labs are increasingly looking to add more advanced genetic testing to their assay menus.

While 31 percent of molecular labs surveyed already offered cystic fibrosis testing, an additional one-third plan to add the test within the next five years. A similar proportion (31 percent) reported that they plan to add CYP450 genotyping, a pharmacogenomic test that only 17 percent of labs said that they already offered. Meanwhile, as available Food and Drug Administration (FDA)-approved HER2/neu breast cancer tests proliferate, 26 percent of labs said that they plan to add the testing within the next five years. HER2/neu testing was also among the list of the top 10 most commonly offered molecular tests among the labs surveyed, with 48 percent already performing it. For more results from G-2's molecular diagnostics survey, see *Inside the Diagnostics Industry*, pp. 5-6.

Planned Molecular Diagnostic Offerings

(% of labs surveyed that plan to add test within five years)



Source: Washington G-2 Reports 2008 Molecular Diagnostics Survey (n=117)

FDA Clears Pathwork Diagnostics Tumor Origin Test

The United States Food and Drug Administration (FDA) has cleared the Pathwork Tissue of Origin test for use in determining the origin of certain tumors, Pathwork Diagnostics (Sunnyvale, Calif.) announced on July 31. The molecular diagnostics company will sell the test to clinical laboratories as an in vitro diagnostic (IVD) kit, as well as continue to offer it as a service through Pathwork's CLIA-certified laboratory.

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▲ **Tumor Origin Test** *from page 1*

The first test of its kind to receive FDA clearance, the Pathwork Tissue of Origin test can help determine the source of hard-to-identify tumors, which can in turn enable better, targeted cancer treatment. The test uses a microarray to measure the expression pattern of more than 1,500 genes in the uncertain tumor and compares it to expression patterns of a panel of 15 known tumor types to help determine the tumor's origin.

"Hard-to-identify tumors are a significant clinical problem," said Dr. James Abbruzzese, professor of medicine at M.D. Anderson Cancer Center, in a statement issued by Pathwork. "They are time-consuming and frustrating for both physicians and patients. Accurately identifying a tumor's origin—and thus knowing what kind of cancer the patient has—is necessary for beginning standard-of-care, cancer-specific treatment per the *National Comprehensive Cancer Network Clinical Practice Guidelines*. Knowing the tumor's origin can also enable patients to get into—and benefit from—appropriate clinical trials."

Medicare Legislation Kills Lab Competitive Bidding Demo

After a four-year lobbying campaign, America's clinical laboratory industry is sleeping a little easier now that the Medicare competitive bidding demonstration project for clinical lab services, slated to launch on July 1 in San Diego, has been repealed. The repeal went into effect on July 15, after Congress overrode the president's veto of the Medicare Improvements for Patients and Providers Act of 2008. The move by Congress also enacted major program changes advocated by clinical laboratory and pathology organizations, including a physician fee fix.

Competitive bidding was touted by the Bush administration as a fee-for-service alternative intended to inject more market forces into the Medicare program. The new Medicare law repeals the authority of the Centers for Medicare and Medicaid Services to conduct a Part B lab bidding demonstration, as was required under the 2003 Medicare reform law passed by the Republican-controlled Congress.

Congress has replaced the cut of 10.6 percent in Medicare physician fees that took effect July 1 under the sustainable growth rate update formula with a 0.5 percent increase, retroactive to July 1 and effective through December 31. For 2009, fees will rise an additional 1.1 percent.

Additionally, for the first time in five years, the Part B lab fee schedule will get a positive update starting Jan. 1, 2009, though it will not be the full Consumer Price Index (CPI) update currently projected to be 5 percent. Congress reduced the CPI update to the lab fee schedule by 0.5 percent for a net gain of 4.5 percent.

AutoGenomics Files for IPO

On July 24, molecular diagnostics company AutoGenomics (Carlsbad, Calif.) filed papers with the Securities and Exchange Commission (SEC) for an initial public offering worth up to $86.3 million. The company, which intends to reincorporate in Delaware after the IPO, plans to list its shares on the Nasdaq under the symbol AGMX.

Founded in 1999 as Neuron Technologies by Abbott Laboratories veteran Fareed Kureshy, AutoGenomics specializes in automated multiplex molecular testing. The company's fully automated INFINITI system is designed to process its proprietary BioFilmChip microarrays, which can be multiplexed and configured to assess disease signatures from a single sample. The U.S. Food and Drug Administration (FDA) cleared its benchtop INFINITI analyzer in February of 2007. In June, the analyzer received the CE mark, allowing it to be marketed in the European Economic Area.

AutoGenomics's Top Tests

- ❑ Warfarin sensitivity
- ❑ Human papillomavirus
- ❑ Cystic Fibrosis
- ❑ CYP450 2D6

Source: AutoGenomics

The FDA has cleared four INFINITI assays: those for Factor II, Factor V, Factor II-V, and warfarin sensitivity. The company sells 22 other INFINITI assays on a research use only (RUO) basis and plans to introduce six additional applications by the end of the first quarter of 2009. The FDA is now considering AutoGenomics's proposed protocol for a clinical trial for use in the premarket approval (PMA) application for its human papillomavirus (HPV) screening test.

AutoGenomics has big hopes for HPV testing. It currently sells two RUO assays for HPV, one a primary screening test for high-risk types of the virus and another for genotyping. "Our strategy is to become a key provider of HPV testing products," the company noted in its SEC filing. The company estimates that securing PMA approval for its HPV screening test will take at least two to three years. Meanwhile, it intends to apply for 510(k) clearance for the HPV genotyping test next year.

To date, AutoGenomics has placed 58 INFINITI systems in reference laboratories, hospital laboratories, and specialty clinics in North America, including ARUP Laboratories, Cleveland Clinic, Louisiana State University Hospital Health Science Center, and New York Presbyterian Hospital.

Harms of Prostate Cancer Screening Outweigh Benefits for Men Over 75

One-third of men in the United States over 75 are receiving prostate-specific antigen (PSA) testing, but the U.S. Preventive Services Task Force warns that such testing could do more harm than good. According to a recommendation and analysis published in the August 5 issue of the *Annals of Internal Medicine*, men age 75 and older should not be screened for prostate cancer, and younger men should discuss the benefits and harms of the PSA test with their clinicians before being tested.

The task force found evidence that screening for prostate cancer provided few health benefits but led to substantial physical harms and some psychological harms in men age 75 and older. In men younger than 75, the group concluded that current evidence is insufficient to assess the relative benefits and harms of prostate cancer screening. Two ongoing clinical trials should help to clarify the potential benefits of screening in men under the age of 75.

Although a PSA test is more likely to detect prostate cancer than a digital rectal exam, prostate cancers detected with a PSA test take years to affect health; most

An estimated 218,890 U.S. men were diagnosed with prostate cancer in 2007, and one in six men will be diagnosed in his lifetime.

prostate cancers that grow serious enough to cause death take more than 10 years to do so. Since a 75-year-old man has an average life expectancy of about 10 years and is more likely to die from other causes, such as heart disease or stroke, prostate cancer screening is unlikely to help men over 75 live longer.

There are also harms associated with prostate cancer screening. These include biopsies, unnecessary treatment, and false-positive results that may lead to anxiety. Treating prostate cancer can result in such complications as urinary incontinence and impotence, while slow-growing cancers may never have affected a patient's health or well-being had they not been detected by screening.

Most major medical organizations suggest that prostate cancer screening may be discontinued in men with a life expectancy of fewer than 10 years, but the task force is the first group to define an explicit age cutoff above which screening is likely to be ineffective or harmful.

Inverness Debuts Rapid HIV Test, Plans POC Molecular Test

Inverness Medical Innovations (Waltham, Mass.), the rapid diagnostics company that has moved aggressively into the health management market through acquisitions, premiered its newest HIV test at the International AIDS conference (AIDS 2008), held in August in Mexico City and attended by approximately 25,000 people. Meanwhile, the company plans to launch a more advanced, multi-array HIV test late this year.

At AIDS 2008, Inverness announced its fourth-generation rapid HIV diagnostic test, the Determine HIV-1/2 Ag/Ab Combo. The company will launch the test in the developing world during the third quarter and in certain other markets next year.

As the first test to allow simultaneous detection of HIV p24 antigen (Ag) and antibodies (Ab) for HIV-1 and HIV-2, the Determine Combo test can detect HIV infection earlier than tests that detect only antibodies. The p24 antigen is present during the first weeks of HIV infection and can be identified before HIV antibodies are produced.

The Determine Combo test is a rapid, point-of-care lateral flow test that provides visual results in 20 minutes. The user-friendly format makes the test appropriate for a range of clinical settings. The test can be used with human serum, plasma, or whole blood samples.

Inverness also has a test in development that is more closely linked to its increased focus on disease management, an area that is increasingly relevant to HIV's status as a chronic disease in the developed world. Using the multiplex molecular diagnostic platform that it acquired in its 2006 purchase of German company Clondiag, Inverness plans to launch a multi-array system that can combine molecular immunoassays and other technologies in a point-of-care format.

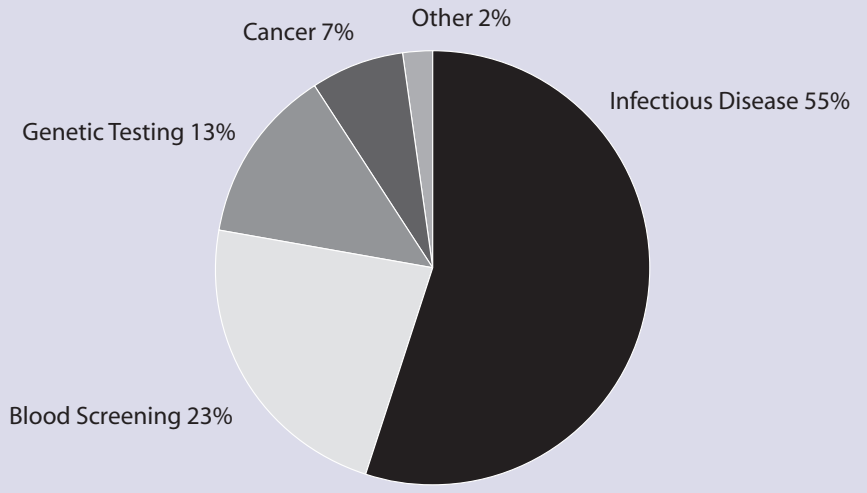
The Inverness Clondiag platform's first application, scheduled to launch later this year, is a test that will aid in the management of HIV by staging the disease and measuring the patient's response to therapy. The company plans to follow the HIV product with tests for cardiology and infectious diseases applications.

Growing Field of Molecular Diagnostics Still Dominated by Infectious Disease Testing

Washington G-2 Reports estimates that approximately 65 million molecular diagnostics tests will be performed in 2008, and an increasingly diverse array of clinical laboratories—community hospitals and independent labs as well as the academic medical centers that pioneered the clinical use of molecular testing—are focusing on adding or expanding their offerings in this rapidly growing area, which continues to be dominated by testing for infectious diseases.

In a recent survey, Washington G-2 Reports found that nearly two-thirds (65 percent) of 117 U.S. laboratories surveyed currently offer molecular diagnostic tests. Of those labs, 38 percent have added molecular diagnostic testing to their offerings within the last five years. An additional 9 percent of all laboratories surveyed noted that they have a plan in place to add molecular diagnostic capabilities in the near future. Meanwhile, labs with no specific plans to offer molecular testing cited the ease of sending out these tests to reference laboratories, the lack of available information concerning how to develop a molecular testing program, and insufficient demand for this type of testing.

Global Molecular Diagnostics Testing by Segment



Source: Washington G-2 Reports

Among the labs surveyed that offer molecular tests, the average number of molecular assays offered was 19 and the median number offered was 10. When asked about their specific molecular diagnostic test offerings, labs reported test menus that are in step with the global market for molecular diagnostic testing, which remains dominated by infectious disease testing followed by blood screening, genetic testing, and cancer testing.

The list of the 10 tests most likely to be offered by labs that perform molecular testing is weighted heavily toward infectious disease tests. At least half of the labs offer testing for chlamydia / gonorrhea (CT / NG) and human papillomavirus (HPV), while 48 percent offer cytomegalovirus (CMV) testing. Qualitative testing for the hepatitis C virus (HCV), offered by 45 percent of molecular labs surveyed, is only slightly more common than a quantitative test format,

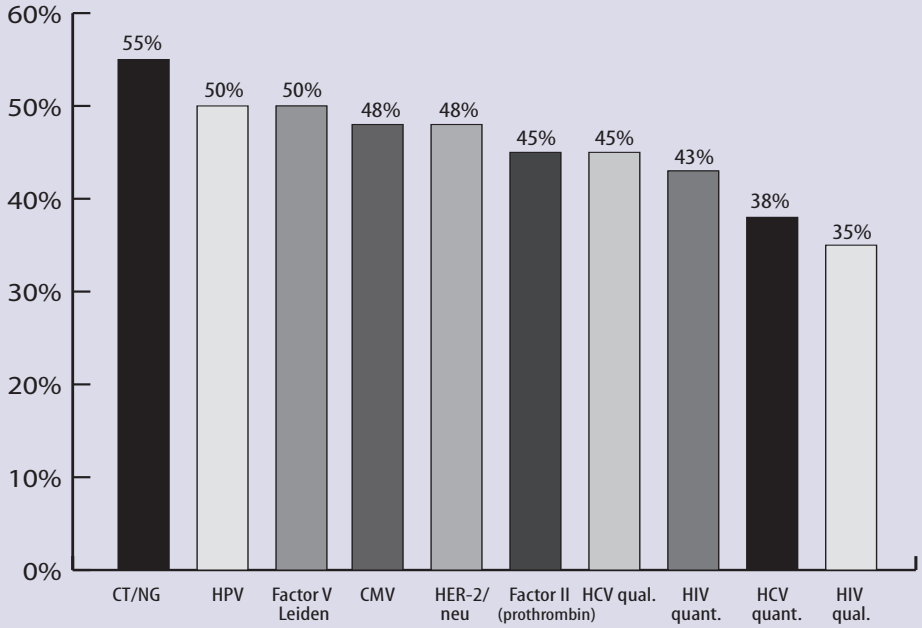
while the reverse was true for HIV, with 43 percent offering quantitative HIV testing and 35 percent offering testing in a qualitative format.

Not surprisingly, tests for the Factor V Leiden and for Factor II (prothrombin) mutations were also among the top 10 tests performed by labs with molecular capabilities. Half of labs surveyed offered Factor V testing and 45 percent offered Factor II testing. Also high on the list of top tests was HER2/neu. This testing, which is used to guide treatment and determine prognosis of invasive breast cancer, was performed by 48 percent of labs surveyed.

Beyond the top 10 most commonly performed molecular tests, a third of labs said that they offered testing for herpes simplex virus (HSV), while just under that proportion offered testing for cystic fibrosis (31 percent) and human leukocyte antigen (HLA)-typing (31 percent). A little over one-fifth (21 percent) of labs reported that they offered prenatal testing, while CYP450 genotyping was offered by 17 percent of labs surveyed.

While molecular testing continues to grow in popularity, G-2 survey results show that this area remains challenging on several fronts. Among the most difficult aspects is outreach to clinicians regarding molecular testing, which nearly half (47 percent) of laboratories that perform molecular testing classified as something that has been harder or much harder than they expected. A similar proportion (43 percent) said that finding appropriate personnel for molecular testing and/or budgeting/cost control was more difficult than anticipated. Finally, more than a third of respondents pointed to deciding which tests to offer (38 percent) and training or retraining personnel (34 percent) as harder or much harder than expected.

Top 10 Molecular Tests Offered
(% of labs surveyed that offer test)



Source: Washington G-2 Reports *2008 Molecular Diagnostics Survey*

FDA Clears Invitrogen's CISH Test for HER2

The U.S. Food and Drug Administration has granted Invitrogen (Carlsbad, Calif.) premarket approval (PMA) for a novel genetic test that can determine whether patients with breast cancer are good candidates for treatment with the drug Herceptin (trastuzumab). The SPOT-Light HER2 CISH kit uses chromogenic in situ hybridization (CISH) to quantify HER2 gene expression in tumor tissue. The approved test kit, Invitrogen's first to receive PMA, will be available in mid-August.

A healthy breast cell has two copies of the HER2 gene, which sends a signal to cells telling them when to grow, divide, and make repairs. Between 18 percent and 30 percent of breast cancer patients have more than two copies of the gene, leading to the overproduction of HER2 protein and prompting cells to grow and divide too rapidly. Patients who overproduce HER2 are typically treated with Herceptin, which targets HER2 protein production. Current medical practice requires that all patients who are considered for trastuzumab treatment be tested for HER2 amplification or overexpression.

Using a DNA probe for the HER2 gene, the SPOT-light test assesses the amplification of HER2 in a small sample of removed tumor. The excised tumor is stained with a chemical that causes any HER2 present to change color. This color change can be visualized under a standard bright-field microscope, eliminating the need for more expensive and complex fluorescent microscopes that are required to read immunohistochemical assays. The SPOT-Light test also allows labs to store tissue for future reference.

"The current protocol for assessing HER2 gene status is for labs to initially screen tissue samples with immunohistochemistry to gauge whether there is an overabundance of the HER2 protein, as an indirect measure of gene amplification," said August Sick, vice president and general manager of Invitrogen's cellular analysis business. "In the case of an inconclusive test, the samples are typically sent to an outside lab for confirmation." The SPOT-Light test allows histology labs to assess amplification of the HER2 gene while simultaneously examining tissue morphology.

The FDA based its approval of the test on a study of tumor samples from patients with breast cancer in the United States and Finland. Findings confirmed that the test was effective in assessing HER2 gene copy number in these patients.

"When used with other clinical information and laboratory tests, this test can provide health care professionals with additional insight on treatment decisions for patients with breast cancer," said Daniel Schultz, M.D., director of the FDA's Center for Devices and Radiological Health.

HandyLab Raises $19M

Molecular diagnostics company HandyLab (Ann Arbor, Mich.) has raised $19.2 million in a Series D funding round co-led by Dow Ventures and

Lurie Investments. Other backers included EDF Ventures, Ardesta, Arboretum Ventures, and Pfizer Strategic Investments. The company has raised a total of approximately $44 million to date.

In July, HandyLab released its automated Jaguar system, a real-time PCR platform that integrates sample preparation, nucleic acid extraction, and microfluidic amplification and detection into a single instrument. The system can run as many as 24 tests within 90 minutes on a raw patient sample.

The company also recently teamed up with Nanogen (San Diego, Calif.) and the Medical College of Wisconsin (Milwaukee, Wis.) on a two-year, $10.4 million project for the U.S. Centers for Disease Control and Prevention. The goal of the project is to develop a multi-analyte molecular diagnostic assay for influenza that will be significantly faster and more sensitive than current rapid flu tests. The project is expected to use HandyLab's Raider system, a microfluidic real-time PCR technology released in February. The system provides results from purified nucleic acid in less than 15 minutes.

Gene Express Partners With NeoGenomics for Test Validation, Commercialization

Molecular diagnostics company Gene Express (Wilmington, N.C.) announced on August 11 that it will use the clinical trials service division of NeoGenomics (Ft. Myers, Fla.) to validate its lung cancer risk prediction and BCR/ABL tests, commercialize its tests, and validate future Gene Express technology to meet requirements of the U.S. Food and Drug Administration (FDA). Additionally, a licensing agreement allows NeoGenomics to use Gene Express's standardized reverse transcription polymerase chain reaction (StaRT-PCR) platform technology for its own commercial activities.

Gene Express plans to complete clinical validation and submission for FDA approval of its lung cancer risk prediction test in the fourth quarter of this year and will begin clinical trials to support an FDA-approved BCR/ABL test by the first quarter of 2009.

In July, Gene Express announced its receipt with BioTrove (Woburn, Mass.) of a two-year National Institutes of Health grant for research of genetic biomarkers for lung cancer. Using PCR-based technology from both companies, the project aims to create a standardized genetic profiling test for lung cancer biomarkers that can be used at the point of care.

Gene Expression Predicts Lung Cancer Survival

Microarray measurements of gene expression can help to predict the survival of lung cancer patients. This finding could lead to a test that would allow physicians to determine which lung cancer patients need the most aggressive treatment. The study, the largest of its kind, appears online and in the August issue of *Nature Medicine*.

According to the American Cancer Society, 215,020 Americans will be diagnosed with lung cancer this year and 161,840 will die from the disease.

Typically, lung cancer patients receive chemotherapy after surgery to reduce the risk of cancer recurrence. However, some patients with stage I disease have an aggressive disease with poor prognosis, while other patients with more advanced stage II disease have a relatively good prognosis. The challenge is identifying which patients are which so that the information can be factored into treatment decisions.

The researchers looked at 442 lung adenocarcinoma tissue samples collected from six cancer hospitals in North America. They tested the tumor samples to look at the expression of hundreds of genes and factored in clinical data such as tumor stage and the patients' gender and age. The results showed that the lung cancers could be divided into groups that exhibited better and worse survival rates. Most of the prognostic models tested performed better with clinical data, supporting the combined use of clinical and molecular information.

"We found that looking at clinical data along with gene expression can be a more reliable indicator. Gene expression is not just a black box approach, which a lot of researchers think it is," says David Beer, Ph.D., professor of surgery and radiation oncology at the University of Michigan Medical School and senior author of the study. "Sometimes knowing the context actually helps you use that information more efficiently."

A gene test for a complex disease such as lung cancer would need to accurately model the known cellular diversity and the potential differences underlying the aggressiveness between lung cancers. "Our findings suggest that there is a potential for successfully predicting lung cancer prognosis based on gene expression, but it is likely to be more difficult to develop a clinically useful test than has been suggested by previous studies," says co-author Kerby Shedden, Ph.D., associate professor of statistics at U-M. "It's going to require more assay standardization and a large prospective study to identify a signature that is ready for clinical use."

The researchers will continue to identify important genes and testing findings with tissue samples. They also plan to test their predictors in a prospective trial, enrolling patients as they are diagnosed and following their progress.

New Assay Shows Promise for Anemia Diagnosis

Researchers from the University of Utah School of Medicine and University of California have developed an assay that facilitates diagnosis of chronic-illness related anemia and diseases of iron overload. The results of a study detailing the new tool are published in the August 2008 issue of the journal *Cell Metabolism*.

Iron balance in the body is regulated by the interaction between the liver-produced hormone hepcidin and the iron transporting receptor ferroportin. Hepcidin binds to ferroportin, resulting in decreased export of iron out of cells. An excess of hepcidin in the blood can result in anemia, and a deficiency of hepcidin causes a build-up of iron that is damaging to body organs.

Unlike the anemia that is caused by iron deficiency, vitamin B12, or folate deficiency, anemia of chronic disease is thought to be related to abnormally high levels of hepcidin. Meanwhile, inappropriately low levels of hepcidin in the blood are associated with hereditary hemochromatosis, the most common iron overload disorder in humans.

Distinguishing among the causes of anemia and iron overload can be difficult. "It is hard to diagnose the anemia of chronic disease," said senior author Jerry Kaplan, Ph.D., a professor of pathology at the University of Utah. "Having an assay for hepcidin would make it much easier, and it would also help in diagnosing iron overload diseases."

In the study, Kaplan and researchers identified the hepcidin-binding domain (HBD), the site where hepcidin binds to ferroportin. By placing a synthetic version of that binding site on agarose beads, the researchers developed the HBD assay, a rapid, sensitive test for measuring the concentration of active hepcidin in the blood.

The HBD assay developed by Kaplan and colleagues detects biologically active hepcidin. This assay can readily detect variations in hepcidin levels in the blood due to mutations in genes that are known to affect hepcidin levels, as well as mutations in other genes involved in iron metabolism. It can also measure hepcidin concentration in response to inflammation. Such a test would allow physicians to distinguish anemias and diseases of iron metabolism that arise from abnormalities in hepcidin from those that have other causes.

Rosetta Genomics Completes Purchase of Parkway Clinical Labs

On July 24, microRNA (miRNA)-focused Rosetta Genomics (Rehovot, Israel, and Jersey City, N.J.) completed its acquisition of Parkway Clinical Laboratories (Bensalem, Penn.) for $2.9 million in cash and stock, with an additional payment to be triggered by the achievement of certain milestones.

Parkway's privately held, CLIA-certified lab is expected to have 2008 revenues of approximately $2.7 million and break-even operating income. Rosetta has said that it will retain Parkway's 33 employees and the lab's CEO, Raza Bokhari, M.D., has been named Rosetta's chief development officer.

Eight-year-old Rosetta acquired Parkway to expedite development and validation of its miRNA-based diagnostic tests. The lab will also be used to control the commercialization of those tests, including marketing, sales, and reimbursement strategy. Columbia University Medical Center's high complexity molecular pathology laboratory and the University of California Irvine School of Medicine's CLIA lab are also expected to offer diagnostics based on Rosetta Genomics's microRNA technology.

This year, three of Rosetta's tests are expected to enter development and validation at Parkway's 5,000-square-foot lab: a test designed to differentiate squamous from non-squamous non-small cell lung cancer, one that distinguishes between

mesothelioma and adenocarcinoma, and a test that uses miRNA biomarkers to identify tumor origin. On August 11, Rosetta initiated a 100-subject clinical validation study of its tumor origin test with the University of Texas M. D. Anderson Cancer Center. Rosetta expects predictive tests for ovarian cancer, gastric cancer, and lung cancer to enter development within the next two years.

Bone Disease Marker May Predict Risk of Death in Dialysis Patients

Chronic kidney disease patients with alkaline phosphatase levels above the upper limit of normal had a 25 percent increase in mortality rate.

High levels of alkaline phosphatase—a routinely measured laboratory marker of bone disease—may signal an increased risk of death in patients with chronic kidney disease (CKD), reports a study in the November *Journal of the American Society of Nephrology* (*JASN*). The study was published online on July 30.

"This large epidemiologic study shows, for the first time, a consistent and robust association between a high blood level of alkaline phosphatase and cardiovascular death in thousands of dialysis patients across the United States," says Kamyar Kalantar-Zadeh, M.D., of the University of California Los Angeles, one of the study authors. "If the association between alkaline phosphatase and mortality has a causal link, treatment strategies that reduce alkaline phosphatase levels may improve survival in patients with CKD, and probably in many other patients with chronic diseases and active bone disorders."

The researchers analyzed data from nearly 74,000 hemodialysis patients in dialysis clinics during a three-year period. Laboratory measurements of alkaline phosphatase level measured were analyzed as a possible predictor of mortality risk. In dialysis patients, alkaline phosphatase levels are routinely measured to monitor metabolic bone disease, a common complication of CKD. However, current guidelines do not include specific recommendations or targets for serum alkaline phosphatase in CKD patients.

The results showed that patients with higher alkaline phosphatase levels were at higher risk of death during the three-year follow-up period. After adjustment for a wide range of other risk factors, patients with alkaline phosphatase levels above the upper limit of normal (>120 IU/L) had a 25 percent increase in mortality rate.

The link between alkaline phosphatase and mortality was significant across various subgroups of dialysis patients—including patients without hepatitis or other liver diseases, which can also cause increased alkaline phosphatase levels, as well as patients who had normal serum liver function or normal nutritional status. In addition, patients whose alkaline phosphatase level increased during the first six months of the study were at higher risk of death over the subsequent two and one-half years.

However, the study doesn't allow researchers to determine that high alkaline phosphatase levels are actually responsible for the increase in mortality risk. Kalantar-Zadeh concludes, "For the ultimate proof of causation, treatment trials are needed to target high bone turnover diseases to reduce serum alkaline phosphatase effectively and then to ascertain whether these interventions can improve survival."

Bill Calls for Overhaul of Medicare Lab Fee Schedule

A new bill, H.R. 6761, makes a controversial call to modernize the 24-year-old Medicare lab fee schedule. The bill was introduced July 31 by Reps. Bart Stupak (D-Mich.) and Michael Burgess (R-Texas) through the efforts of the Clinical Laboratory Management Association (CLMA) and the American Society for Clinical Laboratory Science (ASCLS). Stupak and Burgess are members of the Energy and Commerce Committee. CLMA and ASCLS are urging their members to get their representatives to sign on as cosponsors.

"The Medicare lab fee schedule was adopted in 1984 and has not been subject to a fundamental review and updating since then to reflect changes in the delivery of clinical lab medicine, resulting in real reductions in reimbursement," said CLMA in statement. "Today, clinical labs are paid only 75 percent of the 1984 level when adjusted for inflation."

Negotiated rulemaking has been used to resolve lab industry concerns in the past by establishing uniform national Medicare coverage decisions for 23 frequently performed clinical lab tests and thus eliminating carrier variations in payment.

Gene Variations Affect Response to Antidepressant Celexa

A study published early online by the *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* shows that variations in the serotonin transporter gene could explain why some people with depression respond better than others to treatment with Celexa (citalopram), an antidepressant. The Mayo Clinic study of 1,914 subjects shows that two variations in the serotonin transporter gene (SLC6A4) have a direct bearing on how individuals might respond to citalopram.

According to the Centers for Disease Control and Prevention, antidepressants are the most prescribed medication in the United States with about 10 percent of adults taking prescription medication for depression.

In the study, researchers evaluated the influence of variations in SLC6A4 in response to citalopram treatment in white, black, and Hispanic patients. They found that white patients with two distinct gene variations were more likely to experience remission of symptoms associated with major depression. No associations between the two variations and remission were found in black or Hispanic patients.

"The findings of this study represent another step in advancing individualized medicine for psychiatric patients," says David Mrazek, M.D., chair of the Mayo Clinic department of psychiatry and psychology and the study's senior author.

According to the Centers for Disease Control and Prevention, antidepressants are the most prescribed medication in the United States with about 10 percent of adults taking prescription medication for depression. Studies show that less

than 50 percent of people treated for depression experience complete remission of symptoms. Many stop taking medication early because of negative side effects or lack of response. Pharmacogenomic tests could improve patient outcomes by matching patients with the right drug from the start.

The study is based on the analysis of a data sample from the *Sequenced Treatment Alternatives to Relieve Depression Study*, or *Star-D*, a National Institute of Mental Health seven-year study that analyzed treatment for adult patients diagnosed with major depression. The Mayo Clinic study's final analysis included the DNA of 1,503 subjects: 1,074 whites, 233 blacks, and 196 Hispanics.

Next steps in this field include examining how other genes predict response to treatment with citalopram and how variations within SLC6A4 might influence how other medications work.

"I would predict that within two years there will be more extensive tests available that will be more accurate than tests that focus on one gene," says Mrazek. "We already know there are half a dozen genes that can provide clues in selecting the right medication for patients."

Private Equity Firm Buys GTI Diagnostics

The Riverside Company (Cleveland and New York City), a global private equity firm focused on the smaller end of the middle market (companies valued up to $200 million), has acquired GTI Diagnostics (Waukesha, Wis.), which develops, manufactures, and markets in vitro diagnostic assays for the transplantation (HLA), blood bank, and coagulation laboratory markets. GTI's more than 20 test kits are used by approximately 400 labs around the world. Financial terms of the deal were not disclosed.

Riverside acquired GTI from the BloodCenter of Wisconsin Research Foundation, the not-for-profit blood bank and research institution where GTI was founded in 1985 by Jim Tidey, the company's CEO. Tidey will continue as both CEO and an investor in GTI., which leases 23,500 square feet of laboratory, manufacturing, and administrative space in Waukesha, a suburb of Milwaukee.

"Riverside has developed expertise with similar medical diagnostics companies such as platform company Diatron and its recent add-on acquisition of Novamed," said Loren Schlachet, managing partner of Riverside. "GTI has a significant base of recurring revenue from the sale of consumable test kits, has an outstanding management team, and has a cutting-edge R&D department."

Biomarkers Show Promise for Early Diagnosis of Alzheimer's Disease

Biomarker-based tests could be used to diagnose Alzheimer's disease (AD) in its earliest stages, according to a number of studies presented at the 2008 Alzheimer's Association International Conference on Alzheimer's Disease (ICAD2008), held in Chicago in July. Detecting AD-associated proteins and

enzymes in cerebrospinal fluid (CSF) could identify affected individuals while they are still cognitively normal so that future AD therapies can preserve normal function.

A study led by Leslie Shaw, Ph.D., professor of pathology and lab medicine at the University of Pennsylvania, examined CSF samples from more than 50 study sites and determined baseline levels of three proteins associated with AD (total tau, phosphorylated tau, and ß-amyloid42). The researchers found significant differences in the level of these biomarkers among the three populations they studied: elderly who were cognitively normal, those with mild cognitive impairment, and those who had AD.

"Analyzing changes in these CSF biomarker levels in people with mild cognitive impairment can detect the conversion to Alzheimer's disease, especially when used in conjunction with neuroimaging and psychological tests," said Shaw.

Another study presented at ICAD2008 focused on the diagnostic potential of ß-amyloid42 (Aβ42), a type of amyloid protein fragment that is more likely to aggregate into small clusters and eventually into the plaques that are considered a hallmark of AD, was led by Anne M. Fagan, Ph.D., of the Washington University School of Medicine. Fagan and colleagues broadened the scope of their previous smaller study to demonstrate that a low level of Aβ42 in CSF is an effective marker for determining the presence of amyloid in the brain.

The 132 subjects studied ranged in age from 45 to 88 years old and included cognitively normal, very mildly demented, and mildly demented individuals. In addition to observing a striking inverse relation between the presence of amyloid in the brain and levels of Aβ42 in CSF regardless of cognitive status, the researchers observed that three non-demented, low CSF Aβ42 study participants were subsequently diagnosed with AD, suggesting that low CSF Aβ42 may be useful as markers of "preclinical Alzheimer's."

A third study focused on the enzyme β-secretase (BACE1), which has been found at increased levels in the brains of patients with AD compared to healthy individuals. Researchers investigated whether BACE1 in CSF may be a feasible biomarker candidate for predicting AD in people with mild cognitive impairment, a transition stage between the cognitive changes of normal aging and the more serious problems caused by AD.

Researchers found that subjects with mild cognitive impairment showed increased BACE1 activity when compared to normal elderly control subjects and those with AD. BACE1 activity was also significantly correlated with levels of Aβ42.

Additional research compared the value of BACE1 compared to other biomarkers for predicting the development of AD in individuals with mild cognitive impairment. Analysis showed that BACE1 protein levels and Apolipoprotein E genotype (a genetic risk factor for AD) were the strongest predictors of conversion to AD, after controlling for age and gender. A blood-based diagnostic test for BACE1 is in development.

IVD Stocks Climb 14%; Clinical Data Soars 39%

The August 8 stock market rally fueled by a $4.82-a-barrel drop in oil prices helped the G-2 Diagnostic Stock Index to rise an average of 14 percent in the five weeks ended August 8, with 14 stocks up in price and three down. The G-2 index is down 6 percent so far this year, while the S&P is down 11 percent and the Nasdaq has fallen 8 percent.

Leaving the index this month is **Third Wave Technologies** (Madison, Wis.), known for its Invader chemistry-based testing platform. On July 24, a wholly owned subsidiary of **Hologic** (Bedford, Mass.) completed its cash tender offer for all outstanding shares of Third Wave for $11.25 per share in a deal valued at approximately $600 million. The purchase price represented a premium of about 24 percent to Third Wave's average trading price in the three months before the deal was announced on June 9. Women's health-focused Hologic is now completing the acquisition of Third Wave through a short form merger, in which Third Wave will become a wholly owned subsidiary of the developer, manufacturer, and supplier of diagnostics, medical imaging systems, and surgical products.

Making up for recent losses was **Clinical Data** (Newton, Mass.), which soared 39 percent to close at $18.98 per share and a market capitalization of $401 million. On August 6, Clinical Data announced its acquisition of privately held Adenosine Therapeutics (Charlottesville, Va.), a developer of drugs that act on adenosine receptors, for approximately $11 million in cash, with plans for future payments.

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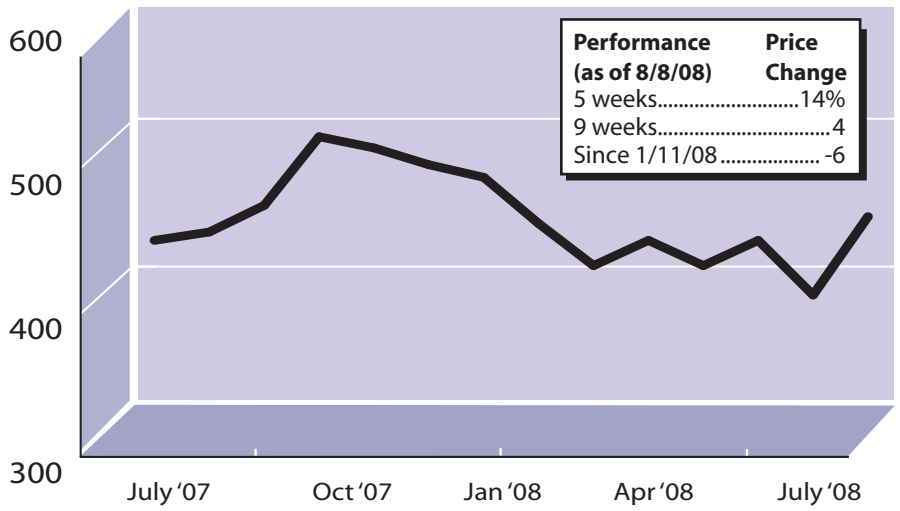
Founded in 1999 by University of Virginia professor Joel Linden, Ph.D., and entrepreneur Robert Capon, Adenosine Therapeutics earned 2007 revenue of $5.1 million and has 26 employees. The acquisition is expected to boost the pipeline of Clinical Data's PGxHealth division, which develops targeted therapeutics as well as proprietary biomarker and pharmacogenomic tests. Adenosine's drug candidates include those for cardiac disease, diabetes, inflammatory diseases, and sickle cell anemia.

G-2 Diagnostic Stock Index



Source: The G-2 Diagnostic Stock Index is tabulated weekly by *DTTR* from the average percentage change in the stock price of 17 IVD companies.

Up	Price	% Chg
Abbott Labs	$59.03	8%
Beckman Coulter	74.94	9
Becton Dickinson	87.41	6
Bio-Rad	106.50	32
Clinical Data	18.98	39
Gen-Probe	60.20	27
Immucor	31.92	28
Inverness Medical	35.70	11
Johnson & Johnson	71.55	10
Luminex	23.38	18
Nanogen	0.40	3
Nanosphere	10.91	48
OraSure	4.06	1
Quidel	19.97	25

Up	Price	% Chg
Affymetrix	8.83	-10
Abaxis	22.12	-7
Meridian	26.59	-3

G-2 Insider

Lab Institute 2008 to Tackle Changing of the Guard . . . Join Washington G-2 Reports for its 26th annual Lab Institute, September 17-19 at the Crystal Gateway Marriott in Arlington, Virginia. This year's program, "Changing of the Guard: Working With a New Administration, the New Millennial Generation, and a New Health Care System," examines fundamental realignments in politics, Medicare and health care reform policy, personalized medicine, and the molecular diagnostics market. At this year's Lab Institute, you will:

- ❑ Hear from the nation's foremost thought leaders on the future of health care policy and lab industry trends;
- ❑ Go inside the boardroom and hear what the lab industry's top CEOs are saying about the lab and IVD sectors;
- ❑ Improve your bottom line and reduce your risk with two intensive half-day workshops on coding and reimbursement and avoiding legal minefields for labs;
- ❑ Train your future lab leaders, residents, and administrators at Lab Leaders' Boot Camp, a special all-day seminar in which lab professionals will address six core issues for future managers; and
- ❑ Recognize industry stars with the presentation of the Washington G-2 Reports' Laboratory Public Service National Leadership Award and the Washington G-2 Report/Dennis Weissman Scholarship Award for Excellence in the Clinical Laboratory Sciences.

To register or get program details, visit *www.g2reports.com/labinstitute08*.

References

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Clinical Data 617-527-9933

FDA OIVD 240-276-0450

Gene Express 419-380-9930

GTI Diagnostics 262-754-1000

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