G2 INTELLIGENCE

Diagnostic Testing &Technology Report

Competitive Intelligence & Analysis for an Expanding Global Market

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CONTENTS

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Gene Fusion Test Shows Promise for Early Detection of Prostate Cancer

A study conducted by researchers at the University of Michigan Comprehensive Cancer Center and the Michigan Center for Translational Pathology suggests that testing for a common genetic anomaly could help clinicians to detect prostate cancer at an earlier stage and determine which men are at highest risk for clinically significant prostate cancer. The new urine test, when used in addition to an "elevated" prostate-specific antigen (PSA) screening result, could also help some men delay or avoid a needle biopsy.

The noninvasive test looks for fusions between the transmembrane protease, serine 2 (TMPRSS2) and v-ets erythroblastosis virus E26 oncogene homolog (avian) (ERG) genes. These fusions are found in approximately 50 percent of PSA-screened prostate cancers and were found to be associated with indicators of clinically significant cancer at biopsy and prostatectomy. The researchers also found that including another marker, prostate cancer antigen 3 (PCA3), allowed them to better predict cancer. Results of the study were published in the Aug. 3 issue of *Science Translational Medicine*.

"We think this is going to be a tool to help men with elevated PSA decide if they need a biopsy or if they can delay having a biopsy and follow their PSA and urine TMPRSS2:ERG and PCA3," says Scott Tomlins, M.D., Ph.D., a pathology resident at the U-M Health System and lead author of the study.

The Michigan Center for Translational Pathology is working with Gen-Probe (San Diego), which has licensed the technology, to offer the combined TMPRSS2:ERG and PCA3 test to patients by the end of the year. U-M currently offers PCA3 screening alone as follow-up to elevated PSA.

For more on the latest developments in cancer testing, see the special focus section starting on page 8.

Chinese Diagnostic Partnerships Increasing; Mayo Enters China Through Collaboration

Mayo Medical Laboratories (Rochester, Minn.) has entered into a strategic agreement with China's Wuhan Kindstar Globalgene Technology Inc. to provide specialized laboratory support that will advance Kindstar's esoteric testing capabilities and will expand Mayo's international activities. The arrangement is representative of expanding interest in Chinese-American partnerships in both the clinical laboratory and diagnostics industries. *Continued on p. 2*

▲ Chinese Diagnostic Partnerships Increasing, *from page 1*

Mayo's Department of Laboratory Medicine and Pathology and its reference laboratory, Mayo Medical Laboratories, will provide advice on tests, laboratory quality, and accreditation standards. Through the partnership, Kindstar—which currently offers 750 tests to 2,000 Chinese hospitals—could add several thousand tests in a few years without heavy investments in research and development, according to Mayo. As part of the collaboration agreement, Mayo Clinic will receive equity in Kindstar. Mayo Clinic also participated in Kindstar's $11 million Series B financing that closed earlier in the summer.

"We see quite an opportunity. . . . There is an increased appetite for esoteric testing with a growing middle-class population, which may be close to 300 million people," says Franklin Cockerill, M.D., CEO of Mayo Medical Laboratories, of the Chinese market in which health care is largely paid for out of pocket. "The deal, of course, extends our business around the world and allows an extension of our tests into the Chinese market." The added revenue will be reinvested in research at the Mayo Clinic.

An Enticing Market

Mayo is not alone in recognizing the opportunity in China both because of the size of the market and the rapid evolution of the Chinese health care system. China is in the midst of a five-year, $124 billion health care reform initiative intended to distribute health care more widely outside of its big cities.

> ***"There is a great push to kick the birds out of the nest. We will see a major surge in acquisition activity. Chinese companies are going global in a big way and have to spend their cash. [Acquisitions] give them an immediate footprint without having to do it the old-fashioned way by developing a brand."***
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> ***—Luke Treloar, NC China Center***

"The Chinese medical device and equipment market is a phenomenal opportunity. It really boggles my mind," says Luke Treloar, executive director of the North Carolina China Center in Raleigh and manager of the Hamner-China Biosciences Center. The Hamner Institute and North Carolina are recognized by the Chinese Ministry of Commerce as one of five globally designated investment "platforms" that economically link local and Chinese development interests. "They didn't have modern surgery 20 or 30 years ago. Now with modern equipment migrating into tier two and three hospitals, it is an explosion of opportunity.... Tier two and threes were off-limits for foreign companies. The restrictions have been removed and it is a huge deal."

While diagnostics companies recognize the importance of China strategically, generally only the larger companies have been able to penetrate into the market. "They understand China is looming on the near horizon and there is a competitiveness in establishing a presence in China. But they are not on the front end getting a plan together yet," Joseph Panetta, CEO of BIOCOM, says of Southern California diagnostics companies. BIOCOM (San Diego) is a regional life science association with 550 members.

American life science experts on the ground in China say partnerships are a preferred way for western companies to enter China. Domestic companies are familiar with Chinese business practices and can access government funding and other incentives that foreign companies can't. The Chinese seek partners with entrepreneurial experience. When carefully selected, partnerships afford mutual benefit.

"For western companies coming to China, access to market is an obvious [attraction]," says Greg Scott, president, ChinaBio, a consulting firm and merchant bank focusing on

China's life science industry. "Chinese companies are getting more advanced technology and international branding. . . . You have to pick your partner very carefully—one that respects western rule of law and intellectual property (IP)."

"China is the second-largest economy in the world but we know remarkably little about it. It has an insular economic policy and despite its size, it is remarkably difficult to do business there," says Treloar.

"I see from our members a general anxiety about IP protection in China," says Panetta. "They are anxious, cautious, and concerned that as soon as they step foot in China somebody will steal their IP. . . . They don't want to have to give up too much in the way of trade secrets to gain access to the market."

Looking to the Future

Despite cultural business differences, those familiar with demand for diagnostics testing in China say that the rapidly evolving market is moving toward that of the United States. In the coming years experts believe the "nascent" clinical lab industry in China will decentralize and there will be increased demand for clinical labs outside of major hospitals.

"They do understand testing—the latest testing and what it can do," says Cockerill. There is demand for oncology and infectious disease testing and companion diagnostics are catching on. In the coming years Cockerill says there will be increased interest in newborn screening and total genomic screening.

Experts expect Chinese companies will develop more novel products and will reach out to the West both for partners and for acquisition targets.

"There is a great push to kick the birds out of the nest," says Treloar of the Chinese desire to be a bigger player in the international economy and have a bigger global footprint. "We will see a major surge in acquisition activity. Chinese companies are going global in a big way and have to spend their cash. [Acquisitions] give them an immediate footprint without having to do it the old-fashioned way by developing a brand. Chinese think their brands are not as competitive, not as trusted or recognized. They don't know how to market to Americans so there is a push towards acquisitions."

PPACA Provision to Offer Women 'No-Cost' Preventive Screenings; HPV Screening Impact Uncertain

A new provision of the Patient Protection and Affordable Care Act (PPACA) mandates that health insurance plans cover expanded women's preventive screenings, including human papillomavirus (HPV) testing and screening for HIV and gestational diabetes. Experts predict the provision may increase HPV screening volumes.

New health insurance plans (as of Aug. 1, 2012) must cover and eliminate all cost sharing (including copays, coinsurance, or deductibles) for HPV DNA testing in women over 30 years of age every three years, regardless of Pap smear results. Other women's

preventive health care services, such as mammograms and screenings for cervical cancer, were already covered by PPACA.

"I believe that the provisions, if implemented and if there are adequate numbers of providers, will increase the number of women participating in screening," says Walter Kinney, M.D., a gynecologic oncologist at Kaiser Permanente's Sacramento Medical Center. "Currently in the United States we screen about 80 percent of eligible women in the preceding three years. That should go up 5 percent to 10 percent."

Philip Castle, Ph.D., executive director of the American Society for Clinical Pathology's Institute and Center for Health Services Research, cautions that HPV testing is already being overused.

"Only a fraction [of patients] are getting screened [for HPV] the way they should," says Castle. "My gut is that the copay is not a big deterrent. Patients seek [HPV screening] more than it is recommended and ultimately whether [HPV screening] is used and used correctly largely falls to the clinician."

Both Castle and Kinney agree that the PPACA provision won't change the rampant nonadherence to practice guidelines, which dictate a three-year no-test interval following a negative test result. They say only changes in reimbursement structures will alter improper test utilization.

Colorectal Cancer Screening Increasing but Not Reaching Target

The Centers for Disease Control and Prevention (CDC) recently released new data showing that more Americans are receiving lifesaving colorectal cancer screenings but that the national target of a 70.5 percent screening rate has not been met yet, according to the agency's *Vital Signs Report*.

Colorectal cancer screening increased from 52 percent in 2002 to 65 percent in 2010. But survey data from the 2002 to 2010 Behavioral Risk Factor Surveillance System shows that still nearly one-third of people between the ages of 50 and 75 (approximately 22 million people) are not up-to-date with recommended colorectal cancer screening. Racial differences exist among those receiving colorectal cancer screening tests. Two out of three white adults aged 50 to 75 reported receiving a stool test within one year or a lower endoscopy within 10 years, but only 54 percent of Hispanics reported receiving the same screening tests.

Increased screening adherence prevented 33,000 cases of colorectal cancer from 2003 to 2007 and saved 16,000 lives during that time, the CDC estimates. If the Healthy People 2020 target of 70.5 percent screening for colorectal cancer is met, an additional 1,000 colorectal cancer deaths could be prevented each year.

The CDC believes that the elimination of cost sharing (copays, coinsurance, or deductibles) for preventive health measures that is mandated for new health insurance plans and Medicare under the Patient Protection and Affordable Care Act (PPACA) will increase access to and utilization of preventive services including colorectal cancer screening tests (fecal occult blood test, sigmoidoscopy, or colonoscopy). Adults aged 50 to 75 are eligible for the "no-cost" screenings.

G2 INTELLIGENCE
Inside the Diagnostics Industry

Technology Pushing Point-of-Care Testing Ahead; TB Molecular Test Gaining Traction in Low-Resource Areas

Despite headline grabbing stories of development of lab on a chip technology capable of rapid, bedside tumor diagnosis, point-of-care (POC) technology is making quiet, persistent inroads into routine clinical care. The most immediate promise for adoption of POC technology is in infectious disease diagnosis, particularly in low-resource settings, where rapid, accurate diagnosis is imperative for effective treatment and patient communication.

While most consumers experience with POC testing may be over the counter pregnancy tests or home glucose meters, patients also may have encountered POC testing throughout the spectrum of health care settings including in a physician's office with a rapid strep test or rapid flu test.

"The first problem is that point of care is not a great word or label," says Harry Glorikian, founder and managing partner, Scientia Advisors, a life science consulting firm based in Cambridge, Mass. "The overarching theme [in POC] is faster turnaround and easy to use tests and that is moving forward. . . . It doesn't physically have to be done at the bedside. It just depends how you draw your boundary around what is POC. We use time as a big factor, not just the location of the test."

Rapid, molecular testing is pushing the envelope of POC testing and experts advise that pathologists and laboratorians have knowledge of current developments to be on the front line of POC testing.

"If it is within the hospital it is under their domain anyways and they almost need to bless it before it is on the floor. They will be looked to to see if it is running correctly and doing what it should be doing," says Glorikian. "If it is looked at as a threat, then adoption will be slower and slow down what could be a really great technology. If we look at it as an advancement to patient care, adoption could go much quicker. Molecular in the central lab had double-digit growth. We believe double-digit growth in possible in POC if the right technology comes to market."

Scientific advances, including in micro-fluidics—combined with decreasing manufacturing costs of these technologies—makes the latest POC tests more cost-effective as well as increasingly portable but not yet small enough to fit in a clinician's back pocket. But it is not just the technical or market availability of these product that dictates adoption of POC technologies.

"POC [adoption] is driven by medical value. Faster, definitive results have greater medical value," says David Persing, M.D., Ph.D., chief medical and technology officer, Cepheid. "Molecular testing is the gold standard but is almost exclusively in a centralized lab performed on a batch basis. It takes a one-hour procedure and turns it into one- to two-day turnaround. . . . If we develop a model with the same sensitivity and performance and it is decentralized and we bring it closer to the patient with rapid turnaround, one to two hours and 100 percent actionable

information—who to treat and who to not treat—the bottom line is that that has the most medical value. It is the missing link between rapid antigen testing and a reference lab."

TB, a Leading Test in Low-Resource Areas

Acceptance of POC testing is not uniform either geographically or by medical specialty.

"I think developing countries will take the lead in rapid decentralization of testing. This technology is placed in environments considered hostile to conventional testing. They need it and recognize the impact."

—David Persing, M.D., Ph.D., Cepheid

"In the United States there is less momentum," says Bernard Weigl, Ph.D., principal investigator at Center for Point of Care Diagnostics for Global Health (GHDx Center; Seattle), a collaboration between the international nonprofit PATH and the University of Washington. "Here everybody has phones and addresses and can be informed of their results. Medical necessity drives POC. It is hard to argue for POC just for convenience. Do you really need the results at an office visit or can you wait a day or two? There are exceptions for infectious disease where time is critical, but for measuring creatinine levels [you don't need POC]. In the developing world you are not able to get [the patient] back."

Need for POC testing in the developing world is driven by logistics and infrastructure deficits.

"I think developing countries will take the lead in rapid decentralization of testing," says Persing. "This technology is placed in environments considered hostile to conventional testing. They need it and recognize the impact. They have no infrastructure or means to transport [patients or specimens] to a central lab."

Tuberculosis (TB) testing, in particular, is taking off due to the World Health Organization's (WHO) Stop TB program and related Global Laboratory Initiative that includes policy recommendations on the use of new diagnostics. In December 2010 WHO endorsed the Xpert MTB/RIF a rapid, automated, cartridge-based nucleic amplification assay for the simultaneous detection of TB and rifampicin resistance developed by the Foundation for Innovative New Diagnostics (FIND; Geneva, Switzerland), Cepheid (Sunnyvale, Calif.), and the University of Medicine and Dentistry of New Jersey. WHO gave a "strong recommendation" for the Xpert MTB/RIF rapid test for initial diagnostic test in people suspected with MDR-TB or HIV/TB. The test, run on Cepheid's GeneXpert platform, can be run with minimal training directly from sputum in under two hours and can be housed in unconventional laboratories.

"Centralized TB testing doesn't work," says Persing. "About 20 percent of results never get to the patient and even if they do it can take weeks or months. Even rapid molecular testing if performed in a central lab can take more than 50 days." Persing tells *DTTR* that the Xpert MTB/RIF test is run 24/7 in a Ugandan clinic that has no electricity and relies on solar panels for energy. In other parts of Africa the system is run off of a car charger and transported in mobile vans driven village to village.

According to WHO, 9.4 million people developed active TB last year and TB killed more than 1.7 million people in 2009. Rapid diagnosis and appropriate treatment can cut transmission rates significantly. Cepheid, the test's manufacturer,

is offering a 75 percent price reduction for the governments of 116 countries and nongovernment organizations operating in those countries. Organizations like the Gates Foundation, USAID, and Reach are all working with health ministries and are playing a big role in supplying funds for system replacement. The pricing for cartridges is "a very low margin price compared to other diagnostic products," says Persing. The initial cartridge price is $16.86 "and as with many things, as volumes increase, prices come down and we will pass on the volume dependent savings." Once there is more than 3.5 million in order volume, the price will be in the $10 to $11 range, says Persing.

Cepheid's GeneXpert At-a-Glance

Systems: 2,224 GeneXpert systems placed (as of June 30, 2011); 2011 second quarter included 148 GeneXpert commercial placements and 38 system placements in High Burden Developing Countries program.

Tests: 11 tests currently available in the United States and 12 tests outside the United States; A total of 47 tests are expected to be available globally by the end of 2016.

In addition to the endorsement of molecular TB testing, in July WHO called for countries to ban the use of serological (blood) tests to diagnose active TB disease describing the results from these blood tests as "inconsistent and imprecise" and "a major risk to the health of patients."

These tests, despite having sensitivities in some cases of less than 10 percent are widely used, particularly in India, where tests to detect TB antibodies are a "giant industry," says Persing. Experts caution that while evidence exists that proves molecular tests to be more sensitive, adoption is still a challenge despite the glaring need for this technology. Service, supply chains, and training in remote areas hamper adoption.

Looking Forward

So, what does the future hold for the development and acceptance of POC diagnostics?

Cepheid's GeneXpert is "a trailblazer device," says Weigl. He notes that in impoverished areas, even at steep discounts, it is still cost-prohibitive. "At $10 to $17 a test it is still out of reach for many." Weigl predicts the next generation of machines will be made in India and China and sold for one-tenth of the cost and $5 a test or less.

Experts predict in the coming years further penetration of POC testing in emerging markets and expansion of POC infectious disease test options. Weigl expects we will see more multiplex testing to differentiate the cause of fever or diarrhea-causing diseases that lack specific symptoms.

"In the United States flu and STD testing will have a big impact," says Persing. "The way it is done in the United States is centralized with high throughput labs. Hospitals would prefer to have [STD testing] on-site to reduce turn around time and cost [of send outs]. If they can run STD on an existing platform it is a no-brainer and then they can service the emergency department and local ob/gyn offices."

Regulation impacts the acceptance of all POC testing, but reimbursement will determine in part the trajectory POC testing may take in the United States.

"The big issues are reimbursement and regulation and can the system handle it," says Glorikian. "How will [POC tests] interface with the IT system? If it is over the counter, it is an out-of-pocket expense. If a physician does it, how does it get logged? How do you get paid for it?"

Roche to Acquire Cancer IVD Maker Mtm Laboratories

Roche (Basel, Switzerland) is expanding its cervical cancer diagnostic offerings into tissue-based tests with the planned acquisition of Mtm Laboratories (Heidelberg, Germany). The Swiss health care company has agreed to acquire privately held Mtm for 130 million euros (approximately $185 million at current exchange). An additional payout of approximately 60 million euros ($85 million) is contingent upon reaching certain performance-related milestones. Mtm will become part of Roche's tissue diagnostics (Ventana Medical Systems) business unit. The transaction is expected to close by September.

Mtm's proprietary tests are based on p16, a biomarker used to identify and diagnose precancerous cervical lesions. The p16 gene is an established marker of the early oncogenic process, and the level of p16 protein becomes markedly increased after persistent human papillomavirus (HPV) infection.

"The identification of overexpression of p16 allows us to identify those women specifically with cancer and those that need to be referred on to additional treatment," said Daniel O'Day, COO of Roche Diagnostics, during the company's July 21 earnings call with analysts and investors.

The Mtm CINtec Plus cytology kit is approved for use in Europe to identify overexpression of p16 in cervical Pap test samples to detect precancerous lesions. The company's CINtec histology assay also detects overexpression of p16 and is used in conjunction with traditional staining techniques to aid in the identification of high-grade cervical intraepithelial neoplasia and cervical carcinoma in biopsy samples. Roche plans to seek U.S. Food and Drug Administration (FDA) premarket approval for both tests.

News of the Mtm deal comes only months after Roche received FDA approval for its HPV test. The cervical cancer screening tool, Cobas HPV, was launched in the United States in May. O'Day is enthusiastic about the potential of adding a tissue-based diagnostic tool to the high-volume, high-sensitivity HPV genotyping test. "We're very excited about this," he said on the call. "Look for the ability to leverage our tissue diagnostics and molecular diagnostics business together against one cancer."

Radient Pharmaceuticals Adds New Lab Partner for Onko-Sure Test

In vitro diagnostics developer Radient Pharmaceuticals (Tustin, Calif.) continues to expand the availability of its Onko-Sure cancer test kit. The company's newest clinical laboratory partner is NeoloMed BioSciences (Monmouth Junction, N.J.), a CLIA-certified, College of American Pathologists-accredited clinical laboratory that will offer the test to physicians' offices and hospitals in New Jersey, Connecticut, Delaware, Pennsylvania, Washington, D.C., Virginia, and Maryland.

Focused on cancer testing, NeoloMed currently offers flow cytometry, karyotype, and fluorescence in situ hybridization analysis.

"We have been looking to expand our menu of oncology diagnostics that provide valuable information for doctors and their patients," said CEO Faribouz Payvandi, Ph.D., who founded the company in 2007 as CytoMab Biosciences. "Onko-Sure is the first blood test we've chosen to offer."

The FDA has cleared Onko-Sure for colorectal cancer monitoring during treatment and for post-treatment recurrence monitoring.

Onko-Sure is an enzyme-linked immunosorbent assay designed to monitor or detect solid tumor cancers by measuring the accumulation of fibrin and fibrinogen degradation products (FDP) in the blood. Cancer cells are known to overproduce FDP, including D-dimer, and Onko-Sure simultaneously measures multiple FDP species in a serum sample.

The test has been cleared by the U.S. Food and Drug Administration for colorectal cancer monitoring during treatment and for post-treatment recurrence monitoring. Outside of the United States, the test has received regulatory approval as a general cancer tumor marker (for 15 different types of cancer) as well as for lung cancer detection, treatment, and recurrence monitoring. Payers are not yet reimbursing for the test.

"Our goal is to significantly expand the availability of Onko-Sure throughout the U.S. and to work with regional and national diagnostics labs in doing so," said Douglas MacLellan, chairman and CEO of Radient.

Onko-Sure is also performed by GenWay Biotech (San Diego), which offers the test through its clinical laboratory and has signed exclusive, multiyear agreements with Radient to market, sell, and distribute the test in several international markets. Genway markets the test as the FirstMark ONC Oncology Health Monitoring Test at a price of $189 per test. Results are available within two weeks. Because prostate and breast cancer do not correlate with FDP, Genway includes a PSA test or CA15-3 test at no additional charge.

Novel Biomarker May Be Key to Effective Ovarian Cancer Screening

An antibody to a well-studied protein may be useful for screening and early detection of ovarian cancer. Researchers at Rush University Medical Center (Chicago) identified the antibody, which is produced in response to the protein mesothelin, in the bloodstream of infertile women. The study was published on Aug. 17 in the online version of *Cancer Epidemiology, Biomarkers, Prevention*, a journal published by the American Society for Cancer Research.

"Our approach to discovering cancer biomarkers was unique in this study," said Judith Luborsky, Ph.D., professor of pharmacology, obstetrics, and gynecology and preventive medicine at Rush and lead author of the study. "Instead of investigating molecules specific to ovarian cancer alone, we asked what molecules women with a risk of ovarian cancer and those with ovarian cancer had in common."

Mesothelin is found in abundance on the surface of ovarian cancer cells but present only in limited amounts in normal human tissue. The researchers tested for

mesothelin antibodies in the bloodstream of 109 women who were infertile for a variety of reasons, 28 women diagnosed with ovarian cancer, 24 women with benign ovarian tumors or cysts, and 152 healthy women.

The American Cancer Society estimates that there will be approximately 21,900 new cases of ovarian cancer in the United States in 2011 and about 15,460 deaths from the disease. The poor prognosis for women with ovarian cancer is due to the lack of clinical symptoms when the cancer first develops and the absence of laboratory tests specific to the disease.

Significant levels of mesothelin antibodies were found in women with premature ovarian failure, ovulatory dysfunction, and unexplained infertility, as well as in women with ovarian cancer, although not in women with endometriosis and not in healthy women or women with benign disease. Endometriosis is generally associated with a different kind of ovarian carcinoma than other types of infertility, which may explain why mesothelin antibodies were not found in these cases.

"We think that antibodies may arise in response to very early abnormal changes in ovarian tissue that may or may not progress to malignancy, depending on additional triggering events," said Luborksy. "Or, alternatively, antibodies may bind to normal cells in the ovary, causing dysfunction and leading to infertility—and, in a subpopulation of women, to the development of ovarian cancer."

Ongoing research in larger populations will further explore the applications of the mesolithin antibody for ovarian cancer screening. Currently, there is no standard or routine screening test for ovarian cancer, and existing ovarian cancer screening methods have not been proven to decrease the death rate from the disease. Adds Luborksy, "With the discovery of the mesothelin antibody, we now have what appears to be a biomarker that can potentially be used in screening tests to help us conquer ovarian cancer."

Clinical Genomics, Quest Diagnostics Extend Partnership for Colorectal Cancer Test Development

Sydney, Australia-based biotechnology company Clinical Genomics has extended its longtime alliance with Quest Diagnostics (Madison, N.J.). The latest agreement, announced in July, calls for Quest to make milestone payments to Clinical Genomics for the development and validation of new molecular blood tests for the early detection of colorectal cancer. Financial terms of the deal were not disclosed.

Clinical Genomics was founded in 2006 by Lawrence LaPointe, Ph.D., and Howard Chandler after their previous company, Enterix, was acquired by Quest for approximately $43 million. Enterix manufactures, markets, and distributes InSure, a fecal immunochemical test for colorectal cancer screening. In the wake of the sale, LaPointe and Chandler decided to spin off the company's research and

development arm to expand and commercialize a proprietary set of candidate biomarkers for colorectal neoplasia purchased from Enterix.

Now Clinical Genomics is focused on transitioning its research on colorectal cancer gene targets into clinical testing services. At the Digestive Diseases Week conference held in May in Chicago, the company presented preliminary data supporting the development of a blood-based RNA screening assay for colorectal cancer.

Sequencing Reveals New Genetic Links to Head and Neck Cancer

Large-scale genetic analysis is providing new insights into head and neck squamous cell carcinoma (HNSCC), the sixth most common cancer worldwide. Two research groups studied HSNCC primary tumors using whole-exome sequencing and gene copy number analysis and revealed their findings in studies published July 28 in the online version of *Science*.

> ***"Head and neck cancer is complex and there are many mutations, but we can infer there is a convergence on a cellular process for which we previously did not have genetic evidence. . . . It shows that if you do a genome sequencing project of this size you can gain major new biological insights."***
>
> ***—Levi A. Garraway, M.D., Ph.D.***

In addition to confirming previously suspected genetic abnormalities, such as defects in the p53 tumor suppressor gene, the researchers found mutations in the NOTCH family of genes, suggesting that their role as regulators of cell development may be impaired.

"Head and neck cancer is complex and there are many mutations, but we can infer there is a convergence on a cellular process for which we previously did not have genetic evidence," said Levi A. Garraway, M.D., Ph.D., a senior associate member of the Broad Institute, an assistant professor at Dana-Farber Cancer Institute and Harvard Medical School, and a senior author of one of the *Science* papers. "It shows that if you do a genome sequencing project of this size you can gain major new biological insights."

Both Garraway's group and one led by researchers at Johns Hopkins Kimmel Cancer Center and the University of Texas M. D. Anderson Cancer Center found that approximately 15 percent of the HNSCC tumors they analyzed had mutations in NOTCH1, a gene that controls how cells differentiate, mature, and die. The mutations turned off NOTCH1, blocking cell differentiation and trapping them in a proliferative, precancer state.

"Both of our studies reveal few clues to the significance of NOTCH mutations. Further studies will be necessary to define its role in prognosis, diagnosis, and/or treatment," said Nishant Agrawal, M.D., a surgical oncologist at Johns Hopkins and a lead author of one of the *Science* papers. "The idea is to use these genetic alterations to predict a patient's prognosis and define personalized treatment strategies tailored to their cancer's genome."

Repeated Family Histories Important for Appropriate Cancer Screening

Between the ages of 30 and 50 a patient's family history of cancer can change significantly enough to affect recommendations for cancer screening. A study in the July 13 issue of the *Journal of the American Medical Association* found that regularly updating family histories is needed to ensure high-risk patients are identified for earlier or more sensitive cancer screening for colorectal, breast, and prostate cancer.

"To assess the need for screening, it's crucial that a clinician has knowledge of how an individual's family history changes over time," said Sharon Plon, M.D., Ph.D., director of the Baylor College of Medicine Cancer Genetics Clinic and senior author of the study. "Our hope is that this new information will help educate physicians to more frequently ask patients these important questions."

Family medical data both at baseline (from birth to registry enrollment) and over an average of eight years of follow-up was examined from nearly 11,000 participants in the Cancer Genetics Network, a national population-based cancer registry. The researchers looked for changes in cancer history among participants' closest relatives (parents, siblings, grandparents, and aunts and uncles). Colorectal, breast, and prostate cancer were the focus because they have effective, early screening methods.

From ages 30 to 50 the percentage of patients recommended for high-risk screening of colorectal cancer increased from 2 percent to 7 percent. The percentage of women recommended for magnetic resonance imaging screening—a more sensitive test for breast cancer than standard mammography—increased from 7 percent to 11 percent. The percentage of men who met criteria for high-risk prostate cancer screening increased from 1 percent to 2 percent. The authors acknowledge that while the number of men who qualified for prostate-specific antigen (PSA) screening increased slightly, the merits of PSA screening are not universally accepted in the medical community. While currently there are no guidelines suggesting how frequently family cancer histories should be updated, these findings led the researchers to recommend that a comprehensive family history is needed by age 30 and that it should be updated at least every five to 10 years. G2

Fasting May Not Be Necessary Before Lipid Screening in Kids

A new study found that only small, clinically insignificant differences exist between fasting and nonfasting lipid panel screenings in children. The findings, published online Aug. 1 in *Pediatrics*, indicate fasting before lipid screenings in children might not be necessary which, when applied clinically, could increase screening efforts in high-risk children.

The researchers analyzed data on 12,744 children ages 3 to 17 from the National Health and Nutrition Examination Survey (1999 to 2008). They found fasting had a small, positive effect for total cholesterol (TC), low-density lipoproteins (LDL), and high-density lipoproteins (HDL), resulting in a mean value that was 2 to 5 mg/dL higher with a 12-hour fast compared to no fast. Fasting time had a larger, negative effect on triglycerides, resulting in values 7mg/dL lower in the fasting group.

The differences, while statistically significant, were deemed "unimportant" from a clinical perspective and were not likely to change classification or treatment. Approximately 1.2 percent with "borderline" fasting LDL levels would be reclassified as having normal results postprandially and 1.6 percent of children with increased fasting LDL levels would have borderline results postprandially. For triglycerides, 4 percent of children classified with normal fasting levels would have elevated values postpradially. The authors note that this was a populational study and did not track individual patients over time. It is likely some children will have either more or less dramatic differences in fasting and nonfasting values.

"I have always thought that if results are totally normal not fasting, I am confident I would take that and not need to retest fasting. But if the results are abnormal not fasting, how concerned should I be?" asks co-author Michael Steiner, M.D., an assistant professor of pediatrics at the University of North Carolina at Chapel Hill and medical director for the North Carolina Children's Hospital clinics. "These findings are very reassuring to me and add to the understanding in adults for the role of nonfasting screening."

The American Academy of Pediatrics and the American Heart Association currently recommend fasting lipid panel screenings for high-risk children as young as two. But removing the fasting requirement could increase screening efforts by removing the burden of the fast and often a second office or laboratory visit.

23andMe Validates Proof of Principle of Web-Based GWAS Research, Finds Parkinson's Associations, Launches Cancer Initiative

Personal genetics company 23andMe (Mountain View, Calif.) is expanding its research arm following publication of a proof-of-concept study that validated the power and reliability of the company's use of Web-based enrollment and data collection. The study, published online in *PLoS Genetics*, found two, significant, novel genetic associations with Parkinson's disease (PD) and provided new evidence that there is a substantial genetic component to the disease that remains undiscovered.

The study, which the company says is the largest case-control, genomewide association study of PD to date, included more than 3,400 cases and 29,600 controls and was completed and published in two years. In addition to the discovery of two novel genetic associations, the researchers replicated 20 previously discovered genetic associations, providing support for the nonconventional study design. Analysis found that genetic factors explain at least one-fourth of the variation in PD liability, of which currently discovered factors only explain a small fraction—roughly 6 percent.

By using the Internet for surveys and enrollment, 23andMe's platform significantly increases the efficiency and reduces the cost of research. The company believes this methodology for study design will prove advantageous for other conditions where the advantage of having a large cohort is paramount for detecting subtle genetic effects. Currently, more than three-quarters of 23andMe's 100,000 plus customers have consented for their DNA data to be used in research efforts.

"One of the additional remarkable features of 23andMe's approach is that our single unified platform is, by its nature, disease-agnostic," says Ashley Dombkowski, Ph.D., 23andMe's chief business officer. "So academics, patient-focused research organiza-

tions, and innovative companies are coming to 23andMe driven by their interest in including their patients in a database that stretches beyond the single disease registries of the past. . . . Given the interest we are seeing along these lines, I expect we will have a steady stream of new communities to talk about in the months and years ahead."

In the beginning of August, 23andMe launched a research initiative for myeloproliferative neoplasms (MPN), a group of "orphaned disease" blood cancers. The program will focus on enrolling 1,000 individuals with these rare blood cancers. The company's PD and sarcoma research efforts continue with the goal of enrolling a total of 10,000 PD patients and 1,000 sarcoma patients.

Myriad Ruling: No Clear Victor

In what was not a unanimous victory for any party, the U.S. Court of Appeals for the Federal Circuit ruled in a 2-1 decision that isolated DNA and cDNA of the BRCA1 and BRCA2 genes are patentable material, overturning a lower court's ruling.

The panel unanimously upheld the lower court's ruling that Myriad Genetics' (Salt Lake City) methods to compare those gene sequences were not patentable. This decision may provide temporary relief for many in the diagnostics industry who fear upheaval if ultimately genes are found to be a product of nature and not patentable, but final resolution of the case and the broader patentability question is not expected soon.

The court found isolated genes, cDNAs, and partial isolated gene sequences patentable subject matter. The two judges who supported the patentability of isolated genes differed in their reasoning, but both majority judges emphasized the dangers of upsetting 30 years of patent practice—what Judge Kimberly Moore called "settled expectations and extensive property rights." Judge William Bryson did not defer to patent office practice and wrote in his dissent that patenting isolated genes presents "a significant obstacle to the next generation of innovation in genetic medicine—multiplex tests and whole-genome sequencing."

The three judges ruled that the therapeutic screening methods claims were patentable since they involve "transformative" steps. They invalidated the comparing or analyzing methods claims saying that such claims in the end "recite nothing more than the abstract mental steps necessary to compare two different nucleotide sequences."

In a statement Myriad said they "strongly agreed" with the court's patentability ruling and said they have "237 method claims for BRACAnalysis which were not affected by this ruling and remain in full force and effect providing Myriad with equally strong method of use patent protection."

Both Myriad and the plaintiffs are eligible and expected to seek further review by all 10 judges of the Federal Circuit. Either following a full review or if the request is denied, the parties could petition the Supreme Court, legal experts say. The Supreme Court, if it takes the case, could take it in its entirety or could just take the product claims issues if methods issues are settled by the *Prometheus* case. One concern is that the appeals process may take so long as to have little impact on these parties, as Myriad's product patents will begin to expire in 2014.

IVD Stocks Fall 18% as Stock Market Tumbles

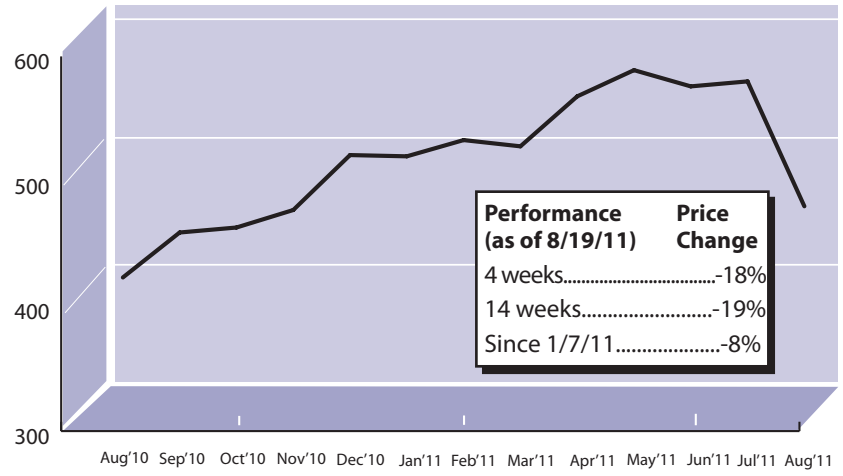
In what was an abysmal month for the stock market, the G2 Diagnostic Stock Index was down 18 percent for the four weeks ending Aug. 19, with 17 stocks down in price and one remaining unchanged. The G2 Index declined more than either the Nasdaq or the S&P, with the Nasdaq declining 16 percent and the S&P dropping 15 percent over the same period.

Among the companies losing the least ground this period was multiplex instrument maker **Luminex** (Austin, Texas) losing only 4 percent on positive second-quarter results. Consumable revenue reached a record $18.4 million, a 90 percent increase over the second quarter of 2010. The company's assay group, led by the cystic fibrosis and respiratory viral panels, grew 24 percent, reaching $9.3 million in revenue. Luminex expanded their installed base with shipment of multiplexing analyzers, up 13 percent from 2010. The company raised its 2011 annual revenue guidance to a range of $180 million to $185 million, an increase of 27 percent to 31 percent over 2010 annual revenue.

Tumultuous market conditions combined with poor second-quarter results drove several companies' stock prices down by more than a third and led to reductions of full-year revenue estimates. Excluding **Alere's** (Waltham, Mass.) North American influenza revenues, currency-adjusted organic growth in the company's professional diagnostics segment was up 7 percent, with cardiology diagnostics up 10 percent. But $50 million of new product revenue anticipated for the year "might be slightly at risk," CEO Ron Zwanziger said, so the company revised its full-year 2011 guidance to an adjusted earnings per share of $2.50 to $2.60 from the $2.75 original estimate.

Similarly, **Meridian Bioscience** (Cincinnati) had "disappointing" results due to continued weakness from their European diagnostics business (down 6 percent) and from their core life science businesses (down 12 percent). The company revised downward its fiscal 2011 guidance to anticipated net sales of $160 to $163 million.

G2 Diagnostic Stock Index



Source: The G2 Diagnostic Stock Index is tabulated weekly by *DTTR* from the average percentage change in the stock price of 18 IVD companies.

Unchanged	Price	% Chg
Immucor	$26.81	0%
Down		
Abbott Labs	49.08	-7
Abaxis	22.25	-23
Affymetrix	4.53	-30
Alere	23.20	-37
Becton Dickinson	76.92	-12
Bio-Rad	96.83	-18
Cepheid	30.58	-5
Gen-Probe	54.48	-15
Illumina	46.79	-36
IRIS	7.94	-23
Johnson & Johnson	63.14	-6
Luminex	19.89	-4
Meridian	17.10	-36
OraSure	6.44	-34
Qiagen	14.44	-21
Quidel	13.40	-14
Sequenom	5.28	-30

Denied Payment for Hospital-Acquired Conditions to Bring Greater Focus on Accuracy . . . The Centers for Medicare and Medicaid Services (CMS) issued a final rule that will deny Medicaid payments to providers for the treatment of preventable health care-acquired illnesses or injuries, effectively bringing Medicaid policy in alignment with Medicare, which implemented similar rules in 2008.

"This CMS decision places increased emphasis on accuracy—the accuracy of a specific diagnosis and the location of the patient at the time of infection," says Patrick Joseph, M.D., associate clinical professor at the University of California San Francisco School of Medicine and chief of epidemiology and infection control at San Ramon Regional Medical Center. "They want to know if it was hospital-acquired or incubating at the time of admission. Accuracy is almost always a good thing in medicine. Accuracy leads to increased patient care quality."

The Medicaid rule became effective on July 1, although states have until Sept. 30 to submit plans and have until July 2012 to implement it. The states' list of conditions must include at a minimum the 10 hospital-acquired conditions identified under the Medicare rule including some "never events" like leaving an instrument in during surgery. But several of the conditions such as blood incompatibility and infections (catheter-associated, pressure ulcers, and at a surgical site) could be prevented or identified through laboratory testing or blood bank services.

Because there is greater emphasis on detection and location of the patient at the time of infection, there will be increased emphasis on documentation and additional screenings of higher-risk patients at the time of admission. "It might increase fixed costs, but it won't break the bank," says Joseph. For instance, patients with in-dwelling devices or who present with pressure ulcers may be cultured at the time of admission, but Joseph says not all screenings need to be done with rapid testing.

"The turnaround time for making the diagnosis is not critical," he says. "Accuracy is not time dependent. Payment is not made at the time of admission. I am very much in favor of newer lab technology [rapid diagnostics testing], but Medicare is not driving this as much as we think." G2

Company References

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