Diagnostic Testing and Technology Report

Competitive Intelligence & Analysis for an Expanding Global Market

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Issue 10-07/July 2010

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WASHINGTON G-2 REPORTS

Established 1979

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FDA Stepping Up Oversight of Lab-Developed Tests

Shortly after notifying five manufacturers that their genetic tests marketed directly to consumers are not considered laboratory-developed tests (LDTs) but are medical devices subject to premarket review, the U.S. Food and Drug Administration (FDA) announced its plans to move to a risk-based application of LDT oversight. The agency has invited comments from stakeholders, including laboratory professionals, clinicians, patients, and industry, to help define the issues that pose the greatest risk to public health. Additionally, the FDA will convene a public meeting to discuss issues surrounding oversight of LDTs as well as direct-to-consumer (DTC) testing. The FDA is accepting comments through Aug. 15.

The meeting, to be held July 19-20 in Hyattsville, Md., will feature an overview of the history and current regulatory status of LDTs, as well as discussions concerning patient considerations, challenges for labs, DTC test marketing, and education and outreach. The FDA will review comments from the meeting and develop a draft oversight framework for public comment "with the goal of providing a level of predictability as quickly as possible." Such a framework would likely be phased in over time based on the level of risk of the test. For more on this story, see *Inside the Diagnostics Industry*, p. 5.

Supreme Court Takes Broad View on Business Method Patents

Hotly anticipated for its potential to profoundly alter the patent landscape, the Supreme Court's June 28 decision in the case of *Bilski et al.* v. *Kappos* created more questions than it answered. Given the opportunity to define the scope of patent law to take into account emerging technologies, the high court allowed business method patents to survive, although the extent of that patent protection remains unclear.

The court affirmed the lower court judgment, holding that the specific invention in this case, a method of predicting business or economic cycles, was ineligible for a patent. In a majority opinion authored by Justice Anthony Kennedy, the court also ruled that the so-called "machine or transformation test," which had been applied by the Federal Circuit in deciding the case, is not in fact the sole test for eligibility to obtain a patent.

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Although the categories of patent-eligible inventions are broadly defined in statutory text, Supreme Court precedents provide three specific exceptions: "laws of nature, physical phenomena, and abstract ideas." In deciding *Bilski*, the court focused on the latter criteria. "Petitioners seek to patent both the concept of hedging risk and the application of that concept to energy markets," wrote Kennedy, who referred to precedents under which "these are not patentable processes but attempts to patent abstract ideas."

In rejecting Bilski et al.'s patent application on the grounds that abstract ideas are unpatentable, wrote Kennedy, the court "need not define further what constitutes a patentable 'process,'" beyond pointing to the statutory definition and looking to guiding precedents.

The court's ruling in the case, which was argued before the court on Nov. 9, 2009, could have been a bellwether for patent law. However, the decision did little to address issues surrounding the patentability of complex technologies and the information generated by those technologies, including sequencing technology used to identify human genes.

Myriad Genetics (Salt Lake City) recently appealed the summary judgment in *Association for Molecular Pathology, et al. v. U.S. Patent and Trademark Office, et al*., the lawsuit filed by the American Civil Liberties Union and the New York-based Public Patent Foundation. In his March 29 ruling, Judge Robert W. Sweet of the U.S. District Court for the Southern District of New York invalidated some of the patents on the BRCA1 and BRCA2 genes granted to Myriad and the University of Utah Research Foundation.

Various mutations in BRCA1 and BRCA2 are associated with hereditary breast and ovarian cancer, and the patent holders claim the exclusive right to perform diagnostic testing on them and to license the testing to others. As with *Bilski*, the Myriad case centers around questions of what is patentable, specifically whether human gene sequences satisfy statutory patent requirements such as novelty and nonobviousness. The recent Supreme Court decision may be incrementally positive for Myriad Genetics since it weakens the judge's ruling.

FDA Approves OraSure's Point-of-Care Test for HCV Antibodies

The U.S. Food and Drug Administration (FDA) has approved the first rapid blood test for antibodies to the hepatitis C virus (HCV) for individuals 15 years and older. Manufactured by OraSure Technologies (Bethlehem, Pa.), OraQuick HCV has been approved for use in detecting HCV antibodies in venous whole blood specimens. The qualitative test, which can be performed at the point of care, is for use in individuals who are at risk for infection with HCV and people with signs or symptoms of hepatitis. The test is not approved for HCV screening of the general population.

The U.S. Centers for Disease Control and Prevention estimates that approximately 3.2 million people in the United States are chronically infected with HCV, and each year, about 17,000 people are newly infected. HCV is transmitted through exposure

to infected blood. The virus can also be transferred from an infected mother to her child. Hepatitis C can lead to liver inflammation and dysfunction and, over time, to liver disease and liver cancer.

Developed in collaboration with Merck & Co. (Whitehouse Station, N.J.), OraQuick HCV is a strip-based test that does not require an instrument for diagnosis. The test works on oral fluid, whole blood, serum, and plasma. Results are available within approximately 20 minutes.

"Approval of OraQuick means that more patients can be notified of their HCV infection faster so that they can consult with their physicians for appropriate health measures," said Jeffrey Shuren, M.D., J.D., director of the FDA's Center for Devices and Radiological Health, in a statement announcing the approval.

In December 2009, OraSure received the CE mark for the test for use with a broader variety of sample types, including oral fluid, serum, and plasma specimens. The company previously received FDA approval for its rapid HIV-1/2 antibody test for use with oral fluid, fingerstick, and venous whole blood and plasma samples.

FDA Approves Abbott Test for Detection of HIV Antigen, Antibodies

The U.S. Food and Drug Administration has approved the Architect HIV Ag/Ab Combo assay, making it the first test approved in the United States that can simultaneously detect both HIV antigen and antibodies. Developed and manufactured by Abbott Laboratories (Abbott Park, Ill.), the test is approved for use as an aid in the diagnosis of HIV-1/HIV-2 infection in adults, including pregnant women. It is also the first assay to be approved for use as an aid in the diagnosis of HIV-1/HIV-2 infection in children as young as 2 years old.

While not intended to be used for routine screening of blood donors, the test is approved as a donor screening assay for HIV-1/HIV-2 infection in urgent situations where licensed blood donor screening tests are unavailable or their use is impractical.

The Architect HIV Ag/Ab Combo assay is a chemiluminescent microparticle immunoassay (CMIA) that is run on Abbott's Architect family of diagnostic testing instruments. The assay was approved for use in Europe in 2004.

The Centers for Disease Control and Prevention (CDC) reports that approximately 18 million people in the United States are tested for HIV each year. The CDC estimates that there are about 56,000 new HIV infections in the United States each year and that more than 1 million people in the United States are infected with HIV.

"The approval of this assay represents an advancement in our ability to better diagnose HIV infection in diagnostic settings where nucleic acid testing to detect the virus itself is not routinely used," said Karen Midthun, M.D., acting director of FDA's Center for Biologics Evaluation and Research. "It provides for more sensitive detection of recent HIV infections compared with antibody tests alone."

Meridian Bioscience Inks Deal with DiaSorin

Meridian Bioscience (Cincinnati) and DiaSorin (Vercelli, Italy) are partnering on infectious disease diagnostics. The Italian immunodiagnostics specialist, which recently acquired Abbott's Murex line of tests, will use Meridian technology to develop infectious disease products for use on its fully automated Liaison platform.

The exclusive development and distribution agreement is royalty-based. The actual royalty amount will be paid to Meridian dependent on type of test and specific geographic market. No further financial details were disclosed.

The first two products to be developed through the deal will be for the detection of *Clostridium difficile and Helicobacter pylori*. DiaSorin will have exclusive distribution rights for the tests in all geographic markets except the United States and United Kingdom, where Meridian will have the option for distribution.

The deal is part of DiaSorin's move to expand the testing menu for its Liaison platform, a random access system based on chemiluminescense detection. Approximately 3,000 Liaison instruments are installed in laboratories worldwide. A high-throughput model of the system is slated to launch later this year.

In June, DiaSorin completed its $58 million all-cash acquisition of Abbott's Murex line of tests for HIV, HBV, and HCV.

Obama Signs Bill for Medicare Physician Fee Fix

On June 25, President Obama signed into law legislation that provides a 2.2 percent update to fees paid under the Medicare Part B physician fee schedule retroactive from June 1 through Nov. 30, 2010.

The bill, the Preservation of Access to Care for Medicare Beneficiaries and Pension Relief Act of 2010, passed the House June 24 following Senate approval of the measure June 18.

The measure cancels the 21 percent cut in Medicare physician fees that took effect June 1 when the congressionally mandated freeze keeping fees at their 2009 levels expired May 31.

The Centers for Medicare and Medicaid Services (CMS) had directed contractors to hold physician claims with a date of service on or after June 1 through June 17, anticipating congressional action by then. But on June 18, with no legislative reprieve, CMS began processing the claims with the cut required under the Sustainable Growth Rate (SGR) formula used to update fees each year.

The agency now has directed Medicare contractors to discontinue processing claims at the negative update rates and to temporarily hold all claims for services rendered June 1, 2010, and later, until the new 2.2 percent update rates are tested and loaded into the contractors' claims processing systems. "Effective testing of the new 2.2 percent update will ensure that claims are correctly paid at the new rates. We expect to begin processing claims at the new rates no later than July 1, 2010."

FDA Moves to Actively Regulate Lab-Developed Tests

As the U.S. Food and Drug Administration (FDA) follows through on its long-discussed plan to more actively regulate laboratory-developed tests (LDTs), the clinical laboratory and in vitro diagnostics industries find themselves revisiting a familiar and sensitive issue. Since the implementation of the 1976 Medical Device Amendments, the FDA has generally exercised enforcement discretion and not enforced applicable regulations with respect to LDTs. Instead, the agency has focused its attention on analyte-specific reagents and a subset of genetic tests known as In Vitro Diagnostic Multivariate Index Arrays, which use a proprietary algorithm to generate a patient-specific result.

LDTs and diagnostic test kits are subject to different standards and uneven enforcement, the FDA has acknowledged. Seeking to level the playing field, biopharmaceutical giant Genentech and AdvaMed, lobbying for major medical device makers, have petitioned the agency to treat all LDTs the same as test kits, except for low-risk tests. The American Clinical Laboratory Association and the College of American Pathologists oppose this stance, arguing that further FDA regulation would stifle innovation and impede patient access to cutting-edge technological advances. Moreover, they point out, LDTs are subject to the most stringent requirements under CLIA and these are sufficient to ensure the tests' validity and utility.

On June 10, the FDA sent warning letters to deCode Genetics, Illumina, 23andMe, Navigenics, and Knome about their DTC genetic tests. In the letters, Alberto Gutierrez, Ph.D., director of FDA's Office of In Vitro Diagnostic Device Evaluation and Safety, said the companies' respective tests are medical devices requiring premarket approval but the agency has not received the required information on their validity.

In an interview with Washington G-2 Reports, Gutierrez said letters seeking information have been sent to more than the above five companies, and representatives have met with FDA officials to discuss their test offerings and related claims. "Some of the letters just sent refer to information gathered at those meetings," he said, "and how that led us to believe the tests were not LDTs."

While the LDT area is fairly fluid, he said, what is clear is that DTC tests do not fall within the agency's enforcement discretion. DTC testing is a separate category from LDTs, even though some DTC tests may be lab-developed, he continued. "When an LDT is marketed to the consumer, FDA clearance is required. When an LDT is sold to a physician, it is not at this point."

The FDA has generally used its enforcement discretion for LDTs. Initially, the agency saw them as relatively simple, well-understood, low-risk tests that diagnosed rare diseases and conditions, and were intended for use by physicians and pathologists in a single patient care setting. But over the last 15 years, the nature of LDTs has changed dramatically, the FDA said. "These tests, which are becoming more complex and high risk, are playing an increasingly important role in clinical decisionmaking. As a result, LDTs not properly validated put patients at risk, such as for missed diagnosis, wrong diagnosis, and failure to receive appropriate treatment."

FDA Convenes Meeting on Array-Based Tests

On June 30, the U.S. Food and Drug Administration (FDA) convened a meeting on array-based cytogenetic tests. The regulatory body solicited feedback on more than a dozen questions concerning how to evaluate the performance, interpret results, and report findings of array-based cytogenetic tests for copy number variation (CNV).

Cytogenetic tests provide much higher resolution than traditional karyotyping, with expansive capabilities to diagnose and identify causes of genetic syndromes due to chromosome abnormalities. The standard of care in molecular and cytogenetic laboratories as well as genetics clinics is shifting from traditional karyotyping to array-based cytogenomic analysis.

Professional societies are currently working to develop professional practice guidelines to address many of the questions raised by the FDA that focus on interpreting and reporting results of array-based cytogenetic tests.

The Association for Molecular Pathology (AMP; Bethesda, Md.), for example, believes that the interpretation of these tests falls within the scope of professional practice and that while the FDA should evaluate the technology platform for analytical validity, the FDA does not need to review each possible CNV result. "It is important to remember that all testing is performed in the context of the phenotype of the patient, and interpretation of laboratory data is a collaboration between the clinical scientist and the treating physician," said Mark Sobel, Ph.D., executive director of AMP, which is encouraging the FDA to partner with professional associations to standardize the use and reporting of array-based tests.

AMP believes that to advance the use of array-based cytogenetic tests, the molecular cytogenetic field needs to collect data on both the laboratory results and clinical information. Sobel added, "Such a database will enable the community to continually assess the validity of results and accelerate the understanding of the results."

Pathologists Call for Training Program to Support Personalized Medicine

In the June issue of the *American Journal of Clinical Pathology*, senior author Jeffrey Saffitz, M.D., Ph.D., and colleagues issue a "call to action" for the medical profession to catch up with the technology and business communities in the application of genomics to personalized health care. The authors call for genomics and personalized medicine to become a core competency for all pathology trainees by 2012. "Genomics and 'medical sequencing' will revolutionize clinical laboratory diagnostics as the foundation for the new era of personalized medicine," write the authors. "Pathologists must take the lead in the application of genomics technologies, including whole genome sequencing, laboratory technologies and personalized medicine."

As a critical first step in leading this charge, the Department of Pathology at Beth Israel Deaconess Medical Center (BIDMC), in collaboration with BIDMC's genetic counseling service, last year launched the Genomic Medicine Initiative, a novel compulsory program to prepare doctors-in-training to apply genomics and personalized medicine in their day-to-day practices.

A novel curriculum offers the blueprint for a new medical specialty built on three pillars: laboratory medicine, genetic counseling, and health information technology.

"This is emerging as one of the most significant shifts in medical education in decades," said Saffitz, chief of pathology at BIDMC and Mallinckrodt Professor of Pathology at Harvard Medical School. "Diagnostic pathology is the medical specialty where the results of multiple diagnostic tests and other patient data are analyzed and interpreted. Why should a patient's genotyping results be any different? We feel that it is our responsibility as the diagnostic enablers of clinical medicine to understand genomics information and to serve as primary consultants for physicians and patients who need to know how to interpret and act on this data."

The new BIDMC pathology curriculum addresses these key issues, with the new medical specialty built on three pillars: laboratory medicine, genetic counseling, and health information technology. As Richard Schwartzstein, M.D., vice president for education at BIDMC and a faculty dean for medical education at Harvard Medical School, explained, "The integration of genetic information will be the core of 'patient-centered' care."

When it comes to genomic testing and applications of data generated by initiatives such as the Human Genome Project, the medical profession has lagged far behind the technology and business communities.

"At the present time, no single discipline in medicine has developed a comprehensive approach to train a cadre of physicians who will be prepared to meet the coming challenge of personalized medicine," added Mark Boguski, M.D., Ph.D., an associate professor in the Department of Pathology BIDMC and the Center for Biomedical Informatics at Harvard Medical School. "As a result, control of personal genomics has shifted directly into the hands of consumers, with confusing results. We would like to ensure that, going forward, pathologists are the interpreters and integrators of genomic information."

Molecular Testing, Automated Results Reporting Increase HIV Detection Yield

Community-based HIV testing programs generally use only HIV antibody testing, but nucleic acid testing (NAT) can detect the presence of HIV earlier. Researchers at the University of California, San Diego School of Medicine studied more than 3,000 patients who sought HIV testing in community-based clinics in or near San Diego to examine the yield of testing with a rapid test plus NAT and to see whether patients would be willing to access their results by phone or computer.

Their study, published June 14 in the *Annals of Internal Medicine*, showed that

Extending the use of nucleic acid testing to routine HIV testing programs might help decrease the HIV incidence rate.

NAT testing increased the HIV detection yield by 23 percent and that a large majority of study participants received their negative test results by automated phone or Internet systems.

"While the findings may not be generalized to all populations and testing programs, we did find that NAT programs that include automated systems for result reporting can increase case yield," said Sheldon Morris, M.D., lead author of the study and an assistant clinical professor at UC San Diego.

"Extending the use of NAT to routine HIV testing programs might help decrease the HIV incidence rate by identifying persons with acute infection that would otherwise be missed through routine screening," said Morris. "In addition, automated reporting of negative results may prove an acceptable and less resource-intense alternative to face-to-face reporting."

The patients were first tested for HIV with a rapid saliva test. If the result was positive, a counselor informed the patient and blood was obtained for a standard HIV test. If the result was negative, blood was obtained for a NAT. Nearly one quarter of persons with identified cases of HIV had positive results only by NAT testing. More than two-thirds of patients with negative NAT results retrieved them via computer or voice mail.

Biomarkers Linked to Alzheimer's Disease Do Not Help Predict Risk

Although genomewide analysis identified two genetic variations associated with Alzheimer's disease (AD), these variations did not improve the ability to predict the risk of AD, according to a study in the May 12 issue of the *Journal of the American Medical Association.*

One of every five persons aged 65 years is predicted to develop Alzheimer's disease in their lifetime, and genetic variants may play an important part in the development of the disease.

Monique M. B. Breteler, M.D., Ph.D., of University Medical Center Rotterdam in the Netherlands, and colleagues conducted a study to identify and strengthen associations of additional loci (the position of a gene on a chromosome) with AD and confirm these in an independent sample. The researchers also examined the contribution of recently identified genes to AD risk prediction in a three-stage analysis of new and previously published genomewide association studies on more than 35,000 people (8,371 AD cases).

After conducting various analyses from different AD patient and population groups, in the gene discovery phase, the researchers found genomewide significance for two loci related to AD, one on chromosome 2 and a second locus on chromosome 19, that had not previously been found to achieve genomewide significance and that appear to be independent of apolipoprotein E (APOE), the gene well established to be associated with AD.

"These findings were replicated in an independent population. Two recently reported associations were also confirmed. [In analyses including age, sex and

APOE genotype], These loci did not improve AD risk prediction," the authors wrote. "The value of these associations may lie in the insights they could provide for research into the pathophysiological mechanisms of AD."

In an accompanying editorial, Nancy L. Pedersen, Ph.D., of the Karolinska Institutet (Stockholm, Sweden), noted that the findings of this study are a reminder that family history is very important, even for late-onset AD, which was once thought to occur sporadically.

"Findings such as those reported [in this study] reinforce the futility of using individual genetic risk profiling for AD beyond collecting information on age, sex, family history, and APOE status," wrote Pedersen.

Predictive Biosciences Raises $25 Million

Molecular diagnostics developer and anatomic pathology laboratory Predictive Biosciences (Lexington, Mass.) has completed a $25 million funding round led by ProQuest Investments. All of the company's current investors also joined in this third round of growth capital financing, including Flybridge Capital Partners and Kaiser Permanente Ventures.

Predictive Biosciences seeks to become "a leading, innovative provider of molecular diagnostic cancer assays and anatomic pathology lab services," according to President and CEO Peter Klemm, Ph.D. Launched in 2006, the company develops biomarker-based diagnostic tests for cancer. Its first tests will be for the monitoring of bladder cancer recurrence through the detection of proprietary urinary biomarkers, including matrix metalloproteinases and a disintegrin and metalloproteinases.

Proceeds from the Series C financing will be used to complete multicenter clinical trials for Predictive's bladder cancer assay, CertNDx, and support its commercial launch as a laboratory-developed test through the company's CLIA-certified lab. The test utilizes Predictive's novel approach of combining DNA and protein biomarkers into a single assay to assist physicians in non-invasively determining the presence or absence of cancer.

The capital infusion will also help fund the continued commercial and operational growth of OncoDiagnostic Laboratory (ODL), the CLIA-certified anatomic pathology and molecular diagnostics lab acquired by Predictive in January. ODL continues to operate from its Cleveland headquarters, where it performs histopathology, immunohistochemistry, cytopathology, as well as testing for a range of prognostic markers, including Bcl-2, p53, and HER-2/neu. The laboratory's menu of molecular diagnostic tests includes UroVysion, human papilloma virus, and chlamydia/gonorrhea.

Predictive will focus on expanding ODL's facilities to support its growing national customer base. Additionally, ODL will continue to invest in informatics, including optimized test ordering processes and effective integration with electronic health records.

Clinicians May Overscreen for Cervical Cancer, Study Finds

Clinical guidelines recommend screening low-risk women for cervical cancer every three years after age 30, but most primary care clinicians report that they would advise testing for the disease more frequently, according to a study published in the June 14 issue of *Archives of Internal Medicine*. Adding a test for human papillomavirus (HPV) to screening protocols does not increase clinicians' reported adherence to guidelines but may make them less likely to extend screening intervals.

Many physicians reported overscreening women by using both the HPV and Pap tests annually.

Based on evidence that annual screening does not improve outcomes relative to screening every three years, the U.S. Preventive Services Task Force has long recommended extending screening intervals up to every three years. Improved understanding of HPV infection and its role in cervical cancer, along with tests for HPV, have also resulted in recommendations from the American Cancer Society (ACS) and American College of Obstetrics and Gynecology (ACOG) to extend screening intervals without requiring prior normal Papanicolaou (Pap) tests.

Mona Saraiya, M.D., M.P.H., of the Centers for Disease Control and Prevention (Atlanta), and colleagues asked 1,212 primary-care physicians, of whom 950 performed Pap tests and had ever recommended the HPV test for their patients, to report their screening recommendations in response to clinical vignettes.

For a 35-year-old woman with no new sex partners in the past five years and three normal Pap test results, 31.8 percent of clinicians reported they would recommend the next Pap test in three years and 31.7 percent would recommend the next Pap test in one year. However, for a 35-year-old woman with one normal Pap test and a normal HPV test, 19 percent of clinicians would extend the screening interval to three years, whereas 60.1 percent would recommend annual testing.

Cost-effectiveness models "suggest that the practice patterns we found in our study are likely to increase costs with little improvement in reducing cervical cancer incidence and increasing survival," write the authors. "Overuse of screening is expensive for the health care system and may result in unnecessary follow-up testing, increased risk of colposcopy-associated morbidities and adverse birth outcomes and distress for patients."

The results of the study highlight the need for measures to reinforce extended screening intervals among patients with negative HPV and normal Pap test results. Without such measures, the authors conclude, "there is no advantage gained with HPV co-testing, and it is more expensive."

Society for Biomolecular Sciences and Association for Laboratory Automation Agree to Merge

The Society for Biomolecular Sciences (SBS; Danbury, Conn.) and the Association for Laboratory Automation (ALA; Chicago) have merged, creating a single organization known as the Society for Laboratory Automation and Screening (SLAS). SBS and ALA will live on as individual sections of SLAS, which will begin operating as a united entity

later this year.

"SLAS will become the premier international community dedicated to advancing scientific research and discovery through laboratory automation and screening technology," said inaugural SLAS President Michelle Palmer, Ph.D., director of screening at the Broad Institute of MIT and Harvard.

The SBS and ALA sections will continue to pursue their current missions while collectively addressing the SLAS mission, which is to provide forums for education and information exchange to encourage the study of and improve the science and practice of laboratory automation and screening.

Studies Support Genetic Screening for Fragile X Syndrome

There is adequate research to support population screening of women of childbearing age for fragile X syndrome—the most common inherited cause of cognitive impairment, according to a review published online ahead of print in *Genetics in Medicine.*

Fragile X syndrome affects about one in 4,000 males in the United States (it also occurs in females but causes less severe impairment). The condition is caused by relatively common mutations in the FRMR1 gene. Approximately one in 300 to 400 U.S. couples may be carriers of such a mutation.

Undertaken by a group of researchers in Australia, the review identified 11 studies evaluating the use of fragile X screening in women of reproductive age. The women in the studies found fragile X screening acceptable and appreciated having the option of screening, whether or not they chose to be tested.

The studies varied in terms of the percentage of women who agreed to screening, as well as the rate of abnormal FMR1 gene carriers. Studies that examined the psychological issues involved in screening revealed challenging issues for genetic counseling—especially related to the lack of awareness or personal experience with fragile X syndrome in the general population.

Despite the limitations of the research, fragile X screening in women of reproductive age "clearly meets established criteria" for genetic screening programs, the researchers concluded. However, they emphasized the need for "targeted educational and counseling strategies," as well as further research to evaluate the potential impacts of fragile X screening. "It is crucial that future studies offering screening for fragile X syndrome explore a range of psychosocial aspects in addition to looking at uptake of screening and mutation frequency," they noted.

The review found just one study evaluating the benefits of testing for fragile X syndrome in newborns—far short of the evidence needed to recommend screening. However, testing for the condition later in infancy might be a good alternative, according to an accompanying editorial by Bradford Coffee, Ph.D., of Emory University. He suggests that performing fragile X screening around 1 year of age would allow early education for affected infants. It would also avoid the "diagnostic odyssey" experienced by families of children affected by fragile X syndrome. Currently, the average age at diagnosis is about 3 years.

Coffee agrees that effective public education will be an essential part of any large-scale fragile X screening program. "Given that the vast majority of the general public has never heard of fragile X syndrome, much less are aware of the complexities of screening and predictive testing of premutation-associated disorders, educational and counseling services need to be developed to inform families of the risks and benefits of the screening," he wrote. He added that any type of fragile X screening program is far more likely to be successful if the process is "voluntary and transparent."

In addition to counseling and educational strategies, the review offers several suggestions for future research in this area. These include longitudinal studies to look at pretest and posttest outcomes, the inclusion of health economic measures in studies where screening is offered, and clinical trials to establish the benefit of early interventions in fragile X syndrome to guide policy decisions on whether to introduce newborn screening.

Cancer Screening Tests Found Lacking in Hodgkin Lymphoma Survivors

A population-based study that followed Hodgkin lymphoma (HL) survivors for 15 years discovered that while many survivors had multiple X-rays and CT scans years after treatment was finished, they often did not receive recommended cancer screening tests.

Survivors of HL, a highly curable malignancy that occurs in young patients, are known to have increased risks of screen-detectable cancers, including cancers of the breast, cervix, colon, and rectum.

CT scans appeared to be overused in early follow-up, while rates of recommended cancer screening were suboptimal.

The study, which was published online in advance of the July 15 issue of *Cancer*, followed 2,071 survivors for up to 15 years after their HL diagnosis by evaluating physician visits, imaging studies, and the use of routine and HL-specific cancer screening tests.

Survivors had CT scans at a rate three times greater than in the general population, even 10 to 15 years after their original diagnosis. "It is not clear why the CT scans were ordered, but they certainly did not appear to be an efficient way to detect relapse, particularly this long after treatment was finished," said principal investigator David Hodgson, M.D., a radiation oncologist at the Princess Margaret Hospital Cancer Program (Toronto) and investigator at the Institute of Clinical Evaluative Sciences.

Despite frequent contact with both specialists and primary care providers, many of the survivors did not receive recommended cancer screening tests. Among those who met criteria for routine screening, 62.5 percent were not screened for colorectal cancer, 32.3 percent were not screened for breast cancer, and 19.9 percent were not screened for cervical cancer.

"Our results indicate that the optimal follow-up care did not happen, even though most patients had visits with both a primary care provider and an oncologist in years two through five," said Hodgson. "So there are opportunities to improve post-treatment

surveillance for relapse and late effects."

Of particular concern is the finding that 87.1 percent of young women potentially at high risk of breast cancer because of prior radiation therapy were not screened. In the past decade, clinical practice guidelines have recommended that some patients start breast cancer screening before the usual starting age.

"Most HL patients are cured, but they can be at risk many years later of developing secondary cancers or other late effects of their initial treatment," said Hodgson. "This is why quality of follow-up care post-treatment is so important. And, increasingly, it is also important for other survivors as cure rates for several forms of cancer improve."

Enzo BioChem Denied Rehearing on Interference Patent

The Board of Patent Appeals and Interferences of the U.S. Patent and Trademark Office has denied a request for rehearing filed by Siemens Healthcare Diagnostics (Deerfield, Ill.) in a patent interference proceeding related to Enzo Biochem Life Science's application for nucleic acid signal amplification and a Siemens patent relating to branched DNA diagnostic systems.

Siemens filed the rehearing request in response to a Feb. 22, 2010, decision by the patent office awarding priority of the invention to Enzo, based in New York City. The result of this latest decision is that the judgment of the patent office is now final. Subject to any appeals that Siemens might file in federal court, Enzo will receive a full 17-year patent for all the invention covered by the claim, commencing on the date of the patent's issuance.

"This technology is the basis for a number of significant products in clinical diagnostics and in the life sciences field which currently are marketed or licensed by various commercial entities," said Elazar Rabbani, Ph.D., chairman and CEO of Enzo. "Additionally, we plan to expand the application of this key technology beyond the scope of gene-based applications into the field of immunodiagnostics."

According to trade reports, industrywide annual sales of diagnostic products utilizing the nucleic acid signal amplification technology are estimated to exceed $100 million in the United States. Using Enzo's signal amplification technology, direct detection of nucleic acid can be carried out without the need for target amplification and without compromising the sensitivity of the detection assay.

Health Plans Get a Break on Preventive Service Mandates

A provision in the health care reform law requires that for plan years (policy years in the individual market) on and after Sept. 23, 2010, private insurers must cover, at a minimum, without cost sharing, a range of preventive services. But the law—the Patient Protection and Affordable Care Act—also provides an exemption from this mandate for health plans that qualify for "grandfather" protection.

A grandfathered plan is a group health plan or health insurance coverage in which an individual was enrolled on the date of enactment of the law (March 23, 2010). Renewal of the plan after such date does not alter the grandfather status of the plan.

"New employer plans will not be able to have copays and deductibles after Sept. 23, but some existing plans will be grandfathered and thus not required to drop their cost-sharing policies," said attorney Peter Kazon of Alston & Bird (Washington, D.C.).

"But when the health exchanges become effective in 2014, they will not be able to have cost sharing for the preventive services specified in the law," he noted. Private plans participating in state-based exchanges will be required to comply with full coverage of the mandated preventive services.

Congress included this protection and other grandfather provisions in PPACA to give employers and insurers time to transition to the new law. But the law is vague on what constitutes a grandfathered plan and when, if ever, the protection will end. Plans that do not qualify must abide by all the consumer protections in the new law, including mandated preventive service reforms.

A lot is riding, legal analysts say, on whether the Department of Health and Human Services (HHS) takes a narrow or broad interpretation of the statute.

With health plans preparing their offerings for next year, they are particularly anxious to learn how any changes, including changes to benefits and cost sharing, would affect their grandfather status. Some speculate that any change would trigger loss of this status. That was included in the House version of health care reform but not in the final bill that became law. Other analysts speculate that it may take substantial changes to coverage to lose the status.

Under PPACA, the services that must be covered with no cost sharing include preventive services with an A or B rating from the U.S. Preventive Services Task Force; recommended immunizations from the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention; and with respect to infants, children, and adolescents, evidence-informed preventive care and screenings stipulated in comprehensive guidelines supported by the Health Resources and Services Administration.

Cost sharing is defined as deductibles, coinsurance, copayments, or similar charges, as well as any other expenditure required of an insured individual which is a qualified medical expense with respect to essential health benefits covered under the plan. There are certain exceptions: premiums, balance billing amounts for non-network providers, and spending for noncovered services.

An interval of one year is allowed from the time a preventive service recommendation or guideline is issued and the plan or policy year for which it takes effect.

The requirement to provide the mandated services is one of numerous provisions in the law aimed at accelerating the shift to prevention and wellness to help reduce and manage disease complications and avoid costly hospitalizations while rewarding quality and cost-saving outcomes.

On the immediate horizon, Medicare is authorized to add an annual wellness visit with health risk assessment in 2011 and to waive most beneficiary cost sharing, as of Jan. 1, 2011.

IVD Stocks Fall 6%; Inverness Plummets on Lowered Outlook

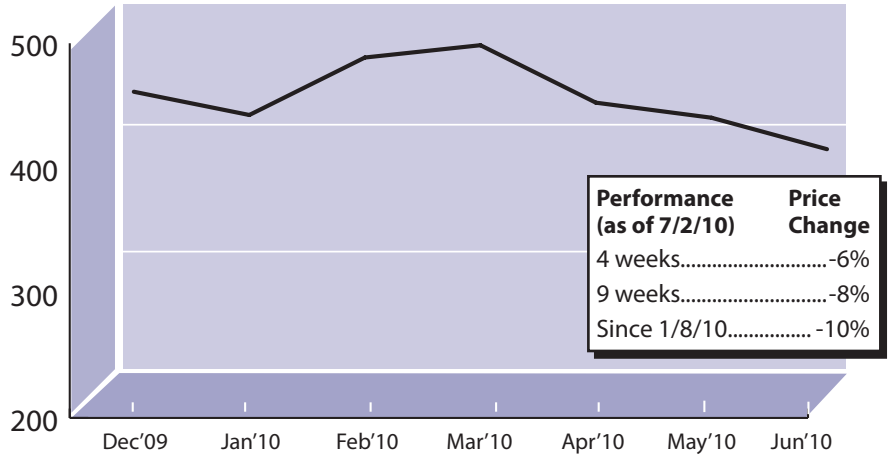
The G-2 Diagnostic Stock Index lost an average of 6 percent in the four weeks that ended July 2, with 12 stocks down in price, four up, and two unchanged. The G-2 index is down by 10 percent since January, as is the Nasdaq, while the S&P 500 has dropped 11 percent over the same period.

Inverness Medical Innovations (Waltham, Mass.) plummeted 25 percent to close at $25.80 per share and a market capitalization of $2.3 billion. The company recently lowered its full-year earnings outlook from $2.90 per share to $2.60 per share. Management attributed the reduction to a weaker-than-expected flu season as well as the decline of the euro and greater research and development costs.

Also losing a quarter of its value was **Clinical Data** (Newton, Mass.). Shares in the biotechnology company closed at $11.92 with a market capitalization of $344 million. Results for the fourth fiscal quarter and fiscal year ended March 31 fell below analysts' expectations. While quarterly revenue increased 5 percent to $3.8 million from $3.6 million compared to the same period a year ago, the company reported a loss of $38.4 million, or $1.44 per share, due largely to a hefty payout to Merck. The payment was tied to the FDA's acceptance of a new drug application for vilazodone, the novel therapeutic candidate for the treatment of depression that would be Clinical Data's first drug.

Meanwhile, Clinical Data's revenue boost was primarily driven by an increase in gross sales of its Familion genetic tests. The company recently expanded the product line with two new tests and one enhanced test for detecting inherited cardiac conditions. In the fiscal year that ended March 31, Clinical Data saw sales of its genetic tests grow by 36 percent, or $3.8 million, compared to the previous year. Third-party payer coverage for Familion tests is approximately 280 million lives in the United States, and Clinical Data's PGxHealth division is an approved Medicare provider and a Medicaid provider in most states.

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 18 IVD companies.

Up	Price	% Chg
Beckman Coulter	$61.37	9%
Gen-Probe	46.25	3
Johnson & Johnson	59.08	2
Quidel	12.31	8
Unchanged		
Abbott Labs	46.03	0
Meridian	17.22	0
Down		
Affymetrix	5.86	-8
Abaxis	21.18	-3
Becton Dickinson	67.97	-2
Bio-Rad	85.57	-5
Cepheid	15.45	-9
Clinical Data	11.92	-25
Immucor	18.58	-4
Inverness Medical	25.80	-25
Luminex	16.38	-5
Nanosphere	4.12	-18
OraSure	4.45	-3
Sequenom	5.37	-13

G-2 Insider

Cernostics completes funding round, partners with Geisinger Health System . . . Cernostics (Pittsburgh and Danville, Pa.), the pathology company founded in 2008 as a spin-off of Cellumen (Pittsburgh), has raised $2.6 million in a Series A funding round led by Novitas Capital, Geisinger Health System, and the Pittsburgh Life Science Greenhouse. In a related agreement, Cernostics has partnered with Geisinger to develop diagnostic technologies that can more effectively predict cancer progression and identify patients who are most likely to benefit from specific cancer treatments.

Cernostics has developed a proprietary approach known as TissueCipher Pathology (TCP) to integrate digital imaging pathology, highly multiplexed panels of fluorescence biomarkers, informatics, and electronic medical record systems. TCP combines measurement of biomarkers of key tumor system functions, including malignant, immune, and stromal processes, with advanced informatics for improved diagnostic, prognostic, and predictive testing.

The personalized medicine-focused collaboration with Geisinger, a $2.1 billion integrated health services organization, will bring together Cernostics' technological expertise in digital pathology and tissue-based diagnostics with Geisinger's robust biorespository and tumor bank, which is linked to its advanced electronic health records. The partnership will focus on developing cancer tests that can increase quality and decrease costs, assess the safety of traditional cancer treatments, and spur the creation of new cancer treatments. The initial focus is expected to be on gastrointestinal cancers and breast cancer.

Company References

Abbott Labs 847-937-6100
ACLA 202-637-9466
ALA 888-733-1252
AMP 301-634-7939
Cellumen 412-481-5690
Cernostics 570-214-6365
Clinical Data 617-527-9933
DiaSorin 651-439-9710
Enzo Biochem 212-583-0100
FDA OIVD 301-796-5450
Geisinger Health System 800-275-6401
Immucor 770-441-2051
Inverness Medical Innovations 781-647-3900
Meridian Bioscience 513-271-3700
Navigenics 650-585-7743
OraSure 800-869-3538
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SBS 203-743-1336
Siemens Healthcare Diagnostics 847-267-5300

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 Diagnostic Testing & Technology Report (ISSN 1531-3786) is published by Washington G-2 Reports, 1 Phoenix Mill Lane, Fl. 3, Peterborough, NH 03458-1467. Tel: 973-718-4700. Fax: 973-622-0595. Web site: www.g2reports.com.

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