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Competitive Intelligence & Analysis for an Expanding Global Market

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DTC Genetic Testing Regulation Debated by FDA Panel

At a two-day public meeting, the Food and Drug Administration's (FDA) Molecular and Clinical Genetics Panel (MCGP) discussed and made recommendations regarding direct-to-consumer (DTC) clinical genetic tests. FDA will draw upon the opinions and input of the panel as it considers how to most effectively regulate this burgeoning area of testing as well as the companies that offer DTC genetic testing services.

Last year, the agency advised DTC companies such as 23andMe (Mountain View, Calif.), Decode Genetics (Reykjavik, Iceland), and Navigenics (Foster City, Calif.) that it considers many DTC genetic tests to represent medical devices subject to regulation. However, it has not yet issued regulation guidance on DTC genetic tests and it remains unclear when it may be forthcoming.

Many panel members, invited speakers, and public commenters expressed their beliefs that these tests should only be accessible through doctors. Future regulatory approaches may require firms to establish clinical validity or utility, support labeling and advertising claims, engage in post-test follow-up, or comply with data-handling requirements due to the privacy issues involved. Additionally, the agency is open to a framework in which regulatory requirements differ based on the type of DTC test.

For a more detailed account of the FDA's MCGP meeting and more on genetic testing, please see the special focus section on p. 5.

First-Quarter Diagnostic IPOs Miss Targets

Initial public offerings (IPOs) of diagnostics companies have had mixed results during the first quarter. While several companies successfully raised money in the public markets, they consistently had to lower target stock prices, with net proceeds ranging from 14 percent to 40 percent below initial expectations. In a span of 10 days in February three molecular companies went public, including BG Medicine, Fluidigm, and Vermillion, while Atossa Genetics withdrew its application for an IPO.

After abandoning a planned 2007 IPO, BG Medicine (Waltham, Mass.) was the first of the trio to enter the public markets on Feb. 4, selling 5,750,000 shares of common stock at a price of $7 per share, including the overallotment option exercised by the underwriters. The net proceeds are a fraction of the original target of $86.3 million declared when the company first filed to go public a year ago and was even well below the revised $67 million target price that BG Medicine set in November.

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▲ **First-Quarter Diagnostic IPOs Miss Targets,** *from page 1*

The company said that $15 million of the net proceeds will fund the commercial launch of its lead product, the BGM Galectin-3 test for diagnosing chronic heart failure. The patented test was cleared by the U.S. Food and Drug Administration in November and is marketed by Laboratory Corporation of America. An additional $8 million of the proceeds will be used for other cardiovascular diagnostic candidates, and $3 million is expected to fund research and development (R&D).

Microfluidic systems maker Fluidigm (San Francisco) priced its initial public offering of 5,558,333 shares of common stock at $13.50 per share on Feb. 10. The company netted $78 million, following the overallotment option and deducting expenses payable by the company. The offering price was at the low end of the proposed range of $13.50 to $15.50 that Fluidigm disclosed in a prospectus filed in January with the U.S. Securities and Exchange Commission (SEC). In a statement the company estimates $15 million in proceeds will be used to enhance resources for product commercialization, $12 million will be used for R&D, and $4 million will be used for capital improvements and purchases.

On Feb. 14 Vermillion (Austin, Texas), a diagnostic developer, offered 4 million shares of common stock at $5.45 per share, netting approximately $20.2 million, down from an anticipated $34 million quoted in an amended SEC S-1 form, just a few weeks prior to the company's IPO. Proceeds from the offering will be used to expand the company's sales force and to accelerate clinical trials of its diagnostic test for peripheral arterial disease and its OVA2 test.

On the same day that Vermillion went public, Atossa Genetics (Seattle) notified the SEC it was withdrawing its IPO filing, saying it was not practical to pursue an IPO at this time. In October the company said it hoped to raise $17.6 million and planned to use the proceeds to launch its FDA-cleared Mammary Aspirate Specimen Cytology Test (MASCT), which it intends to launch in the Pacific Northwest this year.

While the reception has been tepid, more diagnostics companies are anticipated to enter the public markets. It has been reported that Netherlands-based Agendia is considering an IPO filing later this year. G2

Urinary Antigen Tests Underused in Diagnosing Pneumonia

Urinary antigen tests appear to be underused in clinical settings despite that fact that the pneumococcal urinary antigen has a high positive predictive value in diagnosing pneumococcal pneumonia, according to a study published in the Jan. 24 issue of the *Archives of Internal Medicine*. The findings, when clinically applied, have the potential to help optimize anti-microbial therapy selection thereby, reducing the incidence of antibiotic resistance.

Researchers conducted a yearlong study of adults hospitalized with community-acquired pneumonia (CAP) to evaluate the accuracy of the test. Antibiotic modifications, complications, and mortality were analyzed. Specificity was 96 percent and the positive predictive value ranged from 88.8 percent to 96.5 percent. Of the 474 cases of CAP that were included, streptococcus pneumoniae was the causative pathogen in 171

cases (36.1 percent). The urinary antigen test was performed in 153 of 171 patients (89.5 percent) with pneumococcal pneumonia, and it was positive in 130 (85 percent).

Despite the positive identification of s. pneumoniae, the test results led the clinicians to reduce the spectrum of antibiotics in only 41 patients (8.6 percent), all of whom had good clinical outcomes.

"A small percentage of doctors used that information. It's almost illogical," says Victor Yu, M.D., a professor of medicine at the University of Pittsburgh School of Medicine, who was awarded a National Institutes of Health grant to compare narrow-spectrum anti-microbial therapy to standard of care in patients with CAP. "Guidelines recommend all patients get urinary antigen test, but it is not adopted as widely as it should. The disadvantage is with broad spectrum antibiotics, you don't have to do any tests, [you're covered], but it's like using a cannon instead of a sniper rifle."

"Urinary antigen tests (both the pneumococcal and Legionella urinary antigen) and the Gram stain should become standard in-house tests of pneumonia at the [point of care] in the clinic, emergency department, and the hospital. The results are available within 20 minutes of processing, so diagnosing pneumococcal pneumonia accurately and then administering targeted penicillin therapy is eminently feasible," wrote Yu in an accompanying perspective piece in the *Archives of Internal Medicine*. "Rational use of antibiotics, using an appropriate pathogen-focused agent or narrowing empirical therapy, may decrease cost, drug adverse events, and the threat of antibiotic resistance."

CDC Recommends Use of Traditional Screening in Diagnosing Syphilis; Reverse Sequence Screening Has Higher False Positives

Reverse sequence syphilis screening can lead to a higher incidence of false positives, says the Centers for Disease Control and Prevention (CDC), which recommends use of the traditional screening alogorithm. The recommendations is contained in the Feb. 11 issue of *Morbidity and Mortality Weekly Report*, in which the CDC reports on a performance evaluation of reverse sequence syphilis screening with discordant results at five laboratories.

The CDC recommends syphilis screening with a nontreponemal test (rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test) to identify persons with possible infection followed by confirmation using one of several treponemal tests. But, in an effort to reduce time and labor, some laboratories are shifting to automatable treponemal enzyme and chemiluminescence immunoassays (EIA/CIA), leading to the adoption of a reverse sequence for syphilis screening in which a treponemal EIA/CIA is performed first, followed by testing of reactive sera with a nontreponemal test.

This reverse sequence can result in identification of discordant sera that are reactive with a treponemal test but nonreactive with a nontreponemal test. Discordant testing results could be caused by a previous syphilis infection with persistence of treponemal antibodies but seroreversion of nontreponemal antibodies, a false-positive

treponemal test result, or early primary syphilis in a person who has yet to develop nontreponemal antibodies.

CDC researchers analyzed data from five laboratories that used reverse sequence screening from 2006 to 2010. A total of 140,176 sera screened with a treponemal EIA/CIA were included in the analyses. Among the 4,834 cases of EIA/CIA-reactive sera, 2,743 (56.7 percent) were RPR-nonreactive, of which 866 (31.6 percent) were also nonreactive by treponemal testing (using treponema pallidum particle agglutination (TP-PA) or fluorescent treponemal antibody absorbed (FTA-ABS) tests), indicating that the initial EIA/CIA result was a false positive. Among discordant sera, the rate of nonreactive confirmatory treponemal tests was 2.9 times higher in a population with low prevalence of syphilis, suggesting that the low-prevalence population had a higher percentage of false-positive test results.

CDC continues to recommend the traditional screening algorithm, saying it performs well in identifying persons with active infection, while minimizing false-positive results in low-prevalence populations. However, if reverse sequence screening is used, CDC recommends that a specimen with reactive EIA/CIA results be tested reflexively with a quantitative nontreponemal test (RPR or VDRL). If test results are discordant, the specimen should be tested reflexively using the TP-PA test as a confirmatory treponemal test.

The specimens in this study were not assessed using the same screening immunoassay or the same confirmatory treponemal test. So, the CDC plans to conduct studies to directly compare the performances of EIAs, CIAs, the TP-PA test, the FTA-ABS test, and a new treponemal test that utilizes an alternative format, microbead immunoassay.

Lab Interoperability Cooperative to Help Achieve 'Meaningful Use'

Surescripts (Arlington, Va.), the American Hospital Association (AHA), and College of American Pathologists (CAP) have received a two-year, $4.9 million grant from the Centers for Disease Control and Prevention (CDC) to help laboratories achieve meaningful use in electronically transmitting data. The newly formed Lab Interoperability Cooperative will provide technical assistance to connect hospital laboratories with public health agencies to transmit reportable laboratory results.

While technical standards exist to securely transmit lab results, the implementation and use of these standards by the commercial labs, hospitals, and providers has been limited. AHA will assist in the education and recruitment of hospitals, while CAP will work to involve its 17,000 member pathologists in the program. Surescripts, the company says, operates the nation's largest health information network. The cooperative will connect a minimum of 500 hospital labs—at least 100 will be critical-access or rural hospitals—to the appropriate public health agencies.

CDC hopes to encourage hospital labs to advance electronic lab interoperability, which is a requirement in Stage 1 of the meaningful use program. The CDC grant will help hospital laboratories meet criteria established by the Office of the National Coordinator for Health IT for Stage 1 of the meaningful use program, which includes submission of electronic data on reportable laboratory results to public health agencies.

FDA Advisory Panel Examines Risks, Benefits of Direct-to-Consumer Genetic Tests

Consumers may soon no longer be able to simply spit, send, and click to gain insight into medical information associated with their own DNA—at least not without the involvement of a physician. The U.S. Food and Drug Administration's (FDA) Molecular and Clinical Genetics Panel, part of the Medical Devices Advisory Committee, recently convened to discuss and make recommendations on scientific issues concerning direct-to-consumer (DTC) genetic tests that make medical claims. Over the course of the two-day meeting in Gaithersburg, Md., a 22-member panel heard from a range of invited speakers and public commenters as they deliberated on complex issues related to oversight of DTC clinical genetic testing and considered appropriate approaches to rapidly advancing technology and scientific knowledge.

FDA's Elizabeth Mansfield, Ph.D., set the stage with an overview of the history and landscape of DTC testing, including the agency's 2010 letters to 20 firms informing them that their DTC tests appeared to be medical devices. Through meetings with the companies, the FDA determined that the offerings of many DTC companies did not fit the model for laboratory-developed tests (LDTs) and proceeded to request premarket submissions for all genetic tests that will be offered on a DTC basis. There is plenty of variation among the companies themselves. Some have CLIA certificates, while others do not, and not all DTC tests are multiplexed; some test for a single clinical claim, such as Alzheimer's disease, cystic fibrosis, or celiac disease.

Among the key challenges presented by DTC testing, according to Mansfield, is how to ensure that patients are protected from misleading and false information just as the health care community is working to understand how genetic information can be effectively utilized.

The panel's deliberations centered around three main questions:

- What are the risks and benefits of making clinical genetic tests available for direct access by a consumer without the involvement of a clinician?
- What are the risks of and possible mitigations for incorrect, miscommunicated, or misunderstood test results for clinical genetic tests that might be beneficial if offered through direct access testing?
- What level and type of scientific evidence is appropriate for supporting DTC genetic testing claims?

Invited speaker Teri Manolio, M.D., Ph.D., director of the National Institutes of Health's Office of Population Genomics of the National Human Genome Research Institute, provided background on the clinical applications of genomewide association studies. The disease-associated genetic variations identified in these studies underlie most DTC tests. Noting that few such studies have been narrowed to functional significance, Manolio highlighted the limitations of genetic markers in disease risk assessment. "Most are not deterministic and are not linked to outcomes," she advised. "In general, these are not predictive tests. You can do a much better job predicting diabetes by looking at obesity and family history [than searching for genetic markers that have been linked to the disease]."

During the public comment period, Ashley Gould, general counsel of 23andMe (Mountain View, Calif.), noted that her company, which has genotyped 75,000 individuals to date, is eager to provide customers with a broader and potentially more useful clinical analysis. "We would like to add other factors, including family history and environmental factors," said Gould, who added that 23andMe welcomes FDA oversight. "We want to come under regulation."

"The majority of physicians in the U.S. couldn't interpret a genetic test if their life depended on it. Is any of this ready for prime time? Maybe not."
–Gregory Tsongalis, Ph.D.

Among the most vocal opponents of allowing consumers to directly order and receive the results of genetic tests was Nancy Wexler, Ph.D., president of the Hereditary Disease Foundation and a professor of neuropsychology at Columbia University. In her invited presentation, Wexler, a pioneer in the effort to identify the genetic underpinnings of Huntington's disease, cautioned against the potentially "catastrophic results of predictive testing" for conditions that have no cure and minimal treatment options. "I think we need to be aware of the seductiveness of these offerings," said Wexler, who called for DTC testing to be prohibited. "I think that most people don't understand this information and what to do with it when they get it."

Gregory Tsongalis, Ph.D., of Dartmouth-Hitchcock Medical Center, a nonvoting member of the panel, noted that consumers weren't the only ones flummoxed by genetic test results. "The majority of physicians in the U.S. couldn't interpret a genetic test if their life depended on it," he said, while later advising against an overly restrictive approach. "Is any of this ready for prime time? Maybe not. But it could have a lot of impact on the health care system."

In its deliberations, the panel considered several types of tests and considered the value, risks, and benefits that each would have as a direct-to-consumer offering. While a range of views were expressed, the panel generally agreed on the recommendation that several categories or specific genetic tests should be offered solely upon prescription. These categories include presymptomatic tests that are highly predictive of disease, with potentially severe consequences, and pharmacogenetic tests. The panel also expressed concerns that the current state of scientific knowledge may not warrant the risk assessment claims being made by DTC companies.

David Ransohoff, M.D., another nonvoting member of the panel, emphasized the complex nature of many genetic tests and suggested that the FDA consider a systematic approach to evaluation. "You may have to go through each [genetic test] one by one, like the U.S. Preventive Services Task Force did when they deconstructed the yearly physical exam, and examine the evidence for each test." Celeste Ng, M.D., Ph.D., who was also joining the panel on a temporary basis, suggested a more simple method of evaluation. "Any result that you can do something about, I want that funneled through a physician."

The director of FDA's Office of In Vitro Diagnostic Device Evaluation and Safety, Alberto Gutierrez, Ph.D., reminded the panel that, "The agency is not looking to clear one of these categories or tests specifically. We're asking for general concepts that will allow us to decide whether to move forward or not." As the agency considers whether to allow consumers to order and receive the results of genetic tests without the involvement of a physician, the regulation of companies that provide such tests is a separate matter. "This is not under dispute," said Gutierrez. "They *will* be regulated."

CardioDx Raises $57 Million, Looks to Further Commercialize Genetic Test for Heart Disease

CardioDx (Palo Alto, Calif.), which develops genetic tests for cardiovascular diseases, has raised $57.5 million in equity and options-based investments from a total of 17 undisclosed investors. A March 2 filing with the Securities and Exchange Commission indicates that the new capital is part of a total $78.3 million funding round, the company's fifth since it was founded in 2004.

CardioDx plans to use the new funding to increase commercialization of its lead product, a test for coronary artery disease (CAD), and to develop other heart disease tests. Launched in 2010, CardioDx's Corus CAD test is a laboratory-developed test that uses data such as gene expression levels and other patient characteristics to assess the likelihood that a patient has obstructive CAD. The genomic test, which is priced at $1,195, can help cardiologists to make more informed decisions on how best to diagnose and treat patients. Corus CAD is offered exclusively through CardioDx's CLIA-licensed commercial laboratory.

Vanderbilt Creates Online Hub for Cancer Information

Vanderbilt-Ingram Cancer Center (VICC; Nashville, Tenn.) is making it easier for busy clinicians to keep abreast of the rapidly expanding area of cancer genetics. In March, the National Cancer Institute-designated Comprehensive Cancer Center launched "My Cancer Genome," a Web-based cancer decision support tool designed to help physicians and researchers track developments in personalized cancer medicine and connect with clinical research trials for their patients. It is part of VICC's Personalized Cancer Medicine Initiative, which was launched in 2010.

"Once we test a patient's tumor for specific mutations, the test results stay in a patient's medical record, so as new treatment options become available for each mutation, our physicians will have that information at their fingertips."
–Mia Levy, M.D., Ph.D.

Universally accessible at *www.MyCancerGenome.org*, the new site collects and disseminates knowledge about the prevalence and clinical significance of genomic alterations that predict response to cancer treatments. My Cancer Genome annotates mutation-drug-disease relationships via literature review, summarizes the comparative effectiveness of treatments for a given cancer by mutation status, and highlights genotype-driven therapeutic clinical trials.

"Next-generation, or genetically informed, cancer medicine holds the promise of tailoring anti-cancer treatment according to individual patient tumor characteristics," said William Pao, M.D., Ph.D., associate professor of medicine and director of personalized cancer medicine at VICC. "Staying abreast of these fast-paced research changes may be difficult for time-pressed oncologists and medical caregivers. In particular, knowledge about rare variants found in cancers may be hard to track down, especially in busy clinics. We launched this Web-based tool to enable a genetically informed approach to cancer medicine that we believe can be more efficient and effective."

A physician who receives tumor profiling results from the laboratory can consult My Cancer Genome to find the latest information about the clinical implications about a particular genetic mutation. The physician can then recommend treatment that is currently available or refer the patient to a clinical trial that is testing a targeted therapy

for that gene. Patients can also use the site to learn more about their diagnosis.

Vanderbilt University Medical Center has already linked its electronic medical record database to My Cancer Genome. "Once we test a patient's tumor for specific mutations, the test results stay in a patient's medical record, so as new treatment options become available for each mutation, our physicians will have that information at their fingertips," said Mia Levy, M.D., Ph.D., assistant professor of biomedical informatics and medicine and cancer clinical informatics officer for VICC.

My Cancer Genome launched in early March with two forms of cancer: lung cancer and melanoma. Other cancers, including breast and colon, will be added to the site over the next few months.

Study Finds New Genetic Links to Coronary Artery Disease

A massive meta-analysis has linked 13 new gene regions to coronary artery disease (CAD), the most common cause of death worldwide. The results of the study, published online on March 6 in *Nature Genetics*, could provide valuable insights into the development of the disease and improve the performance of current risk profiling strategies for CAD prediction.

An international consortium of researchers analyzed data from 14 genomewide association studies. They examined the complete genetic profiles of more than 22,000 people of European descent with CAD or a history of heart attack along with 60,000 healthy controls, making for a sample size almost 10 times larger than the next-largest whole-genome study to date.

"The signals from these gene regions are all rather subtle, making large-scale collaborations a prerequisite for any meaningful progress," said Themistocles Assimes, M.D., Ph.D., an assistant professor of medicine at Stanford University and study author.

After examining an average of 2.5 million common single nucleotide polymorphisms (SNPs) in each of the 14 genomewide association studies, the investigators focused on variants in 23 regions that appeared most likely to predispose people to coronary atherosclerosis. These regions were then studied in about 25,000 subjects with disease and about 25,000 healthy subjects from multiple additional studies. Thirteen of those 23 regions passed the threshold of statistical evidence for validation.

Only three of the 13 new gene regions appear to be linked to CAD through traditional risk factors such as high cholesterol and blood pressure, diabetes, smoking, and obesity. "This leaves open the possibility that many of the other gene regions are pointing to biological processes in the vessel wall that are reacting to the plaque-promoting effects of traditional risk factors," said Assimes. Interestingly, five of the CAD risk variants were also strongly associated with various other human disease traits in genomewide association studies.

The results of this study could translate into genotyping to assess risk of CAD. "With such information we should be able to better identify people at high risk early on in life and quickly take the steps to neutralize that excess risk by strongly recommending lifestyle and pharmacological therapies that we already know substantially reduce risk," Assimes said. "Although we are inching closer to that day, we will probably need to reliably identify many more variants predisposing to heart attacks over the next few years before it becomes useful to perform this genetic profiling in a doctor's office."

G2 INTELLIGENCE
Inside the Diagnostics Industry

Drug Testing Rebounds as Alternative Specimens, Expanded Panels More Widely Adopted

A dip in the economy, increased use of instant testing products, and pricing pressures have driven many drug testing laboratories out of business. In 2010, the Substance Abuse and Mental Health Services Administration (SAMSHSA) certified 37 laboratories to conduct testing in federal agency employees, down from 71 laboratories in 1998. But, despite these grim figures, the outlook for the drug testing market looks promising.

An executive order issued by Ronald Reagan in 1986 mandating a drug-free federal workplace led to standardization in an expanding drug testing industry. It helped establish technical guidelines and the NIDA 5, renamed the SAMHSA 5, a urine test panel for marijuana, cocaine, amphetamines, opiates, and phencyclidine (PCP) used to test safety-sensitive workers including pilots, bus and truck drivers, and workers in nuclear power plants, for whom routine drug testing is mandated by the U.S. Department of Transportation and the Nuclear Regulatory Commission.

Today, the federal government is no longer the largest user of drug tests and has not altered its mandatory testing program much since inception. Private industry is driving innovation in drug testing, including use of alternative specimens and instant screening tests, and expanded drug panels. Now that the economy is rebounding, experts expect to see increased adoption of these newer technologies.

Pre-Employment Testing Picking Up

As the economy improves, testing volumes and associated revenue is once again increasing, but companies are reporting a shift in the types of tests ordered.

Medtox Scientific Inc. (St. Paul, Minn.) reported that in 2010 drugs-of-abuse (DOA) testing revenues increased 9.9 percent to $39.6 million, from $36 million in the prior-year period. The increase resulted from "more stable testing volumes from existing workplace clients and an increase in revenues from new clients," the company said in a statement. Medtox's diagnostic segment saw similar revenue increases that were attributable to improved sales of their Profile products, an instant screening product that can be shipped to Medtox for confirmatory testing of positive results.

Quest Diagnostics (Madison, N.J.) similarly reported an uptick in testing volumes, with an 8.2 percent increase in DOA testing in the fourth quarter of 2010. DOA testing revenue for 2010 was $170 million, representing 2.5 percent of the company's total clinical testing revenue.

Growth in Alternative Specimens and Instant Testing

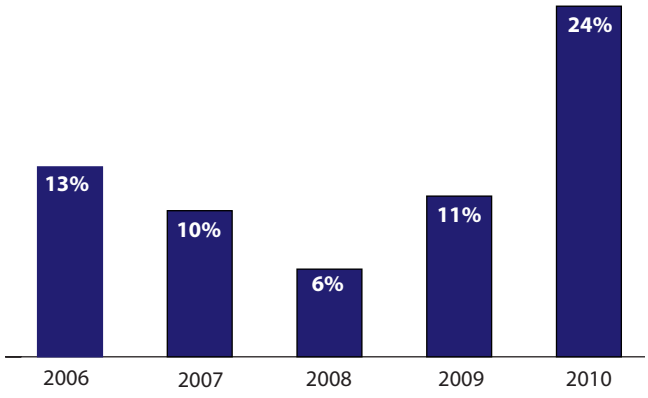
Drugs of abuse are absorbed into the bloodstream and are deposited into tissue including saliva, urine, and hair. Urine testing is the gold standard for drug testing as drugs exist in concentrations several hundred to a thousand times more than they do in saliva, blood, or hair. But urine testing poses collection challenges, and without direct supervision, can be easily adulterated to produce false negatives.

"It is a cat and mouse game with adulterators. I think a lot more people serious about drug testing are moving away from urine tests to alternative specimens because they are much more difficult to adulterate," says Laura Shelton, executive director, Drug and Alcohol Testing Industry Association. "The new technology has been around long enough and now there are legal cases upheld in court."

Hair testing allows for direct observation of specimen collection and shows drug abuse that occurred in the past 90 days, making it an ideal specimen for pre-employment and random drug tests. But since it takes an average of five to 10 days after a drug is abused to enter a hair follicle and grow above the scalp line in sufficient length to be tested, it is not a suitable test for post-accident testing. Saliva samples can be easily collected under direct observation and can be tested instantly. A survey conducted by G2 Intelligence determined the average price per drug test was $34.12 for urine, $25.25 for oral fluid, and $51.50 for hair.

"Urine testing is still dominating, but we are seeing a market increase in newer technologies. Oral fluids represent roughly 10 percent of workplace drug testing in the U.S. general workforce and probably 13 percent of all private-sector testing," says Barry Sample, Ph.D., director of science and technology for employer solutions at Quest Diagnostics. "We will continue to see increased utilization of oral fluids and will likely see increased utilization of hair testing in manufacturer facilities and in random testing to detect patterns of repeat use."

Drugs of Abuse CLIA-Waived Tests



Source: Adapted from G2 Intelligence, FDA

Sample said a large part of a recent drug testing advisory meeting agenda was dedicated to oral fluids testing. He is "hopeful" that in the next 18 months the U.S. Department of Health and Human Services will issue new proposed guidelines considering alternative specimens.

"As the economy comes back, pre-employment testing is picking up, but more companies, in an effort to control cost, are using point of care (POC) or instant testing to screen and only non-negatives are sent to laboratories," says Shelton.

Negative tests account for up to 90 percent of routine employment drug tests. Screening on site saves companies time and money. Technical performance characteristics of POC testing are similar to lab-based tests and are now available in expanded test panels.

Panels to Incorporate 'Drugs of Choice'

Over the last 20 years there have been several small revisions in the Mandatory Guidelines for Federal Workplace Testing Programs, mostly involving testing cutoffs. The latest revision was implemented in October 2010 and expanded the

drug testing panel to include methylenedioxymethamphetamine (MDMA), also known as ecstasy, and 6-acetylmorphine, an active metabolite of heroin.

The Quest Drug Testing Index (DTI) has tracked employment testing for the last 19 years and has noted a steady decline in drug testing positives, from 13.6 percent in 1988 to 3.6 percent in the combined U.S. workforce in 2008. The index, which reports positivity rates on drug tests performed by Quest among three major testing populations—federally mandated, safety-sensitive workers, the general workforce, and the combined U.S. workforce, has documented shifts in positive tests over the years.

Average Price of Drug Tests

TYPE	*PRICE*
Urine	$34.12
Oral Fluid	$25.25
Hair	$51.50

Source: G2 Intelligence survey, *Laboratory Industry Strategic Outlook: Market Trends & Analysis 2009*

Among those transportation workers subject to the October 2010 changes in mandated testing rules for the heroin marker, DTI analysis revealed a nearly 20 percent jump in positive results in the fourth quarter of 2010 compared to the same period in 2009, with the previous heroin detection program.

"In the first three months, we saw a 20 percent increase in positive results of private-sector transportation workers," Sample told *DTTR*. "While it is still very low incidence, nine in 100,000, we wanted to call it out because of safety concerns."

The government also required testing for ecstasy beginning in October 2010. During the first three months of testing under the new requirements, the additional test for ecstasy yielded a positivity rate (0.004 percent) consistent with expected rates based on historical nonregulated testing data.

While nonmandated testing programs initially mimicked the federal drug panel, expanded panels have become commonplace to capture trends in drug abuse and can test 12 to 50 classes of drugs.

"Fads in drug use change panels," says Shelton. "We see a switch to prescription panels, as that is now the drug of choice. If you aren't testing for the drug of choice in a specific area, you're not going to get the return on investment for your program you're looking for."

In September 2010 Quest reported a jump of 18 percent in American workers and job applicants testing positive for prescription opiates from 2008 to 2009 and an increase of 40 percent from 2005 to 2009 in the general U.S. workforce. Positive opiate results were found nearly four times as often in 2009 post-accident drug tests, as compared with pre-employment drug tests.

"There is a large increase of interest in the use or misuse of prescription drugs, prescription opiates. We are seeing repeated and large increases in hydrocodone," says Sample. "It is not surprising that with greater prescribing, there is greater use and a similar increase in workplace positivity rates."

States Attempt to Regulate Genetic Testing and Information

While the industry waits for a comprehensive, federal overhaul of genetic testing regulation, state legislators have begun to introduce their own legislative reforms—from mandating insurance coverage of genetic tests to expanding privacy rights of genetic information.

New York state Assemblyman Gary Pretlow (D-Mount Vernon) introduced a bill (A02325) in late January that would require insurance companies in the state to provide coverage for genetic testing for people who are deemed to be at "significant risk" for contracting cancer. It is unclear if the bill would require genetic tests for all cancers or just breast cancer, which was explicitly mentioned in the bill's accompanying memorandum. The bill has been referred to the insurance committee but is not likely to pass in the face of significant opposition from the insurance industry.

"A bill which would create separate insurance coverage criteria for a subset of genetic tests and follow-on services in a single state would further complicate the existing personalized medicine landscape for national insurers, healthcare providers, genetic test developers, and patient advocacy groups," wrote Dan Vorhaus, attorney and editor of the *Genomics Law Report*, while acknowledging improvements to the regulatory framework are necessary for genetic testing and personalized medicine which, he says, currently remain a "messy, patchwork affair."

A bill sponsored by state Sen. Harriette Chandler (D-Worcester), known as the Massachusetts Genetic Bill of Rights (S01080) attempts to expand upon current federal laws. The legislation establishes property and privacy rights for genetic information and genetic material, while proposing civil and criminal penalty provisions for violations. If enacted, these would be the strongest set of protections yet against surreptitious genetic testing, experts say. Additionally, the legislation expands upon the federal Genetic Information Nondiscrimination Act of 2008 by prohibiting genetic discrimination in the pricing of long-term care, life, and disability insurance. Opponents are concerned that the legislation could impose unintended barriers that could hamper research in the state. In late January the legislation was referred to the Joint Committee on Public Health.

New Launches: Breast Cancer Assays to ID Screening Tests

ARUP Laboratories (Salt Lake City) has announced the availability of a new laboratory-developed test designed to classify breast cancer into clinically significant molecular subtypes. The test, known as the PAM50 Breast Cancer Intrinsic Classifier, is an RT-qPCR assay that measures the expression of 50 classifier genes and five control genes to identify the intrinsic subtypes known as Luminal A, Luminal B, HER2-enriched, and Basal-like along with quantitative values for proliferation, luminal gene expression, ESR1, PGR, and ERBB2.

Meridian Bioscience Inc. (Cincinnati) has received clearance from the U.S. Food and Drug Administration (FDA) for pediatric usage of its illumigene Clostridium difficile molecular amplification test. C. difficile is a bacterium that is frequently associated with antibiotic therapy often causing diarrhea and, in severe cases, a life-threatening inflammation of the colon. Studies have shown the bacterial infection is becoming

more frequent and more severe. C. difficile products are expected to account for 22 percent of the company's 2011 revenue.

Roche (Basal, Switzerland) has launched the cobas TaqScreen DPX Test in the United States. It is the first commercial test to quantify parvovirus B19 and detect hepatitis A virus (HAV) simultaneously in one assay in human plasma, the company says. The in vitro nucleic acid amplification test adds to the company's offerings for the blood and plasma screening market.

Agendia (Amsterdam) has received an additional FDA clearance for its MammaPrint assay, now allowing it to run on two more Agilent microarray scanners and two Agilent Bioanalyzers. The assay, based on analysis of 70 genes, stratifies patients based on risk of distant recurrence of breast cancer. The additional clearance will expand laboratory capacity at the company's labs in Amsterdam and Irvine, Calif.

Noninvasive Test Accurately Identifies Melanoma, Could Improve Current Detection Methods

DermTech International (La Jolla, Calif.) has released data on its genomic assay for melanoma, showing the test is able to identify skin cancer with 100 percent accuracy. The results, published online in the *British Journal of Dermatology*, are an important step toward commercialization of the test that could prove more accurate than current detection methods and could impact care for more than 7 million people at high risk for developing melanoma in the United States alone.

The test is based on the company's Epidermal Genetic Information Retrieval (EGIR) technology that noninvasively collects cells from the surface of suspicious lesions using a custom adhesive. RNA isolated from the tapes was amplified and a 17 gene biomarker was characterized that accurately differentiates in situ and invasive melanomas from nevi (birthmarks or moles) with 100 percent sensitivity and 88 percent specificity.

Each of the 13 false-positive specimens was re-reviewed using serial sectioning and it was determined one of the false positives actually harbored an invasive superficial spreading melanoma. The authors hypothesize that the EGIR-based genomic assay can detect molecular changes prior to the development of morphological abnormalities in melanoma cells, making the EGIR-based genomic assay a more sensitive way to detect melanoma than standard histopathological practice.

"This is all about being objective, removing subjectivity, and in so doing catching melanoma in the earliest stages," says George Schwartz, CEO, of DermTech. "To me this is bringing focus to help physicians better determine which lesions need to be biopsied, identifying melanoma at a stage prior to what a pathologist's toolbox can allow him to see today, by providing a fuller molecular picture of a lesion than the standard of care can today, at less than today's cost."

DermTech is now translating this discovery data onto a quantitative polymerase chain reaction (PCR) platform and will initiate a pivotal trial with sample collection activities ongoing in the United States, Australia, and Europe.

If DermTech develops the test on its own, it intends to seek FDA approval. But the company is interested in engaging in discussions with possible laboratory partners,

Schwartz tells *DTTR*. Commercialization is expected to occur first in Australia, which has the highest incidence of melanoma in the world, followed by introduction in Europe. Adoption in the United States is expected in two to three years and will initially target high-risk populations, which offer the greatest hope of swift regulatory clearance and reimbursement. While Schwartz declined to discuss pricing specifically, he said it is assumed the test will cost less than the sum of a biopsy and related pathology.

Small Setbacks for PGx, but Development Continues

While many tout the promise of codevelopment of drug therapies and diagnostic tests, some industry experts are wondering aloud if recent high-profile drug failures could have been prevented if companion diagnostic strategies had been more aggressively pursued by pharmaceutical companies.

In the beginning of February, AstraZeneca (London) informed the U.S. Food and Drug Administration that it will be withdrawing the accelerated approval new drug application for IRESSA (gefitinib) effective September 2011 and will no longer pursue approval for IRESSA. The drug was approved under Subpart H for life-threatening illness for use as monotherapy in the treatment of locally advanced or metastatic non-small-cell lung cancer after failure of other chemotherapies. But the drug failed to show a significant survival benefit in required confirmatory studies. The company effectively dismissed a relaunch with a pharmacogenomics strategy.

"There is no sort of blanket statement that could possibly cover the nuances of these different situations," says Harry Glorikian, managing partner in the life science consulting firm Scientia Advisors (Boston). "In the background they are doing return on investment with assumptions and risk calculations going into the model. We aren't privy to the economics that drive these decisions."

In January Sanofi-Aventis (Paris) reported disappointing results from a phase III study conducted with the company's oncology candidate, iniparib (BSI-201), in women with metastatic triple-negative breast cancer. Results showed that iniparib failed to prolong overall survival and progression-free survival. Salt Lake City-based Myriad Genetics CEO Pete Meldrum has publicly commented that his company's BRCA test could have helped Sanofi-Aventis's iniparib succeed, as parp inhibitors have been shown more effective in women with mutated BRCA genes.

"A lot of organizations are still figuring out the path that works for them," says Glorikian. "It's an individual decision, not a systemic decision. We are going to have ups and downs. As time goes on we will see more [companion diagnostics]."

At least one company is taking the lesson to heart. In February, Invivoscribe Technologies Inc. (San Diego) announced a collaboration with Novartis (Basel, Switzerland) to develop a companion diagnostic test to identify acute myeloid leukemia patients positive for the FLT3 mutation. The diagnostic will be used in connection with the Novartis development compound, midostaurin (PKC412), which is in phase II clinical trials. FLT3 mutations, present in approximately one-third of all AML patients, are associated with poor prognosis.

IVD Stocks Fall 1%; Weak Earnings Contribute to Decline

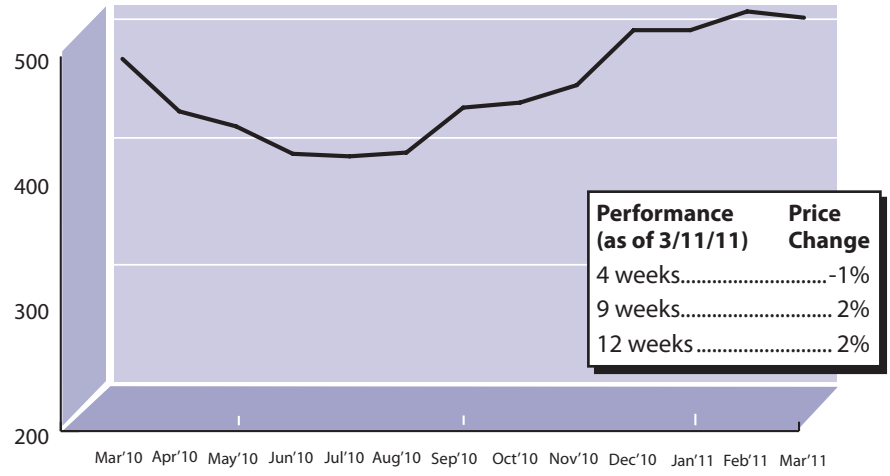
The G2 Diagnostic Stock Index lost just over 1 percent in the four weeks that ended March 11, with 11 stocks down in price, seven companies up, and one remaining unchanged. During the same four-week period the Nasdaq was down 3 percent and the S&P 500 was down 2 percent.

Losing the most ground was **Sequenom** (San Diego), whose stock price dipped to $5.72 per share, down 18 percent. The company reported its financial results on March 8 for the fourth quarter and fiscal-year 2010. Total annual revenues were $47.5 million, an increase of 25 percent from the $37.9 million reported in 2009. For the full year, the company lost $120.8 million, or $1.69 per share. Fourth-quarter losses increased due to a $6.5 million charge for revaluating settlement of a lawsuit, as well as increased costs. In a conference call the company said they expect to incur further losses for the foreseeable future and that the company needs to secure additional financing this year.

Also losing more than 11 percent during the last four weeks were **IRIS International** (Chatsworth, Calif.), **Illumina** (San Diego), and **Quidel** (San Diego).

Despite announcing record revenue fourth-quarter revenue of $29.3 million, IRIS stocks closed at $9.02 per share, down 13 percent. The company's full-year 2010 revenue was $107.7 million, an increase of 16 percent from $92.6 million in 2009. The company also reported lower earnings both for the fourth quarter and for the full year. Full-year 2010 earnings per share were 17 cents versus 35 cents in 2009. Decreased earnings resulted from the dilutive impact of IRIS's Arista Molecular Laboratory, estimated to be approximately $2.1 million, or 9 cents per share. Fourth-quarter and full-year earnings also reflect, the company said, chief financial officer severance and transition expenses, unfavorable foreign currency exchanges, and higher instrument costs of approximately $800,000, or 3 cents per share. G2

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 19 IVD companies.

Up	Price	% Chg
Abbott Labs	$48.46	6%
Abaxis	28.20	7
Bio-Rad	115.90	6
Cepheid	26.18	5
Gen-Probe	65.01	2
OraSure	6.91	3
Qiagen	20.30	6
Unchanged		
Beckman Coulter	82.99	0
Down		
Affymetrix	4.90	-8
Alere	36.85	-8
Becton Dickinson	78.87	-3
Illumina	19.16	-5
Immucor	22.58	-1
IRIS International	9.02	-13
Johnson & Johnson	59.69	-2
Luminex	18.26	-6
Meridian	21.46	-5
Quidel	12.10	-11
Sequenom	5.72	-18

G2 Insider

Learn how clinical laboratories are capitalizing on molecular diagnostics . . . "MDx Goes Mainstream" is the theme of G2 Intelligence's sixth annual molecular diagnostics conference, which will take place April 13 to 15, 2011, at the Fairmont Copley Plaza in Boston. A roster of experts will discuss how to best apply the emerging science, novel business models, and rising demand for molecular diagnostic testing to grow your lab in the current regulatory and business environment. Scheduled sessions include:

- The Future of Molecular Diagnostics, a keynote address by **Randy Scott, Ph.D.**, executive chairman of Genomic Health;
- Demystifying MDx: The Path to Profitability, presented by **Kevin Krenitsky, M.D.**, president of Enzo Clinical Labs;
- Driving Data Discovery Through Integration and Analysis, a keynote address by **John Quackenbush, Ph.D.**, professor of computational biology and bioinformatics at Harvard School of Public Health;
- Pharmacogenomics in the Clinical Laboratory, presented by **Karen E. Weck, M.D.**, professor and director of the molecular genetics laboratory at the University of North Carolina School of Medicine; and
- A two-part look at reimbursement and how it is inextricable from regulation, presented by Foley Hoag's **Bruce Quinn, M.D., Ph.D.**, formerly the contractor medical director for the California Medicare Part B program, and **Patrick Terry**, partner and principal with Scientia Advisors.

For full program details or to register, visit *http://www.mdxconference.com/* or call Jeff Watkins at 973-718-4709.

Company References

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