G2 INTELLIGENCE

Diagnostic Testing & Technology Report

Competitive Intelligence & Analysis for an Expanding Global Market

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Self-HPV Testing Quality Comparable to Liquid-Based Cytology

In what is said to be the largest study to examine the diagnostic accuracy of self-collected cervicovaginal specimens for human papillomavirus testing (self-HPV testing), researchers found that the sensitivity of self-HPV testing compared favorably with liquid-based cytology (LBC). The results suggest that self-HPV testing could complement current screening programs by increasing testing coverage in areas lacking access to cytology-based screening, according to the study published online Jan. 23 in the *Journal of the National Cancer Institute*.

The researchers analyzed pooled data from five cervical cancer screening studies in China in which more than 13,000 participants were screened using self-HPV testing and three other methods. The researchers found that self-HPV testing was more sensitive and less specific than either visual inspection with acetic acid or LBC but less sensitive and similarly specific to physician HPV testing.

"Although it is not specific enough to be a stand-alone test, self-HPV testing provides sensitive results without pelvic exams, medical professionals, or health-care facilities and thus has the potential to serve as a primary cervical cancer screening method for women," write the authors led by You-Lin Qiao, M.D., Ph.D., of Peking Union Medical College. For more on the growing interest in self-collected testing specimens, please see *Inside the Diagnostics Industry* on page 5.

Oxford Nanopore Shakes Up Sequencing Market; Novel Sequencing Technology to Enter Market in 2012

The first commercial sequencing instruments to use nanopore technology are expected to enter the commercial markets in the second half of 2012. Oxford Nanopore Technologies' (United Kingdom) presentation of their two nanopore platforms Feb. 17 at the Advances in Genome Biology and Technology conference in Marco Island, Fla., immediately set the sequencing world abuzz with the promise of ultralong read lengths, high throughput, and real-time sequencing results, all without cumbersome sample preparation.

Oxford's nanopore technology, which reads a strand of DNA as it is pulled through a microscopic hole, will be available on two platforms—the GridION, a scalable electronic platform, and the MinION, a miniaturized, disposable instrument the size of a USB memory stick.

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▲ **Oxford Nanopore Announcement Shakes Up Sequencing,** *from page 1*

"The exquisite science behind nanopore sequencing has taken nearly two decades to reach this point; a truly disruptive single molecule analysis technique, designed alongside new electronics to be a universal sequencing system," said Gordon Sanghera, Oxford Nanopore's CEO, of the unveiling in a statement.

The Technology

Nanopore technology uses an array of proprietary protein nanopores embedded in a robust polymer membrane. Each nanopore sequences multiple strands of DNA from a solution in succession. Individual strands are pulled through the nanopore by a proprietary processive enzyme. As the DNA bases pass through the hole they are identified by an electronic chip that measures disruptions in electrical current through the nanopore. The changes in current produce data that, when decoded, identify the sequence of the DNA bases.

The advantages of nanopore sequencing platforms over other commercially available instruments are that the DNA is sequenced as contiguous reads and that no sample preparation is required—no amplification or chemical labeling steps are necessary. The downside of the technology is that the error rate is currently approximately 4 percent, although the company anticipates being able to reduce that to a reported 2 percent by product launch.

The GridION system consists of scalable instruments or nodes, as they are called, which are used with consumable cartridges that contain proprietary array chips for multi-nanopore sensing. In the first release each cartridge is designed for real-time sequencing by 2,000 individual nanopores. But more powerful configurations are already in the works with instruments with 8,000 nanopores expected in 2013. When 20 nodes are installed together using an 8,000 nanopore configuration, the company says, sequencing results of a complete human genome could be delivered in 15 minutes. The company says the instrument will be competitively priced in a "price per base" comparison. Upon launch even the portable MinION will be able to deliver read lengths of up to 100 kilobases and is expected to retail for less than $900. The MinION is expected to make sequencing widely accessible with no large capital investments—"it's pay-as-you-go sequencing," Clive G. Brown, the chief technology officer of Oxford Nanopore Technologies, told the *New York Times*.

Shuffling of Sequencing Players

News of the GridION and the MinION immediately caused share values of sequencing instrument makers like Life Technologies, Pacific Biosciences, and Illumina to fall. Illumina (San Diego), though, may be somewhat sheltered from Oxford Nanopore's attempt to gain market share with its 2009 $18 million investment in Oxford Nanopore. While Illumina owns approximately 15 percent of privately held Oxford Nanopore, Illumina does not have the marketing rights to the newly unveiled machines.

Nanopore's low cost and ability to read long DNA fragments along with its minimal sample preparation, which frees up time, space, and money, have the potential to drastically simplify the sequencing work flow. But the two primary

Other Sequencing News

There is continued evidence that sequencing technology is continuing its march into the clinical realm. On Feb. 13 Complete Genomics (Mountain View, Calif.) announced it will provide outsourced whole-genome sequencing for Mayo Clinic's Center for Individualized Medicine (Rochester, Minn.). While Mayo operates a comprehensive sequencing laboratory in its own Medical Genome Facility, it is expected that this outsourcing arrangement will help expedite Mayo Clinic's translational genomics-based programs. Financial details of the agreement were not disclosed.

challenges with nanopores have been accuracy and speed.

"While [Oxford Nanopore Technologies'] product is potentially game changing, we have witnessed many similar announcements before and history has reminded us patience is a virtue," says Jon Groberg, an analyst from Macquarie Capital in New York in a recent report.

Groberg expects the consequences of Oxford Nanopore's announcement to play out in a few ways. First, he thinks other sequencing players will up their research and development spending, and second, he says, "A price war is no longer coming, it is here." With three new sequencing technologies expected to ship in 2012 (Oxford Nanopore's platforms along with Life Technologies' Benchtop Ion Proton sequencer and Illumina's upgraded HiSeq) users are in a great position to negotiate pricing as each company is eager to maintain or gain market share.

Affymetrix GeneChip Approved for Use in China

Affymetrix (Santa Clara, Calif.) announced in mid-February that its GeneChip System 3000Dx v.2 is the first microarray instrument system granted approval by China's State Food and Drug Administration (SFDA) for clinical testing. With the clearance of the instrument, Affymetrix is hoping to gain a share of China's emerging personalized medicine market. Prior to the announcement approximately 2,200 systems had been shipped worldwide, but the company says it is seeing "robust demand" for the system in China.

"We feel very confident about the China diagnostic market and our advantage of being the first microarray platform that is SFDA cleared," says Chris Barbazette, Affymetrix's vice president of commercial operations in international markets. "This will enable us to expand into the clinical diagnostics applications."

The GeneChip System already received regulatory approval in the United States, Japan, and Europe. Affymetrix's microarray platform has a record of successful development and commercialization of molecular diagnostics tests through partnership. Currently there are two U.S. Food and Drug Administration-cleared tests (Roche's AmpliChip CYP450 test and Pathwork Diagnostics' Tissue of Origin Test), four CE-marked tests, and several more tests in the process of clearance all based on the GeneChip microarray platform. But, Barbazette says, the diagnostic test developers will have to independently submit their own assays or diagnostic kits to SFDA for clearance.

Gene Co. (Hong Kong) is Affymetrix's distribution partner in China. The list price of a typical GeneChip 3000Dx unit starts at $229,000 in China, Barbazette says.

NIH's Genetic Testing Registry Officially Launches

The National Institutes of Health (NIH) launched its Genetic Testing Registry (GTR) on Feb. 29 with an initial list of tests for 2,500 diseases. The database is expected to expand along with the growing number of molecular tests offered nationally, but not without some lingering displeasure from consumer and industry stakeholders.

Submission of genetic tests is voluntarily provided by genetic test providers. The NIH says the entered information will include the purpose of each genetic test and its limitations, the name and location of the test provider, whether it is a clinical or research test, what methods are used, and what is measured.

GTR will offer detailed information on analytic validity, including how accurately and reliably the test measures the genetic target; clinical validity, including how consistently and accurately the test detects or predicts the outcome of interest; and information relating to the test's clinical utility. NIH will not verify the content but will require submitters to agree to a code of conduct that stipulates that the information they provide is accurate and updated annually.

With no oversight, the quality of the content and data submitted remains a point of contention among some stakeholders. Consumer advocacy organizations are concerned about the lack of oversight, while the laboratory industry remains concerned about the requirements for data provided. Throughout the process the NIH has sought stakeholder comment and involvement. In comments submitted by the Association for Molecular Pathology in fall 2011, the organization said that it "continues to have concerns regarding the format and the data elements proposed for the Genetic Test Registry" including the fact that some data elements address detailed issues of laboratory policy "that are inappropriate for inclusion in the GTR and raise legal and liability concerns." G2

New Colorectal Cancer Screening Guidance

The Clinical Guidelines Committee of the American College of Physicians (ACP) has issued new guidance on appropriate colorectal cancer (CRC) screening in adults. The guidance, published in the March issue of *Annals of Internal Medicine*, was based on a critical review of four existing U.S. guidelines and was intended to clarify conflicts between existing guidelines for practicing clinicians. The new guidelines suggest that reliance on annual fecal occult testing for CRC in average-risk patients is acceptable.

Among the committee's four recommendations are clinicians should perform individualized assessment of risk for colorectal cancer in all adults; clinicians should screen for colorectal cancer in average-risk adults starting at the age of 50 years and in high-risk adults starting at either age 40 or 10 years younger than the age at which the youngest affected relative was diagnosed with CRC; stool-based testing, flexible sigmoidoscopy, or optical colonoscopy can be used as screening tests in patients who are at average risk, while optical colonoscopy is recommended in high-risk patients; and clinicians should stop screening for colorectal cancer in adults over the age of 75 years or in adults with a life expectancy of less than 10 years.

Current CRC screening rates in the United States remain low. According to data from the U.S. Centers for Disease Control and Prevention only 50 percent of U.S. adults age 50 or older had undergone a sigmoidoscopy or colonoscopy within the previous 10 years or had used a fecal occult blood test within the preceding year. The ACP committee says that since "currently available colorectal cancer screening tests are believed to be similarly efficacious" patient preference should play a role in screening test selection.

The recommendations say that noninvasive stool-based tests, which are assumed to be preferred by patients, are to be used annually, although the interval for stool DNA panels remains uncertain. The other recommended stool-based tests are guaiac-based fecal occult blood test and immunochemical-based fecal occult blood test. Positive stool tests will require a follow-up colonoscopy. G2

G2 INTELLIGENCE
Inside the Diagnostics Industry

Industry Interest in Patient Self-Sampling Growing; STD and Anti-Coagulation Testing Moving Ahead

Diabetes monitoring is typically viewed as the quintessential example of patient self-sampling – patients drawing their own blood sample to test glucose levels. In the comfort of their own office or home, diabetic patients can draw their own blood sample to test their glucose levels. Technological advancements have enhanced testing sensitivity and improved available mediums for the collection of specimens, expanding the possibilities of using patient-collected samples for diagnostic testing or monitoring.

Health care providers and the diagnostic industry are taking note of other clinical areas, including testing for sexually transmitted infections (STIs) and chronic anti-coagulation monitoring, where patient self-sampling can both provide added convenience and increase access to testing in underserved areas.

STD Self-Sampling

In the beginning of February, Roche (Basal, Switzerland) announced that the U.S. Food and Drug Administration provided 510(k) clearance to the cobas CT/NG test for the detection of Chlamydia trachomatis (CT) and Neisseria gonorrhoeae (NG) infections using self-collected vaginal swabs or male urine. Previous trials confirmed that self-collected vaginal specimens and male urine specimens provide increased sensitivity and specificity compared to alternative specimen types across patient populations with both low and high disease prevalence. These specimen types, in addition to being less invasive and more private to collect, are the preferred specimen types for CT and NG testing, according to a 2009 summary report from the U.S. Association of Public Health Laboratories and U.S. Centers for Disease Control and Prevention. With the approval of the CT/NG test, Roche has been able to expand its offerings for STI testing on the cobas platform and demonstrates increasing interest in expanding patient-collected test offerings.

The accuracy and feasibility of using self-collected samples for human papillomavirus (HPV) have been the subject of numerous recent studies both in the United States and abroad. Experts believe that by using self-collected samples for HPV testing, underserved areas will be able to expand their cervical cancer screening programs.

In one study published in *Lancet* in November 2011, researchers found that HPV testing of self-collected vaginal samples from poor, rural women in Mexico was both acceptable to the women and was more sensitive than routine local cervical cytology. The study, partially funded by Qiagen (Hilden Germany), tested more than 25,000 women aged 26 to 65 years. The participants were randomly assigned to either HPV DNA testing of a vaginal sample self-collected at home or cervical cytology at the nearest health center. Qiagen's digene cervical sampler, a conical-shaped brush, was used to take the samples and the digene HPT assay for the high-risk variants of the virus most likely to cause cervical cancer was used for testing.

Participation was higher in women randomized to the HPV group (98 percent) compared to women in the cytology group (87 percent). The relative sensitivity of HPV testing was 3.4 times greater than cytology and detected 4.2 times more

invasive cancers than cytology testing, but its positive predictive value was only 12.2 percent, compared to 90.5 percent for cytology.

"HPV testing is lower in cost, easier to implement, and has lower false-negative rates than cytology," said lead author, Eduardo Lazcano-Ponce, Ph.D., of the Centro de Investigación en Salud Poblacional of INSP, the national institute of public health in Mexico. Lazcano-Ponce and co-authors wrote in the paper that, "because women at these sites will be screened only a few times in their lives, the high sensitivity of a HPV screen is of paramount importance." But, given the low positive predictive value, the challenge of implementing a HPV testing strategy for cervical cancer prevention in low-income countries is identification of the most effective triage for HPV DNA-positive women because the test substantially increases the number of colposcopy referrals.

"The primary issue is trying to increase access to cervical cancer screening and self-HPV testing is a real move in that direction. Many women remain outside the guidelines with barriers to access [testing]. "
–Jennifer Smith, Ph.D., University of North Carolina, Chapel Hill

"The primary issue is trying to increase access to cervical cancer screening and self-HPV testing is a real move in that direction," says Jennifer Smith, Ph.D., associate professor of public health at University of North Carolina, Chapel Hill. "Many women remain outside the guidelines with barriers to access [testing]. We think one-quarter of [U.S.] women have not received screening in the last three years and that is not a non-negligible portion of the population."

Smith conducted a study offering free home HPV screening kits to underserved women in North Carolina to determine the feasibility and acceptability of self-collection. Nearly 70 of participants reported the testing was"mostly positive" and 64 percent saying they preferred home self-collection to clinic visit, although a positive test requires a referral to a clinic for a Pap smear.

While experts are hopeful that self-collected HPV testing can improve access to testing, barriers to widespread adoption of such programs exist.

"Reimbursement is always an issue. Ensuring that coverage translates to self-sample is a very big issue and remains to be seen," cautions Smith, who explains that industry buy-in is also necessary to bring down the cost of the consumables.

Self-Sampling for Chronic Monitoring

One other clinical area for which patient self-sampling is garnering increased attention is in the field of anti-coagulation monitoring. An estimated 4.2 million patients are on anti-coagulation therapy (warfarin therapy) in the United States.

"This is a little different [than STI testing]. This is for monitoring a chronic condition. Testing and monitoring diabetes is a better analogy," says Hanna Bloomfield, M.D., director, Center for Chronic Disease Outcomes Research at the University of Minnesota School of Medicine. "Warfarin is an unusual situation in medicine where the drug has a tight therapeutic index and outside of that range it is not safe. In no other place in medicine does a basically healthy person have to come in every four to six weeks for testing."

Current estimates are that 50 percent to 60 percent of warfarin patients are being followed by private physicians (usual care), 30 percent to 40 percent are managed

by a specialty hospital-based anti-coagulation clinic, with only a few percent of patients currently self-testing at home. Many in the field had hoped that home anti-coagulation monitoring would have taken off by now, but adoption has been hampered by cost as well as ongoing debate about whether or not outcomes are really improved by more frequent, costly patient self-testing and also which patients should be permitted to self-test.

Several large studies have been published since late 2011 suggesting that home testing of prothrombin time/INR in patients receiving anti-coagulation therapy is safe. A prospective, randomized trial published in October in the *New England Journal of Medicine* found that weekly home INR testing was slightly superior to monthly clinic INR testing in the average percentage of time the 2,922 patients spent in therapeutic range. But there was no real benefit found in terms of major clinical outcomes including the reduction of the risk of a major event like stroke, major bleeding episode, or death. Unlike other studies published in this area, this one did not limit the selection to highly qualified patients and dosing management was still managed by the clinic, even though testing was done by the patient. The authors, led by David Matchar, M.D., director of the Center for Clinical Health Policy Research at Duke University (Durham, N.C.), made the guarded recommendation that self-testing should "be considered for patients whose access to high-quality anti-coagulation care is limited by disability, geographic distance, or other factors."

"In no other place in medicine does a basically healthy person have to come in every four to six weeks for testing. . . . Patients can do [self-anticoagulation monitoring] safely, but you have to choose the right patients. Not all patients can do it."
–Hanna Bloomfield, M.D., University of Minnesota School of Medicine

But a study published in January 2012 in *Lancet* found that patient anti-coagulant monitoring and dosing managed by patients at home is safe and does significantly decrease clotting risk. Thromboembolic events were nearly halved by self-monitoring with even greater benefits in patients younger than 55 years of age. The authors, led by Carl Heneghan, Ph.D., of Oxford University (United Kingdom), wrote that the results "will lead to a systematic change in practice" and that "patients should be offered the option to self-manage their disease with suitable healthcare support as back-up."

But not all clinicians agree. In an accompanying editorial in the same issue of *Lancet*, Paul Alexander Kyrle, M.D., and Sabine Eichinger, M.D., both of the Medical University of Vienna, only agreed that self-management should be offered to young, mechanical heart valve patients, but wrote that they "do not see a place for self-monitoring in other areas of this treatment except for individual patients for whom access to routine usual anti-coagulation care is restricted."

"I think it is getting to a tipping point. Patients can do this safely, but you have to choose the right patients. Not all patients can do it," Bloomfield tells *DTTR*. "It is a huge patient convenience but cost is the bigger issue. The strips are very expensive."

Bloomfield adds though, that just as this testing is catching on, it faces a challenge from new drugs in clinical trials that don't require monitoring. "This might blow up. If newer therapeutic agents are proven safe, warfarin might be done or a second-line drug," Bloomfield says.

While Not Final, Proposed 2013 Federal Budget Could Spare Tool Makers

When President Obama unveiled his proposed fiscal year 2013 budget on Feb. 13, tool makers breathed a temporary sigh of relief as he announced flat funding for the National Institutes of Health (NIH), with a requested budget of $30.86 billion for the agency, the same as in 2012. While this proposal in no way guarantees what the final funding will resemble, analysts quickly touted this proposal as good news for life science tool makers, who are dependent upon academic and research funding for their grants.

Life Technologies (Carlsbad, Calif.) and Illumina (San Diego) are two companies particularly sensitive to constraints on academic spending. Analysts say about 80 percent of Illumina's revenues come from academic and government researchers as do about 45 percent of Life Technology's revenues. Uncertainty over NIH's budget during the budget debate in late 2011 led to declines in instrument purchases in the second half of 2011 and sharp declines in both companies' stock values. While the proposed budget brings hope for tool makers, the failure of the Joint Select Committee on Deficit Reduction (the so-called "super committee") in 2011 to come up with $1.2 trillion in budget savings keeps automatic, across-the-board 8 percent cuts as a "potential issue," analysts say.

"The request preserves NIH's highest priority activities within overall budgetary constraints," the agency said in a statement. "One of the current priorities in NIH basic research is to capitalize further on the revolution in genome sequencing."

Among Obama's NIH requests in his budget is a reduction of $1 million to the National Human Genome Research Institute to $511 million, which reflects the drop in the cost of sequencing. There is a requested increase of $3 million for the National Cancer Institute, whose budget could reach $5.1 billion. The budget also includes a proposed 11 percent increase in funding (to $639 million) for the recently established National Center for Advancing Translational Sciences (NCATS), which funds the development of new diagnostic tools and technology. The budget, experts say, reflects a slight shift toward translational science.

NIH says 54 percent of its budget is in basic research with 46 percent devoted to applied research. In an attempt to address the "exceedingly complex, costly, and risk-laden endeavor" of translating basic research into clinical applications, the NIH is pursuing efforts to streamline and shorten the pathway from laboratory discovery to clinical application through the establishment of the NCATS, the forging of public-private partnerships to hasten commercial development pipeline, and the creation of a network of health care delivery organizations to conduct research that will quicken the translation of research results to "real-world" health practice.

In its budget report the NIH acknowledges the importance of emphasizing sequencing technologies given that China is assuming the leading position in genomic sequencing. With its recent purchase of 128 highly advanced genome sequencers, the Beijing Genomics Institute alone now has more DNA sequencing capacity than all of the NIH-supported genome centers combined, the agency says.

New Blood Test Offers Hope for Early Diagnosis of Parkinson's Disease

Phosphorylated α-synuclein (α –syn) can be detected in blood plasma and is potentially a useful biomarker for Parkinson's disease (PD), according to a study published in the December issue of the *Journal of the Federation of American Societies for Experimental Biology*. The researchers say that if future larger studies confirm the utility of the biomarker, the test can be used for early diagnosis of presymptomatic Parkinson's and may have potential to monitor disease progression.

Immunoassays for total and oligomeric (oligo-) forms of both normal and phosphorylated (phospho-) α –syn were used to test plasma samples from a longitudinal cohort of 32 patients with PD sampled at baseline and then sampled monthly for three months, as well as single plasma samples from a group of 30 healthy control participants. The researchers designed individual sandwich immunoassays that can distinguish between total α –syn, oligo- α –syn, pS- α –syn, and oligo-pS- α –syn (pS129 capture and detect). The assays for oligomeric forms of α –syn use a double-antibody approach, where the same monoclonal antibody is used for both antigen capture and detection.

The levels of α –syn in plasma varied greatly between individuals but were consistent over time within the same individual with PD. The mean level of phospho- α –syn was found to be marginally significantly higher in the PD samples than in the controls, but there was no significant difference between the PD group and controls for total α –syn, oligo- α –syn, or oligo-phospho- α –syn. Phospho- α –syn can be detected in blood plasma and shows more promise as a diagnostic marker than the nonphosphorylated protein. Longitudinal studies undertaken over a more extended period will be required to determine whether α –syn can act as a marker of disease progression, the researchers say.

"Our ultimate aim is to develop a relatively simple test for the early diagnosis of PD, or a surrogate marker for monitoring the progression of PD," writes study author David Allsop, Ph.D., professor of neuroscience at Lancaster University in the United Kingdom.

High Cadmium and Lead Blood Levels Lead to Pregnancy Delay

High blood levels of heavy metals (cadmium and lead) are significantly linked to a delayed ability for couples to conceive, according to a study published online Feb. 4 in *Chemosphere*. If the findings are validated by additional research, examination of exposure to heavy metals may play a role in the search for causes of infertility.

The researchers assessed 501 couples who were attempting to get pregnant in both Michigan and Texas from 2005 to 2009. Recruited couples completed interviews and provided blood specimens for the quantification of cadmium (μg L^{-1}), lead (μg dL^{-1}), and mercury (μg L^{-1}) using inductively coupled plasma-mass spectrometry. When assessing partners' exposures separately and adjusting for other variables, female cadmium exposure was associated with approximately a 22 percent reduction and male lead exposure with approximately a 15 percent reduction in the odds of conception per standard deviation increase of blood concentrations. When jointly modeling couples' exposures, only male lead concentration significantly reduced the odds of pregnancy (0.82), though the odds remained less than one for female cadmium (0.80).

"The findings highlight the importance of assessing couples' exposure jointly, in a single, combined measure," said Germaine M. Buck Louis, Ph.D., director of the Division of

Epidemiology, Statistics, and Prevention Research at the National Institute of Child Health and Human Development. "Males matter, because couples' chances of becoming pregnant each cycle were reduced with increasing blood lead concentrations in men."

Cigarette smoke is the most common source of exposure to cadmium with smokers estimated to have twice the levels of cadmium of nonsmokers. Louis says that before heavy metals testing should be translated into clinical guidance or practice, additional research needs to be completed.

Biomarker Profile Differs Between Primary and Recurrent Ovarian Tumors

Recurrent ovarian cancer tumors have different protein expression profiles of drug targets and candidate drug response markers from the patient's corresponding primary tumor or from prior recurrences. These differences may be sufficiently large as to impact selection of therapy and, according to a pilot study published in the February issue of *Molecular Cancer Therapeutics*, suggest the need to analyze tumor specimens at the time of ovarian cancer recurrence.

The researchers analyzed the tumor samples of 168 patients with advanced-stage ovarian cancer for expression of 18 biomarkers by immunohistochemical analyses at Clinical Laboratory Improvement Amendments-certified laboratories. Analysis of 56 primary and 50 recurrent tumors showed that P-glycoprotein (PGP) and excision repair complementation group 1 (ERCC1) were significantly upregulated in recurrent lesions. But when the researchers analyzed 43 matched tumor specimens from 19 patients, immunohisotchemical analysis confirmed the overexpression PGP and ERCC1 observed in the cohort analysis but revealed that the expression levels of breast cancer resistance protein, ribonucleotide reductase regulatory subunit M1, and cyclooxygenase-2 were discordant in more than 40 percent of the matched tumor specimens.

"These results demonstrate the dynamic genetic changes in ovarian cancers between diagnosis and recurrence. While the expression of these and other candidate response biomarkers should be evaluated in larger studies to better understand the clinical utility of profiling recurrent tumor specimens, this report highlights our urgent need to individualize our treatment approaches in order to improve ovarian cancer survival," said co-author Beth Karlan, M.D., director of the Cedars-Sinai Women's Cancer Program (Los Angeles), in a statement.

The authors suggest that the results may have implications both for the use of biomarkers in therapy selection as well as for future biomarkers discovery and validation.

"Expression of these and other candidate response biomarkers must be evaluated in much larger studies and, if confirmed, support the need for profiling of recurrent tumor specimens in future clinical trials," write the authors.

G2 Index Mixed, Ends Down 1%

The G2 Diagnostic Stock Index was mixed for the period but closed the four weeks ending March 9 down 1 percent. Eight stocks were up for the period, four stocks were unchanged, and five stocks declined. The Nasdaq and the S&P were both up modestly over the same period, gaining 3 percent and 2 percent, respectively.

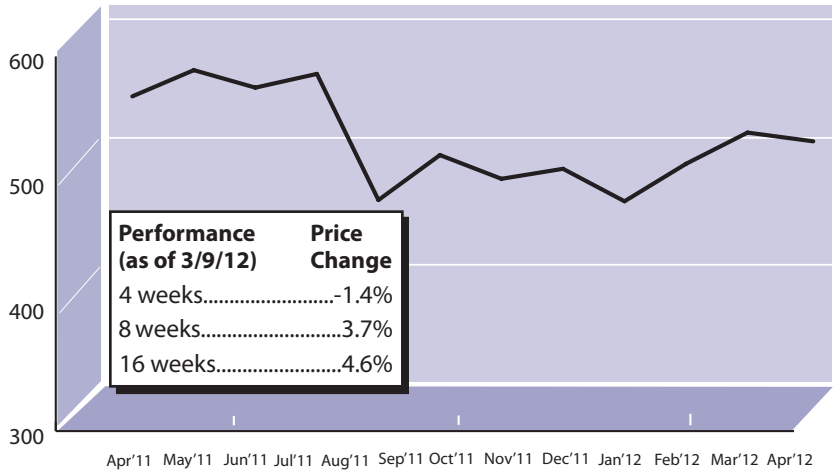
Among the stocks gaining ground was **IRIS International** (Chatsworth, Calif.), which reported full-year 2011 financial results. Its stock rose 13 percent this period on news that its 2011 year-end revenue of $118.3 million beat analysts' expectations. The full-year revenues were pushed higher by IRIS's diagnostics division, which increased sales by 11 percent over 2010 and by a record number of instrument placements and related consumable sales. The company says it expects its consumables to continue to grow "at double digit rates" and reaffirmed its 2012 guidance of revenues in a range from $127 million to $131 million (a 7 percent to 11 percent increase over 2011) and earnings per share of 30 cents to 35 cents.

Another stock up this period was **Quidel** (San Diego), which gained 10 percent. The company reported "terrific" financial results for the full year of 2011, with total revenues growing 40 percent to $158.6 million from $113.3 million in 2010. The revenue increase was primarily driven, the company says, by a 53 percent increase in sales of infectious disease products over 2010, a light flu year. Among the 17 products currently in development, five are Sofia assays, based on the company's next-generation fluorescent immunoassay analyzer system, Sofia, which received Food and Drug Administration clearance for analyzer as well as the Sofia Influenza A+B Fluorescent Immunoassay in the fourth quarter 2011.

Correction – In the March issue of *DTTR* Qiagen's stock price should have been listed as $15.15, a 0 percent change from the previous period.

Illumina (San Diego) was one of the companies whose stock performance dragged the G2 Index down this period. Despite its early March announcement of the launch of its TruSeq Amplicon—Cancer Panel, a highly multiplexed panel that allows researchers to sequence hundreds of cancer loci simultaneously, Illumina's stock declined 7 percent in part over the ensuing stalemate with Roche (Basal, Switzerland) over its attempted takeover of Illumina.

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 17 IVD companies.

Up	Price	% Chg
Abbott Labs	57.95	5%
Alere	26.01	1
Becton Dickinson	76.82	1
Bio-Rad	103.82	1
Cepheid	42.78	1
IRIS	11.71	13
Luminex	22.69	8
Quidel	16.14	10
Unchanged		
Abaxis	27.41	0%
Johnson & Johnson	64.74	0
Meridian	17.93	0
Qiagen	15.08	0
Down		
Affymetrix	4.21	-9%
Gen-Probe	66.94	-3
Illumina	50.12	-7
OraSure	9.48	-9
Sequenom	4.18	-9

G2 Insider

Chloride: An Undervalued Marker of Potential Mortality in Critically Ill. . . Every single standard chemistry panel run on critically ill patients in hospitals every day includes evaluation of chloride. Chloride levels are frequently abnormal in critically ill patients, resulting from either underlying conditions or as a consequence of fluid therapy, yet its values are widely ignored, even though new research suggests it may be an important predictor of mortality.

"We basically ignore chloride. Nobody thinks much about it," says Kenneth Christopher, M.D., of Brigham and Women's Hospital in Boston. "Hypochloremia, there is basically nothing out there on it. Low chloride has never been evaluated and this shines light into that evidence gap."

Calling it an "underappreciated and understudied" electrolyte, Christopher undertook a study to evaluate the association between chloride levels and mortality in a database of more than 50,000 critically ill patients treated between 1998 and 2009. Categorizing chloride levels into deciles (≤98mEq/L, 99-101, 102-103, 104, 105, 106, 107-108, 109, 110-111, or ≥112), Christopher found that after adjusting for sodium, hypochloremia—but not hyperchloremia—is a robust predictor of increased risk of all-cause patient mortality in the critically ill. He presented these findings at the Society for Critical Care Medicine's annual meeting (Feb. 4-8 in Houston). When adjusting for sodium levels, compared to patients with chloride values of 107-108, patients with chloride values less than 98 carried a 66 percent increased risk of dying in the 30 days following critical care.

"When you adjust for sodium, only low chloride is associated with mortality, which tells me that hyperchloridea has more to do with sodium, and chloride basically goes along with it," says Christopher. "[Conditions associated with abnormal chloride levels] are all present in sick patients, so it is a very complicated interaction with significant comorbidity. Elucidating the mechanism is challenging. Low chloride is probably not a warning sign in that you probably already know the patient is sick. But if chloride levels are low [in a sick person] it is a robust, independent predictor of increased risk of adverse outcomes."

Company References

Affymetrix 408-731-5000

American College of Physicians 215-351-2400

Complete Genomics 650-943-2800

Illumina 800-809-4566

IRIS International 818-527-7000

Life Technologies 760-603-7200

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