G2 INTELLIGENCE

Diagnostic Testing & Technology Report

Competitive Intelligence & Analysis for an Expanding Global Market

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CONTENTS

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Grants Aid Labs in Transition to NGS Clinical Testing

GenomeQuest Inc. (Westborough, Mass.) is providing software and services grants to six laboratories to aid in the transition from multiple Sanger-based gene tests to consolidated next-generation sequencing (NGS)-based tests for diagnosis of a wide variety of conditions.

"Lab directors are recognizing the enormous opportunity to improve patient care by screening larger and larger regions of the genome while simultaneously lowering costs and turn-around times with next generation sequencing. This program supports GenomeQuest's commitment to empowering laboratories with the knowledge-base and interpretation tools they need to bring new NGS-based diagnostics to the clinic," said GenomeQuest CEO Richard Resnick in a statement. "The six grant recipients were selected from a competitive field of applicants based on their clear, actionable vision for utilizing NGS-based diagnostics in the clinic."

GenomeQuest will provide the software, annotation data, and the infrastructure required to process and store NGS data and produce diagnostic reports. The grants, totaling $120,000, were announced in early January and went to Cincinnati Children's Hospital Medical Center (Cincinnati), University of Medicine & Dentistry of New Jersey (Newark), Nationwide Children's Hospital (Columbus, Ohio), University of Massachusetts Medical School (Worcester, Mass.), University of Minnesota Medical School (Minneapolis), and University of Nebraska Medical Center (Omaha).

For more on the transition of NGS technology into clinical practice, please see the special focus section starting on page 8.

Layoffs, Restructuring Capped Off Difficult Year for Tools Companies; Stabilization Expected in Coming Year

In response to falling revenues and poorer than expected financial performance, there was a rash of layoff and restructuring announcements at the end of 2011, particularly among the battered diagnostic tools sector. WaferGen (Fremont, Calif.), Illumina (San Diego), and Pacific Biosciences (Menlo Park, Calif.) were among nearly a dozen companies in the diagnostics field ending the year by reducing head counts and expenses. Experts say that while macroeconomic uncertainties compounded company-specific challenges, the industry should stabilize during 2012.

"A lot of the restructuring was company-specific, made worse by the funding situation," says Amanda Murphy, an analyst at William Blair & Co. (Chicago). "The restructuring has probably settled out. There may still be a one-off case."

Continued on p. 2

▲ **Layoffs, Restructuring Capped Off Difficult Year,** *from page 1*

The restructuring afforded companies a way to rectify internal missteps including over-optimistic estimates of instrument placements and inflated hopes of market demand.

"For Pac-Bio it was a strategic misstep," says Peter Lawson, Ph.D., executive director and senior equity analyst at Mizuho Securities USA (New York). "They built up too fast for a product in its infancy and some doubt the position of that product in the market." Pac-Bio recently introduced a third-generation DNA sequencing system that incorporates single molecule sequencing.

Analysts reacted favorably to restructuring announcements, particularly in the case of Illumina, where they expect community demand to catch up with the company's excess capacity.

"Illumina was exposed to spending cuts, but the capabilities of sequencing increased so much and they kept upgrading their machines, they frankly misjudged the community demand," explains Murphy. "Going forward funding is still volatile, but we are at the peak of uncertainty right now for 2013 [funding]. We have a positive outlook [for this year]. Both the uncertainty and Illumina's capacity issue should resolve itself over time."

But, Lawson says, while investor expectations and company guidance account for known uncertainties like funding, utilization, and reimbursement issues, few have taken into account the potential impact the 2.3 percent medical device fee (scheduled to take effect in 2013) will have on the diagnostic industry. While Lawson says the impact will be "modest" among diagnostic companies compared to companies in the med tech industry, the fee has not been adequately addressed. Hope for a repeal of the fee, uncertainty over the constitutionality of the larger health care reform bill, and a lack of understanding over which elements are included in the fee (Food and Drug Administration-approved tests) and not included (non-FDA approved products like analyte-specific reagents and laboratory-developed tests) may contribute to the current failure to incorporate the calculation of the fee into company estimates.

In a Jan. 9 research note, Lawson writes that the fee needs to be accounted for in 2013 estimates, and in Mizuho's assessment Cepheid (Sunnyvale, Calif.), Alere (Waltham, Mass.), and Gen-Probe (San Diego) have the greatest exposure among diagnostic companies. The analysts believe share repurchases, price increases, and possibly restructuring initiatives will be needed to counter the impact of the fees.

Sampling of Fall 2011 Restructuring Announcements

WaferGen (Nov. 21, 2011)—As part of a revised commercialization plan for its SmartChip Real-Time PCR System the company cut 24 percent of its workforce. The restructuring was expected to result in a $1.3 million savings in operating expenses and the company took a one-time $400,000 charge related to the job cuts in the fourth quarter of 2011.

Illumina (Oct. 25, 2011)—Responding to uncertainties associated with academic and government research funding, the company eliminated 200 jobs, about 8 percent of its workforce. The restructuring charges of $15 million to $17 million were expected to be recorded in the fourth quarter of fiscal 2011.

Pacific Biosciences (Sept. 20, 2011)—Citing economic uncertainties the company announced a 28 percent reduction of its total workforce, with heaviest impact on the operations and research and development divisions. The company expected to incur $5.2 million in restructuring charges, mainly in the form of compensation and benefits to terminated employees.

Breath Test Successful in Differentiating Lung Cancer

A noninvasive breath test can tell not only if the sample breath came from a cancerous lung, but it can differentiate what specific type of cancer is present. Once commercialized, the test could revolutionize lung cancer screening and diagnosis.

The test, employing electronic nose technology developed at Technion University in Haifa, Israel, uses an array of gold nanoparticle sensors in conjunction with pattern recognition software. According to a proof-of-concept study published online in *Nanomedicine*, the device was able to classify lung cancer histology by significantly discriminating between cancerous and healthy cells, small cell and non-small cell lung cancer (NSCLC), and between two subtypes of NSCLC—adenocarcinoma and squamous cell carcinoma. While the study used in vitro samples, the researchers will soon publish results of a study demonstrating the successful application of this technology to exhaled breath samples.

"The data is very encouraging; however we have to emphasize this is in the early stages of development and we are not expecting to go to the commercial market tomorrow," says co-author Fred R. Hirsch, M.D., Ph.D., a professor of pathology at the University of Colorado Cancer Center in Denver. "This technology lends itself to a noninvasive approach. You can almost imagine standing in a grocery store giving a sample."

Results from the National Lung Cancer Screening Trial on more than 50,000 people demonstrated that employing low-dose computed tomography (CT) scans for lung cancer screening can reduce mortality rates by 20 percent. But the approach yields high rates of false positives with 95 percent of positive scans actually revealing noncancerous nodules, which unnecessarily subjects patients to invasive biopsy procedures.

Researchers are hopeful that this breath test could provide a cost-effective, noninvasive compliment to CT scans—to identify which patients do need a biopsy and could possibly expand screening in high-risk populations. A future test may have a hierarchical order with the first phase intended for screening purposes and then, subsequently, delivering a differential diagnosis in lung cancer-positive subjects by distinguishing between the most prevalent histological lung cancer types.

Hirsch says when the product is commercialized he expects it to be "relatively cheap," costing less than a biopsy or spinal CT. G2

New Staining-Based Test Could Aid in Identification of GI Conditions

Researchers have discovered that two staining-based tests—for major basic protein (MBP) and eotaxin-3—can help clinicians distinguish between two gastrointestinal conditions, eosinophilic esophagitis (EoE) and gastroesophageal reflux disease (GERD), which can have overlapping clinical symptoms and shared endoscopy and biopsy findings. The early results, which were presented at the American College of Gastroenterology annual meeting (Washington, D.C., Oct. 28–Nov. 2), demonstrate the potential clinical utility of the tests.

The investigators examined 51 patients with EoE and 55 GERD patients with inflammation including eosinophils on biopsy. Immunohistochemistry was performed for MBP and eotaxin-3, known markers of eosinophil activation and migration. The mean eosinophil count was higher in EoE patients compared to GERD patients (143 eos/hdf

versus 20 eos/hdf). Patients with EoE also had significantly higher levels of MBP and eotaxin-3 staining in the esophageal epithelium compared with GERD patients.

"Staining with MBP and eotaxin-3 provides added diagnostic value beyond eosinophil counts alone, and MBP staining in particular may have utility as a diagnostic assay for EoE," writes lead author Evan Dellon, M.D., assistant professor of medicine at the University of North Carolina in Chapel Hill, in the abstract presented at the conference.

Dellon says the performance of the stains as a diagnostic test needs to be prospectively validated before they can be used in routine clinical practice, but he says they do show promise for the future.

Improved Tn1 Assay and Novel Cardiac Marker to Speed MI Diagnosis

Two new tests being developed to improve diagnosis of heart attacks—one using a highly sensitive troponin I (hsTnI) assay and the other using a novel marker, cardiac myosin binding protein-C (cMyBP-C)—may improve the speed with which a definitive myocardial infarction (MI) diagnosis can be made.

Researchers from the University Heart Center Hamburg in Germany evaluated the diagnostic performance of the hsTnI assay and currently used troponin assays (cTnI) in a study published Dec. 28 in the *Journal of the American Medical Association* that involved 1,818 patients with suspected heart attack or angina. The cTnI and hTnI assays were both superior to the 10 other cardiac biomarkers evaluated. The hsTnI, the next-generation Architect STAT High Sensitive Troponin I assay (Abbott Diagnostics), could detect troponin at lower levels than the cTnI (3.4 pg/mL versus 10 pg/mL). Using the 99th percentile cutoff of 32 pg/mL, hsTnI on admission had a sensitivity of 82.3 percent and negative predictive value (NPV) of 94.7 percent. After three hours hsTnI had a sensitivity of 98.2 percent with NPV of 99.4 percent. Compared with hsTnI, the cTnI assay had comparable sensitivity and NPV.

"Combining the 99th percentile cutoff at admission with the serial change in troponin concentration within 3 hours, the positive predictive value (for ruling in acute myocardial infarction) for hsTnI increased from 75.1 percent at admission to 95.8 percent after 3 hours, and for cTnl increased from 80.9 percent at admission to 96.1 percent after 3 hours," the authors write. The difference between the two assays was nonsignificant.

While worldwide guidelines utilize troponins as the preferred biomarkers to diagnose MI, not all acute MI patients will have elevated troponin levels within three hours of onset of chest pain. Researchers have identified another biomarker released into the blood post-MI that has twofold higher plasma levels than the gold-standard of TnI. With higher plasma concentrations of cMyBP-C, there is a greater chance of achieving 99th percentile separation at an earlier time, increasing both the sensitivity and specificity necessary to detect non-ST elevation MIs, says Sakthivel Sadayappan, Ph.D., an assistant professor of physiology at Loyola University Chicago.

In pilot studies Sadayappan's group reported in the *Journal of Molecular and Cellular Cardiology* that cMyBP-C can be detected within 30 minutes of ischemia in a rat model. While the biomarker appears to be "robust," Sadayappan says the time of release, half-life, peak concentration, and association with MI severity still need to be studied before the biomarker could be used clinically to diagnose heart attacks.

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Inside the Diagnostics Industry

New Technology and Market Differentiation Key to Growth at Bio-Reference Laboratories

Marc Grodman, M.D., founder and CEO, Bio-Reference

Few companies can claim they have achieved 20 percent compound annual growth for 18 consecutive years. Bio-Reference Laboratories Inc. (Elmwood Park, N.J.), is planning on extending that record for a 19th year in 2012 through a strategy focused on providing differentiating service in specialty markets.

By most metrics, 2011 was a dazzling year for Bio-Reference with annual increases in patient volume, company revenue, and net income. The company ended its 2011 fiscal year with $559 million in revenue, up 22 percent over fiscal year 2010, and despite industrywide utilization concerns, Bio-Reference saw an increase in the number of patients served in 2011, servicing 6.7 million, up 20 percent from 5.6 million the previous fiscal year.

Marc Grodman, M.D., founder and CEO of Bio-Reference, recently spoke to *DTTR* about how the company manages to sustain such growth organically, the company's pipeline of specialized tests, and the future of the clinical laboratory industry.

How do you account for Bio Reference's continued track record of growth and what specifically made 2011 a great year for the company?

The clinical diagnostic market is comprised by multiple smaller markets that are defined by specialty, by region, by type of payer, type of physician or physician group or customer or client. What Bio-Reference has tried to do is to go look at ourself in the scope of the submarkets and where we can go in and be differentiating. This is what we have done over the years.

We are a regional laboratory that has grown in capabilities and footprint, infrastructure, and insurance contracts in the regional market. But at the same time we are a national women's health laboratory that provides differentiating services with a dedicated sales group that live and breathe selling women's health services to ob/gyns. We are a national oncology laboratory that sells what we think is the latest in cancer diagnostics.

We invest in new technologies to differentiate our services at all times. We have a state-of-the-art genetics laboratory, GeneDx, which while platform agnostic, provides more types of genetic diagnoses and testing than quite frankly any laboratory in the world. The resources and intelligence we gain from one area feeds the other. The capabilities we build for one helps all parts. We are absolutely geared to be able to grow the business. It is not by chance that it has been 18 years of [cumulative annual growth]. We have created new markets and created new business because we constantly go in and try to make the market smaller and therefore find the elements that will allow us to be differentiating.

Esoteric testing has been a driver of Bio-Reference's growth. How will you continue to grow esoteric testing as a percentage of total revenue?

By nature once you are in a specialty market, of course, more of the work you do will be considered esoteric. The high esoteric number as it relates to a percentage

of our overall business is the result of the strategy. It is not the end-all. It is reflective of what our business has been, which is to grow in specialty markets.

Part of the value we have is the fact that when we work in these areas we not only are able to do the esoteric work, but we can do the routine work as well for specialty clients. So it is not just the testing, it is the market. The value of the laboratory market is that we can go in and be full-service. The key isn't to do specialty work, but everything there. It is hard to survive in a doctor's office when you only do one test. What can we provide that is specialty, not because it represents a huge profit, but because it will convince the doctor to use us for all of his services?

Do you believe growth in testing volume can be sustained in 2012? Also, what is the outlook for increasing testing volume throughout the industry in 2012?

Bio-Reference Laboratories by the Numbers

Year founded: 1986

3,000 employees

25 million tests run annually

$559 million in revenue for FY 2011

15 percent expected revenue growth for FY 2012

Given our track record I don't think I am going out on an extreme limb. I've said that we will do 15 percent growth. This is routine guidance we give every year based on our capabilities. The battle we fight every year is a larger denominator.

The opportunities that we have [as an industry] from a technical point of view are tremendous. How will the laboratory industry do? We have great value to provide—answers to questions that are out there. We also have real pressures—pricing pressures, utilization pressures. . . . In the coming year we have the opportunity as an industry to grow, but we have to provide more value for the dollars.

The company has previously announced several new diagnostic initiatives planned for 2012. Can you please apprise us of the progress on the InheriGene and OnkoMatch programs?

There are two initiatives that we think are important. OnkoMatch is a joint collaboration with Massachusetts General Hospital where we are going to be offering solid tumor genotyping—the ability to go in and look at different oncogenes and see if the samples are positive for these. It is more than doing testing for testing itself. There are so many clinical trials that are available now for many types of cancers, but by and large nobody knows if they are candidates. OnkoMatch is really the commercialization of a program that has been carried out at MGH over the last three years. . . . However, we can do this more efficiently than has been done in the past. We are going to provide all this extra information for the same cost as what it would be to test a handful of oncogenes themselves . . . more technology, more answers that can be actionable for less money.

Another new program we are doing is InheriGen, a pan-ethnic carrier screen. Right now there are a lot of tests being conducted on people for carrier screening. What conditions would you like to know before baby is born? Part of this is normal practice like cystic fibrosis, Fragile X. There are some other tests, most

of them known as Ashkenazi Jewish tests. We have come up with a way of not looking for eight or 16 carrier tests but over 160 of these carrier conditions. Those conditions can represent up to 600 mutations that we will be looking for and we will be doing this at basically the cost of what an Ashkenazi Jewish panel would normally be. . . . This is something we will introduce a little later in winter or early spring and will be sold by our women's health sales force in collaboration with their other women's health testing.

Given both macroeconomic challenges and uncertainties in the health care industry, what are you looking for in 2012 as signs of well-being in the clinical laboratory and diagnostic testing industries?

There are certain basic [signs] we have to look for. We have to be cognizant of Medicare reimbursement.

> ***"I think the industry needs two things: price and competition. If the price can drop, but we can still compete for the business, then I think all parties will find a level in which they can survive. The part I am most concerned about is the effort to lower price and limit competition, meaning insurance companies can have exclusive relationships that won't even let the local laboratory compete for the nursing home business."***
>
> ***–Marc Grodman, M.D.***

One of the other things we look at is the ability of insurers to go in and negotiate not only for good price but for good service. We think a healthy sign of the industry is open contracts, where all laboratories, if they meet requisite standards—licensure and the ability to provide electronic data—can participate in all plans. I think the industry needs two things: price and competition. If the price can drop, but we can still compete for the business, then I think all parties will find a level in which they can survive. The part I am most concerned about is the effort to lower price and limit competition, meaning insurance companies can have exclusive relationships that won't even let the local laboratory compete for the nursing home business. That is, I think, the greatest threat to our business.

How do you see the clinical laboratory industry evolving in the next five years?

Quite frankly I think we are all going to be part of larger companies. The asset for the clinical laboratory is much greater than sum of its parts. We provide consistent contact with physicians, we have consistent access to his desktop, and we are absolutely integrated into therapeutics and care. You cannot have an [electronic medical record] without a lab interface. You can't have decision support models without laboratory data. You can't have any type of pay for performance or evaluation of care without laboratory data. More importantly, only clinical laboratories can deal with the ongoing complexities and rapid advances in genetic testing.

These are incredible assets and somehow they are being mired under even what some of our own want to present as just a commodity of care. We are more than a commodity of care. It may take other kinds of entities to unlock the true value. Laboratories are information companies and there is a lot of information that we need to manage care in the future years.

Sequencing Technology Rapidly Expanding Into Clinical Care

With the recent announcement that the $1,000 genome has been achieved, there is renewed optimism that there will be an explosion of clinical applications for sequencing-based testing. 2011 and 2012 are characterized as pivotal years in the transition of genome sequencing from the domain of the researcher to the world of the clinician. With advancements in sequencing platforms, strategic government and institutional commitment to bioinformatic investment, and improving interpretation of variations of clinical significance, early targeted sequencing applications are expected to give way to more widespread adoption of broader sequencing platforms.

"In some settings there are ethical or regulatory questions, but it is not a question of when or if—sequencing applications are already in practice and there is no way to stop their rapid expansion," says David Ledbetter, Ph.D., chief scientific officer, Geisinger Health System (Danville, Pa.).

Much of the early focus of clinical sequencing has been focused in the field of oncology where sequencing-based tests aid in personalizing medicine by matching mutations in the patient's tumor to drugs that target those mutations. Next-generation sequencing (NGS) technology is also enabling more rapid identification of infectious disease pathogens including those responsible for costly and even deadly hospital-acquired infections, like methicillin-resistant staphylococcus aureus or MRSA. But sequencing-based testing is expected to penetrate every clinical discipline and eventually will become so commonplace that an individual's entire genome could be routinely sequenced at birth with the raw data becoming part of their permanent medical record.

Evolution of Clinical Sequencing

Several labs were early groundbreakers in offering NGS-based tests as a clinical service. In 2008 GeneDx (Gaithersburg, Md.), a subsidiary of Bio-Reference Laboratories, became the first lab in the United States, it says, to offer clinical NGS-based services with a test for cardiomyopathy. In 2010 the Emory Genetics Laboratory (Atlanta) became the first academic laboratory to offer NGS-based clinical services with the introduction of three multigene panels: the X-Linked Intellectual Disability panel (92 genes), the Congenital Muscular Dystrophy panel (13 genes), and the Congenital Disorders of Glycosylation panel (24 genes).

Now, as the cost of sequencing plummets, labs are finding it more cost-effective to consolidate multiple individual Sanger-based gene panel tests into a single NGS test. Until recently scientists at the University of Iowa had to individually sequence up to 66 genes to make a diagnosis of genetic hearing loss. Now the comprehensive OtoSCOPE test screens in parallel all known genes associated with inherited deafness and uses GenomeQuest's (Westborough, Mass.) GQ-Dx clinical decision-support system for whole- and partial-genome diagnostics to compare a patient's DNA with the human reference genome for known hearing loss mutations. This advance will reduce the total cost of a molecular diagnosis from $75,000 to under $2,000 and will give a clinically relevant, genetic diagnosis of a patient's specific cause of deafness in less than three months, rather than one year using the individual Sanger sequencing method.

Efforts like those in the University of Iowa's Molecular Otolaryngology and Renal Research Laboratory are expected to play out in laboratories across the nation given the enhanced strategic attention government and institutional players are giving to translating sequencing into clinical practice.

A Changing Strategic Outlook

The federal government is undertaking strategic initiatives to help accelerate sequencing's foray into clinical practice. In keeping with its 10-year strategic plan published in February 2011, the National Institutes of Health's National Human Genome Research Initiative said in January it plans to undertake a broad restructuring plan to organize the institute around its strategic domains of research activities. The reorganization will expand the institute's structure from two divisions to six, including the Division of Genomics Medicine, which would lead the institute's efforts to advance genomic technologies and clinical applications and care.

Nongovernmental efforts are under way to expand collaboration and pool sequencing data to facilitate more rapid discovery of variations of clinical significance. Efforts include expansion of the International Standards for Cytogenomic Arrays (ISCA) Consortium to include sequencing data. The ISCA Consortium was established in 2007 with the goals of standardizing genotype and phenotype data and creating a publicly available database through the National Center for Biotechnology Infor-

Recent Advancements in Sequencing Technology Unveiled at the J.P. Morgan Healthcare Conference

Life Technologies (Jan. 10) introduced the Benchtop Ion Proton sequencer. It is designed to sequence the entire human genome in a day for a cost of $1,000 and is based on semiconductor sequencing technology. The Ion Proton I Chip, ideal for sequencing exomes, will be available mid-2012 and the Ion Proton II Chip, ideal for sequencing whole human genomes, will be available about six months later. The machine is priced at $149,000. Life Technologies reiterated that it will seek U.S. Food and Drug Administration (FDA) approval for the Ion PGM (personal genome machine) platform later this year.

Illumina (Jan. 10) introduced an upgrade to its NGS, HiSeq system that will enable researchers and clinicians to sequence an entire genome in approximately 24 hours. It is able to sequence 20 exomes in a day and 30 RNA-seq samples in five hours. Illumina expects to begin full commercial shipment of the HiSeq 2500 in the second half of 2012. It is reported to cost $740,000 or $50,000 for an upgrade from the HiSeq 2000. Illumina also said it plans to seek FDA clearance this year for its MiSeq sequencing platform.

Complete Genomics (Jan. 11) announced the signing of a third order from the Institute for Systems Biology (Seattle) for the sequencing of an additional 615 genomes for research into neurodegenerative diseases. A few days earlier Complete Genomics announced that it had delivered 3,000 sequenced whole genomes in 2011, slightly off from earlier company expectations. The company's lab expansion will improve the company's capacity to handle the 5,800 genomes on order.

mation for the research and clinical communities. The database now includes more than 150 cytogenetics and molecular genetics laboratories and will soon have more than 50,000 cases. Through access to shared data generated from routine clinical use and research, an understanding of what variation is pathogenic versus benign can be accelerated. The founders of the ISCA Consortium are applying for grants and facilitating dialogue with sequencing experts so that their model, which facilitated acceptance of cytogenomic arrays, can be applied to NGS technology.

Drastic Improvements in Instrumentation Pushing Clinical Sequencing

Above all, technological improvements in the speed and power of sequencing instruments, coupled with their declining cost, will continue to make clinical applications of the technology more appealing for labs from both a time savings and financial perspective.

"The ability to sequence an entire genome in a day . . . will enable new opportunities for researchers to develop medically relevant whole-genome applications," said Jay Flatley, CEO of sequencing equipment maker Illumina (San Diego), in a statement.

> ***"I hope clinicians won't use [sequencing] as a first-line test. It is like using an atom bomb to kill an ant. I hope clinicians won't use it to cover ignorance and generate more laziness."***
>
> ***—Sherri Bale, Ph.D., GeneDx***

Under Moore's Law, computing power and affordability have predictably doubled every two years. DNA sequencing is outstripping that pace. The last five years have seen exponential leaps forward in speed and exponential reductions in cost. At the J.P. Morgan Healthcare Conference (San Francisco; Jan. 9-12, 2012) competitors Illumina and Life Technologies (Carlsbad, Calif.) both introduced instruments capable of sequencing a genome in a day for costs nearing the anticipated $1,000 mark. That price tag is expected to continue to drop to the point that it will be cheaper to sequence an entire genome than to examine individual genes. Experts predict the day will come, possibly in just a decade, when entire genome sequencing will be considered routine and possibly done as part of newborn screening.

"You can filter the analysis to only analyze genes appropriate for that clinical setting in an age-appropriate manner. You don't need to know about adult onset disease risk in a newborn screen," says Ledbetter. "If you use that model you eliminate the huge, major concerns over data handling and interpretation. You can generate the data in one cost-effective step and analyze the portions you need to at that time and the rest sits there. . . . You can give it to the parents on a hard drive or store it in a personal health vault and it may be used in a future encounter with the health care system."

There are no doubts the technology exists and the worldwide sequencing capacity will improve so that every person can have their genome preemptively sequenced, but the mystery of the genome still lies in the ability to clinically interpret it. Sequencing the entire genome is not the same as applying sequencing technology to solve a clinical question.

"I hope clinicians won't use [sequencing] as a first-line test. It is like using an atom bomb to kill an ant," says Sherri Bale, Ph.D., managing director, GeneDx (the genetic testing lab of Bio-Reference Laboratories). "I hope clinicians won't use it to cover ignorance and generate more laziness. They still need to go through a differential in a complete but cost-effective manner. Look at the patient and let's look at a specific gene."

Given the current quality of raw sequencing data, Bale sees a difference between clinical sequencing for diagnosis and preemptive sequencing to have on file in a medical record.

"Specificity and sensitivity must be a lot higher for a diagnostic," says Bale. "To answer a specific question about a disease you must be very sure that all of the genes of interest or parts of genes of interest are covered at good enough depth. Sequencing may not have the cleanest, highest-quality data to rule in, but time will tell."

"We will see some disruption in who the leading reference labs are because not all of the biggest labs move quickly enough. It is an opportunity for new companies that focus on genomics and bioinformatics and smaller academic and commercial labs that can rapidly expand if they have the right combination of expertise."

—David Ledbetter, Ph.D., Geisinger Health System

This targeted sequencing approach is initially where there will be the most growth. Whole-genome sequencing will, for the next several years, remain a tool used in research laboratories, but multigene sequencing panels will increasingly evolve in pathology laboratories.

"Gene panels based on next-generation sequencing are already clinically available and will continue to increase," says Ledbetter. "It is more cost-effective way to look at 10 to 20, 100 genes."

Analysts say low-cost sequencing platforms will gain traction in clinical laboratories, but outsourcing of sequencing will remain a viable commercial model. The question is over time will clinical laboratories bring sequencing-based tests in-house?

"Certain types of sequencing, targeted DNA tests, will absolutely go in-house, even point-of-care panels will happen," predicts Bale. "But big-time sequencing panels, complex genotypes—they will remain the purview of a handful of good laboratories to perform."

Will today's leading reference labs be at the forefront of sequencing-based testing in the coming years?

"The skillset and expertise for bioinformatics and interpretation is different than what exists in most traditional reference laboratories," says Ledbetter. "We will see some disruption in who the leading reference labs are because not all of the biggest labs move quickly enough. It is an opportunity for new companies that focus on genomics and bioinformatics and smaller academic and commercial labs that can rapidly expand if they have the right combination of expertise." G2

One in Four Women Screened for Gestational Hypothyroidism; Condition Much More Prevalent Than Previously Thought

A nationwide analysis of more than half a million pregnant women shows that gestational hypothyroidism is more common than previously thought and screening rates for the condition are low with only one in four women screened for the condition, according to a study published online in December in the *Journal of Clinical Endocrinology & Metabolism.*

Researchers from Quest Diagnostics (Madison, N.J.) found that 15.5 percent of pregnant women tested for gestational hypothyroidism (either subclinical or overt) were positive using criteria in the 2011 clinical guidelines issued by the American Thyroid Association. Previous estimates indicated prevalence rates were closer to 3 percent.

The researchers believe low testing rates may contribute to the underdiagnosis of the condition. Their analysis found that only one in four pregnant women (aged 18 to 40 years) was tested for thyroid stimulating hormone (TSH) levels and that among those women diagnosed with gestational hypothyroidism, only 20.7 percent were tested within six months postpartum. The findings are based on a review of laboratory tests of 502,036 pregnant women who received lab testing through Quest Diagnostics between 2005 and 2008.

The researchers also found test selection was variable. Twenty-four percent (22,650) of women with TSH within range and 33 percent of women with elevated TSH were also tested for gestational hypothyroxinemia and 0.2 percent and 2.4 percent, respectively, tested positive for gestational hypothyroxinemia. Only 0.3 percent of women with TSH within range received a thyroid peroxidase antibody (TPO Ab) test, with 15 percent testing positive while 0.66 percent of women with elevated TSH received a TPO Ab test and 65 of them tested positive.

"Our findings should reinvigorate the medical community's long-standing debate about the best approach to clinical assessment and management of thyroid function during pregnancy," said co-investigator Jon Nakamoto, M.D., Ph.D., medical director for Quest Diagnostics, in a statement. "With the growing awareness of risks that even subclinical hypothyroidism can pose for the mother and fetus, it's important that practitioners recognize the true prevalence of this condition in a statement." G2

HIV Testing Rates Low in Sexually Active Teenagers; More Comprehensive Testing Strategy Urged

Only one in five sexually active high school students is being tested for HIV, according to a study published online in January in *Archives of Pediatric and Adolescent Medicine*. While students with added known risk factors are tested at higher rates, experts believe a reexamination of testing strategies is needed to ensure more young people are tested.

Analyzing data from the national 2009 Youth Risk Behavior Survey, researchers from the U.S. Centers for Disease Control and Prevention (CDC) found that only 17.9 percent of sexually experienced adolescent males and 27.5 percent of sexually experienced adolescent females have ever been tested for HIV. Among adolescents who reported a risky behavior, less than half of the students reported ever being tested: 28.7 percent

for those students who did not use a condom, 34.7 percent for those having sexual intercourse with more than four people in their life, 36.2 percent for those who had been physically forced to have sexual intercourse, and 41.3 percent for those who had ever injected illegal drugs.

While the researchers suggest it is necessary to increase teenage HIV screening in health care settings through improved provider assessment of sexual risk and through expanded testing in confidential, youth-oriented testing sites, Lawrence D'Angelo, M.D., chief of adolescent and young adult medicine at Children's National Medical Center (Washington, D.C.), calls for a more comprehensive screening approach in adolescents. In an accompanying editorial D'Angelo proposes a stricter protocol than either the CDC guidelines or those put out by the American Academy of Pediatrics. He suggests a universal screening of all adolescents at age 13 followed by repeat annual testing for at-risk teenagers and repeat testing for teens not considered at risk at least every three years after the initial screening.

Rapid HbA1c Testing to Debut in 600 MinuteClinics

In a move that might foretell the expansion of laboratory testing in retail clinics, MinuteClinic (a division of CVS Caremark Corp.; Woonsocket, R.I.) is deploying 600 Afinion analyzers made by Axis-Shield (Dundee, Scotland) for hemoglobin A1c (HbA1c) testing.

The HbA1c assay is Clinical Laboratory Improvement Amendments-waived and will be used in MinuteClinic's 600 retail sites in 24 states. The fully automated analyzer will allow clinic providers (typically nurse practitioners or physician assistants) to collect the patient specimen and obtain test results in three minutes. The deal, previously announced in November, will allow MinuteClinic to expand its chronic disease management offerings.

According to Axis Shield, C-reactive protein testing is also available on the Afinion desktop analyzer and prothrombin time international normalised ratio (PT-INR) and homocysteine tests will be introduced later. The company has not acknowledged whether the additional tests will eventually be deployed in MinuteClinic sites. Axis Shield was acquired by Alere (Waltham, Mass.) in the fall, reportedly for its point-of-care technology.

One-Time Baby Boomer HCV Test May Be Cost-Effective Strategy

Adding a one-time screening for hepatitis C virus (HCV) in baby boomers (born from 1945 to 1965) to existing risk-based testing strategies is a cost-effective model for identifying undiagnosed HCV, according to a study published online in the November *Annals of Internal Medicine*. Without new strategies to identify and treat asymptomatic cases of HCV, the health care system is forecast to face mounting costs and deaths associated with the infection over the next two decades.

Using data from the National Health and Nutrition Examination Survey, U.S. Census, and Medicare reimbursement schedule, the researchers estimate that 2.4 million baby boomers are antibody-positive for HCV and 1.9 million are chronically infected, with 1.2 million of the chronically infected unaware of their status. Under birth-cohort screening models with standard treatment, 60.4 million persons would receive antibody testing, 1 million new cases would be identified with 552,000 patients receiving treatment and 229,000 patients achieving a sustained viral response (SVR), compared

to 14.8 million screened, 135,000 treated, and 53,000 achieving SVR under risk-based screening alone. Under birth-cohort screening with standard treatment an additional 82,000 HCV deaths could be prevented, compared to risk-based screening.

Compared with the status quo of high-risk screening, birth-cohort screening identified 808,580 additional cases of chronic HCV infection at a screening cost of $2,874 per case identified. The authors say birth-cohort screening with standard treatment (when compared with risk-based screening) ranks equivalently to colorectal cancer screening, hypertension screening, and pneumococcal vaccination of adults age 65 years or older in terms of cost-effective prevention approaches and is a "reasonable strategy" to identify undiagnosed cases of HCV.

New Rapid, POC Tests for Meningitis, HCV

HiberGene Diagnostics Ltd. (Dublin, Ireland) has licensed the patent and exclusive worldwide commercialization rights for a novel, rapid molecular diagnostic test for the detection of neisseria meningitidis. The test, which could simplify diagnosis of the potentially deadly but clinically ambiguous infection, is already being used at Royal Victoria Hospital, where it was originally developed.

The rapid, point-of-care meningitis test provides a reliable diagnosis in 40 minutes, compared to 24 hours for standard laboratory tests. HiberGene plans to market the test worldwide, where it can be used as a front-line test in emergency departments without the need for laboratory referral. Clinical validation of the test shows a 100 percent sensitivity and a specificity of 99.7 percent, the company says. The assay uses an emerging molecular method known as loop-mediated isothermal amplification.

According to Brendan Farrell, CEO of HiberGene, the test does require 510k approval from the U.S. Food and Drug Administration (FDA) and CE marking in Europe, but the company expects the test should be commercially available in the fourth quarter of 2012 in Europe and in the United States the following quarter. While pricing is not yet final, Farrell anticipates the test will list for approximately $30 per test.

Following years of anticipation, in November the FDA granted a Clinical Laboratory Improvement Act (CLIA) waiver for the OraQuick HCV Rapid Antibody test, manufactured by OraSure Technologies Inc. (Bethlehem, Pa.). The CLIA waiver will broaden access to the test and may lead to higher disease detection rates by permitting use of the rapid hepatitis C test in decentralized and nontraditional sites, including doctors' offices, health department clinics, and mobile counseling and testing sites. The test is the first rapid blood test for the hepatitis C virus for use with either fingerstick or venous whole blood specimens. OraQuick is a visually read test strip that delivers results in 20 minutes.

"It is absolutely on everyone's radar," says Eric Rude, director, Office of Viral Hepatitis Coordination, New York City Department of Health and Mental Hygiene, whose office helped with field testing. "Coupled with more effective treatment options, this will lead to more testing."

Rude says two projects involving community-based organizations, one in New York City and one through the state of New York, have received public health funding to use the rapid test and will commence within a month. OraSure had previously announced an agreement with Merck & Co. (Whitehouse Station, N.J.) to promote the OraQuick HCV test in physicians' office worldwide.

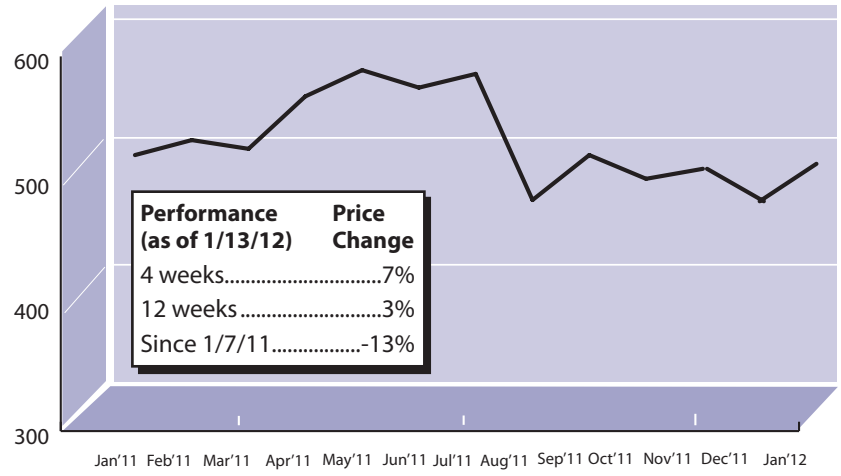
G2 Index Gains 7%, Driven by Some Big Gainers

The G2 Diagnostic Stock Index was up 7 percent for the four weeks ending Jan. 13. Thirteen stocks were up, three stocks were unchanged, and just one stock declined. The Nasdaq and the S&P were also up, with both indexes gaining 6 percent.

Among the stocks gaining this ground were five companies whose values increased more by more than 10 percent. In the opening weeks of 2012 **Qiagen** (Hilden, Germany) had several positive announcements that drove its stock up 12 percent, including the approval of its Therascreen EGFR Mutation Detection Kit RGQ in Japan. The approval advances Qiagen's personalized health care strategy, allowing the companion diagnostic to be marketed along with EGFR-inhibiting drugs. Japan is one of the world's largest markets for companion diagnostic tests, with EGFR and KRAS testing in Japan estimated at approximately 100,000 patients per year. Qiagen's Therascreen KRAS Mutation Detection Kit had previously been approved in Japan. In another to move to expand its future personalized health care pipeline, in early January Qiagen entered into two new strategic codevelopment partnership and licensing agreements—one with Insight Genetics Inc. (Nashville, Tenn.) for a genetic test covering the ALK biomarker, a promising target for a novel class of lung cancer drugs, and the other with Personal Genome Diagnostics Inc. (Baltimore) gaining worldwide exclusive rights to test for mutations of the IDH1 and IDH2 genes, which likely play a role in brain cancers and acute myelogenous leukemia.

Also among the highest-performing stocks of the period was **Sequenom** (San Diego). The company said it met its 2011 research and development goals with the October launch of the MaterniT21 lab-developed test (LDT). The company says it billed more than 21,000 prenatal and retinal diagnostic tests for the year and received its first payments as an out-of-network provider from major commercial payers within the first billing cycle post-launch of the MaterniT21 LDT. In 2012 the company plans to expand commercialization of the test with a corporate goal of billing a minimum of 25,000 MaterniT21 tests this year.

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	55.43	1%
Affymetrix	4.63	22
Becton Dickinson	74.91	6
Bio-Rad	98.14	1
Cepheid	35.73	14
Gen-Probe	60.39	7
Illumina	35.71	33
IRIS	9.80	9
Johnson & Johnson	65.26	1
Meridian	19.22	5
OraSure	9.80	8
Qiagen	15.09	12
Sequenom	4.50	21
Unchanged		
Abaxis	27.79	0%
Luminex	20.63	0
Quidel	15.88	0
Down		
Alere	22.22	-3%

G2 Insider

CYP2C19 Genotype Testing: Is the time now? ... As previously reported by *DTTR*, pharmacogenomic testing for cardiovascular patients is poised for increasingly widespread clinical adoption with large academic medical centers implementing routine, and even preemptive, genotype testing for patients. But a recent meta-analysis published in the Dec. 28 issue of the *Journal of the American Medical Association*, while acknowledging the association between the CYP2C19 genotype and responsiveness to the anti-coagulant clopidogrel (Plavix), cites a lack of evidence demonstrating a clinically important association between the genotype and cardiovascular outcomes.

So, will these findings put the brakes on CYP2C19 genotype testing among already reluctant clinicians, just as cardiovascular pharmacogenomic testing was gaining traction?

Nearly one-third of labs responding to an October G2 Intelligence survey cited cardiovascular testing as a clinical area in which they are likely to add tests to their menu in the near future. But gauging physician demand for exactly what type of cardiovascular genetic testing they are receptive to will be key to successful menu expansion.

"At this time there isn't enough evidence for genetic testing before starting these medications," says Gordon Tomaselli, M.D., president of the American Heart Association and chief of Cardiology at Johns Hopkins School of Medicine (Baltimore). But the evidence isn't the only issue. "First, it is not trivial to do the testing and secondly, in most cases when you start these medications at a time of cardiovascular intervention, you don't have the luxury of time to wait for test results."

While Tomaselli and other experts don't doubt that pharmacogenomic testing will make clinical inroads, single-gene testing of CYP2C19 or other gene variants will not gain significant acceptance. More meaningful inroads will be made, Tomaselli says, with the implementation of "broad-based genetic testing that is easy to digest and organized in a fashion that is clinically useful."

Company References

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