G2 INTELLIGENCE

Diagnostic Testing & Technology Report

Competitive Intelligence & Analysis for an Expanding Global Market

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New Bio-Ink Improves Cell Viability in Bioprinting

Researchers from the University of Wollongong (Australia) have advanced the realm of bioprinting with the development of a new improved bio-ink capable of printing living human cells into three-dimensional structures, according to a study published in the November issue of *Biomaterials Science*. The new bio-ink improves the viability of the cells.

"To date, none of the available inks has been optimized in terms of both printability and cell suspending ability," said Cameron Ferris, co-author and associate researcher at the Australian Research Council Centre of Excellence for Electromaterials Science, in a statement. "Our new bio-ink is printable and cell-friendly, preventing cell settling and allowing controlled deposition of cells."

The bio-ink is based on a biopolymer and two surfactants in a standard tissue culture medium. The ink was able to reproducibly print different cell types from commercial inkjet print heads, the researchers reported. For more information on how advances in bioprinting will affect laboratories, please see *Inside the Diagnostics Industry* on page 5.

How Will the Supreme Court's Gene Patent Ruling Affect the Diagnostics Industry?

The Supreme Court in early December agreed to hear a case challenging Myriad Genetics' (Salt Lake City) patent of two genes linked to hereditary breast and ovarian cancer. In agreeing to hear the case, the court limited the appeal to a single question—are human genes patentable? Despite the attention the case has garnered over the past three years, there are questions over how great of an impact the decision will have on the diagnostics industry.

The question of patentability of genes stirs great passion. Some, like the American Civil Liberties Union in this case, say gene patents interfere with scientific progress by slowing research, increasing clinical and research costs, and impeding access to diagnostic tests. Meanwhile, the biotech industry argues exclusive patent rights are imperative to the in vitro diagnostics industry's success by allowing companies to recoup initial research and development costs.

In 2001 the U.S. Patent and Trademark Office established utility guidelines that allowed patenting of a "genetic composition isolated from its natural state" as long as the patent applicant "discloses a specific, substantial, and credible

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▲ **How Will the Supreme Court's Gene Patent Ruling,** *from page 1*

utility for the claimed isolated and purified gene." But as molecular diagnostics has evolved, technologies like next-generation sequencing may be making isolated gene patents irrelevant.

"In my mind diagnostics [methods] patents are always more important and restrictive than patents on isolated DNA," says Daniel Vorhaus, a lawyer at Robinson Bradshaw in Chapel Hill, N.C., and editor of the online *Genomics Law Report*. "A gene sequence by itself is not that valuable; it's the informational content in the diagnostics method patents [that's significant]."

> ***"Companies can work around the types of patents going to the Supreme Court."***
> ***—Daniel Vorhaus***

Legal experts say that the claims of Myriad's CEO Peter Meldrum that "this case has great importance for the hundreds of millions of patients whose lives are saved and enhanced by the life science industry's products" may be hyperbole. Myriad is a unique business and legal case, as few diagnostics companies have built successful monopolies around isolated DNA patents.

"Companies can work around the types of patents going to the Supreme Court," Vorhaus tells *DTTR*. "Plus, there is the significant cost and consequences of asserting gene patents, as Myriad has seen. I wouldn't expect to see follow-on litigation. . . . The case has driven significant policy discussion, but I don't buy into the rhetoric that it will be broadly detrimental to the biotech industry."

Proprietary Data Outlives Patents

Myriad may not even be too affected by the court's ultimate decision, say experts. With its BRCA-related patents expiring over the next five years the company will rely upon the added insulation it has built around its testing monopoly in the form of its proprietary database of DNA sequence variants (including variants of uncertain significance [VUS]) and associated clinical information relating to the breast cancer genes BRCA1 and BRCA2.

"Myriad clearly sees its proprietary database as a source of competitive advantage, one that will persist after its underlying patents expire or are invalidated in court," writes lead author Robert Cook-Deegan, M.D., from Duke University in Durham, N.C., in a case study published online Nov. 14 in the *European Journal of Human Genetics*. Myriad deliberately retains the data as a trade secret, he argues, while the majority of clinical testing services do provide their data to public databases.

"In an environment in which new technologies, including whole-genome and whole-exome sequencing, are already beginning to change clinical practices in genetic testing, a proprietary database gives Myriad indefinite exclusivity independent of patent protection," writes Cook-Deegan. "Until the data and interpretive algorithms are re-created in publicly accessible form, competing services will be able to manage VUS results in only two ways: by having samples analyzed at Myriad . . . or by rendering inadequate interpretations based upon incomplete public data and algorithms. . . . Current practice permits the privatization of valuable clinical data obtained from patients."

Cook-Deegan and colleagues call for payers, regulators, and providers to enact policies to bring such clinical data into publicly available resources. A similar call was issued in November by the American College of Medical Genetics and Genomics (ACMG) in its position statement *Public Disclosure of Clinically Relevant Genome Variants*.

"The next phase of the human genome project, which is to annotate the human genome sequence with the clinical and biological meaning of the sequences and variants, will require capturing information from a very large number of people from diverse populations," said ACMG's executive director Michael S. Watson, Ph.D., in a statement. "Information that informs us about the meaning of genome sequences should be in the public domain where it can be used for the benefit of all."

As the industry awaits the Supreme Court's decision, there is growing consensus that proprietary genetic data, protected by patents or not, is what poses the greatest challenge to advancing genomic medicine.

DTC Genetic Testing Market Further Consolidates for the Sake of Data

In a surprising move, biotech giant Amgen (Thousand Oaks, Calif.) announced the acquisition of deCODE Genetics (Reykjavik, Iceland) on Dec. 10, further consolidating the direct-to-consumer (DTC) genetic testing market. The sale of deCODE (as well of Navigenics this past summer) underscores the importance placed on access to genetic data in the drive toward personalized medicine. As was the case with Navigenics, deCODE's DTC testing will halt.

Amgen paid $415 million in an all-cash deal for deCODE in the hope that the company's unique data will speed drug discovery, although tangible benefits from the acquisition are likely years away. Since its inception, more than 140,000 volunteers provided medical and DNA information to deCODE.

"[deCODE's] capability will enhance our efforts to identify and validate human disease targets," said Amgen's CEO Robert Bradway in a statement. "This fits perfectly with our objective to pursue rapid development of relevant molecules that reach the right disease targets while avoiding investments in programs based on less well-validated targets."

Sean Harper, M.D., Amgen's executive vice president for research and development, told the *New York Times* that two of the most promising drugs in Amgen's pipeline—one for osteoporosis and one for high cholesterol—were identified from human genetic studies and that the company had previously dropped some targets based on published findings from deCODE.

The Other Original DTC Players

- **23andMe** (Mountain View, Calif.), the last remaining of the original DTC genetic testing companies, improved its financial position in early December with the closing of a $50 million round of series D financing. The company said it would partially use the capital to reduce the price of its DTC genome analysis service from $299 to $99. The company hopes the price drop will aid in growing its base from 180,000 to 1 million customers. The company will also use the funds to expand its research and operational capabilities and necessary infrastructure to support its anticipated growth.
- **Navigenetics** (San Francisco) was acquired by Life Technologies (Carlsbad, Calif.) this past July. The purchase was part of Life's strategy for entering the clinical diagnostics market. From the purchase Life gained both Navigenics' Clinical Laboratory Improvement Amendments-certified laboratory and its data system to speed up diagnostic assay validation and companion diagnostic development. Following the acquisition, the DTC portion of Navigenics' business was immediately closed.

"Clearly Amgen wanted deCODE for more than its patents, genetic testing business, or drug development projects—although there is plenty of value there," wrote Terry McGuire, managing general partner of Polaris Venture Partners, in his blog. The venture capital firm was an investor in deCODE. "Amgen bought deCODE for its powerhouse research engine—including its talented genomics scientists, tools, and data."

deCODE has had a turbulent run since its 1996 inception. From reporting a market capitalization of $1.2 billion in 2000 the company plummeted into bankruptcy in 2009 but re-emerged as a populational genetics research-oriented company. While publishing more than 400 papers on discoveries linking genetic variants to common conditions like Alzheimer's and autism, deCODE remained unable to financially capitalize on those discoveries with therapeutic or diagnostic products.

deCODE's founder Kari Stefansson reportedly is staying on board to run deCODE and plans to continue publishing genetic findings. The transaction does not require regulatory approval, Amgen says, and is expected to close before the end of 2012.

Family of Joint Infection Detection Assays Nearing Launch

CD Diagnostics (Wynnewood, Pa.) completed the purchase of Citrano Medical Laboratories (Towson, Md.), a family-run Clinical Laboratory Improvement Amendments-certified laboratory, in October as a final step in readying the company to launch its first tests. The company's synovial fluid-based assays are aimed at improving diagnosis of joint conditions and will initially target detection of infections.

The company says that 51 million people are tested annually for joint pain resulting from an infection, osteoarthritis, gout, or other disease. Synovial fluid samples offer greater specificity than blood to detect the cause. CD Diagnostics' assay employs a lateral flow design and uses antibody-coated cellulose strips to analyze the joint fluid. While initially launching as a lab-developed test, the company will pursue 510(k) clearance to approve the test as a moderately complex point-of-care test (results are read in 10 minutes, much like a pregnancy test). The company hopes to receive regulatory approval in 2014.

Richard Birkmeyer, Ph.D., the CEO of CD Diagnostics, tells *DTTR* that the case for the test is pretty straightforward. Joint fluid is currently analyzed with a series of tests that can include culture, gram stain, and C-reactive protein, which is not specific to joint infections culture, as well as expensive radiographic assessments. Simple analytic assays for joint fluid analysis are currently lacking, Birkmeyer says. While declining to pinpoint a specific price for the test, Birkmeyer says the company is in talks with insurance companies and Medicare and expects the test to be reimbursed in the neighborhood of $40 to $80, a "dramatic" cost savings from current diagnostic methods.

The synovial test, which launched as a pilot program in November, tests for infection in artificial joints and is the first released under a development agreement between CD Diagnostics and Zimmer (Warsaw, Ind.). The agreement includes development of a total of four diagnostic products. CD Diagnostics receives milestone payments of roughly $3 million per test developed. A similar test for infections in native joints is expected to be available in February or March of 2013. The company anticipates completing 300,000 infection tests in the first year.

G2 INTELLIGENCE
Inside the Diagnostics Industry

3-D Bioprinting to Improve Cell Modeling in the Laboratory

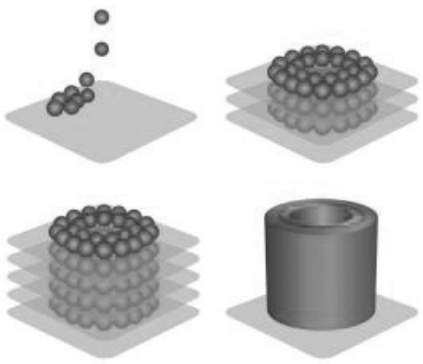
Using a printer to create tissues sounds like like science-fiction, but researchers are making rapid progress in the field of bioprinting. While printing off replacement organs for human transplantation may be years off, early applications of bioprinted tissues are currently being used in pharmaceutical development and academic research laboratories for biomarker discovery, drug screening, and toxicology testing. Bioprinted tissues may also reach clinical laboratories in the not-so-distant future.

"The concept of bioprinting, which is essentially an extension of the philosophy that uses additive manufacturing methods to build complex scaffold structures, can be thought of as a combination of (i) different types of cells in defined locations, (ii) supporting matrix or scaffolds (if required), and (iii) biochemical cues to control behavior," writes Brian Derby, Ph.D., from the University of Manchester in a review piece published in the Nov. 16 issue of *Science*. "Although bioprinting has its origins in the area of tissue engineering and is sometimes described as organ printing, there are other application areas where a printed or artificially fabricated tissue analog structure is useful, including cell-based sensors, drug/toxicity screening."

How It Works

Progress in bioprinting is happening at the intersection of biotechnology and manufacturing. It is based on the computer-controlled delivery of cells into three-dimensional constructs.

Constructing 3-D Tissues



Source: Organovo

Progress in the field has been rapid since Gabor Forgacs, Ph.D., at the University of Missouri, Columbia, made the seminal discovery in 1996 that during embryonic development, cells clump together with liquidlike properties. In 2003 Thomas Boland, Ph.D., then at Clemson University in South Carolina, modified an inkjet printer to dispense cells into scaffolds. Since then researchers have developed technologies allowing 3-D tissues to be engineered without scaffolding. The first commercial 3-D bioprinter was developed in 2009 by a bioprinting company called Organovo (San Diego). Forgacs's discoveries are the foundation for Organovo's technology.

Cells, collected from the patient or stem cells, are cultured and then used to create a bio-ink, which is loaded into a cartridge. The printing process uses layers of an inert hydrogel support matrix and the bio-ink, which allows for control of cell

distribution. Droplets of bio-ink measure 100 microns to 500 microns in diameter and contain more than 10,000 cells each. The computer-controlled printer heads are programmed and layering is repeated in a specified geometry and the cells naturally fuse together in a biocompatible form. Current research efforts are aimed at increasing the diversity of cell lines used in bio-ink and improving the cell viability during the printing process.

The resulting tissue has tremendous biological potential and is superior to animal models, researchers say, because it is made out of human cells. These tissue models have the potential to replace two-dimensional cell-based arrays for studying absorption/distribution/metabolism/excretion (ADME) models, toxicology, and drug metabolism and pharmacokinetics.

Current Applications

Organovo is using the 3-D human tissue printing technology to create tissue on demand. The company's tissues are being used to recapitulate in vivo biology for human disease research, drug discovery and development, toxicology testing, and, eventually, as therapeutics themselves.

"Bioprinting is so valuable because it is an architecturally correct, fully human model."
—Eric David, M.D.

"The big challenge in the pharmaceutical industry and academic labs is the lack of a robust preclinical model," says Eric David, M.D., chief strategy officer at Organovo. "They are surprised too often with a failure in the late stages—in late 2 or stage 3 trials after they have spent $600 million to $1 billion. You can't have failure at that stage for efficacy or safety."

David tells *DTTR* that bioprinting can play an important role in improving the predictiveness of preclinical models, even better than animal models.

"Animal models are a whole organism, but they are not human. Cells in petri dishes are two-dimensional and don't behave like normal human cells," explains David. "Bioprinting is so valuable because it is an architecturally correct, fully human model."

The company's tissues are currently being used in drug discovery research under collaborative research agreements with Pfizer and United Therapeutics, as well as in academic research at Harvard Medical School and the Sanford Consortium for Regenerative Medicine. David says the technology is not used for super high-throughput applications like screening 10,000 compounds, but once the list is whittled down to a dozen or so targets, the model works.

Over the summer the company received its first company patent for multilayered vascular tubes as well as a key founder patent for core bioprinting technologies assigned to the University of Missouri and exclusively licensed to Organovo. The company also moved into larger facilities with three times the laboratory space and approximately four times the cleanroom space of our prior facility, which will provide capacity for near-term product manufacturing needs.

Organovo, David says, is not looking to be in the business of selling the instruments and the consumables, but rather to sell the tissues on 96-well plates or in bigger tissues constructs on 24-well plates. Within a year he sees the company as having "off-the-shelf" tissue options including for researchers testing liver toxic-

ity to research in vivo drug interactions. The earliest successes for the bioprinted tissues will likely be in fibrotic diseases and in liver and kidney disease, which currently have poor disease models. David says he could see uses for bioprinted tissues in clinical laboratories as well in the future—better enabling comparative histological examinations. "Biobanking only goes so far," he says.

Organovo's bioprinting technology is also being used to develop tissues for direct therapy, such as cardiac muscle patches, although the company is not yet actively in clinical trials.

"We are still a long way from organ printing. Although current deposition and fabrication technologies allow us to build structures that are analogous to tissue in their composition, the development of fully functioning tissue is a much greater step," writes Derby in the review. "There is also still considerable uncertainty concerning the level of cell damage that occurs during cell deposition by all bioprinting methods. It is clear that much further work will be needed in this area before regulatory approval can be obtained for translational studies."

Regulatory challenges seem to pose significant concern for researchers involved in biomaterials research. In a special issue focused on regenerative biotissue, experts commented on some of the challenges associated with translating this emerging research into clinical applications.

Bioresponsive materials that boost the maturation and differentiation of therapeutic cells may be treated as combination products requiring regulatory approval of the material or device as well as the cellular components, says Alan Tounson, Ph.D., in comments in the Nov. 14 special issue of *Science Translational Medicine*.

"Drugs and medical devices follow a refined preclinical testing framework: animal models, study designs, statistical plans, and diagnostics practically comprise a 'cookbook,' which facilitates the risk-benefit analysis process for all reviewers," says Tounson, president of the California Institute for Regenerative Medicine. "There is no such cookbook for biomaterials with biologic components."

"Although current deposition and fabrication technologies allow us to build structures that are analogous to tissue in their composition, the development of fully functioning tissue is a much greater step."
—Brian Derby, Ph.D.

"Long development timelines, funding shortages, and regulatory uncertainty hinder the clinical translation and commercialization process for combination biomaterials," adds Chris Mason, M.D., Ph.D., from the Advanced Centre for Biochemical Engineering at the University College London, in the same piece. "Investors and investigators alike focus on removing complexity, by going with either cells or the biomaterial alone, to ease the regulatory burden and reduce uncertainty. Unfortunately, this strategy is in opposition with the diverse range of unmet clinical needs (many of which will not be solved by one technology alone) and the ability of the field to achieve its full potential through the development of multifunctional combination materials."

For the near-term Derby says that it is likely these tissue analog structures will be limited to applications such as toxicity screening and drug testing, and to construct tumor models, allowing variation in physiological conditions in vitro.

KRAS, BRAF Testing Cut Costs but Don't Improve CRC Survival

Conducting KRAS and BRAF testing in all metastatic colorectal cancer (mCRC) patients prior to treatment with anti–epidermal growth factor receptor (EGFR) therapies could save roughly $8,500 per patient or more than $103 million annually, according to a study published Nov. 28 in the *Journal of the National Cancer Institute*. The savings come, though, without any improvements in survival resulting from the testing strategy.

KRAS and BRAF testing are used to identify those most likely to benefit from costly EGFR therapy, thereby avoiding unnecessary toxicity and cost for the roughly one-third of mCRC patients unlikely to respond to these drugs. The researchers developed a cost-effectiveness model in which a cohort of 50,000 mCRC patients was simulated 10,000 times with randomly assigned attributes (metastases site and real-world treatment patterns) based of distributions from previous randomized controlled trials.

The four strategies tested included no anti-EGFR therapy, anti-EGFR therapy without screening, screening for only KRAS mutations before providing anti-EGFR therapy, and screening for KRAS and BRAF mutations before providing anti-EGFR therapy. The model followed each patient for 10 years. The researchers found that providing anti-EGFR therapy to all patients without any screening was the most costly strategy and only improved mean survival by approximately one day. Adding just KRAS testing saved $7,493 per patient, and adding BRAF testing saved an additional $1,023, with little reduction in expected survival.

"Our results are less supportive of the use of anti-EGFR therapy than previous analyses, and they indicate lower cost savings from KRAS testing than previously reported," concludes lead author Ajay S. Behl, Ph.D., a research associate at HealthPartners Research Foundation (Bloomington, Minn.). "Although we cannot confirm that anti-EGFR therapy is a cost-effective use of health care resources, we can affirm that KRAS testing is cost-saving. BRAF testing may offer additional savings."

Preoperative Urine Cultures Unnecessary

With a shift away from treating asymptomatic bacteriuria in men, new research calls into question the value of preoperative urine screening in patients undergoing nonurologic procedures. A retrospective study of nearly 1,700 men treated at a Veterans Affairs medical center published online in the December issue of *Archives of Internal Medicine*, reports that even if bacteriuria is identified, treatment offers "no benefit."

The researchers reviewed the medical records of 1,688 patients who underwent cardiothoracic, orthopedic (1,291 patients), and vascular procedures to identify urine culture (UC) orders or results during the seven days before each procedure. Bacteriuria was defined as high count (more than 100,000 colony-forming units [CFU]/mL), low count (10,000 to 90,000 CFU/mL), or negative (fewer than 10,000 CFU/mL).

Overall, a urine culture was obtained before one-quarter of the procedures, but there was significant variation by medical service (cardiothoracic accounted for 85 percent; vascular, 48 percent; and orthopedic, 4 percent). Patients receiving preoperative urine screening were significantly older (66.9 years versus 60 years) and were significantly more likely to develop post-surgical complications including surgical sight infections, diarrhea,

and Clostridium difficile infections (CDI), although confounding factors are cited as possible.

"We found that preoperative urine cultures were ordered inconsistently, that findings were rarely positive for bacteriuria, and that bacteriuria, when detected, usually was not treated," write the authors, led by Dimitri Drekonja, M.D., from the Minneapolis Veterans Affairs Medical Center in Minnesota. "Our findings document that treatment of preoperative bacteriuria is associated with no benefit."

In 11 percent (54 of 489 cultures) bacteriuria was detected. Preoperatively, 16 patients were treated for urinary tract infection, but half of the treated patients had only low-count bacteriuria or a negative test result for UC.

"Given the few treated patients and the strong likelihood of confounding variables, this study cannot provide conclusive evidence about the risks and benefits of treating preoperative bacteriuria in older men," writes Barbara Trautner, M.D., Ph.D., from the Baylor College of Medicine in Houston, in an accompanying editorial. But "the treatment of asymptomatic bacteriuria in most clinical settings is not necessary and may be harmful in terms of CDI, antibiotic resistance, and unnecessary costs."

Fasting Unnecessary Before Routine Lipid Testing

Fasting for routine lipid testing may be unnecessary. A large community-based study published in the *Archives of Internal Medicine* on Dec. 10 contributes to a growing body of literature demonstrating minimal differences between fasting and nonfasting mean cholesterol levels, leading many experts to say that nonfasting blood draws may be used for cardiovascular risk assessment and therapeutic decisionmaking.

Laboratory data from 209,180 individuals (111,048 females and 98,132 males) seen by Calgary Laboratory Services over a six-month period were analyzed. A 2011 policy change permitted the laboratory to process patient samples for fasting lipid levels regardless of the duration of the fasting time as long as the patient-reported fasting time (in hours) was recorded. High-density lipoprotein (HDL) cholesterol and triglyceride levels were measured directly, while low-density lipoprotein (LDL) cholesterol levels were estimated. For total cholesterol and HDL cholesterol mean levels varied by less than 2 percent across various fasting times. Triglyceride levels varied by less than 20 percent and the calculated LDL cholesterol varied by less than 10 percent.

"Most of the reasons that we measure a lipid profile depend on total and HDL cholesterol levels for most of our decision making. The incremental gain in information of a fasting profile is exceedingly small for total and HDL cholesterol values and likely does not offset the logistic impositions placed on our patients, the laboratories, and our ability to provide timely counseling to our patients," writes J. Michael Gaziano, M.D., from Brigham and Women's Hospital in Boston, in an accompanying editorial. "This, in my opinion, tips the balance toward relying on nonfasting lipid profiles as the preferred practice."

While current guidelines still recommend that blood for lipid profiles should be drawn after a nine- to 12-hour fast, other recent studies suggest that nonfasting lipid profiles may be superior to fasting levels in predicting adverse cardiovascular outcomes as nonfasting values may be more representative of usual metabolic conditions and lipid clearance. While clinicians still believe fasting lipid tests are necessary in individuals with triglyceride

levels greater than 400 mg/dL and in other high-risk patients, the growing consensus is that removing the fasting requirement will improve clinical care and testing compliance.

"The elimination of a fasting requirement for lipid determination could also increase patient compliance with testing, which could have particular benefits for patients with diabetes," writes study co-author Davinder Sidhu, M.D., from the University of Calgary in Canada. "These findings suggest that analysis of fasting time and lipid levels could have a role in identifying individuals for further screening with supplementary tests such as oral triglyceride tolerance testing or more rigorous treatment protocol goals and closer monitoring."

Genetic Variants Alter Clinical Effects of Vitamin D Levels

Genetic variants within the vitamin D receptor (VDR) gene can significantly modify associations between serum 25-hydroxyvitamin D concentrations and major health outcomes. The study, published in the Nov. 14 issue of the *Journal of the American Medical Association*, suggests that a personalized clinical approach may be necessary in evaluating serum vitamin D levels as a modifiable risk factor for common health outcomes because of variants affecting downstream 25-hydroxyvitamin D metabolism.

"Genetic variation within the vitamin D receptor could alter associations of 25-hydroxyvitamin D concentrations with disease outcomes," write the authors, led by Gregory Levin, Ph.D., from the University of Washington, Seattle. "Further studies are needed to confirm these observed associations and to enhance knowledge of how variation in vitamin D metabolism genes may stratify individuals as to their susceptibility to vitamin D deficiency."

In a discovery cohort, the researchers studied 141 single-nucleotide polymorphisms (SNPs) found in 1,514 white participants of the Cardiovascular Health Study with no known prevalent cancer, cardiovascular disease, or hip fracture. Replication meta-analyses were conducted, applying the discovered variants across data from three additional studies of more than 2,700 participants.

The researchers found that over 11 years of follow-up in the discovery cohort, 948 participants (63 percent) experienced a composite outcome-defined event. Consistent with previous studies, there was evidence of a threshold association between serum 25-hydroxyvitamin D levels and higher risk of the composite outcome that remained significant even after adjusting for age and sex.

Of the five variants identified in the discovery cohort, only the VDR SNP rs7968585 significantly modified the association between low 25-hydroxyvitamin D concentration and risk of the composite outcome in the independent replication meta-analyses. However, an additional VDR SNP (rs2239179) significantly modified the low 25-hydroxyvitamin D–disease association in a meta-analysis that included both the discovery and replication cohorts. The two identified VDR variants are common SNPs, with minor allele frequencies of 0.48 and 0.42, respectively.

"These results suggest that individuals with specific 25-hydroxyvitamin D metabolism genotypes may be particularly susceptible to, or protected from, the potential adverse health effects of low vitamin D," write the authors. "The VDR, a member of the steroid-receptor gene superfamily, plays a central role in mediating vitamin D signaling."

G2 Index Ends 2012 Up 14%, Diagnostics Did Not Keep Up With the Broader Market

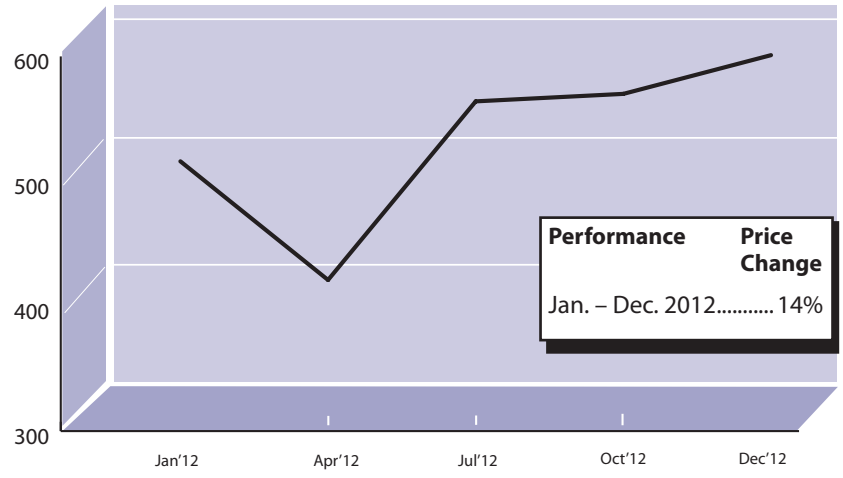
The G2 Diagnostic Stock Index gained 14 percent during 2012. Eleven stocks gained for the period from Dec. 16, 2011, to Dec. 12, 2012, and four stocks declined. Despite closing the year markedly up, the G2 Diagnostic Stock Index underperformed the broader stock markets in 2012. The Nasdaq and the S&P both gained substantially over the same period, with the Nasdaq up 18 percent and the S&P increasing 17 percent.

Among the notable acquisitions in the diagnostics industry over the past year were two G2 Diagnostic Stock Index companies. The sale of **Iris International** (Chatsworth, Calif.) to Danaher (Washington, D.C.) for $355 million closed Oct. 31, and Hologic (Marlborough, Mass.) completed the acquisition of **Gen-Probe** (San Diego) for $3.7 billion on July 31. As a result of the acquisitions both IRIS and Gen-Probe were removed from the index.

The stock gaining the most in 2012 was **Illumina** (San Diego), which began the year fighting off a hostile takeover bid from Roche and ended the year losing in a bidding war with China's BGI-Shenzhen to acquire sequencing competitor Complete Genomics (Mountain View, Calif.). For the year Illumina's shares gained 98 percent, with its Dec. 12 share price of $53.22 just shy of its 52-week high.

OraSure Technologies (Bethlahem, Pa.) ended the year down 20 percent. Despite the much talked about launch of its rapid OraQuick In-Home HIV Test, the company's shares dropped sharply in November, largely due to a weak third-quarter financial report. No revenue was recorded in the third quarter related to the initial shipments of the home HIV test, although approximately $3.6 million in deferred revenue was recorded for the product—an estimated 142,000 tests. The company also forecast weak fourth-quarter results.

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 15 IVD companies.

Up	Price	% Chg
Abbott Labs	66.01	20%
Abaxis	38.15	38
Becton Dickinson	78.61	11
Bio-Rad	104.72	8
Cepheid	32.38	3
Illumina	53.22	98
Johnson & Johnson	70.96	10
Meridian	20.18	10
Qiagen	17.77	31
Quidel	18.10	14
Sequenom	4.86	30
Down		
Affymetrix	3.23	-15%
Alere	19.05	-17
Luminex	16.40	-21
OraSure	7.29	-20

G2 Insider

Have GWASs Been Oversold?… Despite the publication of 1,455 papers and documentation of 8,062 single nucleotide polymorphisms in the Catalog of Published Genome-Wide Association Studies (GWASs) since 2005, personalized medicine has failed to materialize at the hoped-for rate. A research letter published in the Nov. 14 issue of the *Journal of the American Medical Association* makes the case that large GWASs carry some fundamental limitations despite the hundreds of millions of research dollars spent on them.

While effect size is the most important aspect of GWASs, larger sample sizes seem to only elucidate an increasing number of small effect variants. The researchers found that of 1,200 published GWASs only 86 studies (6.8 percent) had odds ratios of greater than 3 at a P value of less than 10^{-5}. Of these studies, half used 300 patients or less.

Even very well-established genetic associations have very limited clinical-diagnostic implications. In a meta-analysis of Parkinson disease GWASs, which included 12,386 cases and 21,583 controls, carriers of selected variants had almost 2.5-times increased odds of Parkinson disease, but based on the disease prevalence, this association translates into a lifetime risk for developing the disease of only 0.35 percent, even in the highest-risk group.

"These considerations lead to two important conclusions: risk prediction for an individual usually cannot be derived even from large-scale GWAS data, and sample size is not a quality marker of GWAS per se, especially in terms of clinical relevance," write the authors, led by Christine Klein, M.D., from the University of Lübeck in Germany.

Complicating current GWAS methodology is the possibility that probands may be more heterogeneous than recognized with phenotypic variants that are difficult to clinically distinguish. Additionally, GWASs of common variants may not delve deep enough into the genetic data.

"Even high-resolution genetic variation will only explain a fraction of the heritability of human diseases and traits," the authors explain. "Thus, the search is still ongoing for future promise beyond simple genetics with gene-gene and gene-environment interactions, as well as epigenetic effects as important but complex targets."

Company References

Amgen 805-447-1000

CD Diagnostics 484-476-4800

Complete Genomics 650-943-2800

Danaher 202-828-0850

Hologic 781-999-7300

Illumina 800-809-4566

Life Technologies 760-603-7200

Myriad Genetics 801-584-3600

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