Diagnostic Testing and Technology Report

Competitive Intelligence & Analysis for an Expanding Global Market

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IVD Companies, Labs Expand Personalized Medicine Plays

Personalized medicine is proving more than a buzzword as in vitro diagnostics (IVD) companies and clinical laboratories align to launch and implement products designed to aid physicians in offering treatments tailored to individual patients. As yesterday's biomarker discoveries emerge in today's multiplex molecular assays, pharmaceutical companies are increasingly prioritizing the collaborative development of companion diagnostics while IVD companies focus on making the case for clinical utility. In this month's special supplement to *DTTR* (pp. 7-11), we highlight a series of recent developments in personalized medicine, from new genetic tests for cancer launched in recent weeks by Genomic Health and Clarient to some landmark studies that may provide the critical research underpinnings for the diagnostic tests of the future.

SACGHS Finalizes Recommendations on Gene Patents

On Feb. 5, the Secretary's Advisory Committee on Genetics, Health, and Society (SACGHS) voted to urge Secretary of Health and Human Services (HHS) Kathleen Sebelius to limit the ability of gene patent holders to keep others from using those genes for diagnostic and research purposes. The report included a statement of dissent from three members of SACGHS, which advises the HHS secretary on the broad range of human health and societal issues raised by the development and use and potential misuse of genetic technologies.

The committee concludes its *Report on Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* with six formal recommendations, beginning with statutory changes that would exempt from liability for gene patent infringement "anyone making, using, ordering, offering for sale, or selling a test developed under the patent for patient care purposes" and those who use patent-protected genes in research. These suggested changes are highlighted as offering "the most expeditious and straightforward way of addressing the identified problems and promoting patient access to emerging genetic advances."

Subsequent recommendations, which could be accomplished more quickly than the proposed legal changes, include promoting adherence to norms (such as nonexclusive licensing) that are designed to ensure access. Additionally, the committee recommends enhancing transparency in licensing, establishing an advisory body on the health impact of gene patenting and licensing practices, and working closely with the U.S. Patent and Trademark Office to provide expertise related genetic testing issues.

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▲ **SACGHS,** *from page 1*

Finally, SACGHS recommends that the secretary work to ensure equal access to clinically useful genetic tests. "Our advocacy for equal access here is part of this committee's longstanding concern about ensuring equality in the provision of genetically related tests and services," noted the authors.

Critics of SACGHS's stance on gene patents are urging Secretary Sebelius to reject the recommendations. "By undermining the value of gene-based patents, these recommendations would chill future investment and innovation, and would undermine the investment-backed expectations of current patent owners and licensees," said Jim Greenwood, president and CEO of the Biotechnology Industry Organization, the industry's main trade and lobbying group.

The SACGHS recommendations were finalized only days after U.S. District Judge Robert Sweet heard oral arguments in a landmark lawsuit challenging gene patents. At issue are patents granted to Myriad Genetics (Salt Lake City) and the University of Utah Research Foundation for BRCA1 and BRCA2 genes, indicators of hereditary disposition to breast and ovarian cancer. On Feb. 2, both sides asked a federal court to rule in their favor without a trial.

At the core of the case is whether the patent claims cover "products of nature" and "laws of nature" and are therefore invalid. The lawsuit, *Association for Molecular Pathology, et al. v. U.S. Patent and Trademark Office, et al.*, was filed in May 2009 by the American Civil Liberties Union (ACLU) on behalf of an estimated 150,000 researchers, physicians, laboratory professionals, and patients.

The suit also alleged that the patents violate the First Amendment by giving exclusive control of the BRCA knowledge to patent holders, restricting scientific research, the development of new tests, and patients' access to medical care, including the right to a second opinion on test results.

Speaking for Myriad, Brian Poisssant said, "This is not a patent on information. This is a patent on a chemical composition." The U.S. Patent and Trademark Office has ruled that genes can be patented if they are "isolated from their natural state and purified." Myriad says its patents cover how to sequence the gene to identify its components, then map that sequence to look for mutations indicative of cancer.

The ACLU's Chris Hansen retorted that "isolating" a gene, no matter how difficult and ingenious, does not alter the structure of the DNA itself, and so what has been patented is indeed a product of nature. "Uncovering a law of nature—while deserving of praise for the time, ingenuity, and hard work that it takes—is not patentable."

CancerGuide Diagnostics Partners with LabCorp, Looks to Raise $10.5 Million

Life science startup CancerGuide Diagnostics (Durham, N.C.) is laying the groundwork for a partnership-based play in the personalized medicine space. The company has raised $2 million of a planned $10.5 million round of private financing in a first tranche that was coled by Hatteras Venture Partners and Intersouth Partners.

CancerGuide has also recently signed a multiyear collaboration and license agreement with LabCorp (Burlington, N.C.), which is also an equity investor in the company.

Under the agreement with the nation's second-largest laboratory testing provider, CancerGuide will collaborate with LabCorp on the development and commercialization of molecular oncology assays.

"Through our unique partnership model, CancerGuide will provide companion diagnostic development services to pharmaceutical and biotechnology companies to maximize the efficiency and effectiveness of the market entry strategies," said Myla Lai-Goldman, M.D., CEO of CancerGuide. Board-certified in clinical and anatomic pathology, Lai-Goldman is the former chief science officer and chief medical officer at LabCorp.

Founded in 2006, CancerGuide is focused on the development and commercialization of genomic-based clinical and pharmaceutical cancer tests and services. In addition to Lai-Goldman, the management team includes president and chief operating officer Bill Haas, who headed LabCorp's esoteric business and oversaw sales, marketing, and managed care for the lab services leader.

Navigenics Raises $18 Million from Investors Including P&G

With competitor deCODE Genetics still reeling from bankruptcy, personal genomics company Navigenics (Foster City, Calif.) has raised approximately $18 million of funding. A notable addition to Navigenics' investors is Procter & Gamble (P&G; Cincinnati), which joined Mohr Davidow Ventures and Kleiner Perkins Caufield and Byers in this third funding round.

Navigenics President and CEO Vance Vanier, M.D., described P&G's "extraordinary track record of consumer understanding" as an opportunity to better address the needs of Navigenics' customers, who pay $999 for the company's genotyping services and results interpretation. "When combined with their commitment to developing innovative consumer health and wellness products and an expanding focus on health services, P&G's insight and brand will strengthen Navigenics' position to embed personal genomics into the prevention dialogue of everyday health care."

P&G recorded 2009 net sales of $79 billion, with approximately 17 percent of net sales coming from health care products including feminine care, oral care, personal health care, and pharmaceuticals. "Navigenics represents an exciting opportunity for future innovation for P&G," said P&G's Nathan Estruth. "Personalized genetic testing can have significant meaning in helping consumers focused on prevention and wellness live better, healthier lives—something that P&G has always been committed to."

According to Vanier, Navigenics plans to use the $18 million in Series C funding to expand its product offerings as well as gain a foothold in employer-sponsored preventive health and wellness programs.

Agilent Divests Clinical Diagnostics Business Hycor Biomedical

Measurement company Agilent Technologies (Santa Clara, Calif.) has sold its clinical diagnostics business to Linden (Chicago), a private equity firm focused on the health care and life science industries. Acquired by Agilent as part of its 2007 purchase of Stratagene, Hycor Biomedical develops, manufactures, and markets in vitro diagnostic products for the global allergy testing, autoimmune testing, and urinalysis markets. Financial terms of the deal were not disclosed.

"Hycor is an innovative, profitable, and growing business, but it does not fit the core focus of our life science business," said Nick Roelofs, president of Agilent's life sciences group, which includes microarrays, microfluidics, and laboratory automation. The group accounted for $969 million of the $4.5 billion in revenue that Agilent reported for the fiscal year that ended Oct. 31, 2009. Agilent's life sciences revenue was down 5 percent in 2009 as compared to 2008, with modest growth in the academic and government markets but weakness in the pharmaceutical and biotechnology markets.

Hycor was founded in 1981 and is based in Garden Grove, Calif. Among its products are tests marketed under the Hytec, Kova, and Autostat brands. The company's fully automated Hytec immunoassay platform can perform allergy and autoimmune antibody testing as well user-defined enzyme-linked immunosorbent assays (ELISAs), while the Hycor ultrasensitive enzyme immunoassay system has been cleared by the Food and Drug Administration for quantitative determination of specific Immunoglobulin E.

Linden operating partner Richard Novak has been appointed chairman of Hycor. Novak previously served as chief operating officer of LabCorp. "The Hycor platform is well-positioned to compete in the high-growth segments of in vitro diagnostics for allergy and autoimmune testing," said Novak, who added that the company's urinalysis products offer a platform for international expansion.

Vanderbilt Launches CardioDX Test for Coronary Artery Disease

Vanderbilt University (Nashville) is the latest institution to offer Corus CAD, a gene expression test that quantifies the likelihood of obstructive coronary artery disease (CAD). The test is manufactured by CardioDX (Palo Alto, Calif.) and performed exclusively in the company's CLIA-certified laboratory.

Launched in August 2009 following a multicenter validation study conducted by CardioDX, Corus CAD integrates the expression levels of 23 genes and other patient characteristics to assess obstructive CAD. The test is intended to be used in an outpatient setting with clinically stable, nondiabetic patients who present with chest pain or who have a high risk of coronary artery disease, but without previously diagnosed myocardial infarction or prior revascularization procedure. Results are reported to ordering physicians in the form of a numeric score that quantifies the likelihood that a patient with stable chest pain has obstructive CAD. Turnaround time for the test is approximately three days.

A gene-based test offers a promising alternative to echocardiography, myocardial perfusion imaging, and computed tomography angiography.

"For now, we will use [Corus CAD] in addition to, and sometimes instead of, our standard approach to evaluating patients for coronary artery disease in the physician office," said John McPherson, M.D., director of the cardiovascular intensive care unit at Vanderbilt University Medical Center and a participant in the validation study. "This is the first of many future tests that will move in the direction of evaluating diseases by looking at a patient's genetics and the dynamic changes in expression of genes when disease is present."

With Focus on Clinical Toxicology and Forensic Testing, NMS Labs Succeeds as a 'Lab's Lab'

Now in its 40th year, NMS Labs (Willow Grove, Pa.) is a national reference laboratory that focuses on clinical toxicology and forensic testing. NMS has annual revenue of approximately $35 million and 210 employees. Clients range from regional laboratories to law enforcement agencies, but "We're really a lab's lab," says NMS Labs President and CEO Eric F. Rieders, Ph.D. NMS provides testing that other labs, including all of the major clinical reference labs, don't or can't provide. "We complement their toxicology menus," explained Rieders. "We've looked on their Web sites to figure out what percentage of testing in our category actually ends up coming here in terms of the actual analyses, and it's a fairly large percentage in many cases—over 50 percent. But these are low-volume tests that aren't really beneficial to the large labs to actually set up." As client labs choose to bring certain tests in-house as their volumes grow, NMS maintains its growth through innovation and a commitment to service. *DTTR* recently spoke with Rieders about what's new and what's next at NMS.

Eric F. Rieders, Ph.D.

How large is the NMS test menu?

Our lifeblood is to be able to offer testing that others don't have, and that means that we've always produced lots of new tests, some of which become a little more important than others with regard to the volume that comes in here. But we keep the low-volume tests on our menu, so I think right now we probably have 3,500 tests on our menu. Many of them are very low-volume.

Give the focus on toxicology, how did you come to add endocrinology tests to your offerings?

We added clinical endocrinology testing to our menu a couple of years ago, largely because of the fact that in our mind, the appropriate technology for performing this testing is tandem mass spectrometry, and we've become rather expert in that technology through the work that we do in toxicology.

Do reference labs constitute the majority of your clients?

A little of over 50 percent of what we do is clinical, and the balance is largely forensic, so our forensic client base is huge. On the clinical side, the majority of work does come from clinical reference laboratories. We work with some smaller ones that are a little more local, but the majority of the work comes from the national and regional reference laboratories.

What are some your growth initiatives on the clinical side?

Our key initiative on the clinical side is to continue to bring up innovative new tests that we believe the market can make good use of. The clinical world is shrinking in the sense of the number of labs that are out there is shrinking, through consolidation, so the number of clients that we can actually serve through our model is not as great as it was even five years ago. So it's been an ongoing interest of ours to maintain those relationships, but our key initiative around that has been to make sure that our service levels are really meeting and exceeding the expectations of the client base that we have. Included in that is to continue to really be aggressive about bringing new tests to market.

Looking at NMS's current offerings, what would you consider some of the top tests, those that are driving growth or for which you're seeing a strong demand?

A good example is pain management testing. We didn't explicitly pursue that area, but a lot of

the testing we provide supports that market. We do both the type of testing that you need to do to monitor compliance, which would be urine testing, as well as what we think is very important, therapeutic drug monitoring. The pain management marketplace is rather large, and we've remained the lab that has had testing available that eventually those labs will bring in-house.

Another market where initially we would have the tests available that would probably eventually be insourced by the major reference labs are tests that neurologists use. For example, anti-convulsant testing—therapeutic drug monitoring—is usually considered to be rather important. Last year, we brought up three new anti-convulsant tests [that use high-performance liquid chromatography] in fairly short order.

NMS is one of the few laboratories that offers testing for endocrine-disrupting chemicals, such as bisphenol A (BPA). Do you see this as a strong growth area?
It's an area that we're very interested in right now—and I won't tell you that the volumes are high, but we think that certainly there should be some interest out in the world these days. With all of the news about things like bisphenol A and thalates and so forth, we think that the tests that we have available may prove useful in assisting both researchers and potentially clinicians in addressing concerns that the general public is inevitably going to have.

Are you seeing a strong response to your recently launched BPA test?
We have not yet seen a strong response to it. Typically, we have seen that the adoption of testing by our clients is becoming more rapid, but frankly, I think some of that has to do with us doing a better job of communicating what tests we have rather than letting people figure out for themselves that we do it. We're proactively reaching out now. We've been in business for 40 years, but we haven't had a marketing department for anywhere near that amount of time. I think it's been about five years now.

Looking ahead, what tests are you looking forward to launching?
One area that I probably should have mentioned sooner is pharmacogenomics, which fits into what we're all about. Like a few other businesses, we were rather excited that testing in connection with warfarin therapy might be the first to bring pharmacogenomics into routine use. That turned out not to be the case, but we continue to look at those types of tests. I would say that we're monitoring both the science and the marketplace to try to decide whether this is something that we should be involved with. We did bring up the relevant testing two years ago, but we haven't even bothered to offer it, because there's simply no demand for it.

In the area of endocrinology, there's sort of a core offering that one needs to have to call oneself a clinical endocrinology service, but we're looking at some of the less available types of tests that we believe are relevant in endocrinology. Primarily this has come to us through contacts we've had through the research community as opposed to with physicians who are demanding something that isn't otherwise available. Some of the less widely tested endocrine steroids are on our menu. We're looking at endocrine peptides, which are currently not widely tested for.

We're also continuing to look at what new drugs are coming to the marketplace. As a toxicology laboratory, we think it's our mission to be as responsive as we possibly can to bringing tests for drugs as they're approved, both in terms of the therapeutic drug monitoring and compliance monitoring, or in some cases, abuse monitoring.

Genomic Health Introduces Colon Cancer Test

Genomic Health (Redwood City, Calif.) has launched its Oncotype DX colon cancer test, a 12-gene test developed for the assessment of risk of recurrence in patients with stage II colon cancer. The laboratory-developed gene expression test is available exclusively through Genomic Health's CLIA-certified laboratory.

There are approximately 30,000 stage II colon cancer patients in the United States. The Oncotype DX colon cancer can predict individual recurrence risk in these patients following surgery, according to results reported at the 2009 American Society of Clinical Oncology (ASCO) meeting.

Genomic Health will follow the commercialization strategy pioneered for its flagship Oncotype DX breast cancer test: launching as a test to predict cancer recurrence and adding clinical indications and clinical value.

"We'd like to take this test and do the same thing that we do with breast cancer and start to answer more questions for colon cancer patients," said Genomic Health President and CEO Kim Popovits at the J.P. Morgan Healthcare Conference on Jan. 11 in San Francisco. "In 2013, our plan is to be able to answer questions around oxaliplatin [Eloxatin] use for both stage II and stage III patients, and then we also want to take a look at targeted therapies in the colon cancer area."

Two studies presented on Jan. 24 at the ASCO Gastrointestinal Cancers Symposium provide further support for the use of the Oncotype DX colon cancer test as an independent predictor of recurrence risk in stage II colon cancer patients. These results also suggest a potential role for the test in patients with stage III disease.

JAMA Study Finds Genetic Links to Lung Cancer Survival

An analysis of genetic and clinical data for nearly 800 patients with non-small cell lung cancer (NSCLC) has identified differences in genetic characteristics that are associated with age- and sex-specific patterns of increased or decreased recurrence-free survival. The study appears in the Feb. 10 issue of the *Journal of the American Medical Association* (*JAMA*).

Researchers at Duke University (Durham, N.C.) retrospectively analyzed 787 patients with predominantly early stage NSCLC. Lung tumor samples with corresponding microarray and clinical data were used. Patients were divided into subgroups based on age or sex.

Low- and high-risk patient groups were identified with the longest and shortest five-year recurrence-free survival, respectively, within the age and sex NSCLC subgroups. The researchers found that these cohorts of NSCLC demonstrated unique patterns of pathway activation. In patients younger than 70 years, high-risk patients, with the shortest recurrence-free survival, demonstrated increased activation of the Src and tumor necrosis factor pathways compared with low-risk patients. High-risk patients ages 70 years or older demonstrated increased activation of the wound healing and invasiveness pathways compared with low-risk patients.

The researchers also found a difference in the biology of lung cancer between men and women. "In women, high-risk patients demonstrated increased activation of the invasiveness and STAT3 pathways while high-risk men demonstrated increased activation of the STAT3, tumor necrosis factor, EGFR [epidermal growth factor receptor], and wound healing pathways," the authors write.

Non-small cell lung cancer accounts for approximately 85 percent of the more than 200,000 lung cancer cases diagnosed each year.

"We believe our findings represent a novel approach to defining clinically relevant cohorts of NSCLC stratified by age and sex that are enriched for specific pathway activity and that would be more apt for therapeutic intervention when planning clinical trials with drugs that target specific pathway-related abnormalities or tumor biology," the authors concluded. "With genomic assays now being increasingly practical and clinically applicable . . . we believe our findings, while hypothesis generating and needing further validation, represent a step forward in defining pathway-driven cohorts of NSCLC that likely explain the age- and sex-specific differences seen in NSCLC."

Pfizer and Qiagen to Develop Companion Diagnostic for Brain Tumor Patients

Pfizer (New York) and Qiagen subsidiary DxS (Manchester, England) have entered into an agreement to develop a companion diagnostic test kit for an immunotherapy vaccine that Pfizer is developing for the treatment of glioblastoma multiforme (GBM). Financial terms of the deal were not disclosed.

Pfizer gained the exclusive worldwide license for the investigational drug from Celldex Therapeutics in April 2008. It is currently in Phase 2 clinical development for the treatment of newly diagnosed GBM, the most common malignant primary brain tumor in adults.

The peptide vaccine targets the tumor-specific Epidermal Growth Factor Receptor variant III (EGFRvIII), a mutated form of EGFR that is only present in cancer cells and occurs in 25 percent to 40 percent of GBM tumors. The Qiagen assay will use real-time polymerase chain reaction (PCR) to detect EGFRvIII RNA in tumor tissue.

The companion diagnostic will be developed and manufactured at the Manchester headquarters of DxS. Qiagen acquired DxS in September 2009 for approximately $95 million in cash, with an additional $35 million tied to specified milestones. Qiagen has indicated that it plans to seek Food and Drug Administration approval for DxS's CE-marked TheraScreen KRAS mutation testing kit this year.

Clarient Launches IHC Test to Aid in Selection of Lung Cancer Therapy

Clarient (Aliso Viejo, Calif.) has launched a laboratory-developed test that helps physicians classify types of lung cancer to identify which therapies may be most effective. Part of Clarient's new Insight Dx line of tests, Pulmotype is intended for use in subclassifying patients with non-small cell lung cancer (NSCLC).

Performed exclusively in Clarient's CLIA-certified laboratory, Pulmotype is a five-antibody immunohistochemistry (IHC) test that uses an algorithm to aid in the histological distinction between adenocarcinoma and squamous cell carcinoma in NSCLC tumor specimens. The test can be performed on formalin-fixed, paraffin-embedded lung cancer biopsies. Turnaround time for the test is 24 hours.

"The correct pathology assessment is essential for therapeutic decisionmaking, given the powerful new drugs currently on the market to treat lung cancer, such as Avastin and Alimta," said Ken Bloom, M.D., Clarient's chief medical officer. "The use of these therapies is predicated on the histologic differentiation of the cancer." Both Avastin (bevacizumab) and Alimta (pemexetred) have been approved by the Food and Drug Administration for nonsquamous histotypes.

Clarient's new Pulmotype test combines staining results for three squamous markers (SLC7A5, CK5/6, TRIM29) with two adenocarcinoma markers (MUC1, CEACAM5) to distinguish adenocarcinoma from squamous cell carcinoma in patients with non-small cell lung cancer.

The Pulmotype test was developed by Applied Genomics, which Clarient acquired in December 2009 in an all-stock merger valued at up to $17.6 million. Applied Genomics validated the test with a clinical study cohort of more than 1,000 patients and published the results of the study in the August 2009 edition of *Modern Pathology*.

"Our goal is to be the first place a pathologist goes after diagnosing NSCLC," said Chief Executive Officer Ron Andrews. "Having the lung cancer sample in our hands at the beginning of the diagnostic process allows us to assist the pathologist and the oncologist throughout the patient care process by delivering information on additional molecular markers, such as EGFR mutation and KRAS."

Researchers Map Genetic Variations Across 26 Cancers

A team of researchers has created a genome-scale map of 26 different cancers, revealing more than 100 genomic sites where DNA from tumors is either missing or abnormally duplicated compared to normal tissues. The study, the largest of its kind, appears in the Feb. 18 issue of *Nature*.

"Our findings show that many genome alterations are universal across different cancers. Although this has been known for some types of changes, the degree to which so many alterations are shared was pretty surprising to us," said senior author Matthew Meyerson, M.D., Ph.D., a professor of pathology at the Dana-Farber Cancer Institute and senior associate member of the Broad Institute of Harvard and MIT. "It suggests that, in the future, a driving force behind cancer treatment will be common genomic alterations, rather than tumors' tissue of origin."

To map genetic changes across different cancers, the researchers focused on somatic copy-number alterations (SCNAs), DNA changes in which segments of

a tumor's genome are present in abnormal copies. They used microarrays to analyze DNA from over 2,500 cancer specimens representing more than two dozen cancer types. Those results were then combined with publicly available data from another 600 tumor samples to assemble a detailed catalog of the SCNAs present in multiple tumor types.

Focusing on the shortest of the common SCNAs (focal SCNAs), Meyerson and his colleagues noticed that the majority did not coincide with genes already known to be amplified or deleted in cancer. Looking more closely at the genes that normally reside in these regions, the researchers found an enrichment of genes with important functions in cancer. Two genes associated with cell death—MCL1 and BCL2L1—emerged as particularly significant for maintaining tumor growth.

Looking across the data for the various cancers it became clear that most focal SCNAs are not unique to one type of cancer but are shared among multiple tumor types. In an analysis of 17 different cancer types, the researchers found that a majority of amplifications and deletions are present in more than one type.

Another study in the same issue of *Nature* also sheds light on genetic aspects of cancer.

British researchers analyzed gene deletions in 746 cancer cell lines and concluded that many deletions found in cancer reflect the position of a gene at a fragile site in the genome, rather than as a recessive cancer gene whose loss confers a selective growth advantage.

Geisinger and TGen Partner for Personalized Medicine Initiative

Geisinger Health System (Danville, Pa.) and the Translational Genomics Research Institute (Tgen; Phoenix) have entered into a research partnership designed to address gaps in clinical medicine. One of the first projects will focus on the genetic underpinnings of obesity, diabetes, and other metabolic conditions. The studies will combine the nearly two decades of data amassed in Geisinger's advanced electronic health records (EHRs) with TGen's expertise in proteomics and genomics.

"Identification of patients at risk for chronic metabolic diseases would provide enormous benefit to health care," said David Carey, Ph.D., director of the Sigfried and Janet Weis Center for Research, located on the Geisinger campus. "Geisinger's ability to obtain detailed, electronic health information in real time for a large, stable patient population will significantly accelerate this research effort."

Possible other areas of focus for the partnership between TGen and Geisinger include genetic variations that predispose individuals to disease, congestive heart failure, abdominal aortic aneurysms, and the potential side effects of prescription drugs.

TGen also is working with the Partnership for Personalized Medicine (PPM), which includes TGen, Arizona State University's Biodesign Institute, and the Fred Hutchinson Cancer Research Center.

Biomarker Could Help Treatment Selection for Rheumatoid Arthritis

A newly discovered biomarker could help physicians identify patients who will best respond to certain therapies for rheumatoid arthritis. The study appears in the February issue of the journal *Arthritis & Rheumatism*.

"While our study was performed on a relatively small group of patients and will need to be confirmed in a larger cohort, the data are promising and may be clinically significant for the medical management of patients," said senior author Mary K. Crow, M.D., director of rheumatology research and co-director of the Mary Kirkland Center for Lupus Research at Hospital for Special Surgery (New York).

The researchers set out to examine whether levels of type I interferon proteins, specifically a type called interferon beta (IFN-beta), could play a role in how patients respond to tumor necrosis factor antagonists. This class of drugs, which includes Enbrel and Humira, are not highly effective in 30 percent to 50 percent of patients. Patients taking TNF antagonists, which have been available for roughly 10 years and cost approximately $16,000 per year, also risk developing bacterial or fungal infections.

While studies have identified factors associated with poor response to TNF antagonists such as expression of certain genes, none of the factors has as yet provided doctors with a tool that will help select patients who are likely to respond to the drugs or identify those less likely to respond.

In a study of three patient groups (35 patients who had rheumatoid arthritis and received a TNF antagonist, 12 arthritis patients who received no drug, and 50 healthy volunteers), the researchers found that patients with higher baseline levels of type I IFN were more likely to respond to therapy with TNF antagonists. Patients who had an increased IFN-beta-to-alpha ratio, meaning they had more IFN-beta, were also more likely to respond to therapy.

Because IFN-beta is known to induce interleukin-1 receptor antagonist (IL-1Ra), another protein, the researchers also tested levels of IL-1Ra. They observed significantly higher baseline levels of IL-1Ra in plasma samples from good responders as compared with those from nonresponders or moderate responders.

"We have drawn attention to a potential biomarker that might provide a tool to predict who might be a responder to this class of biologic rheumatoid arthritis therapies, the TNF antagonists, and who might be less likely to be a responder," said Crow, who has submitted a patent application for an interferon assay. "For those who demonstrate low levels of blood interferon activity, that information might be useful to guide patients to alternative treatments that might be more likely to work for them." This could include the use of other drugs such as Rituximab, which is not a TNF antagonist.

Surgical Pathology Topped $1 Billion in Part B Charges in '08

Surgical pathology (Level IV, code 88305) continues to rank as the highest-volume pathology procedure paid under Medicare Part B. For the calendar-year 2008, this code had approximately 18 million allowed services and $1.18 billion in allowed Medicare charges—which is three times more than any other single procedure on the top 100 list.

It is important to note that 88305 is the first-ever pathology or lab code to top the $1 billion mark in allowed Medicare charges for a single year, according to analysis from the forthcoming updated *Medicare Reimbursement Manual for Laboratory and Pathology Services 2010* from Washington G-2 Reports. This data comes from analysis of the top 100 clinical laboratory and pathology procedures paid under Medicare Part B during calendar-year 2008 according to the annual BESS file (Part B Extract and Summary System) for CPT codes in the 80000 series. Lab and pathology services are represented in the CPT code range 80047-89399.

For 2008, the top 100 laboratory and pathology services encompassed 317 million Medicare-allowed services. Medicare-allowed charges to both providers and suppliers for these services totaled $5.051 billion or an average allowed charge of $15.93 per test procedure. This represents a $294 million increase in allowed charges and a 49 cent rise in the average allowed charge compared to 2007, when the Medicare numbers stood at $4.757 billion and $15.44, respectively.

Not surprisingly, the 90 laboratory codes included among the top 100 procedures accounted for a significant majority of Medicare-allowed services (287.5 million or 90.54 percent). However, these tests constituted only 64.5 percent ($3.26 billion) of the total allowed charges, making for an average allowed charge per procedure of $11.36. This represents an increase of 25 cents per laboratory procedure compared to the $11.11 per-test average allowed charge in 2007.

The 10 pathology codes included within the top 100 list accounted for a relatively small 9.47 percent of allowed services, or about 30 million allowed services. More importantly, these pathology services accounted for a robust 35.46 percent ($1.79 billion) of total allowed charges in 2008 that amounted to an average allowed charge of $59.68.

Overall, the average allowed charge per pathology procedure rose by $1.84 in 2008 compared to the previous year when it stood at $57.84 per procedure. As a result, the average allowed charge for the 10 leading pathology procedures was about 5.3 times the average amount paid by Medicare for the top 90 lab tests.

Continuing a trend in previous years, two pathology procedures had the highest average allowed charges in 2008 among the top 100 list: Level V – surgical pathology (88307) had the best at $88.40 (down from $89.13 in 2007 and noticeably down from $95.72 in 2005) and cytopathology, selective cellular enhancement technique, with interpretation (88112) came in second at $72.23 (down from $75.03 in 2007 and still below its $80.97 in 2005).

Also following a trend in recent years, the highest-volume laboratory procedure in 2008 was blood count, CBC, automated (Hgb, Hct, RBC, WBC, and platelet count) and automated differential WBC count (85025), with 31.4 million allowed services. This code generated $337.3 million in allowed charges, up 1.3 percent from 2007, and had an average allowed charge per test of $10.74, essentially unchanged from the prior year.

The best-paying high-volume (1 million or more in allowed services) laboratory test in 2008 continues to be TSH (84443), with some 13.7 million allowed services that paid $322.2 million in allowed charges and $23.41 in average allowed charge per procedure. Meantime, high-volume lab tests having the lowest average allowed charge per procedure were albumin, serum (82040) at $2.17 and bilirubin, direct (82248) at $2.16. In addition to the CBC and TSH, the five other laboratory tests that generated the highest volume in annual Medicare-allowed charges in 2008 include lipid panel (80061) and comprehensive metabolic panel (80053).

Highest-Volume Lab Tests, 2008

Test	Average allowed services	Allowed charges	Average allowed charges
CBC (85025)	31.4 million	$337.3 million	$10.74
TSH (84443)	13.7 million	$322.2 million	$23.41
Lipid panel (80061)	20.7 million	$298.6 million	$14.39
Comprehensive metabolic panel (80053)	25.5 million	$295.3 million	$11.57
Hemoglobin; glycosylated (83036)	11.6 million	$156.3 million	$13.52
Prothrombin time (85610)	21.7 million	$119.0 million	$5.48
Basic metabolic panel (80048)	9.5 million	$93.8 million	$9.83

Source: *Medicare Reimbursement Manual for Laboratory and Pathology Services 2010*, Washington G-2 Reports

Medco Health Services Acquires DNA Direct

Pharmacy benefit manager Medco Health Solutions (Franklin Lakes, N.J.) has acquired DNA Direct (San Francisco), which provides guidance and decision support for genetic testing to patients, providers, payers, and employees. Financial terms of the deal were not disclosed.

Medco, which posted net revenues of $51.3 billion in 2008, plans to integrate DNA Direct's services with its own portfolio of personalized medicine capabilities, which include a pipeline of pharmacogenetic research, testing programs for drugs like tamoxifen and warfarin, and warnings of approximately 50 drug-gene interactions that are used by the company's specialist pharmacists. Medco envisions broadening its suite of health services to range "from consumer education to clinical decision support," the company noted when announcing the deal on Feb. 2.

Founded in 2005 to facilitate genetic testing for consumers via the Internet, DNA Direct has recently expanded to serve physicians and payers with various guidance and decision support services related to molecular testing. The company's laboratory partners include LabCorp, ViroMed Laboratories, and Myriad Genetics.

In 2009, DNA Direct partnered with Humana to launch a genetic guidance program and also received utilization management approval from URAC, a Washington, D.C.-based accrediting organization that establishes quality standards for the health care industry.

"Together Medco and DNA Direct have envisioned genomic medicine programs for payers, employers, physicians, and patients to lower costs for all stakeholders, increase access for those who need and it, and improve patient care," says Ryan Phelan, president of DNA Direct. According to Phelan, DNA Direct will remain in San Francisco and operate as a wholly owned subsidiary of Medco.

Myriad Genetics Inks Deal with Mammography Reporting System to Identify Potential Patients

Under a recently announced agreement with Mammography Reporting System (MRS; Seattle), Myriad Genetics (Salt Lake City) will be able to identify more high-risk breast cancer patients—and therefore potential candidates for its BRACAnalysis test—through risk flags incorporated into cancer-tracking software that service 2,400 mammography centers in the United States.

"Women who are at a risk for cancer are going in and having mammograms and it's a great opportunity to ask them the questions about whether they might have a hereditary condition in their family," said Myriad President Gregory C. Critchfield, M.D. "We can incorporate red flags that are part of the identification process that are present in the MRS software, which can be captured when patients register in a mammography center."

An estimated 6 percent of women in mammography centers, or approximately 2.4 million women, are estimated to be at high risk for hereditary breast cancer. These women would be considered appropriate candidates for the BRACAnalysis test, which assesses the risk of developing cancer based on detection of mutations in the BRCA1 and BRCA2 genes.

This announcement comes at a time when Myriad is under increased scrutiny for unnecessary testing, with some national insurance providers like UnitedHealthcare and Aetna implementing prior authorization and notification, among other measures, before they will cover the BRACAnalysis test.

But Critchfield appears confident that the test is provided to the appropriate patients. "From time to time, insurance companies may want preapproval processes to be put in place, but this is a situation that is dynamic," he said. "We've had large insurers in the past who have put the processes in place and have abandoned it, because there is too much paperwork on their side and when they look at the data, it doesn't make any difference anyway."

IVD Stocks Slip 4%; Cepheid, Sequenom Join Index

For 2010, the G-2 Diagnostic Stock Index adds molecular diagnostics companies **Cepheid** (Sunnyvale, Calif.) and **Sequenom** (San Diego). The index is down 4 percent in the five weeks ended Feb. 12, with 14 stocks down in price, three up, and one unchanged. In comparison to the G-2 Index's 4 percent drop, the Nasdaq and the S&P each lost 6 percent.

Clinical Data (Newton, Mass.) fell 8 percent to close at $16.89 per share and a market capitalization of $462 million. The company recently reported strong quarterly sales for its Familion line of genetic tests. Gross revenue from the test reached $719,000, an increase of 25 percent compared to the same period a year ago, while gross margins climbed from 35 percent to 53 percent.

Also slipping was **Quidel** (San Diego). Shares in the rapid testing company dropped 7 percent to close at $13.09 with a market capitalization of $394 million. On Feb. 11, Quidel announced 2009 revenue of $164.3 million, up 28 percent from $128.1 million in 2008. Net income increased by 75 percent to $32.9 million from $18.8 million in 2008.

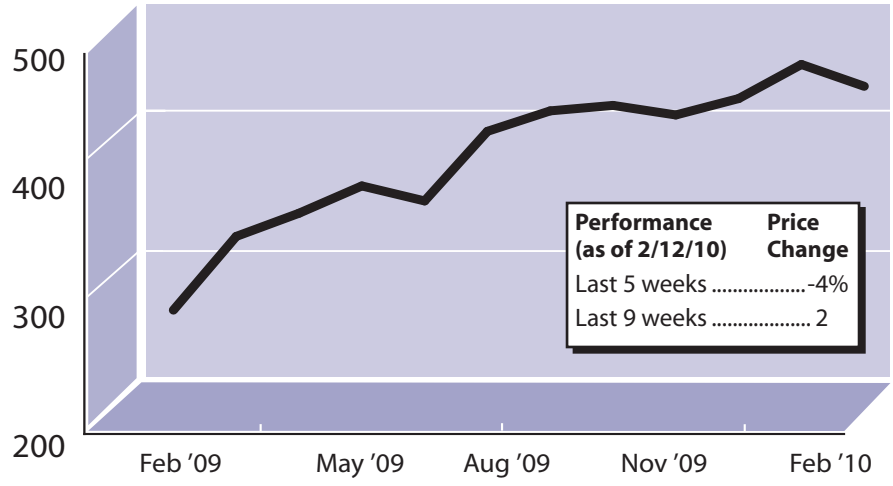
This year, the company expects to introduce five products, including a second-generation fecal immunochemistry test for colorectal cancer screening that is now under review by the Food and Drug Administration.

On Feb. 19, Quidel announced that it had completed its $130 million acquisition of Diagnostic Hybrids, which manufactures and commercializes direct fluorescent in vitro diagnostic assays for diseases including viral respiratory infections, herpes, and chlamydia. The company reported 2009 revenue of $51 million, an increase of 34 percent over 2008.

Sequenom was one of the few gainers, ending the period up 9 percent with a share price of $4.52 and a market capitalization of $350 million. The company recently launched a fetal test for sex determination and a test to detect incompatibility between the mother's and the fetus's blood type.

For up-to-the-minute laboratory and diagnostic firm data, financial news, and company podcasts—go to **www.g2reports.com**

G-2 Diagnostic Stock Index



Source: The G-2 Diagnostic Stock Index is tabulated weekly by *DTTR* from the average percentage change in the stock price of 18 IVD companies.

Up	Price	% Chg
Affymetrix	$7.36	7%
Cepheid	15.56	8
Sequenom	4.52	9
Unchanged		
OraSure	4.95	0
Down		
Abaxis	$25.26	-1
Abbott Labs	53.93	-2
Beckman Coulter	65.18	-5
Becton Dickinson	75.84	-3
Bio-Rad	93.91	-7
Clinical Data	16.89	-8
Gen-Probe	42.97	-4
Immucor	18.73	-8
Inverness Medical	41.25	-6
Johnson & Johnson	62.24	-3
Luminex	15.03	-1
Meridian	20.77	-4
Nanosphere	4.40	-32
Quidel	13.09	-7

G-2 Insider

Will needle and thread sew up cheaper chip-based tests? It's possible, according to a study published in the Jan. 27 issue of *ACS Applied Materials & Interfaces*. Researchers at Australia's Monash University used cotton thread and sewing needles to create a novel microfluidic device. The simple and relatively low-cost version of a "lab-on-a-chip" test stitched thread into paper to form three-dimensional sensors capable of detecting and measuring nitric acid and uric acid in urine.

Chip-based diagnostic tests have traditionally relied on a costly and complex process that etches microscopic channels onto silicon, glass, ceramics, or metal substrates. More recently, paper-based microfluidic devices have been proposed as a more economical alternative, but the Monash team's work is the first to use thread to fabricate the sensors.

"Gaps between fibers of cotton threads provide capillary channels for liquids to wick along threads without the need of an external pump," note the authors, who found that the wicking properties could be controlled by treating or twisting the threads. "The ability to manipulate liquid transport and mixing offers the possibility of using threads to fabricate more sophisticated microfluidic patterns."

The low cost and portability of tests made with this novel approach would make them ideal for use in developing or remote regions. The technique could be used to develop microfluidic diagnostic devices suitable for colorimetric, electrochemical, chemiluminescent, and electrochemiluminesent assays as well as for electrophoresis.

Company References

Agilent Technologies 408-345-8886
CancerGuide Diagnostics 919-474-2439
CardioDX 650-475-2788
Cepheid 408-541-4191
Clarient 949-425-5700
Clinical Data 617-527-9933
Genomic Health 650-556-9300
LabCorp 800-526-3593
Linden 312-506-5600
Medco Health Services 201-269-3400
Myriad Genetics 801-584-3600
Navigenics 650-585-7743
NMS Labs 800-522-6671
Pfizer 212-573-2323
Qiagen 31-77-320-8400
Quidel 858-552-1100
Sequenom 858-202-9000
TGen 602-343-8400

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