Diagnostic Testing and Technology Report

Competitive Intelligence & Analysis for an Expanding Global Market

Stephanie Murg, Managing Editor, smurg@ioma.com

Vol. VIII, No. 2/October 2007

CONTENTS

WASHINGTON G-2 REPORTS

Established 1979

Personalized Medicine: Ready for Its Close-up

Some skeptics predicted that the advent of personalized medicine would coincide with that of the Jetsonian flying car, but it's here—now. Nearly two years after an FDA advisory committee endorsed the use of genotyping to manage dosing for warfarin (Coumadin), the drug's updated labeling has been approved (see below). Microarray-based gene testing for enzymes that are responsible for metabolizing approximately 25% of all prescription drugs is flourishing (see pg. 9), even at $900 a test. Meanwhile, diagnostics companies like Clinical Data are snapping up small companies who specialize in pharmacogenetics research (see p. 4). And personalized medicine encompasses more than genotyping. More routine testing methods are assisting clinicians in figuring out who stands to benefit from the most basic of drugs—aspirin (see pg. 8).

FDA Approves Update to Coumadin Label

In what could be a boon for laboratories that offer pharmacogenomic tests, the U.S. Food and Drug Administration (FDA) has approved updated labeling for the blood-thinning drug Coumadin, manufactured by Bristol-Meyers Squibb. The new labeling, which will also be added to warfarin (the generic version of Coumadin), explains how a person's genetic makeup may influence their response to the drug.

The hotly anticipated labeling change comes nearly two years after an FDA subcommittee recommended testing for variations in the CYP2C9 and VKORCI genes that can confer sensitivity to warfarin and therefore significantly alter a patient's required dose. Molecular tests can identify patients who require a higher or lower dose to achieve a target international normalized ratio (INR), may be at an increased risk for bleeding complications, and without the test, would require a longer period of time to achieve stable warfarin dosing. Labs that currently offer warfarin sensitivity testing include ARUP Laboratories, LabCorp, Mayo Medical Laboratories, Kimball Genetics, and PGXL Laboratories.

First developed as a rat poison by the Wisconsin Alumni Research Foundation (WARF), warfarin is the most frequently prescribed oral *Continued on p. 2*

Looking to hire? Looking for a job? Announcing the new G-2 job board!
Washington G-2 Reports is pleased to announce its newly launched online job board, which features listings for positions in diagnostic company management, laboratory management, hospital management, and pathology, as well as medical technologist and laboratory specialist jobs. Visit the G-2 job board at www.g2reports.com/jobs/

▲ **FDA Approves Update to Coumadin Label,** *from page 1*

Approximately 30 million prescriptions for warfarin and Coumadin are written annually in the United States, and each year, nearly 43,000 patients are seen in emergency rooms for adverse side effects of the drug.

anticoagulant, but it is difficult to manage due to its narrow therapeutic range and inconsistent patient response resulting from inter-individual variability. The dosing range is wide, from 5 mg/wk to 80 mg/wk, and depends on such covariates as age, weight, ethnicity, diet, and vitamin K intake in addition to genetic factors.

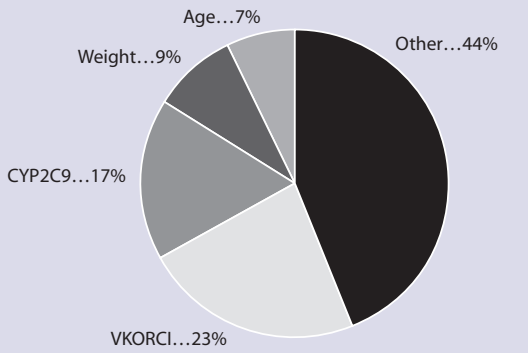
Warfarin testing has been hailed as the first pharmacogenomic test to enter widespread clinical practice. "The FDA labeling change for warfarin is the next step in the pathway toward incorporating genetics into the care of patients who need anticoagulation," says Marc S. Williams, M.D., a board member of the American College of Medical Genetics (ACMG; Bethesda, MD). "The FDA has said that physicians should be aware of the role of genetics in warfarin dosing, but now the hard part is doing the necessary groundwork to determine how best to use genetic testing to improve care."

Labs Offering Clinical Testing in the United States for CYP2C9 and/or VKORC1 Alleles

- ARUP Laboratories
- Cincinnati Children's Hospital
- Esoterix Laboratory Services
- Genelex
- Genomas
- Kimball Genetics
- LabCorp
- Mayo Medical Laboratories
- Molecular Diagnostics Laboratories
- OKU Molecular Pathology Lab
- PGXL Laboratories
- Specialty Laboratories

In December of 2006, a multidisciplinary team of investigators commissioned by ACMG issued a report reviewing the scientific and clinical evidence surrounding the use of genetic testing to guide dosing of warfarin. "The report states that there are situations in which one should perform genetic tests when prescribing warfarin," says Michael S. Watson, Ph.D., executive director of ACMG. "In particular, it states in the conclusion that CYP2C9 and VKORC1 genotypes can reasonably be used as part of diagnostic efforts to determine the cause of an unusually low maintenance dose of warfarin or an unusually high INR during standard dosing."

Known Sources of Variability in Warfarin Dose Needed for a Stable INR*



*Each estimate is based on a summary analysis of partial r^2 values from multivariate regression analysis reported in six studies that included genotyping on both CYP2C9 and VKORC1.

Source: ACMG's *Rapid ACCE* (Analytic validity, Clinical validity, Clinical utility, and Ethical, legal, and social implications) *Review of CYP2C9 and VKORC1 Allele Testing to Inform Warfarin Dosing in Adults at Elevated Risk for Thrombotic Events to Avoid Serious Bleeding* (December 2006)

In analyzing the clinical utility of genetic testing for warfarin dosing, the report notes that the number of individuals that must be tested and warfarin-dose adjusted to avoid one serious bleeding event ranges from 48 to 385. The cost per serious bleeding event ranges from $14,500 to $95,900, an estimate that is strongly influenced by the effectiveness of reduced warfarin dose in avoiding serious bleeding (found in a sensitivity analysis to range from 80% to 20%) and the cost of genetic testing, which ranges from $300 to $500.

Food and Drug Commissioner Andrew von Eschenbach called the approved labeling change an important step in the FDA's commitment to personalized medicine. Additionally, the FDA's Critical Path Initiative has funded a research project to develop genetically based instructions for warfarin dosing. Also underway is planning for a clinical trial that will study warfarin dosing based on genetic test information and another clinical study that will derive personalized warfarin dosing algorithms for patients new to the drug.

FDA Approves Roche's West Nile Virus Screening Test

The U.S. Food and Drug Administration (FDA) has approved the cobas TaqScreen West Nile Virus (WNV) test, which is manufactured by Roche Molecular (Pleasanton, CA). This is the second test approved by the FDA for the detection of WNV in blood and organs. Gen-Probe's Procleix West Nile Virus Assay received FDA approval in December 2005, more than two years after it was first made available for use by U.S. blood centers under an Investigational New Drug Application. The Gen-Probe test is marketed by Chiron (Emeryville, CA), a division of Novartis.

Usually transmitted to humans by mosquitoes, WNV can also be transmitted by blood transfusion or organ transplantation from infected donors. WNV first appeared in the United States in 1999, and since then, it has become endemic in most of the country, with between one million and three million cases between 1999 and 2006, according to the Centers for Disease Control and Prevention (CDC).

The cobas TaqScreen WNV test is an automated test that can detect the genetic material of the virus early in the infection, even before the donor's body has begun to produce antibodies against the virus. The qualitative test is approved for the detection of the virus in plasma specimens from human donors of whole blood and blood components (plasma, red or white cells, platelets) and living donors of cells, reproductive cells, and other tissues. It is also intended for use in testing plasma specimens of organ donors when specimens are obtained while the donor's heart is still beating. The test is not intended for use on samples of cord blood or as an aid in the diagnosis of WNV infection.

The West Nile Virus test is the first test available on Roche's automated cobas s 201 system in the United States. Multiplex tests for HIV, hepatitis C (HCV), and hepatitis B (HBV) are currently under FDA review. Roche launched the system in 2006 in Europe, where it markets the five-parameter multiplex cobas TaqScreen MPX Test, a comprehensive single-assay for the detection of HIV-1 groups M and O, HIV-2, HBV, and HCV in donated blood and plasma.

Jesse L. Goodman, M.D., M.P.H., director of the FDA's Center for Biologics Evaluation and Research, called the approval "the culmination of the dedicated efforts of FDA, our sister agencies, blood establishments, and manufacturers to bring donor screening tests to market for this increasingly common virus." It also gives blood centers and hospitals a choice of two FDA-approved tests for WNV screening in

FDA-Approved WNV Screening Tests

Test	*Company*	*Method/ Platform*	*Qualitative/ Quantitative*	*FDA Approval*
Procleix WNV	Gen-Probe/Chiron	NAT* / Semi-automated (eSAS)	Qualitative	December 2005
		NAT / Automated (Tigris)	Qualitative	March 2007
cobas TaqScreen WNV	Roche Molecular	NAT / Automated (cobas s 201)	Qualitative	August 2007

*Nucleic Acid-Amplification Test via real-time polymerase chain reaction (RT-PCR)

Source: *DTTR*

donated blood and organs, Goodman added. Approval of Roche's WNV test comes as the FDA is preparing guidance on the use of licensed WNV screening tests for blood donors.

Only 20% of people infected with WNV are symptomatic, but about one in 150 to one in 350 infected people will develop serious symptoms, including encephalitis, an inflammation of the brain. Since the introduction of the virus, the reported number of human cases of serious WNV in the United States has grown steadily from 62 in 1999 to 4,269 in 2006. As of late August, 58 blood donors who are possibly positive for the virus had been reported to the CDC.

In March, Gen-Probe received expanded FDA approval for its Procleix WNV test. The test is now approved to run on the company's automated Tigris platform as well as its semi-automated eSAS platform. Meanwhile, Gen-Probe is developing additional assays for the blood screening market. Gen-Probe's blood screening products are marketed worldwide by Chiron.

Clinical Data Buys Genetic Biomarker Company

Biotechnology company Clinical Data (Newton, MA) has acquired privately held Epidauros Biotechnologie (Bernried, Germany), which specializes in pharmacogenetic research, for 8.75 million euros (approximately $11.84 million). Epidauros CEO Michael Lutz, Ph.D., will join Clinical Data as senior vice president of pharmacogenetic partnerships.

Epidauros's services include those related to sample collection, sample preparation, bioinformatics, and quality assurance. A key area of specialization for the company is clinical genotyping services, including sequencing, TaqMan allelic discrimination and real-time assays, fragment analysis of PCR-amplified DNA, and TaqMan-based allelic copy number assays.

Among the most valuable assets Clinical Data will gain from this deal is Epidauros's robust intellectual property portfolio, which includes approximately 1,000 validated assays, including biomarkers related to a number of drug transporters and genes involved in cytochrome P450-mediated drug metabolism. The company has a particular strength in assay development and reports that it can develop and validate novel assays within four weeks.

Epidauros will also provide Clinical Data with insight into and expanded presence within the European clinical market, particularly Germany. Clinical Data already has operations in the United Kingdom and France.

With approximately 300 employees, Clinical Data has three divisions: PGxHealth (genetic tests), Cogenics (molecular and pharmacogenomic services), and Vital Diagnostics (traditional in vitro diagnostics). The company is currently in the process of rolling out a sales force to raise visibility and increase adoption of its new PGxPredict tests, which help to determine patient response to such drugs as clozapine (for schizophrenia), rituximab (for non-Hodgkin's lymphoma), and the anticoagulant warfarin.

A Look at What's Next in HPV Screening

About 5.5 million Americans get a new HPV infection each year, making HPV the most commonly acquired sexually transmitted disease.

Human papilloma virus (HPV), which causes cervical cancer, has become a household name in the last few years. This newfound awareness is due in large part to the media blitz and educational efforts of Digene (now part of Qiagen, based in Venlo, the Netherlands), the company that manufactures and markets the only FDA-approved test for HPV. But what are the pros and cons of the available cervical screening methods, and what assays are on the horizon? *DTTR* looked to Bruce K. Patterson, M.D., medical director of virology, pathology, and laboratory medicine at Stanford University School of Medicine (Palo Alto, CA) and a speaker at Washington G-2 Reports's recent cancer diagnostics conference, for insight into this highly competitive, rapidly growing, and very profitable segment of the in vitro diagnostics industry.

A Brief History of Cervical Cancer Screening and Treatment

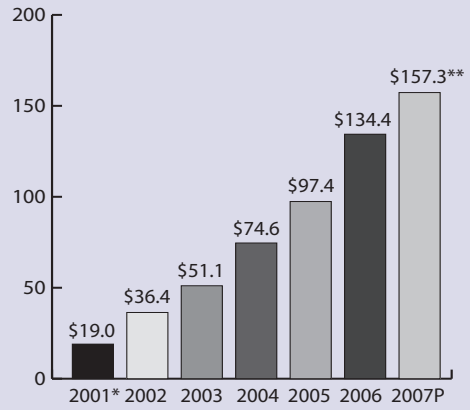
Cervical cancer is the second most common cancer among women worldwide. According to National Cancer Institute estimates, there will be 11,150 new cases in the United States in 2007 and 3,670 deaths. Landmarks in cervical cancer screening include the conventional Pap smear, in wide use since the 1940s, the discovery of liquid-based cytology in the mid-90s, the revised screening guidelines that came into effect in the early 2000s, and the vaccines that were launched in 2006.

While the increase in screening as well as the widespread use of HPV vaccines may come close to eradicating cervical cancer in the United States, the mortality for cervical cancer has not declined since the early 1980s. "It will be interesting to see what the vaccines can do to lower that number," says Patterson.

HPV Diagnostics

Digene's test is used with a Pap test as primary adjunctive screening in women age 30 or older and for evaluation in women with inconclusive Pap results. The test uses the company's proprietary hybrid capture 2 platform, which is pre-PCR technology that uses RNA probes, liquid-based hybridization, antibody capture, and signal amplification. The hybrid is captured onto a solid phase and detected with a chemo-luminescent signal.

Digene's HPV Revenue *(in millions)*



*Years are fiscal years ending June 30
**Projected by Washington G-2 Reports
Source: Digene and *DTTR*

Washington G-2 Reports estimates that approximately 7.5 million HPV tests will be performed in the United States this year, and the growth of this testing is reflected in Digene's climbing revenue from HPV diagnostics. In 2001, the company earned $19 million from HPV testing. In five years, that number had grown by 707% to $134.4 million. In FY2007, Washington G-2 Reports estimates that Digene will earn $157.3 million in revenue from HPV testing.

HPV Diagnostics

"I think people are aware that HPV has extremely high prevalence in the late teens and early twenties. What was surprising to me was that women in their early 20s came down with cervical cancer, or certainly high-grade

lesions, yet all the FDA-approved tests for HPV are for women over 30," notes Patterson. "We really need to think about this younger age group in terms of cervical cancer screening, especially in light of the fact that we are considering this age group for the new vaccine. It's a very important issue today."

According to Patterson, there are a number of clinical issues with current HPV diagnostics. "First, there is no perfect gold standard. Over the last 10 years that I've been doing HPV research, it's always a question of what do you use for a gold standard? What do you use as an objective or cutoff or goal for clinical trials? Second, there is variability in histology and cytology diagnoses from pathologist to pathologist. Third, companies continue to discuss the negative predictive value of HPV DNA tests, while ignoring the positive predictive value for lesions," Patterson says.

DNA-based HPV tests have a very high negative predictive value, which can allow for longer screening intervals. However, at 15% to 25%, the positive predictive value of these tests leaves a lot to be desired. "Some of the HPV genotyping assays improve the positive predictive value to maybe 50% or 60%," notes Patterson. "But certainly not to the extent where we're comfortable in a diagnostic sense."

Another issue is whether HPV-negative cervical carcinomas exist. Patterson cites an editorial published a few years ago in the *Journal of Pathology* that pointed out that HPV DNA at integration sites can result in a deletion of the L1 gene, the target of most of the molecular tests for HPV. "This is a little disturbing," says Patterson. "And we don't really know to what extent this is because there are several small studies looking at this but nothing on a large scale."

Additionally, the presence of HPV may precede abnormal cytology in women developing cervical cancer and signal potentially false-negative smears. Patterson says that by applying two tests—analysis of the expression of HPV oncogenes E6/E7 with testing for high-risk HPV DNA—on a range of cytology diagnoses, "it's very clear that there are women with supposedly normal cytology who have the molecular changes of cellular transformation that are the early stages of cervical abnormalities," says Patterson. "That's something we also want to grab hold of at the earliest possible stages.

Patterson also brings up the relationship between cytology and colposcopic biopsy. "We wanted to come up with a biomarker or some sort of marker that could tell us whether we had a high-grade lesion on biopsy—CIN-2, CIN-3, or cancer—and do some studies to look at the behavior of these particular lesions over time, and how that may relate to E6/E7 expression. High-grade lesions by cytology only had about a 42% sensitivity for high-grade lesions on biopsy. However, in general, that's a disturbing number. The whole goal is to come up with better ways to determine what we might find on colposcopy," he says.

Pathogenesis of HPV

When normal cells are infected by HPV, the infection may be cleared or it may persist. When it persists, the virus may integrate or not integrate. Viral integration leads to upregulation of E6/E7, which degrade the tumor suppressor gene p53 and the Rb gene. "HPV is circular and, in general, it stays in the cytoplasm as an episome," Patterson explains. "Under certain circumstances, it integrates and during integration it knocks out the E2 gene." Since E2 is a negative regulator of E6/E7, upregulation of E6/E7 on a cell-by-cell basis is an indication of the integration event.

Assessing E6/E7 expression PCR, however, can be tricky. "If you take a million cells from a Pap smear and put them into a PCR reaction, and get a million copies back on your instrument, you don't know if you have one copy per one cell, which equals a million, or 1,000 cells that have 1,000 copies of E6/E7, which equals a million and is abnormal," says Patterson. "PCR is the great averager, especially when you have a sample that has millions upon millions of normal cells with normal DNA and normal RNA." Patterson's approach uses flow cytometry, which allows for quantification on a cell-by-cell basis.

Toward New Technology

The histological patterns of cervical cancer and pre-cancer relate to E6/E7 expression in some interesting ways. According to Patterson, in CIN-1 the lower one-third of the epithelium is involved in cellular abnormalities, in CIN-2 about one-half of the thickness of the epithelium is involved, and in CIN-3 the full thickness is involved, with abnormal cells, high nuclear to cyoplasmic ratios, and mitotic figures. "If you look at cells that are a model of cervical cancer, they are very high expression [of E6/E7] throughout the epithelium," says Patterson. "In the W2 cell line [a model of CIN-1], only the lower third is affected, and you'll see the E6/E7 expression in this region. In normal control tissue, there is very little background. This work was done in the 1990s using radioactivity, and we wanted to adapt this type of assay for clinical use."

The key is how E6/E7 expression varies based on CIN status. "When you look at slides from biopsies, it shows the difference in E6/E7 expression in CIN-1 versus CIN-3," he continues. "There is going to be a quantitative difference in the amount of E6/E7 expression in terms of the number of cells that are expressing E6/E7 between these two histologic diagnoses."

A new test takes advantage of this finding. HPV OncoTect uses flow cytometry to quantify E6 and E7 mRNA, avoiding PCR's potential masking effects of normal RNA or a few copies of E6/E7 mRNA expressed in a large number of histologically normal cells. The test is made by Invirion Diagnostics (Oak Brook, IL), a company founded by Patterson in 1999, when he was on the faculty at Northwestern. He currently serves as CEO of Invirion.

"It is a robust technique that uses fluorescence in situ hybridization for E6/E7 messenger RNA in ectocervical cells in liquid-based cytology specimens," says Patterson, describing HPV OncoTect. "Previously, we had used antibodies to unequivocally identify ectocervical cells by either lack of expression of a marker called CAM 5.2, but currently we are able to tell the difference between ectocervical cells and endocervical cells by light scatter on the flow cytometer. In the study we published in 2005, it had a sensitivity of 83.3% and a specificity of 91.3% compared to cervical cytology, and it had a superior positive predictive value compared to HPV/DNA."

In March, HPV OncoTect received approval for reimbursement from two of Spain's largest insurance payors, Sanitas and Aresa. Distributed by Labec Pharma (Madrid, Spain). The test is CE marked and available throughout Spain and Portugal. Invirion also makes kits for monitoring HIV expression in cells and the detection of HCV RNA in extrahepatic reservoirs.

Urine Test to Detect Aspirin Resistance Cleared for Marketing

A new urine test promises to help physicians determine which patients can benefit from the popular aspirin-a-day regimen. By measuring the stickiness of platelets in urine, the test aids in the assessment of the response to aspirin, which approximately 50 million Americans take daily in an attempt to reduce their risk of heart attack and stroke. Research has shown, however, that at least a quarter of the population may reap no benefit from daily aspirin.

AspirinWorks, manufactured and marketed by Corgenix Medical (Denver, CO), is a quantitative enzyme-linked immunoassay that can determine levels of 11-dehydro-thromboxane B2 (11dhTxB2) in human urine. The Food and Drug Administration recently granted the test 510(k) marketing clearance, and Corgenix is now selling AspirinWorks test kits to clinical laboratories at a cost of $695 per test kit, a company representative tells *DTTR*. Each kit contains reagents for a 96-well plate run, which can accommodate up to 37 patient samples. AspirinWorks is also CE-marked, and it is sold throughout Europe.

Among the earliest adopters of AspirinWorks were Emory University and LabCorp; both now offer the test. In late August, direct-access testing provider HealthCheck-USA (San Antonio, TX) began offering the test to consumers nationwide for $85 per test, plus a $12 shipping and handling fee. For an additional $40, HealthCheckUSA offers optional telephone consultation with a physician concerning the test and test results.

AspirinWorks is not the first test of its kind. Light transmission aggregometry (LTA) has long been considered the gold standard for assessing inhibition of platelet function induced by aspirin. Used for over 40 years, this method evaluates luminosity as aggregation occurs in platelet-rich plasma following stimulation with a platelet agonist. However, the use of LTA is limited to specialized laboratories because of poor standardization and the skilled technical manipulation that the method requires.

Other available aspirin resistance tests include VerifyNow Aspirin, a CLIA-waived blood test manufactured by Accumetrics (San Diego, CA). Designed for use at the point of care and in laboratory settings, the qualitative test aids in the detection of platelet dysfunction due to aspirin ingestion in whole blood. The test is run on Accumetrics's VerifyNow system, a turbidimetric-based optical detection system that measures platelet induced aggregation as an increase in light transmittance. The system consists of an instrument, a disposable assay device, and controls.

In a study published in June in the *European Heart Journal*, a Montreal-based research team compared the results of six major platelet function tests in assessing the prevalence of aspirin resistance in a cohort of patients with stable coronary artery disease. The prevalence of aspirin resistance was found to vary widely based on the assay used, and the test results showed poor inter-method correlation and agreement, indicating that they are sensitive to different parameters.

Aspirin Resistance (Platelet Aggregation) Testing Methods

- ❑ Light transmission aggregometry
- ❑ Whole blood aggregometry
- ❑ Point-of-care blood testing
  - —Platelet Function Analyzer, PFA-100 (Dade Behring)
  - —VerifyNow Aspirin (Accumetrics)
- ❑ Urinary 11-dehydro-thromboxane B2 measurement
  - —AspirinWorks ELISA (Corgenix)
  - —ELISA (Cayman Chemical)*
  - —Radioimmunoassay (Gentaur)*

*For research use only in North America.
Source: *DTTR*

In an editorial that accompanied the study, Marco Cattaneo of the University of Milan criticized the available functional assays for lacking sufficient specificity to measure the effects of aspirin on platelet function. He noted that 11dhTxB2-based assays were preferable to other methods but posited that serum levels, not urinary levels, of 11dhTxB2 would provide the most specific test to measure the pharmacological effect of aspirin on platelets. In serum, the level of 11dhTxB2 is less likely to be influenced by blood cells other than platelets.

Center for Molecular Medicine Sees Good Response to CYP450AmpliChip Test

In the spring of this year, the Center for Molecular Medicine (CMM; Grand Rapids, MI), a joint venture between Spectrum Health and Van Andel Institute, added Roche's AmpliChip CYP450 test to its menu. It is the first laboratory in the Midwest to offer the pharmacogenomic test. According to CMM Executive Director Daniel Farkas, Ph.D., the test—and CMM's approach to communicating the results to physicians—is exceeding expectations.

Roche's FDA-approved and CE-marked CYP450 AmpliChip test analyzes variations in CYP2D6 and CYP2C19, enzymes that play a major role in drug metabolism. Approximately 25% of all prescription drugs are metabolized by these enzymes, including many of the most-prescribed drugs for treating depression. Based on CYP450 genotyping, patients can be classified into one of four phenotypic groups: ultra-rapid, extensive, intermediate, and poor metabolizers. These test results may be used by physicians to make more rational drug prescription decisions, reduce "trial and error" prescription and dosing, and guard against adverse drug reactions.

Labs Performing AmpliChip CYP450 Testing

- ❑ Affymetrix Clinical Services Laboratory
- ❑ Center for Molecular Medicine
- ❑ James A Haley VA Hospital (Tampa, FL)
- ❑ Georgia Esoteric and Molecular Diagnostics Laboratories
- ❑ LabCorp
- ❑ Specialty Laboratories
- ❑ Spectrum Laboratory Network

For example, the test can help to address a novel side effect in nursing infants whose mothers are taking codeine and are also ultra-rapid metabolizers of that drug. An FDA advisory issued in August recommended physicians order a CYP2D6 genotyping test to determine how the patient will metabolize codeine in advance of its prescription.

For the CMM, the decision to offer the test was an easy one. "Very simply, the test is cutting edge," says Farkas. "The CMM is designed as a 21st-century molecular diagnostics laboratory, and we're going to bring on the most current, most technologically advanced tests. The AmpliChip test fits the bill extremely nicely." The laboratory performs the test once per week at a cost of $900. Turnaround time is seven to 10 days.

AmpliChip testing at CMM started slowly, but education has led to rapid growth in volume. "I have been out and about in the community, educating physicians about the clinical value, and the test is really gaining traction," says Farkas. "We didn't do our first test for a month or two [after adding it to our test menu], but we've got a batch of 15 that we're running right now, so the volume is really on the upswing."

"We didn't do our first test for a month or two, but we've got a batch of 15 that we're running right now, so the volume is really on the upswing."

In discussing the test with physicians, Farkas emphasizes that the ability to respond to and metabolize certain drugs is genetically controlled. "I give them a list of drugs that are metabolized by the enzymes that are coded for by the genes on the chip, and they put it together rather quickly," says Farkas. "They understand that an ultra-rapid or a poor metabolizer of one of these drugs has sequelae, which could either be a toxic reaction or might require them to manipulate the standard dose."

Physicians are, of course, a highly educated audience, so it's not an issue of them grasping the test's clinical utility but of making the time in their busy schedules to get a handle on the details of the AmpliChip test and how to apply it to patient care. "In large part, it's a matter of exposure as much as education," notes Farkas.

Another critical component of offering AmpliChip testing is results reporting. Using software provided by Roche, the CMM provides physicians with the patient's genotype and phenotype but goes beyond that data, taking advantage of the pharmacological expertise of its partner hospital. "With each CYP450 test result, we also generate a pharmacist's consult, at no extra charge to the physician," explains Farkas, who notes that the cost is absorbed by the CMM. "I think it's crucial, because otherwise the physician, on top of his or her very busy schedule, is now turning into something of a pharmacist."

As noted on the CMM's Web site, the cost of the AmpliChip test is not covered by insurance. "We are in active dialogue with third-party reimbursers in Grand Rapids to explain to them not only the medical benefits but also, in many cases, the economic benefit of doing this test," says Farkas. "That's an ongoing, more challenging educational discussion, but I'm optimistic."

CMS Takes Steps to Reduce HCV Risks

The Centers for Medicare & Medicaid Services (CMS) on August 24 published an interim final rule with comment period outlining requirements for hospitals and other facilities that transfuse blood and blood components to reduce hepatitis C virus (HCV) infections in patients.

HCV infection is the most common chronic bloodborne infection in the United States, and approximately 7% of the estimated 3.9 million Americans ever infected with HCV were infected as a result of blood transfusion before the availability of donor screening tests.

The interim rule requires hospitals and other facilities to establish and maintain a written agreement with a regularly used blood bank governing procurement, transfer, and availability of blood and blood components; quarantine prior collections from a donor who is at increased risk for transmitting HCV infection; extend the time period of maintaining adequate records of the source and disposition of all units of blood and blood components from five years to at least 10 years from the date of disposition; and make reasonable attempts to notify a patient or the attending physician that they have received potentially HCV infectious blood or blood components when this occurs, as well as notify them of the need for HCV testing and counseling.

Collectively, several of these provisions establish a "lookback," requiring hospitals, when notified by blood banks, to quarantine prior collections from a donor who later tested repeatedly reactive for HCV, and to notify transfusion recipients based on further testing of such a donor.

The interim rule is effective Feb. 20, 2008, with comments due October 23. The agency will release a final rule within three years of publication of the interim rule.

IVD Stocks Rise 4%; Clinical Data and Luminex Climb

The 20 stocks in the G-2 Diagnostic Stock Index rose an unweighted average of 4% in the five weeks ended September 7, with 17 stocks up in price and three down. Year to date, the G-2 Index is up a whopping 30%, while the Nasdaq has gained 6% and the S&P 500 is up 3%.

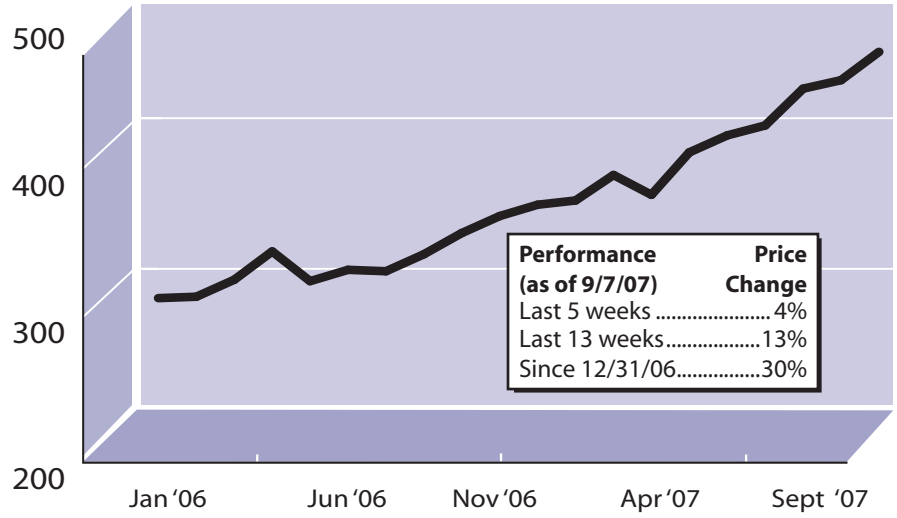
This month, **Cholestech** (Hayward, CA) leaves the index upon the delisting of its shares. On September 12, **Inverness Medical Innovations** (Waltham, MA) completed its acquisition of the company after Cholestech's shareholders approved the deal. The stock deal, valued at $363 million, was announced in June.

The acquisition will dramatically strengthen Inverness's presence in cardiac testing, including cardiac risk assessment and cardiac disease diagnosis. Cholestech also brings Inverness a CLIA-waived testing platform, the LDX system, which can rapidly test for lipids, glucose, alanine aminotransferase, aspartate aminotransferase, and high-sensitivity CRP in physician office laboratories.

Shares of **Clinical Data** (Newton, MA) soared 23% to $27.50 per share for a market cap of $436 million. In addition to its recent acquisition of Epidauros (see p. 4), the company recently announced that vilazodone, its candidate drug for depression, met various goals in a recent Phase III trial. The clinical study of 410 patients also identified potential genetic biomarkers for predicting response to the drug, which Clinical Data acquired the rights to in 2004 from Merck.

Meanwhile, **Hologic** (Bedford, MA) is expected to close on its merger with **Cytyc** (Marlborough, MA) this month. The diagnostic and imaging company began mailing definitive proxy materials in connection with the $6.2 billion deal to stockholders in mid-September, about a month in advance of its October 18 shareholder meeting. Cytyc plans to hold a shareholder meeting on the same day. Shares in the cytology testing leader were up 3% to $43.76 per share for a market cap of $5.2 billion.

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 20 IVD companies.

Up	Price	% Chg
Abaxis	$19.87	10%
Abbott Labs	51.86	2
Beckman Coulter	71.50	1
Becton Dickinson	76.77	1
Bio-Rad	83.14	12
Clinical Data	27.50	23
Cytyc	43.76	3
Dade	75.71	2
Immucor	32.08	1
Inverness Medical	47.33	3
Johnson & Johnson	61.68	2
Luminex	14.46	20
Meridian	26.34	19
OraSure	9.22	5
Quidel	16.77	15
Third Wave	7.89	8
Ventana	83.02	1
Down		
Affymetrix	23.19	-8
Gen-Probe	63.79	-3
Nanogen	1.03	-23

G-2 Insider

Myriad Premieres TV Ad for BRCA Test . . . Myriad Genetics (Salt Lake City, UT) is following the lead of Digene with direct-to-consumer marketing. However, Myriad's BRACAnalysis test, which costs $3,125, has a much smaller candidate pool, and some fear that the marketing push may lead to unnecessary testing.

Myriad's television ads premiered in selected Northeast markets (Boston, Hartford, Providence, and New York City) in mid-September and will run through next spring. They direct women to talk to their doctor and consult Myriad's Web site or call their toll-free number for more information. Four years ago, the company piloted the ad in the Atlanta and Denver markets and found that BRCA testing increased by 30%.

Performed only by Myriad, the BRACAnalysis test detects alterations in the BRCA1 and BRCA2 genes to help determine a woman's risk of developing breast or ovarian cancer and has become the standard of care in identification of individuals with hereditary breast ovarian cancer (HBOC) syndrome.

The ads are part of Myriad's newly launched "BRACAnalysis Awareness campaign." The company says that the campaign is designed to reach women with a family history of breast and/or ovarian cancer and their healthcare providers. Now being conducted across the Northeast, the campaign also includes physician education and outreach, consumer education, and public relations.

Critics say the commercial suggests that any woman with a relative with cancer should be tested for BRCA mutations, but only 2% of women in the general population may be good candidates for testing. In addition, experts question whether there are enough genetic counselors to meet an increase in demand that could result from the ad campaign.

Company References

Accumetrics 858-643-1600
ACMG 301-634-7127
CMM 616-391-4330
Chiron 510-655-8730
Clinical Data 617-527-9933
CMS 877-267-2323
Corgenix 303-457-4345
Cytyc 508-263-2900
Dade Behring 847-267-5300
Digene 301-944-7000
Epidauros 49-8158-99-85-0
Gen-Probe 858-410-8000
HealthCheckUSA 800-929-2044
Hologic 781-999-7300
Inverness 781-647-3900
Invirion Diagnostics 630-572-2800
FDA OIVD 240-276-0450
Myriad Genetics 801-584-3600
Qiagen 800-426-8157
Roche Molecular 925-730-8200

Diagnostic Testing & Technology Report (ISSN 1531-3786) is published by Washington G-2 Reports, 3 Park Avenue, 30th Floor, New York, NY 10016-5902. Tel: 212-244-0360. Fax: 212-564-0465. Order line: 212-629-3679. Web site: www.g2reports.com.

Stephanie Murg, Managing Editor; Dennis Weissman, Executive Editor; Janice Prescott, Sr. Production Editor; Perry Patterson, Vice President and Publisher; Joe Bremner, President.

Receiving duplicate issues? Have a billing question? Need to have your renewal dates coordinated? We'd be glad to help you. Call customer service at 212-244-0360, ext. 2.