



## **New diagnostics: Advances in immunoassay technology, genomic testing are poised to change industry structure.(Report)**

Biomedical Business & Technology

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1 October 2007

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SAN DIEGO The clinical diagnostics industry has been a focus for acquisition activity over the past year, with deals ranging from the purchase of emerging technology-based companies by industry leaders as well as acquisitions that are changing the structure of the industry by integrating in vitro diagnostics with diagnostics imaging.

Two companies in particular, Siemens Medical Solutions (Munich, Germany) and Inverness Medical Innovations (Waltham, Massachusetts), have been involved in many of the industry's key transactions. Siemens has acquired the diagnostics business of Bayer (Leverkusen, Germany) as well as Dade Behring (Deerfield, Illinois) and Diagnostic Products (Los Angeles), while Inverness has expanded to a dominant position in point-of-care testing with the acquisitions of FirstCheck Diagnostics (Lake Forest, California), Biosite (San Diego), Cholestech (Hayward, California), Quality Assured Services (Orlando) and, most recently, HemoSense (San Jose, California). The combined value of those acquisitions was \$16.8 billion. The flood of acquisitions is an indicator of consolidation in the diagnostics market, as well as the value of companies in the sector.

New developments in diagnostic technologies are leading to expanded applications, and driving continued growth in the market. The annual meeting of the American Association for Clinical Chemistry (AACC, Washington), held here in mid-July, highlighted a number of recent developments in segments including immunodiagnosics, pharmacogenomics, molecular diagnostics and point-of-care testing, which are expected to provide a continued stimulus for the market. In particular, the expansion of personalized medicine, although occurring more slowly than some have predicted, is expected to result in an increased demand for diagnostic testing worldwide.

Immunodiagnosics: new developments

Immunodiagnosics, although a \$9.8 billion segment of the global clinical diagnostics market in 2006, continues to be a growth segment as new tests are introduced and advances in technology improve the capability of labs to meet demands for higher test volume. As shown in Table 1, which presents a breakdown of the immunodiagnosics market in 2006 excluding equipment and service revenue, particularly strong growth is expected for infectious disease tests, cardiac markers and tumor markers.

A new, development-stage tumor marker test was described at the AACC conference by Robert Klein, PhD, of IRIS Molecular Diagnostics (San Diego), a division of IRIS International (Chatsworth, California). The assay uses a combination of immunoassay and polymerase chain reaction (PCR) methodologies acquired from Leucadia Technologies (Carlsbad), enabling a significant enhancement in sensitivity compared to existing immunoassays.

Klein said that, in principle, the assay technology, dubbed Nucleic Acid Detection Immunoassay (NADIA), can achieve a sensitivity of 10 molecules with a dynamic range of 10<sup>8</sup>. The first application being developed by IRIS molecular is an ultra-sensitive assay for the tumor marker prostate specific antigen (PSA). The new test will allow tracking of PSA levels below 0.1 ng/mL, the current limit of sensitivity for assays on the market, down to levels as low as 0.2 pg/mL, almost 10,000 times lower than existing tests. That will allow measurement of the low residual PSA level in patients who have radical prostatectomy, an important parameter since it has been shown to be directly proportional to the relapse rate.

About 15% of patients who undergo radical prostatectomy for treatment of prostate cancer exhibit a slowly rising PSA that is below 0.1 ng/mL, according to Klein, and eventually relapse. Those are the patients who will benefit from the test since their relapse will be detected earlier, allowing more effective follow-on therapy. The company is now in the process of obtaining FDA clearance for the NADIA PSA assay.

Such high-sensitivity assays may also have applications in measurement of other tumor markers, providing earlier detection of cancer or of relapse, and in measurement of certain cardiac markers such as cardiac troponin, since recent evidence indicates that low-level elevations of troponin can have prognostic significance. More importantly, as discussed by Klein, high-sensitivity assays are expected to enable about a 50-fold expansion in the number of protein markers that can be analyzed in the clinical lab. At present, due to the sensitivity limitations of existing immunoassays of about 10-15 molar, only about 2,000 proteins are routinely analyzed by clinical labs.

However, about 100,000 proteins are believed to exist in human blood, most of which are not analyzed due to limitations of existing assays. New high-sensitivity tests could potentially drive a significant expansion of the immunoassay market by enabling an entirely new set of markers to be analyzed.

Other new products for the immunoassay segment described at the AACCC conference include AIMS, a new automated multiplex immunoassay system from Inverness Medical; FlexMAP 3D, a new multiplexed analyzer in development by Luminex (Austin, Texas); a new point-of-care cardiac marker test for myeloperoxidase from Biosite; and a development-stage high-volume analyzer from Abbott Diagnostics (Abbott Park, Illinois), the i4000SR.

IMI's AIMS Automated Immunoassay Multiplexing System is a microplate-based analyzer that can perform ELISA assays as well as the AtheNA Multi-Lyte fluorescence assays developed by Zeus Scientific (Raritan, New Jersey). The AIMS incorporates the Luminex 100/200 IS Total System as a component, which provides detection and analysis capabilities for the AtheNA assays. The AIMS menu is initially focused on infectious disease and autoimmune disease serology testing. The system is now in beta testing and is targeted for market introduction during fall 2007.

The FlexMAP 3D from Luminex, which is targeted for market launch in summer 2008, will allow simultaneous measurement of up to 500 analytes in a single microplate, versus the 100-plex capability of the existing Luminex system. In addition, the FlexMAP 3D will add up-front automation with an X-Y platform and on-board fluidics including magnetic bead separation, as well as new software that will, for example, enable a new assay protocol to be automatically stored in the system via a single run. With the i4000SR, Abbott will enter the high-throughput automated immunoassay segment, which includes products such as the UniCel DxI 800 from Beckman Coulter (Brea, California).

#### Mass spec emerging

Mass spectrometry is an emerging technology that is vying to replace existing immunoassay technologies for analysis of certain analytes in the clinical lab, as discussed in a number of sessions at the conference. Mass spectrometry, including liquid chromatography/mass spectrometry (LC/MS) and tandem mass spectrometry (MS/MS), is not a new technique, having been employed for biochemical analysis in pharmaceutical research and industrial testing for many years.

Efforts to use mass spectrometry in clinical diagnostics accelerated four to five years ago, aimed at taking advantage of the technology's ability to eliminate certain analytical limitations of immunoassays. For example, testosterone immunoassays, while providing accurate results for the high levels found in men, are not accurate at the lower levels found in women and children.

LC/MS is less susceptible to interferences from molecules that bind to testosterone or from molecules that are structurally similar to testosterone, and provides more accurate results at low levels. In general, LC/MS and tandem mass spectrometry offer advantages over immunoassays for analysis of most small molecules for similar reasons. In addition, cost per test, at least for consumables and equipment, is typically much lower for mass spectrometry assays compared to commercially available immunoassays.

Suppliers of LC/MS and tandem MS systems, including Thermo Fisher Scientific (Waltham, Massachusetts) and Waters Corp (Milford, Massachusetts), have accordingly promoted their systems for use in clinical diagnostics, and, as discussed by Ravinder Singh, PhD, of Mayo Clinic (Rochester, Minnesota) at the conference, there is increasing interest in the technology in the clinical lab.

However, implementation has not gone as quickly as expected by backers, due to a number of factors, including low throughput, difficulties with regulatory clearance, lack of automation, and the need for highly skilled operators to run the equipment.

There has been some adoption, as discussed by William Clarke, PhD of Johns Hopkins School of Medicine (Baltimore), for applications such as tricyclic antidepressant assays, partly because quantitative

immunoassays are no longer available, and Clarke's lab has developed 13 drug assays performed by mass spectrometry.

Pierre Marquet, PhD, of University Hospital (Limoges, France) described new mass spectrometry assays developed in his lab for immunosuppressants such as cyclosporine, everolimus and sirolimus. Cost was an important incentive to develop the assays in this case, since consumables and equipment costs are typically about 60 cents for a mass spectrometry assay compared to \$2 to as much as \$20 for commercial immunoassays.

In spite of the advantages of mass spectrometry, however, it appears unlikely that there will be a significant degree of conversion from conventional immunoassay technology to mass spectrometry, due mainly to lack of automation, the need for on-going assay support by the lab since most tests are developed in-house, the need for skilled operators, and low throughput.

#### Pharmacogenetic testing expands

Another area addressed in multiple sessions at the AACC conference expected to become a significant segment of the molecular diagnostics market is pharmacogenetic testing, used to predict a patient's response to drug therapy including the potential for adverse drug reactions, response to chemotherapy agents, and response to anti-coagulation therapy. Those applications only represent ones for which pharmacogenetic tests are currently available, but nevertheless comprise over 2 billion physician encounters in the U.S. alone, as shown in Table 2.

As discussed by Kathryn Phillips, PhD of the UCSF Comprehensive Cancer Center (San Francisco) at an AACC plenary session, pharmacogenetic testing has the potential for a major positive impact in reducing adverse drug reactions, which are a major source of morbidity worldwide. According to Phillips, 59% of drugs cited in studies on adverse drug reactions have genetic mutations that affect drug metabolism, versus only 22% of all drugs.

Adverse drug reactions are the fourth leading cause of hospitalization in the U.S. and the fifth leading cause of death. Genetic testing for warfarin response has recently been advocated by the U.S. FDA through an addition to drug labeling requirements that highlights the opportunity for healthcare providers to use genetic tests to improve their initial estimate of what is a reasonable warfarin dose for individual patients.

#### Breast cancer pharmacogenetics

In oncology, the use of pharmacogenetic testing to select breast cancer patients for Herceptin therapy and to identify colorectal cancer patients likely to suffer an adverse response to Irinotecan therapy has been incorporated into drug labeling, making pharmacogenetic testing a requirement for prescribing the drug. The market for pharmacogenetic testing products remains a relatively small percentage of the \$2.4 billion global molecular diagnostics market at present.

One limiter of expansion for pharmacogenetic testing may be related to physician uncertainty about the true predictive value of the tests. For example, Phillips stated that data from insurers shows that only 56% of patients who are treated with Herceptin have a clearly positive test, indicating that, for almost half of patients, physicians (or perhaps patients) believe there is some possibility of benefit for the drug even though the test indicates otherwise. In addition, there is insufficient data from studies to assess the impact of pharmacogenetic testing.

A number of companies have developed or are developing pharmacogenetic tests for clinical diagnostic applications.

As shown in Table 3, Roche Diagnostics has an FDA-cleared microarray manufactured by Affymetrix (Santa Clara, California) on the market used in CYP450 analysis, and a number of other companies are developing microarray-based devices with applications or potential applications in pharmacogenetic testing, as well as for other molecular diagnostics applications.

The Affymetrix microarray technology is also being used to develop chemotherapy response tests for certain cancer drugs. For example, as discussed by William Evans, PharmD, of St. Jude Children's Research Hospital (Memphis, Tennessee) at an AACC plenary session, an Affymetrix array capable of analyzing approximately 30,000 genes has been used to characterize genetic variations affecting response to chemotherapy in acute lymphoblastic leukemia patients. Evans has found that analysis of a relatively small number of genes, ranging from 20 to 42, is sufficient to discriminate sensitivity or

resistance to the four most commonly used anti-leukemia agents, as well as to predict long-term disease free survival.

#### Personalizing via pharmacogenetics

Not all pharmacogenetic tests employ microarray platforms, however. For example, Third Wave Technologies announced a collaboration with Laboratory Corporation of America (Labcorp; Burlington, North Carolina) during the conference to develop a companion diagnostic to help physicians personalize treatment for heart failure patients. The test is being developed with Third Wave's Invader chemistry to analyze genetic variations involved in response to bucindolol, a drug that promises to be the first genetically targeted cardiovascular agent, developed by **ARCA Discovery** (Denver). Third Wave will develop the Invader assay, and Labcorp will handle regulatory approval of the test.

Another molecular diagnostics technology that may find applications in pharmacogenetic testing, as well as in molecular pathology for applications such as cancer staging, is comparative genomic hybridization (CGH), discussed in an AACCC plenary session by Daniel Pinkel, PhD, of the University of California San Francisco. CGH assays are available from a number of companies, but clinical applications have been slow to develop due to regulatory hurdles.

CGH is particularly powerful for analysis of diseases or genetic characteristics that arise from gene duplications or deletions, including mental retardation, renal disorders, diabetes, and autism, according to Pinkel. CGH patterns also are of potential value in diagnosis and management of cancers such as melanoma, where a correlation has been observed between disease grade and CGH patterns, as well as between markers associated with disease severity (e.g., the KIT gene) and CGH test results.

Pinkel said that there is now an explosion in clinical CGH testing for medical genetics and malignancies. However, barriers to expanded use include the current high cost of the technology (which results from the need for pathologist interpretation of CGH patterns) and lack of reproducibility of test results for certain types of genetic changes.

#### Illumina set to enter pharmacogenetics

Illumina (San Diego) is another potential player in the pharmacogenetic testing market, with the development of three molecular testing platforms including a high-throughput sequencing platform, bead array technology, and the Veracode assay technology which is the primary platform for clinical diagnostic applications and was acquired via the purchase of CyVera (Wallingford, Connecticut) in 2005. At present, the primary source of revenue for the company is its high-throughput sequencing platform, sold to the life science research market and employing its high-level multiplexing Bead Array technology.

Illumina's revenue reached \$185 million in 2006, and has increased at a compound annual rate of 107% since 2002. The company is now planning to enter the clinical diagnostics market with its BeadXpress platform, focusing on lower multiplex genotyping, gene expression, and protein assays.

Launch of a BeadXpress system for the molecular diagnostics market along with several assays is targeted for 2007. The system can potentially perform both immunoassays as well as nucleic acid tests on the same microplate simultaneously, providing the capability for labs to integrate both modalities in a single system. The cost of the existing Illumina instrument is \$98,500, and cost for the microbeads used in the assay is comparable to that for other bead-based assays systems now on the market (for instance, those from Luminex).

#### Others in the pharmacogenetic race

Nanogen (San Diego) has been supplying pharmacogenetic testing products for the clinical market outside the U.S. for over a year. Nanogen introduced the DrugMEt assay, which detects variations in genes including CYP2D6, CYP2C9, and CYP2C19, as well as duplication and deletion of the CYP2D6 gene, in May 2006 outside the U.S. The DrugMEt assay was developed by Oy Jurilab Ltd. (Kuopio, Finland) and is distributed exclusively by Nanogen. Nanogen also plans to introduce pharmacogenetic tests for warfarin response for its NanoChip 400 system, which employs reusable electronic microarray technology. The company has already introduced pharmacogenetics research reagents for CYP2C9 and VKORC1, which are the primary genes targeted for analysis in warfarin response testing.

Nanogen views the pharmacogenetic testing market as a high-growth segment, and plans to introduce additional assays for that market.

AutoGenomics (Carlsbad, California) recently has received FDA 510(k) clearance for its pharmacogenetic warfarin response assays for CYP2C9 and VKORC1 that run on its Infiniti analyzer. In addition, 22

Analyte Specific Reagent tests are available on Infiniti including tests for CYP4502D6 and UGT1A1, as well as a genotyping assay for Human Papilloma Virus (HPV). The tests employ the AutoGenomics BioFilmChip platform, and are priced at \$30 per chip. The company has placed 25 Infiniti analyzers to date.

#### Pharmacogenetics attracts IVD segment

The pharmacogenetic testing segment has obviously attracted a number of companies in the in vitro diagnostics market, and more are likely to enter in the future. At present, the market remains in an early stage, with some suppliers (e.g. Roche) experiencing a somewhat slow uptake of their pharmacogenetic testing products, while others such as Nanogen quote market growth rates in excess of 20%.

Initiatives by the FDA to promote the use of pharmacogenomics in drug development are cited by a number of companies expected to drive market expansion, and the recently implemented labeling change for warfarin is an indicator of that trend. However, some barriers remain, such as limitations on reimbursement for pharmacogenetic testing that are likely to limit growth at least in the near term.

Long-term, the large target patient population for pharmacogenetic testing, coupled with the value of testing in reducing adverse events, indicates that pharmacogenetics will become a significant segment of the molecular diagnostics market.

SOURCE-Biomedical Business & Technology

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