

Healthcare & Life Sciences

Vital Signs

Strategic Insights for Healthcare Executives

July 3, 2006

This Week's Industry Focus: Clinical Diagnostics

The Expanding Role of IVD in U.S. Healthcare

Author: Martin Nejat

The in vitro diagnostics (IVD) industry is expected to experience tremendous growth over the near term. Several key areas such as companion diagnostics are predicted to revolutionize healthcare. Due to the increasing utility of IVD in healthcare and predicted growth, Frost & Sullivan recommends increased focus in IVD industries.

What is in vitro diagnostics?

IVD refers to tests performed on a patient sample such as blood, urine, or tissue. Physicians request these tests at various stages of disease diagnosis and patient monitoring. Often a physician speculates about the cause of patient symptoms until a diagnostic test is performed to establish a definitive diagnosis. There is an important distinction between in vitro diagnostic tests and medical imaging diagnostic tests. In-vitro tests, from the Latin "in glass," are performed outside the body on biological specimens; in-vivo tests, from the Latin "in life," are imaging procedures such as x-rays and CAT scans designed to look inside of the body.

Nearly every American has received an IVD test at some point in their lifetime; the first instance usually occurs at birth. It has been estimated that 70-80% of medical decisions are based on results from diagnostic tests. However, diagnostic spending make up approximately 2% of total healthcare costs and 1.6% of Medicare costs. IVD tests cost significantly less than nearly all types of medical procedures such imaging tests, surgeries, and most types of therapy. A relatively small investment by a physician in utilizing the most appropriate IVD tests results in lowering overall healthcare costs while improving the patient quality of life. Avoiding misdiagnosis, establishing diagnosis at an earlier stage, and determining the optimal course of therapy are significant ways that IVD tests can lower overall healthcare costs.

New technologies combined with a greater understanding of biochemistry facilitate an increased utility for IVD tests. Simply put, a significantly greater amount of accurate, clinically actionable information is attainable from a patient sample than ever before.

The IVD Market

In 2005, the IVD market accounted for approximately \$12 billion in annual revenues in the U.S. and was one of the fastest growing segments of the healthcare market. IVD tests are typically classified according to the following types: clinical chemistry, immunochemistry, microbiology,

hematology, point of care, hemostasis/coagulation, and molecular diagnostics.

Currently healthcare spending accounts for approximately 15% of the \$11,134.8 billion U.S. 2005 GDP (Gross Domestic Product), which amounts to staggering \$1,670 billion. Indeed healthcare accounts for a large slice of the US GDP.

With a budget deficit at an all time high, there is substantial incentive to reduce this number. The IVD industry presents solutions that are able to reduce overall healthcare costs.

The Three Ps of Healthcare: Predictive, Preventative, and Personalized Medicine

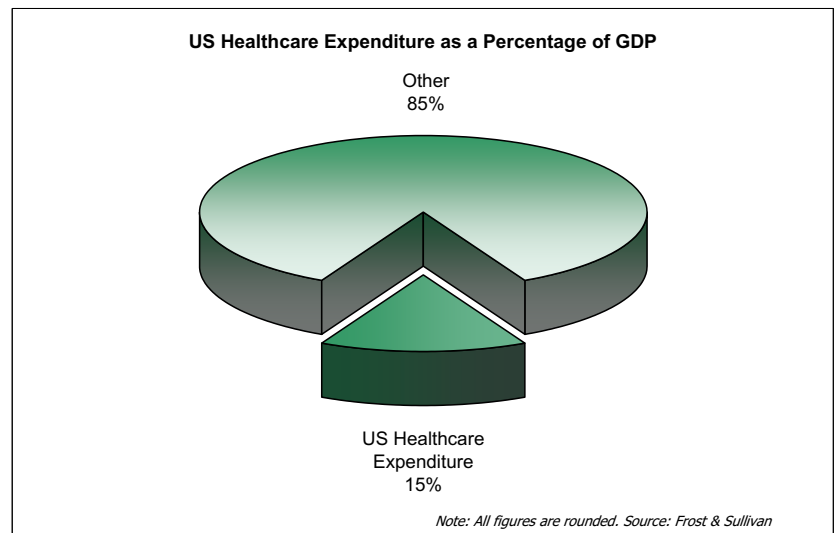
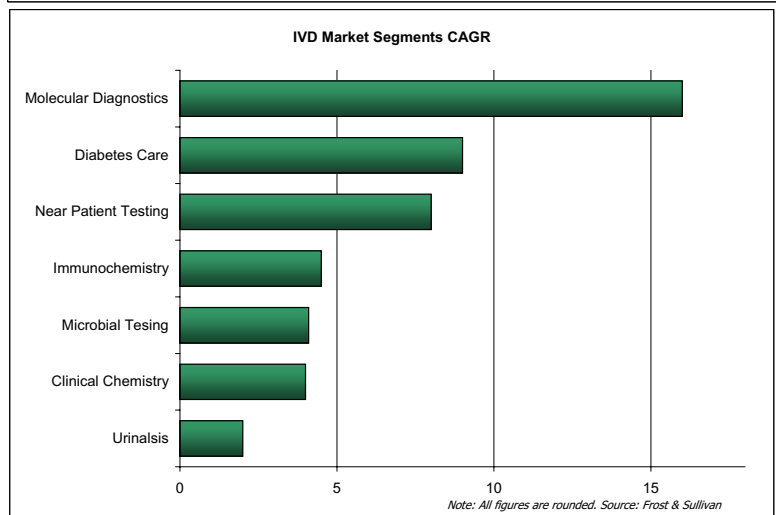
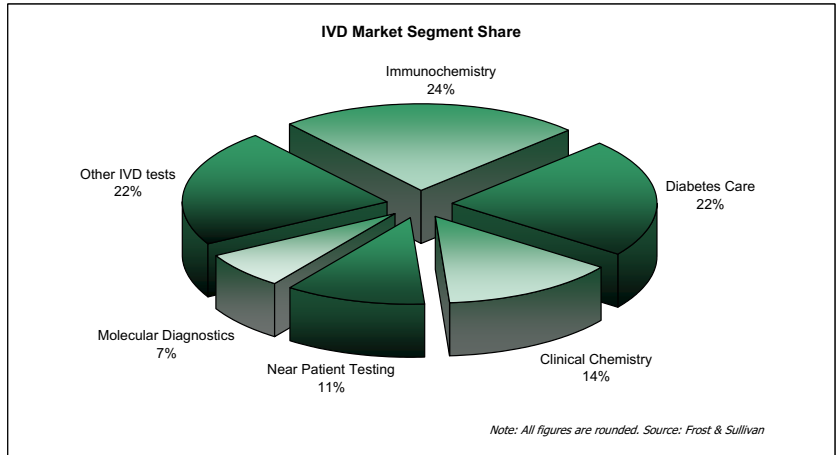
Treatment costs for many common ailments such as cancer, diabetes, cardiovascular problems, and osteoporosis are considerable. Not surprisingly, it is more cost effective to prevent such conditions, or diagnose them at an earlier point, than to treat them after the onset of symptoms. Knowing the likelihood of an event allows a patient and physician to take steps to prevent, delay, or minimize the problem. Moreover, personalizing the medication process has shown to reduce adverse reactions and mitigate unneeded therapy.

Consequently, there exists a significant trend towards predictive, preventative, and personalized medicine. The IVD industry is in line with this trend by offering assays that are predictive and can personalize the treatment process. The new direction of healthcare facilitates an increased role of IVD tests in all aspects of patient management.

IVD companies offer predictive tests and tests that can detect cancer at an earlier stage for several cancer types. Work is underway by companies such as Gen-Probe and Invitrogen to develop such tests for other conditions through the discovery and validation of biomarkers such as genes and proteins that are predictive for the likelihood of medical problems.

The Utility of Companion Diagnostics

Companion diagnostics, the newest paradigm in U.S. healthcare, is a substantial step toward personalized medicine. It essentially consists of the coupling of a therapy, typically drug therapy, with a diagnostic test. Many drugs are prescribed on a trial and error basis. In the past, the factors leading to a therapy decision include patient symptoms and a physicians past experience with the therapy. The persuasive abilities of drug reps are also significant in the equation. Therapeutic concentration (dosage) of drug has normally been determined by considering sex,



weight, age, and level of physical fitness.

Companion diagnostics offer a more analytic alternative to this trial-and-error method of prescribing drugs. A patient's ability to respond to a certain drug is measurable through a variety of means. Metabolic enzyme tests can determine a patient's ability to respond to a drug and help determine the optimal dosage. Cytochrome (CY) P450, a class of enzymes that metabolize approximately 80% of pharmaceuticals, can be genotyped through a variety of methods already available to U.S. physicians. Determining the CYP450 metabolic ability allows physicians to make more informed decisions regarding treatment and dosage decisions. Currently, nearly a dozen pharmaceuticals come with CYP450 warning on the labels.

Another area where companion diagnostics has demonstrated clinical utility is in cancer treatment. Cancer is a serious condition both in terms of high risk of mortality and cost of treatment. Cancer treatment costs thousands of dollars, and adverse side effects are prevalent and severe. Thus any option that allows clinicians to determine an optimal therapeutic strategy is well justified, and has considerable value for clinicians. Her2/neu testing, a prerequisite for Herceptin treatment, has demonstrated this to the medical community. Approximately 20% of breast cancer patients have over expression and multiple copies of this gene, which permits them to respond well to Herceptin treatment.

The companion diagnostic tests that have demonstrated clinical utility are favorable to the insurance industry. It is profitable for them to use a test that deems when a patient should not receive a certain therapy. A reduction in unneeded medication, minimization of adverse side effects, and better dosage decisions are all profitable events for insurance companies.

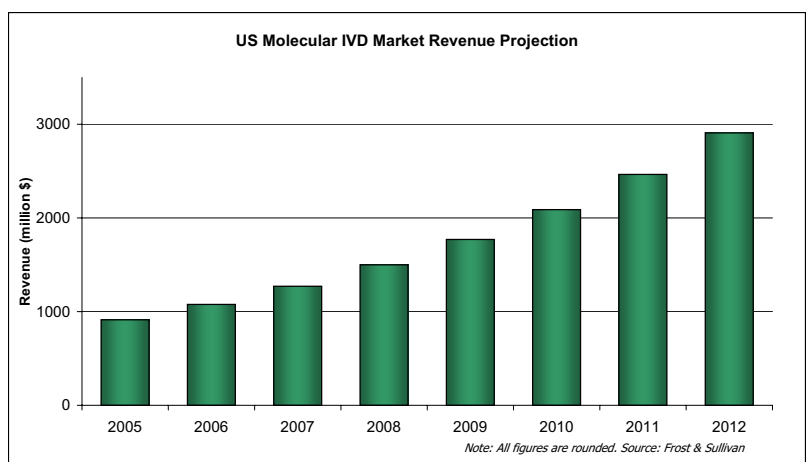
Recently, the FDA has taken steps to pave the way to increase incorporation of pharmacogenomic and other companion diagnostic considerations during drug clinical trials. It has implemented guidelines and procedures for the submission of pharmacogenomic data. The impact has been to encourage pharmacogenomic data to be submitted during the drug approval process.

Companion diagnostics has increased cooperation between diagnostic companies and pharmaceutical companies. Nearly every diagnostic company in the U.S. has established or is seeking opportunities with pharmaceutical companies. For the diagnostic partner, the collaboration typically results in complete marketing rights of the diagnostic tests. The pharmaceutical partner enjoys faster approval time and higher market penetration rates.

Evolving Role of Molecular Diagnostics

Molecular diagnostics is the fastest growing segment of the IVD market. Cancer, pharmacogenomic, and infectious disease testing are the market leaders for this type of testing. Cardiology and neurologic genetic tests are expected to follow.

Molecular tests have currently demonstrated highest utility in infectious disease testing. Infectious agents have smaller genomes compared with complex eukaryotic organisms. Therefore, genetic analysis of bacteria and viruses and has led to subsequent development of a validated diagnostic test for infectious agents. Detection of a bacterial or viral genetic marker in a patient sample has immediate clinical consequences, as it is sufficient to establish a diagnosis for that virus. Genetic tests for infectious diseases also permit diagnosis to occur at an earlier stage as higher sensitivity of molecular tests allow for a lower quantity of infectious agent to be detectable in a patient sample.



Viral load testing is used to monitor a virimically-infected patient's response to drug therapy. Typically, a physician will order a baseline viral load reading before starting the therapy, essentially establishing the number of viruses in the patient. Any change to this viral number indicates

the patient's response to treatment. This makes viral load testing a valuable part of therapeutic management for patients infected with such viruses as HIV or HCV.

Molecular diagnostics are a primary example of the type of innovative solutions offered by the IVD market. They are central to the effort of predictive and personalized medicine. Molecular diagnostics have the potential to decrease the overall cost of healthcare by establishing diagnosis at an earlier stage in the disease cycle before the onset of disease.

Significant steps have been made in this regard with several tests for cancer. The BRCA test offered by Myriad Genetics is a primary example. This molecular test provides the patient and physician information about the likelihood of breast cancer occurrence. Oncotype DX, offered by Genomic Health Inc., provides predictive data to oncologists, which is used for cancer monitoring and treatment.

Pressures Facing the Clinical Laboratory

The clinical laboratory, considered the end-user for the IVD market, is facing a multitude of pressures. In the U.S., there is currently a shortage of qualified medical technologists. Compounding the problem is that volumes of many routine and specialty tests are at an all time high. The laboratory is facing an increasing number of choices in terms of diagnostic platform and testing options. The freeze on Medicare reimbursement rates puts further margin pressure on the clinical laboratory.

The problems of the clinical laboratory present a variety of opportunities for IVD companies. The solutions have come in the form of automated and integrated platforms that increase throughput and reduce workload by eliminating most manual steps. Instruments that offer a black box solution, essentially allowing the technician to place a patient sample in a box and walking away, are highly desired by in the clinical laboratory. Market participants also provide integration of a laboratory's instruments, sample preparation, and data storage. Many solutions are provided by LIS (laboratory information system) companies for system integration, data processing, and information storage.

IVD Presents Growth Opportunities

IVD tests are poised to play an even more significant part in healthcare. They are a critical part of new healthcare trends, and the development of companion diagnostics supported by validation of predictive medicine assays and technologies will support this effort. Consequently, there are many growth opportunities within the IVD market.

The increasing significance of IVD in healthcare spending is driving the recent mergers in the diagnostics arena by large healthcare companies that have not traditionally focused on the IVD market, but are now seeking to benefit from the expected growth. Recently, Siemens entered into acquisition talks with DPC, a manufacturer of immunoassay instruments and tests. Fisher, another large healthcare company, has acquired Athena Diagnostics, and they partly acquired Nanogen in the past year. Traditionally, mergers and acquisitions with IVD companies have allowed pharmaceutical, life science, and biotechnology companies to enter the IVD market.



The increasing role of IVD in U.S. healthcare presents considerable growth opportunities for healthcare companies. As a result, Frost & Sullivan recommends increasing attention towards IVD technologies, applications, and laboratories. The following diagram depicts some specific high growth areas in the IVD market.

Company Spotlight: Target Discovery

Target Discovery, Inc. (TDI), based in Palo Alto California, is an innovative personalized medicine company focused on the development of diagnostic tests to guide treatment decisions by measuring specific protein isoforms. Currently the company focuses on development of diagnostic assays in the area of oncology, particularly prostate cancer aggressiveness. TDI also engages in strategic, sponsored research collaborations with companies who want access to TDI's proprietary isoform discovery and validation technology.

Key Technology or Flagship Product:

In humans, it is estimated that approximately 22,000 genes code for over a million protein variants. About 5-10% of protein variability results from SNPs and splice variants at the genetic level; the vast majority of protein variability, however, results from post-translational modifications (PTMs). PTM's include forms of a given protein that are variably glycosylated, phosphorylated, cleaved into smaller pieces, and even different conformations (shapes) of the same polypeptide chain; all of these different "flavors" of a given protein are termed "isoforms". Protein isoforms may function very differently from their parent protein, and cancers and other diseases can produce altered protein isoforms in the body. Thus detection of specific protein isoforms, which has been historically difficult due to technological limitations, can diagnose human disease.

Current molecular diagnostic and immunodiagnostic products cannot detect and quantify protein isoforms, thus limiting their utility. Target Discovery's proprietary technology allows for rapid identification and validation of this new type of biomarker, allowing for rapid translation into clinically validated diagnostic tests. Central to Target Discovery's market strategy is their patented Mass Defect technology (US patent No. 6,962,818) that uses isotope-differentiated binding energy shift tags (IDBEST™) to validate the levels of clinically relevant isoforms in known biomarkers. Based on this system TDI is uniquely positioned to bring to market diagnostic tests based on isoforms in what is termed Isonostics™.

A growing body of scientific evidence published in peer review journals supports the utility of Isonostic™ biomarkers. Target Discovery is a great example of a company that is expanding the role of diagnostics and personalized medicine in healthcare.

Noteworthy Milestones:

- **February 20, 2002** – TDI secures \$4.6 Million in financing.
- **July 8, 2003** – TDI appoints Juan Santiago, Ph.D, and Evan Williams, Ph.D., to Scientific Advisory Board
- **August 27, 2003** – TDI receives Series A financing, bringing its total to over \$7 million.
- **June 3, 2004** – TDI entered into an OEM reagent supply agreement with Groton Biosystems for their capillary electrophoresis platforms.
- **March 2006** – TDI established collaboration with The Virginia Prostate Center of Eastern Virginia Medical School in the area of prostate cancer theranostics.
- **April 2006** – TDI signed collaboration agreement with M.D.Anderson, one of the leading cancer research and treatment institutions in the world. The scope of this partnership is broad, but it will allow Target Discovery to utilize cancer patient samples in order to discover and validate Isonostic™ biomarkers.
- **Present** – TDI is raising a B-round of investment to speed product development.

Contact Information:

Mailing Address: Target Discovery, Inc.
4030 Fabian Way
Palo Alto, CA 94303-4607
Web Address: <http://www.targetdiscovery.com>

Telephone: 1.650.812.8100
Toll Free: 1.877.834.4620
Facsimile: 1.650.812.8130
Email: info@targetdiscovery.com

Reimbursement & Regulatory News

Recent FDA Announcements:

Date	Company	Device Name	Function	Designation
26-Jun	Styker Corporation	OP-1 Putty	Posterolateral lumbar spine fusion surgeries	premarket approval
26-Jun	Lupin Pharmaceuticals (Baltimore, MD)	Quinapril	Treatment of hypertension	Abbreviated New Drug Approval
23-Jun	Ortho Biotech Products, L.P. (Raritan, NJ)	Prezista (darunavir)	Treatment for HIV infected patients that are not responding to existing drugs	approval
23-Jun	IVAX Pharmaceuticals Inc. (Northvale, NJ), Ranbaxy Pharmaceuticals, Inc. (Princeton, NJ)	Generic Simvastatin	Zocor generic that reduces amount of certain fatty acid substrates	approval
23-Jun	Endo Pharmaceuticals (Chadds Ford, PA)	Opana® ER, Opana®	Relief of moderate to severe pain for patients needing round the clock treatment	New Drug Application final FDA approval
21-Jun	Morphotek Inc. (Exton, PA)	MORAb-003	Treatment for ovarian cancer	Orphan Drug Status

Recent CMS Coverage Announcements:

Wednesday, June 21, 2006

The Centers for Medicare & Medicaid Services (CMS) announced proposed changes to physician fee schedule methodology that will improve accuracy of payments to physicians for the services they provide to Medicare recipients.

The Frost & Sullivan Healthcare Group specializes in closely monitoring the healthcare marketplace to provide critical information, opportunities, and strategic recommendations for market participants. Our global team of highly skilled industry analysts and consultants are educated and experienced in a variety of healthcare market sectors, and maintain well-developed, long-standing relationships with key industry participants. Leveraging these assets, the team provides clients with comprehensive industry knowledge, including detailed coverage of market, technology, economic, and customer-focused trends and forecasts.

The Frost & Sullivan Healthcare team offers extensive coverage of the following markets and sectors:

Drug Discovery

- Proteomics
- Protein Markets
- DNA & Protein Microarrays
- Research Consumables
- High Throughput Screening
- Bioinformatics
- SNP
- Pharmacogenomics
- Mass Spectrometry
- Gel Electrophoresis
- Laboratory Information Systems

Medical Devices

- Cardiovascular Devices
- Orthopedic Devices
- Home Care
- Surgical and Infection Control Products
- General Medical Devices
- Hospital Supplies and Products
- Wound Care/ Management Products

Clinical Diagnostics

- Molecular Diagnostics
- Immuno-chemistry
- Point-of-Care
- Cell Culture
- In Vitro Diagnostics
- Genetic Testing
- Infectious Disease Diagnostics
- Cancer Diagnostics

Medical Imaging

- Core Imaging Modalities
- Imaging Agents
- Imaging Software
- PACS & Imaging IT
- Digital Imaging

Pharmaceuticals & Biotechnology

- Oncology
- Drug Delivery
- Biotechnology
- CNS
- Contract Manufacturing
- Contract Research
- Ophthalmics
- Chronic Diseases

Patient Monitoring

- Cardiac Monitoring
- External Defibrillators
- Multi-Parameter Monitoring
- Glucose Monitoring
- Blood Pressure Monitoring
- Temperature Monitoring
- Pulse Oximetry
- Remote Patient Monitoring
- Patient Monitoring IT
- Sleep Apnea Monitoring

Healthcare & Life Sciences IT

- Electronic medical records
- Data and storage management
- Emerging wireless technologies
- Acute Care Information Systems
- CPOE
- Enterprise clinical information systems
- Claims management through IT
- RFID in Healthcare
- RHIOs

CUSTOMIZED SERVICES

Growth Consulting - Clients may leverage our unique combination of market expertise, global presence, and relationships with key industry players for customized research, business strategy, consumer analysis, and organizational development projects. Clients get powerful and practical solutions to address their unique challenges and develop winning strategies for growth.

Customer Research - Clients gain insights into their customers behaviors and attitudes, find out what end users think of their company, and how their products should look and feel in the future. These analyses are designed to assist you in formulating and applying effective product marketing strategies across your product and service lines.

CONTACT US

Monali Patel
 Director, Healthcare Research
 t) 650.475.4506
 e) mpatel@frost.com

Ryan Goulding
 VP, Healthcare Consulting
 t) 650.475.4508
 e) rgoulding@frost.com

Stephen Mohan
 VP, Healthcare Sales
 t) 210.348.1032
 e) stephen.mohan@frost.com

Greg Caressi
 VP, Healthcare & Life Sciences
 t) 650.475.4555
 e) gcaressi@frost.com