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MOLECULAR DIAGNOSTICS



Molecular Diagnostic ASSAYS:

LEADING A HIGH VALUE EVOLUTION

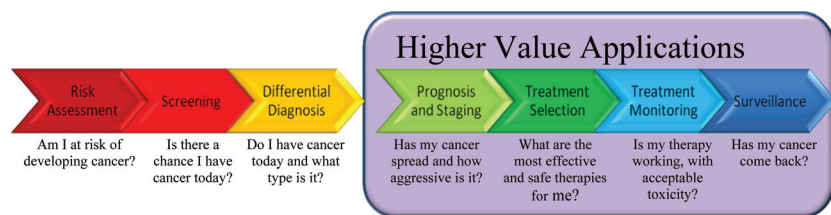
CLINICAL LABORATORY TESTING TODAY IS ON THE VERGE OF SIGNIFICANT CHANGE. DUE, IN PART, TO THE SEQUENCING OF THE HUMAN GENOME, MOLECULAR DIAGNOSTIC ASSAYS ARE BEGINNING TO APPEAR ON THE TESTING MENUS OF LABORATORIES AROUND THE WORLD WITH A POTENTIAL FOR FUNDAMENTALLY IMPACTING HEALTH CARE. THE FIRST WAVE OF THESE HIGH VALUE ASSAYS TO ENTER THE MARKET FOCUSED ON PREDICTING AND DIAGNOSING DISEASES, SUCH AS CYSTIC FIBROSIS, NON-HODGKIN'S LYMPHOMAS AND A VARIETY OF INFECTIOUS DISEASES. THE EXPECTATION IS THAT MOLECULAR DIAGNOSTICS WILL ULTIMATELY BECOME MORE OF A ROUTINE PART OF A PHYSICIAN'S ARSENAL, ENABLING THEM TO NOT ONLY PREDICT AND DIAGNOSE, BUT ALSO TO BETTER TREAT AND MONITOR DISEASE.

Traditional clinical diagnostic assays monitor the chemical and cellular biomarkers of diseases in the blood or other body fluids. Whether measuring electrolytes and liver enzymes, or white blood cells, these assays are performed by highly automated analyzers that quickly and easily provide results with a minimum of intervention by laboratory personnel. Despite the fact that they generate the majority of the data used for medical decisions, insurance reimbursement rates for clinical diagnostics have remained virtually unchanged over the past 30 years at around \$8.50/test. As a result, in-vitro diagnostic (IVD) companies have in the past been an unattractive area for investors, and the market, particularly for clinical

laboratory instrument companies, is in the midst of a consolidation.

The prognosis for the IVD market is changing today, with the development of higher value molecular diagnostics. It all began in 1985 with advances in gene amplification technologies and bioinformatics arising from the Human Genome Project. Based on the data generated through this multi-nation project, scientists now believe the human genome holds approximately 23,000 genes directing the blueprints of more than 100,000 proteins. Industry analysts estimate that if just 5% have diagnostic significance, 1,500 gene-, and 5,000 protein-based tests could be commercialized. Not surprisingly, the competition is on to identify clinically significant biomarkers, and molecular diagnostics has

Figure 1



become one of the fastest growing fields in clinical diagnostics. Its predicted growth rate during the next few years is estimated at 15-20%, reaching \$4 billion by 2010¹.

Newly developed high value tests with these biomarkers are beginning to transform healthcare by allowing physicians to answer a number of key medical treatment questions. In addition to their use as a true diagnostic test (do you or do you not have a disease), tests today can determine a person's predisposition for disease and their prognosis if they develop the disease. These tests can also provide information useful in selecting which medication is optimal and monitoring whether the medication is indeed halting disease progression. The improved sensitivity and specificity of these tests will also be important for monitoring patients for disease recurrence following therapy.

The high quality, quantitative data these molecular diagnostic tests offer and their positive impact on treatment decisions is what is driving their adoption throughout the world. These attributes are also helping to move the cost per test of these diagnostics into the value pricing models seen in the pharmaceutical and device market segments.

Among the first molecular diagnostic tests on the market were Gen-Probe's diagnostic assays for infectious diseases, such as chlamydia, gonorrhea and tuberculosis. Later, predictive assays were developed, such as Myriad Genetics' assays that are used to test for BRCA1 and BRCA2, two genes involved in many cases of hereditary breast and ovarian cancer. Assays for screening the blood supply for such difficult agents as the SARS, HIV and HCV viruses were then developed.

Particularly for complex diseases such as cancer, molecular diagnostics will provide a wellspring of information to help better

diagnose and treat these diseases. Cancer is a general term used to describe a group of over 100 diseases that are characterized by the uncontrolled growth and spread of abnormal cells. Some people develop cancer because of hereditary risk factors, such as the BRCA1 and BRCA2 genes, others because of

“The expectation is that molecular diagnostics will ultimately become more of a routine part of a physician’s arsenal, enabling them to not only predict and diagnose, but also to better treat and monitor disease.”

genetic mutations that accumulate in normal cells over a person's lifetime that can make those cells turn cancerous.

The importance of genetics in cancer was underscored in December 2006 when the U.S. National Cancer Institute and the U.S. National Human Genome Research Institute announced the initiation of The Cancer Genome Atlas, a project focused on uncovering the genetic abnormalities that contribute to cancer. During the three-year pilot phase of the project, \$100 million will be invested

in identifying biomarkers in tumour cells obtained from biopsies and surgery. The project could dwarf the Human Genome Project in cost and complexity.

While the first biomarker assays for cancer used blood as its substrate, companies are increasingly looking at bringing the power of molecular diagnostics to the analysis of human cells and tissues. The gold standard for cancer diagnosis has long been histology, where pathologists examine tissue samples under a microscope to determine whether the cells are normal, abnormal or somewhere in between. Quantitative molecular diagnostic tools add significant value to qualitative assays, identifying patient and tumour-specific information that provides valuable guidance to help better manage the disease.

Efforts in this area have already begun, with companies such as Agendia and Genomic Health launching molecular diagnostic tests for breast cancer prognosis that are performed with tumour tissue samples. The MammaPrint® and OncotypeDX™ assays are designed to assess the risk of breast cancer recurrence in patients, providing valuable information that oncologists can use in their assessments, along with the histopathology reports.

Another company working in this area is DiagnoCure, headquartered in Quebec City, QC. In 2003, the company formed a strategic partnership with Gen-Probe, a leading molecular diagnostics company, to further develop and commercialize a second-generation test for PCA3, DiagnoCure's highly specific genetic marker for prostate cancer. The test detects the presence of PCA3 mRNA in urine, which in clinical testing was shown to be predictive of the result of a repeat prostate biopsy in patients with an initial negative biopsy and elevated PSA, a common clinical dilemma. The test is now available through laboratories in the United States using PCA3 analyte specific reagents (ASR) from Gen-Probe and is available in Europe as the CE-marked PROGENSA™ PCA3 in vitro assay.

Determining whether a cancer has recurred, or has metastasized and spread elsewhere in the body, is an art as well as a science. Pathologists take tissue samples from the original tumour site and from lymph nodes in surrounding areas of the body, examine them under a microscope for the presence of cancer cells and then determine the stage of cancer that is present. Obviously, performing microscopic analysis

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of all the cells in each of many lymph nodes would not be technically feasible. Current molecular detection technologies can identify the presence of one cancer cell in 10 million cells versus the one in 200 cells identifiable by traditional microscopic methods. Clearly, a molecular diagnostic solution would be beneficial in assisting the pathologist in determining the status and stage of a patient's cancer.

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In 2008, DiagnoCure expects to be the first company to introduce a molecular diagnostic test for colorectal cancer that could determine whether the patient's cancer has spread to the surrounding lymph nodes, allowing more accurate disease staging and guiding therapy decisions. The test is based on the detection of GCC (Guanylyl Cyclase C), a gene that appears normally in cells

lining the intestinal track, but has only been found outside the intestine when colorectal cancer has metastasized. For colorectal cancer patients, surgical removal of the primary tumour is a cure only if the cancer has not spread. A patient's lymph node status is one of the most influential predictors of being surgically cured and remaining disease-free. But histological analysis of these lymph nodes is not foolproof. More than 30% of patients with microscopically negative lymph nodes (Stage I and Stage II cancers) experience disease recurrence and most die from disseminated colorectal cancer believed to arise from tumours or micrometastases that were missed during routine pathology examination².

DiagnoCure believes its GCC molecular diagnostic test could more definitively determine if the colorectal cancer has spread to the nodes and, therefore, whether additional treatment such as chemotherapy is required. Dr. Scott Waldman of Thomas Jefferson University in Philadelphia, upon whose work DiagnoCure's test is based, is currently conducting a 1,000 patient multi-center prospective study of the GCC test, with data to be reported in 2008.

Much of the current disease research is based on a systems biology approach that integrates biological data at the gene, protein, cell and tissue and organ levels to generate a comprehensive picture of a disease. With the

increasing availability of molecular diagnostic tests, information at the gene and protein level will soon be available to physicians, giving them a more complete picture and arming them with quantitative information to better diagnose, treat and monitor disease. Clearly, the role of diagnostics in health care and its value to clinicians and patients is changing, for the better.

References

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- 2 Annals of Internal Medicine, V131, December 7, 1999

John C. Schafer, president and chief executive officer of DiagnoCure, Inc., has over 30 years experience in the field of diagnostics along with an excellent track record in management and growth of high technology diagnostic companies.

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