

Executive Summary

The molecular diagnostics market has become a significant segment of the overall in vitro diagnostics (IVD) industry. With worldwide sales of about \$2.5 billion to \$2.8 billion this year for molecular diagnostics products sold to clinical laboratories, plus clinical laboratory testing service revenues of about \$3.2 billion per year in the United States alone in 2007, molecular diagnostics is a major market. Molecular diagnostics is also a rapidly growing and a rapidly changing segment of the overall IVD market.

Infectious Disease Testing

The first molecular diagnostics tests to reach the market were for infectious diseases, and infectious disease testing remains the largest segment of the molecular diagnostics market. This market segment has traditionally been dominated by a limited number of tests that include HIV, hepatitis C virus (HCV), hepatitis B virus (HBV), chlamydia, and gonorrhea.

One additional infectious agent, human papillomavirus (HPV), is joining this list of major tests. Revenues for HPV tests have grown at a rate of approximately 40% per year recently. HPV tests could also be considered to be cancer tests because these tests detect the presence of certain high-risk strains of HPV that are associated with cervical cancer and are used as part of the screening procedure for cervical cancer.

Molecular tests to screen for hospital acquired infections are also emerging as an important market segment. The first of these tests, for methicillin-resistant *Staphylococcus aureus* (MRSA), have already

reached the market. Yet, the infectious disease molecular diagnostics market is not limited to these major tests. Diagnostics companies are developing and commercializing tests for numerous infectious agents. Clinical laboratories have also developed their own in-house tests for many infectious agents as demand for these testing services has preceded the availability of commercial reagents or tests from diagnostics companies.

Molecular Oncology Applications

In addition to the infectious disease area, molecular diagnostics technology is now being applied in a wide range of applications. Another major market segment consists of molecular oncology tests. A significant challenge for diagnostics companies in developing molecular diagnostics tests for cancer has been the identification and validation of biomarkers for cancer, but progress is being made and tests are reaching the market.

These cancer tests can be used for many different indications, including identifying patients at risk of developing cancer, screening for early detection of cancer, determining prognosis, predicting response to therapy, and monitoring patients during and after treatment. One example of an exciting new application of molecular diagnostics in cancer is the development of microarrays to evaluate expression of many different genes to predict prognosis. An early example is Genomic Health's Oncotype DX, which is being offered to physicians as a service, and which provides a quantitative assessment of the likelihood of disease recurrence for a woman with breast cancer. Oncotype DX evaluates expression of 21 cancer-related genes. In addition, Agendia has received FDA clearance for the MammaPrint test, which profiles the expression of 70 genes involved in various aspects of cancer. These and several other examples of molecular diagnostics tests for the field of oncology are discussed in this report.

Genetic Testing

Another important segment of molecular diagnostics is genetic testing, which can be divided into 2 categories: testing for inherited disorders, and testing for genetic changes that increase a person's risk of developing certain diseases. The markets for most tests for inherited disorders are small, although overall this is a significant segment due to the large number of inherited diseases that exist. One inherited disease that has emerged as a significant market opportunity for molecular diagnostics tests is cystic fibrosis, which results from a mutation in the gene for cystic fibrosis transmembrane regulator (CFTR).

Even though the number of babies born with cystic fibrosis each year is small, more than 10 million Americans are carriers for cystic fibrosis. Current guidelines recommend that all couples planning a pregnancy or seeking prenatal care be screened for cystic fibrosis, as well as family members of patients with cystic fibrosis, and partners of individuals who are affected with cystic fibrosis or who are carriers for cystic fibrosis. Cystic fibrosis has emerged as a significant market opportunity, and is becoming a highly competitive area as several molecular diagnostics companies develop and commercialize tests. However, cystic fibrosis is not the only attractive segment of the genetic testing market for inherited disorders. For example, 2 other emerging areas of interest are prenatal diagnostics and Ashkenazi Jewish genetic panel testing.

Another important aspect of genetic testing is predicting which individuals are at increased risk of developing certain disorders, based on their genetic makeup. Early applications in this field include tests offered by Myriad Genetics to predict risk of developing breast cancer, colon cancer, or melanoma. Testing for mutations in the BRCA1 and BRCA2 genes has now become an important part of determining the risk of cancer for women with strong family histories of breast cancer. Another important application of genetic testing to predict disease risk includes testing for mutations in the genes for Factor V Leiden, Factor II (prothrombin), and methylenetetrahydrofolate reductase (MTHFR) to predict a person's risk of developing venous thromboembolism. Several companies are developing and/or marketing products to detect these mutations.

Pharmacogenomics and Personalized Medicine

The segment of the molecular diagnostics market that may have the greatest impact on the pharmaceutical industry is personalized medicine, with the development of pharmacogenomic and companion diagnostic tests. These tests offer the potential of being able to predict which patients are likely to respond to a particular drug, or which patients are likely to develop adverse reactions to a drug.

An early focus of the pharmacogenomics market was on the cytochrome P450 family of enzymes, which have a role in the metabolism of many classes of drugs. Roche's AmpliChip CYP450 Test is currently the only FDA-cleared test for detecting genetic variations in cytochrome P450 genes, although some clinical laboratories offer this service using lab-developed tests. However, a challenge with tests that detect mutations in cytochrome P450 is educating physicians about interpreting the results, since there are multiple mutations, and changes in these genes can affect the metabolism of many different drugs.

A more targeted application of pharmacogenomics testing is to determine a patient's sensitivity to warfarin. The FDA recently approved updated prescribing information for Coumadin (warfarin) to include information on the use of genetic tests to determine a patient's sensitivity to warfarin, and thus, to improve the initial estimates that are being made concerning dosage. Warfarin tests detect variations in 2 genes. One of the genes encodes for CYP2C9, a cytochrome P450 that has a role in warfarin metabolism. The other gene encodes for the C1 subunit of the vitamin K epoxide reductase (VKORC1) enzyme, which is inhibited by warfarin. This action by the FDA, which was announced in August 2007, represents a significant step in the application of pharmacogenomics in health care.

Another important application of personalized medicine in molecular diagnostics has been the development of companion diagnostic tests to identify patients who will respond to the new, targeted therapies that are being developed for cancer. Targeted therapies are drugs that interact with cell receptors, enzymes, or other proteins that are specifically associated with cancer. These targeted therapies are only effective for treatment of cancers that express the molecular target of that drug. Two examples are discussed: testing for overexpression of HER2/neu protein, and for overexpression of epidermal growth factor receptor (EGFR, also called HER1 or ErbB-1).

A third example of a cancer application of molecular diagnostics for personalized medicine is testing for UGT1A1 genetic variants. This test can identify patients with a predisposition to develop side effects if they take Pfizer's Camptosar (irinotecan). An emerging example of a pharmacogenetic test that may be used to personalize treatment of HIV-infected persons, and other molecular diagnostics personalized medicine drugs, are also discussed. Personalized medicine may currently be a small segment of the overall molecular diagnostics market, but it is a rapidly growing segment.

One of the major trends in the molecular diagnostics market is the growing number of biomarkers that have been identified, and the rapidly growing number of tests that are being commercialized to target these biomarkers. Other additional important trends include the development of automated platforms on which these tests can be performed, and the start of a trend to move these tests out of the centralized laboratory and closer to the patient. In addition, an increasing number of molecular diagnostics tests are FDA-cleared or FDA-approved, which is important given the changing regulatory environment in molecular diagnostics. In addition to these trends in the molecular diagnostics products, there are also a number of trends in the overall industry. For example, there has been considerable consolidation in this market, but this remains a highly competitive and rapidly growing market.

Roadmap for this Report

Chapter 1 of this report provides a historical overview of molecular diagnostics, and discusses the wide range of applications for which molecular diagnostics can be used. As noted in this introduction, the focus of this report is on human clinical molecular diagnostics. Chapter 2 provides an overview of current and emerging technologies in the field of molecular diagnostics. While this chapter reviews several broad categories of technologies, many companies have developed their own proprietary versions of these technologies. Chapter 3 discusses many examples of the wide range of applications for which molecular diagnostics is being used. Chapter 4 reviews the overall diagnostics market, selected major trends in this market, the expected impact of personalized medicine and molecular diagnostics on pharmaceutical companies, and selected major challenges facing molecular diagnostics companies. Chapter 5 includes expert interviews with industry leaders, while Chapter 6 provides profiles of several leading companies. Finally, the Appendix summarizes the results of an online survey that include more than 250 individual respondents in molecular diagnostics.

