THE FUTURE OF MOLECULAR DIAGNOSTICS

Innovative technologies driving market opportunities in personalized medicine

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- Given the established importance of DNA in molecular biology and its central role in determining the fundamental operation of cellular processes, it is likely that expanded knowledge in this area will facilitate medical advances in different areas of clinical interest that may not have been possible without them.

- Molecular diagnostics is making it possible to detect infectious disease and cancer more accurately at an earlier stage than before. The technology is also optimizing testing for sexually transmitted diseases and genetic testing. Molecular diagnostics is also addressing the need for tests that monitor the therapeutic efficacy of pharmaceuticals. In this way, it has evolved into an important business opportunity for in-vitro diagnostics makers.

- In the past decade, molecular diagnostics has grown as an industry thanks to major advances in chemistries and instrumentation, including automation, integration, throughput, and the ability to use the instrumentation in a random access mode. Robust chemistries have been adopted, allowing the ability to quantitate using real-time PCR and other chemistries.

- Advances in molecular diagnostics and the ability to automate molecular reactions have the potential to move clinical diagnostics to the front lines of health care.

Trends and drivers

- Molecular diagnostics is expanding beyond just the identification of infections. It is becoming an integral part of disease management and therapy, finding such applications as patient stratification, drug regimen selection, toxicity avoidance, therapeutic monitoring, and detection of predisposition to disease.

- Hospitals and diagnostic laboratories using molecular diagnostic techniques need products that guarantee the highest levels of reliability and the greatest speed. Reliability is essential, because an inaccurate or missed diagnosis can be a matter of life and death.

- Another issue driving the need for new molecular diagnostics involves the ability of microorganisms to evade and even inactivate potent antibiotics, causing health care givers to be faced with substantial infectious disease challenges.

- The variety of technologies used in molecular diagnostics has transformed clinical laboratory medicine. Novel platforms have become the basis for these tests, including PCR and real-time quantitative PCR, as well as high-throughput sequencing.

- There are a variety of challenges facing the molecular diagnostics industry – not only manufacturers of these tests, but also users. With pharmacogenomics, the health care paradigm is shifting from being reactive towards proactive or preventive. This poses a major challenge to IVD manufacturers as this involves educating the medical community.

- Coordination with health care policy makers to solve reimbursement issues involving molecular diagnostic tests is becoming increasingly important for industry. Molecular diagnostics manufacturers should communicate the value of their technologies to healthcare regulators, payors, providers, and even patients to gain timely acceptance.

- More than 50 emerging and re-emerging pathogens have been identified during the last 40 years.

Market developments

- MicroRNAs are a growing class of small, noncoding RNAs (17-27 nucleotides) that regulate gene expression by targeting mRNAs for translational repression, degradation, or both. These molecules are emerging as important modulators in cellular pathways such as growth and proliferation, apoptosis, and developmental timing.

- In November 2009, Ionian Technologies Inc. and Roche Diagnostics Corp. entered into a collaborative agreement based on Ionian's rapid isothermal nucleic acid amplification technology. Under this agreement, Roche will identify new applications and customers for the technology and will bring these opportunities to Ionian.

- British scientists have developed the first blood test for lung cancer. EarlyCDT-Lung measures a panel of six autoantibodies each selected for their involvement in the development of lung cancer. The test detects the body's immune response in the form of antibodies to antigens, which are produced by solid-tumor cancer cells.

- In early 2009, Sequenom Inc., San Diego, CA, signed an exclusive worldwide licensing agreement with Optherion Inc., New Haven, CT. Under the agreement, Sequenom's CAP accredited and CLIA-certified laboratory, Sequenom Center for Molecular Medicine, obtained the rights to develop and commercialize diagnostic tests to predict genetic predisposition to late stage age-related macular degeneration (AMD).

- Qiagen’s wholly owned subsidiary, DxS, has acquired the global and exclusive license for biomarker PI3K - phosphoinositide 3-kinase - from Johns Hopkins University, Baltimore, MD, to develop real-time-PCR and endpoint PCR assays.

Markets

- To facilitate routine testing across a wider range of hospitals and reference laboratories, the market is demanding cost effective and simple-to-perform tests that have cleared the many regulatory hurdles. Automation is playing a key role in the development of tests that are easier and less expensive to operate.

- Infectious disease testing represents a large portion of the current market, given the re-emergence of infectious threats, including multidrug-resistant TB, new strains of HIV, and H1N1.

- Pharmacogenomics may be the most immediate new opportunity in the field.

- Many drug companies are investing significantly in pharmacogenomics in anticipation of shaving years off the drug discovery and approval process, bringing potentially lucrative drugs to market much sooner.

- Also in the future, the molecular oncology diagnostics sector will grow at a CAGR of 18%.

- The traditional trial-and-error practice of medicine is eroding progressively in favor of more precise molecular biomarker-assisted diagnosis and safer and more effective molecularly guided treatments. For the pharmaceutical industry, the outcome of this approach means increased efficiency, productivity, and novel product lines. The diagnostics industry has an opportunity for integration, increased value, and commercial opportunities for molecularly derived tests.

- Through 2015, the molecular diagnostics market will grow at double-digit pace, achieving an overall 14% compound annual growth rate to meet increasing demand for personalized medicine.

- Key areas of growth include infectious diseases, oncology, genetic testing and blood banking. A wide variety of drugs in late preclinical and early clinical development are being targeted to disease-specific gene and protein defects that

will require coapproval of diagnostic and therapeutic products by regulatory agencies.

CHAPTER 1

Introduction

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Summary

- Molecular diagnostics involves the measurement of DNA, RNA, proteins or metabolites in order to detect genotypes, mutations or biochemical changes in the body. The objective is to test for specific states of health or to see if disease exists in blood, tissue or bones. Molecular diagnostics, essentially the analysis of DNA and RNA at the molecular level, is a fast-growing business, made possible by the growing understanding of the human genome, which has driven growth in the diagnostics industry.
- Given the established importance of DNA in molecular biology and its central role in determining the fundamental operation of cellular processes, it is likely that expanded knowledge in this area will facilitate medical advances in different areas of clinical interest that may not have been possible without them.
- Molecular diagnostics is making it possible to detect infectious disease and cancer more accurately at an earlier stage than before. The technology is also optimizing testing for sexually transmitted diseases and genetic testing. Molecular diagnostics is also addressing the need for tests that monitor the therapeutic efficacy of pharmaceuticals. In this way, it has evolved into an important business opportunity for in-vitro diagnostics makers.
- In the past decade, molecular diagnostics has grown as an industry thanks to major advances in chemistries and instrumentation, including automation, integration, throughput, and the ability to use the instrumentation in a random access mode. Robust chemistries have been adopted, allowing the ability to quantitate using real-time PCR and other chemistries.
- Advances in molecular diagnostics and the ability to automate molecular reactions have the potential to move clinical diagnostics to the front lines of health care.

Perspective

Molecular diagnostics involves the measurement of DNA, RNA, proteins or metabolites in order to detect genotypes, mutations or biochemical changes in the body. The objective is to test for specific states of health or to see if disease exists in blood, tissue or bones. Molecular diagnostics, essentially the analysis of DNA and RNA at the molecular level, is a fast-growing business, made possible by the growing understanding of the human genome, which has spurred growth in the diagnostic business. Any gene-based therapeutic that is developed could lead to more efficacious patient outcomes if it is accompanied by a molecular diagnostic test. The molecular diagnostics business is helping to drive the in vitro diagnostics (IVD) industry and the companies involved.

Molecular diagnostics holds immense business potential because these tests are more accurate at identifying viruses and infectious diseases, and do so at an earlier stage of disease than previously possible. Personalized medicine now encompasses any test that modifies or customizes the treatment of a specific disease in a patient. Under this concept, any molecular diagnostic test that improves a health care professional's understanding of a patient's condition, susceptibility or predisposition to an illness can be considered personalized medicine. The science of molecular diagnostics represents a business opportunity for diagnostics companies that want to be on the cutting edge of personalized, or individualized, medicine, in which therapies are tailored to one's specific genetic makeup. These tests make it possible for doctors to monitor the effects of treatment by tracking the molecular properties of a disease.

An emerging science

The medical diagnostic market is playing a key role in the ever-changing health care and drug discovery landscape. Novel platform technologies and a better understanding of the human genome are driving the development of molecular diagnostics. Science and the industry are at the point that genetic tests can optimize drug therapy, and

companion diagnostics are being touted as a method to better define a patient's need or predict clinical outcome from a specific drug.

Key applications of molecular diagnostics include:

- Infectious disease testing;
- Oncology;
- Blood screening;
- Genetic testing.

Companion diagnostics - linking drugs with diagnostics - is expected to become the prevailing health care model, offering advantages for both the prescription drug and diagnostics businesses. For diagnostics companies, combining with a successful companion drug can be a powerful driver of sales, especially when the test is a requirement for prescribing the drug. This is also a crucial factor for achieving a higher price point for the diagnostic product. Pressure from the FDA and insurance payors also may encourage the co-development and co-marketing of drugs and diagnostics. However, not many drug companies are able to develop and market companion diagnostics linked to their targeted therapies. Moreover, pharmaceutical companies without the expertise or infrastructure to handle the regulatory, marketing and distribution aspects of the diagnostic component must chose a diagnostic partner after Phase II clinical drug studies as an option to building up in-house capabilities.

Diagnostics have historically had a commodity status, perceived as being of lesser value than drugs. Low reimbursement rates have contributed to low margins. It is expected that new generation diagnostics will change this cycle, either by linking themselves with companion therapies or by demonstrating value, such as cost reduction through targeted therapies and reduction in the number of adverse effects. It will be

necessary to demonstrate value, because these products, especially those requiring the development of clinically useful biomarkers, tend to require substantial investment and are targeted to niche markets. For companion diagnostics, the trials needed to evaluate a test used with a drug can be as expensive, if not more so, than traditional drug trials[1].

Understanding the human genome

Molecular biology has held out the promise of transforming medicine from a matter of serendipity to a rational pursuit grounded in a fundamental understanding of the human genome and the mechanisms of life. Molecular biology has begun to infiltrate the practice of medicine and genomics is hastening these advances. Within 50 years, comprehensive genomics-based health care should be the norm. Scientists will understand the molecular foundation of diseases, be able to prevent them in many cases and design accurate, individualized therapies for illnesses.

Eventually, genetic tests will routinely predict individual susceptibility to disease. One objective of the Human Genome Project was to identify common genetic variations. Epidemiological studies can show how particular variations correlate with risk for disease. Such studies can reveal the roles of genes which individually contribute to diseases, and how they interact with other genes and with environmental influences, like diet, infection and prenatal exposures, to affect health. Over the period 2010-2020, gene therapy should also become a common treatment, at least for a small set of conditions.

Drugs will eventually be available that derive from a detailed molecular understanding of common illnesses. The drugs will be designer therapies that target molecules logically and are therefore potent without significant side effects. Drugs like those for cancer will routinely be matched to a patient's likely response, as predicted by molecular fingerprinting. Diagnoses of many conditions will be much more thorough and specific than now. For example, a patient who learns that he has high cholesterol will also know which genes are responsible, what effect the high cholesterol is likely to have on his system, and what diet and pharmacologic measures will work best for him[2].

Extensive knowledge of the human genome is translating into advances in medicine and biotechnology. A number of companies, such as Myriad Genetics Inc., Salt Lake City, UT, are marketing genetic tests that can show predisposition to a variety of illnesses, including breast cancer, disorders of hemostasis, cystic fibrosis, liver diseases and others. Also, the causes of cancer, Alzheimer's disease and other areas of clinical interest will benefit from genome information and may possibly lead in the long term to significant advances in their management. There are also many tangible benefits for biological scientists, by visiting the human genome database on the internet, a researcher can examine what other scientists have written about certain genes. Contained in the database is information on a gene, including possibly its three-dimensional structure, its function, its evolutionary relationships to other human genes, or to genes in mice or yeast or fruit flies, its possible detrimental mutations, its interactions with other genes, body tissues in which this gene is activated, and diseases associated with this gene.

Molecular level analysis

A better understanding of the disease processes at the molecular level may help determine new therapeutic procedures. Given the established importance of DNA in molecular biology and its central role in determining the fundamental operation of cellular processes, it is likely that expanded knowledge in this area will facilitate medical advances in different areas of clinical interest. Molecular tests are identifying viruses and infectious diseases more accurately at an earlier stage than currently possible. Molecular diagnostics has also emerged as a potential business opportunity as diagnostics businesses generally fetch higher returns on investment than pharmaceutical and other biotech businesses.

Personalized care

Advances in genomic and proteomic science over the past decade have led to the development of targeted diagnostics and therapeutics that leverage knowledge of an individual’s genetic makeup to create a more personalized approach to healthcare. Genomic testing makes it possible to identify an individual’s susceptibility to disease,

predict how a given patient will respond to a particular drug, and match patients with the proper therapeutics. This new science of personalized medicine has the potential to eliminate unnecessary treatments, reduce the incidence of adverse reactions to drugs, increase the efficacy of treatments and ultimately, improve health outcomes.

The new science is embodied in an approach called P4 medicine by the Institute for Systems Biology and its co-founder, Dr. Leroy Hood, because of its four attributes. It is personalized, predictive, preventive and empowers patients to take more responsibility for their health care decisions. Patient empowerment is part of a broader trend toward consumer-focused health care, enabled by easy access to health information that was once available only to medical professionals. There are many other definitions of personalized medicine. The boundaries of this emerging market are fluid. PricewaterhouseCoopers defines personalized medicine broadly, as products and services that leverage the science of genomics and proteomics (directly or indirectly) and capitalize on the trends toward wellness and consumerism to enable tailored approaches to prevention and care. This definition encompasses everything from high-tech diagnostics to technologies that enable the storage, analysis and linking of patient and scientific data.

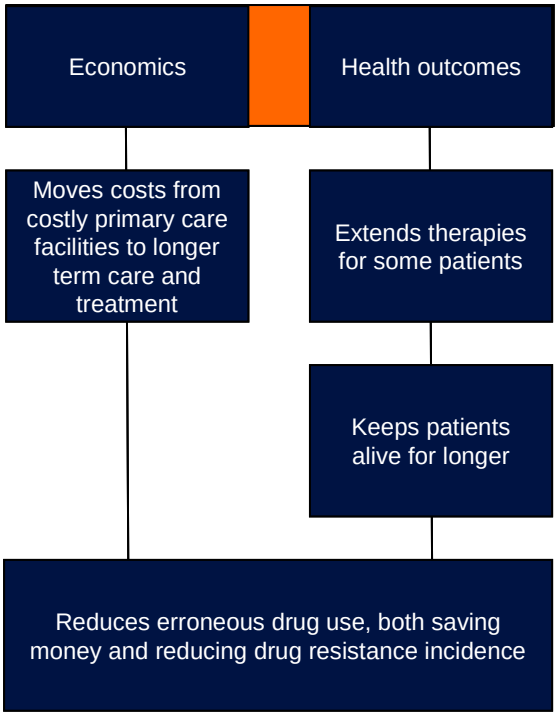
Individualized response

With the increasing number of blockbuster drugs - those individual entities that reach global sales of more than $1 billion annually - being marketed and prescribed, it has become apparent that many of these drugs only benefit part of the intended patient cohort. Estimates suggest that overall effectiveness ranges from 80% to as low as 20%, depending on the disease area addressed. These observations about the relative effectiveness of medicines, equally fuelled by concerns about the safety of medicines, the rising costs of supplying medicines and other macroeconomic factors affecting healthcare budgets, are leading to new models of how medicines are prescribed. Such new models increasingly involve health technology assessments, undertaken by agencies modeled on the UK National Institute of Clinical Excellence (NICE) and

prevalent across Europe and the US, two of the largest geographic pharmaceutical markets[3].

Molecular diagnostics, by targeting individual responses to drug therapy, will also impact health economics. As a general consequence, the prediction of response and the early treatment of disease are likely to have a more favorable outcome on the health of individuals. Individuals may be on therapies for considerably longer treatment periods and, individuals are likely to stay functionally well for much longer. In terms of health economics, costs may well focus away from expensive primary, secondary or tertiary care, such as hospital beds, mechanical interventions and the like, to a focus on long-term treatment for individuals considered well (Figure 1.1). Many healthcare systems already are transitioning toward this scheme of doing business - replacing symptom-based reactive medicine with objective testing-based predictive medicine. Molecular diagnostics could help guide therapeutic treatment and help attain better longer term effects for society as a whole.

Figure 1.1: Molecular diagnostics: predicting response, early treatment of disease



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Early-stage diagnosis

Disabilities impact a fairly large proportion of the population in industrialized countries. It has been estimated that in the US, more than 40 million people have a disability, as defined by the Disabilities Act of 1990 as a limitation in actions or activities because of a physical, mental or other health condition. A disability may result from a variety of acquired or genetic causes. An acquired disability caused by trauma, infections, surgery, endocrine abnormalities or nutritional deficiencies can be recognized when physicians take a history of the patient and give him physical and clinical examinations. Laboratory confirmation can help the physician arrive at a final diagnosis. A wide range of genetic disorders are the known causative factors of a variety of disabilities. Some of the disorders are obvious and present at birth, while

others appear later, either soon after birth or after a few years. Recombinant DNA technology has made it possible to diagnose a large number of diseases. Significantly, the polymerase chain reaction (PCR) has had a tremendous impact on the usefulness of DNA technology as it allows a gene or a DNA fragment of interest to be amplified several thousand times.

Since the first report of the use of DNA techniques to identify the sickle-cell gene in 1978, tremendous progress has been achieved in the field of genetic screening and genetic diagnosis. Early detection of a disease, followed by genetic counseling, is essential in the control and prevention of illnesses. The point of using molecular diagnostics to undertake genetic diagnosis is to identify a disease-producing mutation in any family, essentially before the disease evolves in an individual. The Human Genome Project has advanced gene identification. Genes responsible for disease have been cloned, mutations have been identified and highly accurate molecular tests are available.

Infectious disease

Diagnosing infectious disease involves identifying an infectious agent either directly or indirectly. In practice most minor infectious diseases, such as warts, cutaneous abscesses, respiratory system infections and diarrheal diseases, are diagnosed by their clinical presentation. Conclusions about the cause of the disease are based upon the likelihood that a patient came in contact with a particular agent, the presence of a microbe in a community, or other epidemiological considerations. Given sufficient effort, all known infectious agents can be specifically identified. The benefits of identification, however, may be doubtful. Often there is no specific treatment, the cause is obvious, or the result of an infection is benign.

Specific identification of an infectious agent is usually only helpful when such identification can aid in the treatment or prevention of the disease, or advance knowledge of the course of an illness prior to the development of effective therapeutic or preventative measures. For example, in the early 1980s, prior to the appearance of

AZT for the treatment of AIDS, the course of the disease was closely followed by monitoring the composition of patient blood samples, even though the outcome would not offer the patient any further treatment options. But by understanding how the disease was transmitted, resources could be targeted to the communities at greatest risk in campaigns aimed at reducing the number of new infections. Moreover, the development of molecular diagnostic tools has enabled physicians and researchers to monitor the efficacy of treatment with anti-retroviral drugs. Molecular diagnostics are now commonly used to identify HIV in healthy people long before the onset of illness and have been used to demonstrate the existence of people who are genetically resistant to HIV infection. While there still is no cure for HIV infection, there is great therapeutic and predictive benefit to identifying the virus and monitoring virus levels within the blood of infected individuals, both for the patient and for the community at large.

Viruses

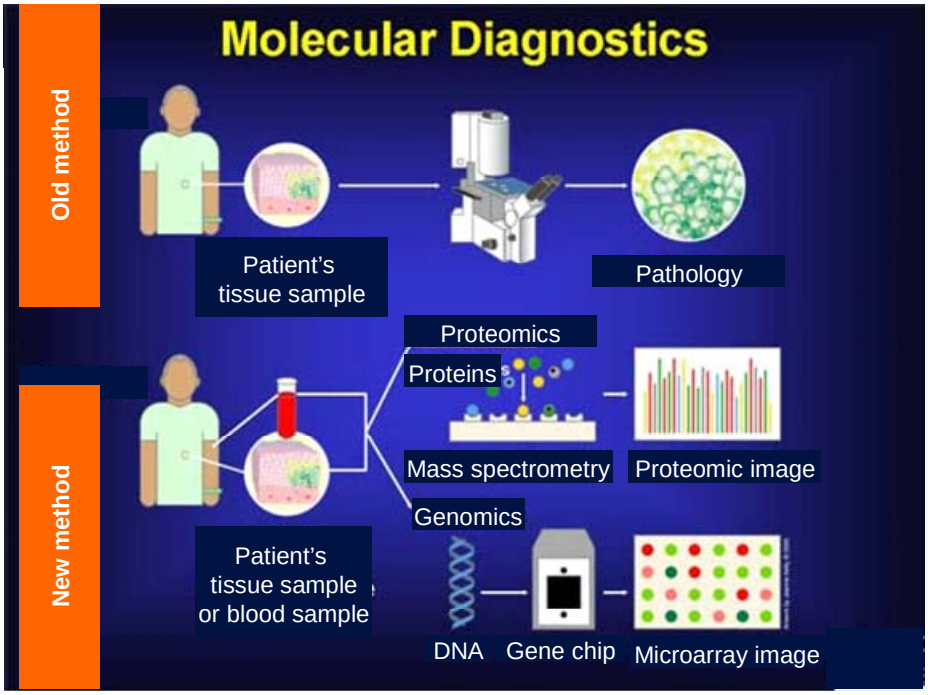
Clinical laboratories historically diagnose seven or eight respiratory virus infections using a combination of techniques including enzyme immunoassay, direct fluorescent antibody staining, cell culture and nucleic acid amplification tests. With the discovery of several new respiratory viruses since 2000, laboratories have been faced with the challenge of detecting up to 19 different viruses that cause acute respiratory disease of both the upper and lower respiratory tracts. The application of nucleic acid amplification technology, particularly multiplex PCR coupled with fluidic or fixed microarrays, has created an important new approach for the detection of multiple respiratory viruses in a single test. These multiplex amplification tests are sensitive enough to diagnose respiratory tract infections at an early stage in individual hospitalized patients. They can also identify the etiological agent in outbreaks of respiratory tract infection in the community. In this manner, molecular testing has made it possible to detect respiratory viruses and to increase an understanding of the roles of various viral agents in acute respiratory disease.

Oncology

Crucial to all normal cell growth is a communication network that functions properly. This network is an intricate collection of pathways built with interactive proteins. Along these pathways, precise protein-to-protein signaling closely regulates growth. The genetic changes involved in the cancer process result in altered proteins that disrupt a cell's communication network. In cancer, altered proteins along many different pathways cause signals to be garbled, intercepted, amplified or misdirected. These changes change what was once normal communication and cause it to achieve uncontrolled tumor growth. The challenge for cancer diagnosis is to locate the renegade genes and proteins - the deranged, defective, and dominating molecules - that change communication in once-normal cells. This requires opening the cell and analyzing the biomolecules inside. The earlier this detection and diagnosis can occur, the better.

Before the advent of molecular diagnostics, clinicians categorized cancer cells according to their pathology - their appearance under a microscope (Figure 1.2). Borrowing from genomics and proteomics, molecular diagnostics categorizes cancer using such technology as mass spectrometry, microarrays and gene chips. Molecular diagnostics determines how these genes and proteins are interacting in a cell. It focuses upon patterns - gene and protein activity patterns - in different types of cancerous or precancerous cells. Molecular diagnostics uncovers these sets of changes and captures this information as expression patterns. Also called molecular signatures, these expression patterns are improving the clinicians' ability to diagnose cancer. All cancers may be diagnosed in this way.

Figure 1.2: Evolution of diagnostics towards molecular diagnostics



Source: Adapted from National Cancer Institute

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Another major focus of molecular diagnostics involves investigations of the proteome - all the proteins produced by a cell. The study of these proteins is called proteomics. Cancer proteomics is making it possible to map, at an early stage, the patterns of proteins involved when normal cellular pathways are hijacked in support of malignant growth. In cancerous tissue, some of the proteins critical for normal communication are damaged, inactive, overactive or missing entirely. The full set of deranged and dominating proteins at work disrupting cellular communications may vary from one type of cancer to another. They may also vary somewhat from one patient to another within a specific cancer type. Scientists have learned that it is not necessary to identify every protein active in cancer. To accomplish a molecular diagnosis, all that may be needed is to separate and preserve a unique subset, a pattern of proteins shared by all patients with the same cancer type[4].

Diagnostics business opportunity

Molecular diagnostics is making it possible to detect infectious disease and cancer more accurately at an earlier stage than before. The technology is also optimizing testing for sexually transmitted diseases and genetic testing. Molecular diagnostics is also addressing the need for tests that monitor the therapeutic efficacy of pharmaceuticals. In this way, it has evolved into an important business opportunity for in vitro diagnostics makers. The molecular diagnostics industry is growing as a result of constant advances in science and technology, and this is generating new opportunities and submarkets. The major factors driving growth include the increasing incidences of various chronic diseases, and the ongoing fight against cancer and other illnesses. In addition, molecular diagnostics is advancing because of the advent of new technologies for genetic testing. It is making possible faster screening and more precise detection of disease. There also is a need for automated techniques, which combine optimized sample preparation, analysis, and data evaluation, and molecular diagnostics manufacturers are addressing this need as well.

The FDA has identified 32 different genomic biomarkers in current product labeling of various drugs, which can be used to leverage a patient's genetic information in order to plan a personalized course of treatment. There already are diagnostic tests that help improve treatment for certain types of cancer, improve matches for organ transplants, and avoid serious side effects or help determine the proper dosage of drugs. These types of advances represent just the start of opportunities for businesses.

A growing role in diagnostics

The molecular diagnostic industry will continue to grow at a double-digit pace to meet increasing demand. A wide variety of drugs in late preclinical and early clinical development are being targeted to disease-specific gene and protein defects that will require co-approval of diagnostic and therapeutic products by regulatory agencies. An increasingly educated public is demanding more information about its predisposition for serious diseases, and how these potential illnesses can be detected at an early stage

when they can be arrested or cured with new therapies custom-designed for their individual clinical status. Drug companies are partnering with diagnostics companies or are developing their own in-house capabilities that will permit efficient production of effective drugs and molecular tests.

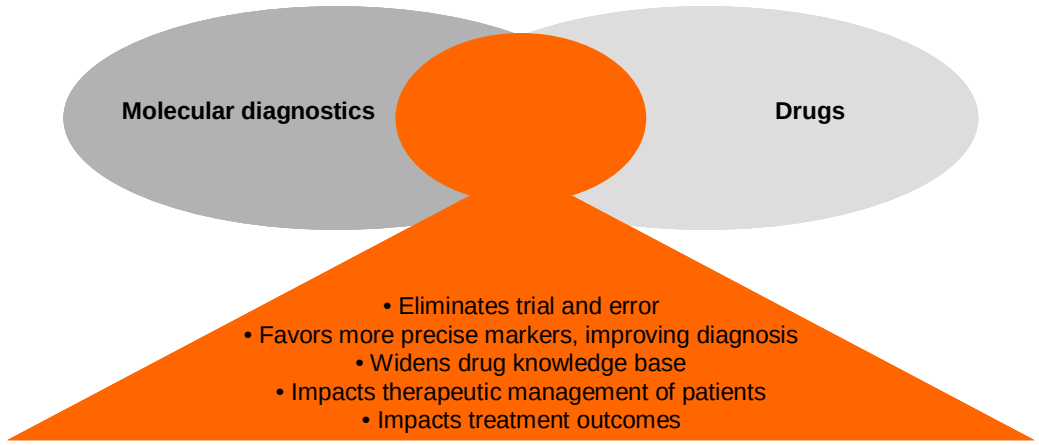
Companion diagnostics and therapies

Most molecular diagnostic tests are for infectious diseases, but there are increasing numbers in other areas, particularly oncology. The biggest challenge to their success is determining clinical utility and subsequent appropriate reimbursement based on the economic and outcome value of the test to the overall management of the disease.

The companion test for a therapeutic is a different type of diagnostic. The importance of this type of test lies in its enabling the success of the therapeutic as measured by the FDA. This requires a distinct process separate from regular diagnostic development. In the companion diagnostic program, the therapeutic requires the companion test. The challenge for the diagnostics company is that this is particularly risky, as the drug may fail. The risk of the failure of the test is compounded by the risk of failure of a drug. Some believe that the pharmaceutical company must be responsible for the costs of developing the test, while the rights of the test remain the property of the diagnostic company. In this way, if the drug fails, the diagnostic company may continue to pursue the development of the test with another related therapeutic being developed by the same pharmaceutical company or another. The commercialization of the test should be the responsibility of the pharmaceutical company as it supports the success of the therapeutic intervention. This may seem like a challenging business model, but it is one that could provide the stimulus for more companies being willing to develop companion diagnostics.

Integration is key when combining molecular diagnostics and therapeutics. The effort should include data collection, aggregation and analysis[5]. Successful integration can eliminate trial and error, favors more precise biomarkers and impacts the therapeutic management of patients (Figure 1.3).

Figure 1.3: Integrating molecular diagnostics with therapeutics



Source: Business Insights

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Diagnostics allowing early detection and treatment

In battling cancer, molecular diagnostics are early detection tools and disease management tools. They will permanently transform the way cancer is managed at every stage of the disease continuum. Colon cancer remains a leading cause of mortality worldwide despite the well-characterized molecular events in the adenoma-to-carcinoma sequence. There has been a strong emphasis on early detection of colon cancer, and fecal DNA-based methods have been developed to assist with early screening.

Tissue-based assays have been utilized for many years to assess tumor aggressiveness and to determine prognosis and response to chemotherapeutic interventions. The most widely used serum marker for colon cancer, carcinoembryonic antigen, is still useful in assessing for occult disease following curative resection. Being able to identify tumor

mutations in CTCs holds a great deal of promise in helping diagnose patients with colorectal cancer. The molecular level inhibitors of apoptosis may be important markers to determine resistance to radiation cytotoxicity in rectal cancer.

Increased efficiency

Molecular-based technologies are revolutionizing diagnostics testing in the clinical laboratory. However, novelty alone is not a sufficient reason to replace existing or implement new assays in the laboratory. Advanced technology must be easy to use, efficient and cost effective. Health care expenditures are rising to unprecedented levels, while aging populations represent an increasing disease burden for the broader community. Technological and biomedical breakthroughs have significantly advanced medical practices; however, the cost of therapeutics continues to spiral upwards. Optimizing treatment for patients remains an ongoing challenge, with uncertainties in identifying disease risk, diagnosing disease and selecting appropriate therapies. New diagnostic biomarkers that improve early disease detection and predict treatment responses will optimize clinical decisions for individual patients and, in doing so, they will improve the efficiency and effectiveness of health systems.

Optimizing drug therapy

Pharmacogenomics involves using molecular-based tests to predict a patient's response to specific therapies and to monitor the response of the disease to the agents administered. Among key examples of pharmacogenomics in infectious diseases are the use of viral load and resistance genotyping to select and monitor the antiviral therapy of AIDS and chronic hepatitis. This application improves disease outcome; shortens length of hospital stay; reduces adverse events and toxicity; and facilitates cost-effective therapy by avoiding unnecessary expensive drugs, optimizing doses and timing, and eliminating ineffective drugs.

Molecular tests can predict disease response to a specific therapy. Molecular-based viral load testing has become standard practice for patients with chronic hepatitis and AIDS. Viral load testing and genotyping of HCV are useful in determining the use of

expensive therapy, such as interferon, and can be used to justify decisions on the extent and duration of therapy. With AIDS, viral load determinations plus resistance genotyping have been used to select among the various protease inhibitor drugs available for treatment. This has improved patient response and decreased the incidence of opportunistic infections.

Significant regulatory concerns

The FDA is responsible for assuring that point-of-care diagnostics are safe and effective. Besides technical issues, another obstacle to the development of molecular assays involves the resources that are needed to optimize, produce and validate assays and develop documentation required for the qualification of techniques and laboratories. In vitro diagnostic companies have clinical and regulatory affairs departments that conduct validation studies and assemble documentation required to get approval of the reagents. However, even for in vitro diagnostic companies, the conception and validation process is time consuming, and time-to-market may be long. This is especially a problem when a diagnostic tool is urgently needed in case of emergence of a new virus.

One way to possibly reduce time-to-market is to release research use only (RUO) assays or assays that have the CE analytical approval in Europe or the status of analyte specific reagent (ASR) in the US. In this case, commercial products that have excellent analytical sensitivity and which are manufactured according to quality standards of the in vitro diagnostics industry can be used by clinical virology laboratories, which have the responsibility to validate their use as diagnostic tools and obtain authorization to use them.

Strengthening oversight

Regarding the consistency of FDA regulation, Genentech filed a 31-page citizen petition in December 2008 urging the FDA to regulate all in vitro diagnostic tests aimed for use in therapeutic decision making. Under the current regulatory system used by the FDA, there are two types of in vitro diagnostic tests: those that are developed by

device manufacturers and sold as diagnostic test kits, and those that are developed by clinical laboratories for use within the laboratory in-house. The FDA has regulated the former, while it has not regulated the latter. This allows developers of in-house diagnostic tests to make claims about the accuracy, validity and effectiveness of their tests that are not subjected to the same scientific scrutiny from the FDA that is required of similar test kits. Genentech argues in the petition that this regulatory inconsistency poses a serious threat to patients' health because "the future of personalized medicine depends on the development of pharmacogenomic tests," and "it is critical that they are accurate, reliable, and clinically valid (i.e., effective)."

As genetic testing plays an increasingly important role in the diagnosis and treatment of disease, proper regulation of genetic tests is crucial. Claims made by developers of genetic tests regarding the validity of the test results are being used by physicians to guide their therapeutic and diagnostic decision making. In some cases, these tests are used to diagnose or recommend treatment for patients with life-threatening diseases, such as some types of cancers. It is crucial for patients' health that FDA oversight be applied to these tests. Genentech has claimed that the FDA allows many tests to go unregulated.

In-house tests have been typically developed to diagnose rare conditions. However, genetic testing technologies are now being used for more common conditions and are being used to select treatment for life-threatening diseases. Genentech suggested that the FDA fix this situation by regulating all in vitro diagnostic tests and employing the risk-based classification system used to regulate medical devices. By placing all developers of in vitro diagnostic tests on an even playing field, the FDA will eliminate disincentives in the market that currently result in very few FDA-approved genetic tests. Successful FDA oversight of all in vitro genetic diagnostic tests is crucial in facilitating a safe and effective future for personalized medicine in the treatment of serious life-threatening diseases[6].

But the FDA has taken notice. The agency had issued a 2008 FDA warning letter to LabCorp (Laboratory Corporation of America) regarding its sales of OvaSure, a

molecular diagnostic test for ovarian cancer. The letter demonstrates the FDA's intent to more closely monitor and regulate the fast growing molecular diagnostic market segment. This increased regulatory scrutiny follows the FDA's July 2007 guidance document on in vitro diagnostic multivariant index assays (IVDMIAs) and the September 2007 guidance document on ASRs. In the past, several companies have decided to use the ASR or IVDMIA route as their go to market strategy for new molecular diagnostic tests, as opposed to filing a 510(k) or PMA. There are obvious advantages to this strategy and also associated risks, as demonstrated by the FDA's warning letters[7].

The FDA told LabCorp that it was illegally marketing the blood test. The test had raised hopes among women and their doctors because it promises to detect ovarian cancer at an early stage, when it is still treatable. But some outside experts, including the Society of Gynecologic Oncologists, said the test had not been proved accurate and might cause women to have unnecessary surgeries to remove their ovaries. The FDA in a previous letter to LabCorp, said the test "may harm the public health." In the second letter, the FDA said that OvaSure required agency approval before it could be marketed. As indicated, usually the agency has not regulated tests that are developed and performed by a single laboratory, as opposed to test kits that are sold to hospitals, laboratories and doctors. But the FDA said that OvaSure did not qualify for this exemption because the test was developed at Yale University, not at LabCorp, and the materials for the test were not manufactured by LabCorp[8]. OvaSure remains off the market.

Improving patient outcomes

Health plans and health care providers need information on how specific genetic tests and related interventions impact and improve patient health outcomes – both those in the near term and future outcomes. It is very important to have information on how cost effective these tests may be. Plans cannot manage what they cannot measure, and as coding information is so nonspecific, plans cannot understand which areas are growing, nor develop specific policies to address any growth. Plans do not know how many or

what kinds of tests they are paying for, and they do not have the data or the guidelines to determine test appropriateness or connect them to outcomes. This often leads to denials and appeals. Plans require specific codes, guidelines, cost, and coverage data for each test.

On the provider side, physicians are seeing more inquiries for genetic tests from their patients, but they do not have a reliable evidence-based source to determine whether they are appropriate. And even when information does become available, it takes an average of 17 years before new medical knowledge has been implemented by half of practitioners[9]. As new tests continue to emerge, physicians are finding it difficult, if not impossible, to stay educated about medical necessity and test efficacy. Compounding this issue is the fact that physicians who graduated from medical school more than five years ago received minimal or no education on molecular diagnostic testing in their curriculum. With about 5% of the US population having had some type of molecular genetic test already, molecular diagnostic testing is a significant concern today for health plans. In addition, 70% of people believe that they will have a genetic test within the next three to five years. Molecular diagnostic testing will be one of the biggest issues plans will be facing over the next decade. Existing health plan policies, written before the age of personalized medicine, must be amended. Objective, evidence-based criteria are needed for assessing these tests. The public, as well as physicians themselves, must be educated. How much of the burden of these and other tasks will fall on health plans is yet to be determined. In the meantime, plans must begin to assess their readiness for molecular diagnostic testing.

There are a number of concerns that must be addressed:

- Physicians must have enough knowledge and education to make appropriate decisions;

- Health care givers must be able to find reliable, credible and current clinical evidence;

- How much evidence is required must be known;
- Medical necessity must be determined;
- Vendors must deliver on test outcomes, analytic validity and clinical utility;
- The type of clinical criteria needed in the short and long term must be determined;
- The type of coverage policies that have to be developed to address these issues must be determined;
- These policies must be coded for consistent assessment in utilization management and claims systems.

Health plans need better tools and information to manage molecular diagnostics as the field grows, especially to support their coverage and appropriateness policies. This effort will require new evidence-based criteria for health plans and providers, with frequent updates needed to keep pace with the onslaught of new tests, many available at the point of care for use within the provider-patient work flow. Plans need this information to help determine test appropriateness and to connect data to outcomes[9].

Optimizing instrumentation and chemistries

There exists an unmet need for robust, reproducible tests that provide consistent results within a lab as well as across different labs. In the past decade, molecular diagnostics has grown as an industry thanks to major advances in chemistries and instrumentation, including automation, integration, throughput, and the ability to use the instrumentation in a random access mode. Robust chemistries have been adopted, making it possible to quantitate using real-time PCR and other chemistries, explains Alice Jacobs, MD, founder, chair, and CEO, IntelligentMDx, Cambridge, MA.

Sample-to-result systems have been embraced, and a broad range of customizable solutions are available for a variety of throughputs to meet the demands of the clinical reference lab. After more than a decade of using molecular methods to diagnose important diseases, it has become increasingly clear that the unmet need is for robust, reproducible, high-quality molecular diagnostic tests whose results are consistent not only within a lab but between labs, she says. She believes that the first step in the genetic detection of disease is a better understanding and characterization of the pathogens that impact human health. Scientists are just scratching the surface in understanding the complex interplay between exogenous factors, such as pathogens and environmental exposures, and their implications in the development of both acute and chronic disease[10].

Advances in sample preparation needed

The process of culture-based testing for microbes has been in use for more than a century. More recently, molecular diagnostic tests have emerged as a more specific, sensitive, and faster alternative. In many cases, however, these tests require multimillion dollar molecular labs and highly skilled technicians to operate them. While molecular diagnostic techniques can generate more sensitive and specific reactions in hours instead of the days needed for a culture-based test, they have remained out of reach for many organizations.

The three key steps to performing real-time PCR - sample preparation and extraction of nucleic acids, amplification of extracted nucleic acids, and detection of a target gene sequence - were first developed in the 1980s. These steps are time-consuming and are not amenable to on-demand testing. Institutions fortunate enough to have a molecular lab typically process samples in batches. First-generation PCR assays for molecular diagnostics require manual sample extraction using reagents prepared by the laboratory staff itself and often involve enzymatic digestion, extraction with organic solvents, and alcohol precipitation. After drying down the nucleic acid pellet, it is resuspended and added to a custom, laboratory prepared buffered cocktail of enzymes, nucleotides, and oligonucleotide primers to carry out the PCR process. After amplification, the real

work of detecting the amplification products begins. For best sensitivity, labeled probes are used to detect PCR amplification products on Southern blots or in microtiter plates. The two-to-three day process of carrying out the complete diagnostic procedure is labor intensive and error prone, which can give rise to false positive results.

The next advance in the development of diagnostic applications of PCR was the development of real-time PCR assays. It is the leading technique in molecular diagnostics. Although a very sensitive method for detection of nucleic acids in very low copy numbers, PCR is highly complex and labor intensive, and easily susceptible to cross-contamination as well as inhibition by sample impurities. For these reasons, molecular diagnostic tests generally are rated as highly complex by the standards of the Clinical Lab Improvement Amendments (CLIAs). They must be performed by technicians with special training and certifications, typically staffed during the day shift at most hospital laboratories, leaving at least 16 hours per day during which these tests cannot be performed. These assays use labeled probes that are part of the initial PCR reaction mixture. The detection of fluorescence accumulation during thermal cycling is used in place of Southern blotting for detecting PCR products within the closed environment reaction tube. Still to be refined, however, is the sample preparation component. No universal method for sample preparation exists. Several kit-based methods are adaptable to a variety of specimens. What is needed is automation of sample preparation procedures.

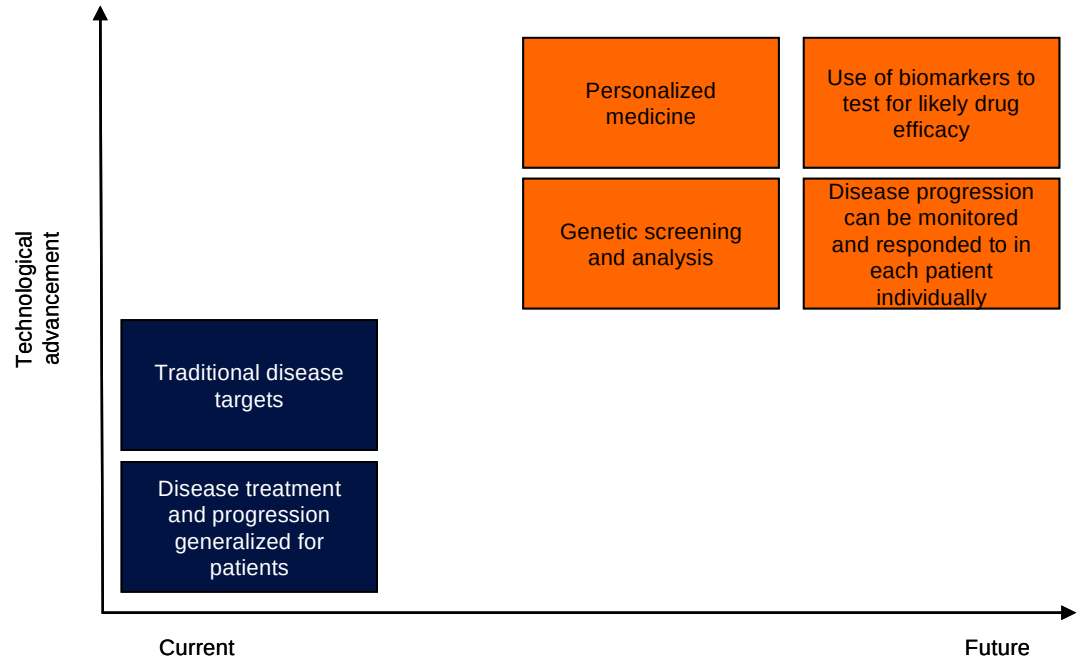
Due to assay complexity, stringent process requirements, and sensitivity to contamination, less than 7% of all clinical laboratories worldwide and virtually no clinics or physician offices are able to perform molecular tests. There is a lack of integrated and automated sample preparation and nucleic acid extraction. Such assays remain difficult to implement. With the exception of high volume tests, such as those for HIV, HCV and HBV, for which automated and semi-automated systems are available, the majority of nucleic acid testing (NAT) is performed using manual assays with non-regulated reagents. Additionally, testing incoming samples is often delayed until the number of samples meets test batch requirements in order to achieve reagent

and labor economics. The resulting long turnaround time, usually on the order of days to weeks, is highly problematic when immediate results are needed[13].

Automation

Advances in molecular diagnostics and the ability to automate molecular reactions have the potential to move clinical diagnostics to the front lines of health care, impacting clinical practice (Figure 1.4). New molecular diagnostic technologies are bringing benefits to a broad spectrum of facilities: large reference labs, regional hospitals, field research units, and first response teams. The key is automation, which enables virtually anyone to collect a sample and carry out a molecular reaction. Automation is a major step in applying the technology to a growing list of public health priorities. Consider the threat of methicilin-resistant Staphylococcus aureus (MRSA). A study published in the Dec. 1, 2006, issue of *The Journal of Infectious Diseases* found that 90 million Americans were colonized with Staphylococcus bacteria, while 2m Americans were colonized with the antibiotic-resistant MRSA strain. Another study published in the Feb. 1, 2006 issue of *Clinical Infectious Diseases* found that from 1992-2003, the percentage of Staphylococcus infections contracted in hospitals rose from 35.9% to 64.4%. In a health care setting, MRSA can be spread among doctors, patients, nurses, and visitors who come in to contact with contaminated surfaces like bed rails or computer keyboards. If MRSA enters the body through the skin, it can cause irritating skin infections, but if it enters the bloodstream or lungs, it can cause serious blood infections, pneumonia, and even death.

Figure 1.4: Changing treatment protocols in clinical practice



Source: Business Insights

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Studies show that diligent surveillance programs, in which patients are screened upon admission to a facility, have a tremendous impact in reducing MRSA infection rates. Identifying MRSA carriers, isolating them, and administering antibiotics is an effective way to stop the spread of MRSA. The Netherlands, Sweden, and Denmark have virtually eliminated MRSA from their hospitals with stringent surveillance programs. Culture-based testing takes days to produce a result. It is too slow to be highly effective in isolating carriers from non-carriers. But automated molecular diagnostics enable hospitals to process a collected specimen in about an hour. This is important because in addition to reducing the spread of MRSA and improving patient outcomes, surveillance can impact cost savings. Unreimbursed costs of treating a single MRSA infection average $25,000 to $40,000. In Pennsylvania in 2006, insurers paid an average of $53,915 for hospitalization of an infected patient compared to $8,311 for patients without infection. Increasingly, payors are refusing to reimburse for the added cost of infections acquired during hospital stays, shifting that financial burden to the hospital.

A growing number of American hospitals are adopting MRSA surveillance programs. Better tests for automated molecular diagnostic instruments make the technology even more accessible and affordable for surveillance purposes. MRSA is a good example of how automated molecular diagnostics can meet an important demand for improving hospital surveillance modalities. The technology offers tremendous benefits by providing critical information at the point of care, such as in emergency or delivery rooms[11]. New molecular systems must enable NAT to be performed at the point-of-care or the bedside rather than the lab. Such decentralized applications require a level of automation, integration, and quality assurance that reduces NAT from a high complexity test to a low complexity test capable of being performed by general healthcare practitioners, such as nurses, doctors and clinicians. Any test must produce results within one hour to meet the needs of intensive care applications, as well as to provide physicians with immediate results to guide drug prescription decisions and increase treatment efficacy while avoiding adverse drug reactions. Because disease and drug metabolism are seldom monogenetic, new systems must be capable of multiplex detection to target multiple genes in one test. Sensitivity must also be high to allow viral or gene quantitation.

Automated molecular diagnostics can also be used to monitor the yearly onset of viruses and the flu, and in developing nations, a rapid molecular diagnostic test for tuberculosis could play a major role in treating HIV-infected populations. Yet another example of a particularly time-sensitive test that would benefit from automation is that for Streptococcus agalactiae or group B streptococcus (GBS). GBS is the leading cause of newborn sepsis and meningitis in the US, with mortality rates of 5% or higher, and can be transmitted from a colonized, asymptomatic mother to her infant during childbirth. Antibiotic intervention immediately pre-partum can substantially reduce the risk to the newborn. The current test for GBS involves a 48 to 72 hour culture, which makes it impractical for testing a woman in active labor whose GBS status is unknown or uncertain. The result is a high incidence of over-prescribing antibiotics, at a time when the medical community is trying to reduce unnecessary antibiotic use in order to fight the rise of drug-resistant pathogens. A molecular diagnostic test could potentially speed the time to results. But if it is moderately complex and can only be performed by

a skilled laboratory technologist, the same problems apply. A low-cost, automated molecular diagnostic could be carried out by technicians at any time, day or night, with results available less than an hour after a woman presents at labor and delivery. Although molecular diagnostic tests represent a vast improvement over culturing protocols for identifying infectious-disease organisms and other nucleic-acid-based targets, they can still be time consuming, labor intensive, and expensive, and contribute to the clinical laboratory staffing problems. The next step in the evolution of molecular diagnostics is to expand the menu of tests that support new automated instruments. As new tests become available, the industry will see molecular diagnostics making a greater and greater impact in clinical settings[12].

In recent years, a number of companies have developed small, automated bench-top analyzers with low-cost, disposable cartridges for performing, on demand, certain routine lab tests, such as tests for hematocrit, blood lipid, creatinine and electrolyte levels, and blood coagulation times. But these technologies are not yet capable of performing PCR-equivalent molecular testing. On the horizon is a new generation of automated laboratory analyzers that will meet the growing demand for moderately complex molecular diagnostic tests. They will be able to reduce the complexity of these tests to the point where they can be run by less experienced lab staff. Although the first such technologies are being commercialized with a relatively high per-test price, these newer products will finally fulfill the need for simple molecular diagnostics at a cost that allows laboratories to realize a reasonable margin on their efforts.

The ideal automated molecular diagnostics system will offer results that are equivalent or superior in sensitivity to current PCR tests, but at a nominal price and with a dramatically reduced need for manual handling and sample preparation. A laboratory technician should simply be able to load a few microliters of a minimally prepared sample, such as whole or heparinized blood, a buffer-suspended swab, or culture samples, into an inexpensive, disposable test cartridge. Then insert the cartridge into the analyzer, start the system, and expect to have a clear result in about an hour.

Such a drastic simplification of the molecular testing process will have far-reaching implications for laboratories, patients, physicians, and hospitals. The most immediate benefit of automated molecular diagnostics will be in relieving the labor squeeze felt by most labs today. While the typical moderately complex molecular diagnostic test is very labor intensive and requires skilled handling, automation at this level enables less experienced lab professionals to produce the same results in far less time. The laboratory personnel structure can be reshaped to reflect a small number of specialized clinical laboratory scientists, focused on hands-on, highly complex tests, supported by a base of round-the-clock personnel running automated diagnostics.

CHAPTER 2

Trends and drivers

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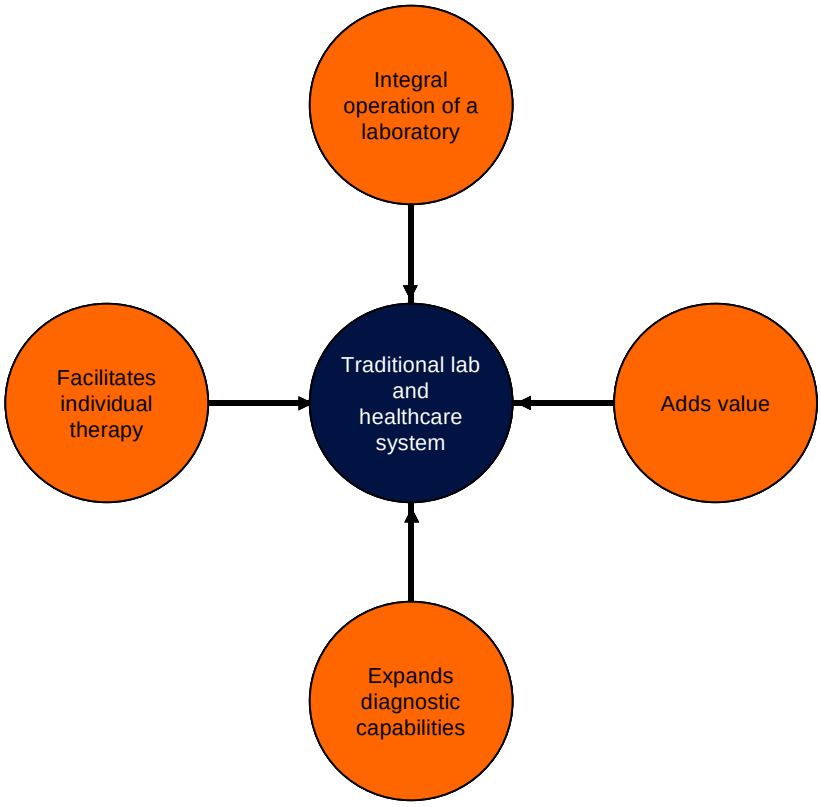
Summary

- Molecular diagnostics is expanding beyond just the identification of infections. It is becoming an integral part of disease management and therapy, finding such applications as patient stratification, drug regimen selection, toxicity avoidance, therapeutic monitoring, and detection of predisposition to disease.
- Hospitals and diagnostic laboratories using molecular diagnostic techniques need products that guarantee the highest levels of reliability and the greatest speed. Reliability is essential, because an inaccurate or missed diagnosis can be a matter of life and death.
- Another issue driving the need for new molecular diagnostics involves the ability of microorganisms to evade and even inactivate potent antibiotics, causing health care givers to be faced with substantial infectious disease challenges.
- The variety of technologies used in molecular diagnostics has transformed clinical laboratory medicine. Novel platforms have become the basis for these tests, including PCR and real-time quantitative PCR, as well as high-throughput sequencing.
- There are a variety of challenges facing the molecular diagnostics industry – not only manufacturers of these tests, but also users. With pharmacogenomics, the health care paradigm is shifting from being reactive towards proactive or preventive. This poses a major challenge to IVD manufacturers as this involves educating the medical community.
- Coordination with health care policy makers to solve reimbursement issues involving molecular diagnostic tests is becoming increasingly important for industry. Molecular diagnostics manufacturers should communicate the value of their technologies to healthcare regulators, payors, providers, and even patients to gain timely acceptance.
- More than 50 emerging and re-emerging pathogens have been identified during the last 40 years.

Integral to traditional labs

Molecular diagnostics is expanding beyond just the identification of infections. It is becoming an integral part of disease management and therapy, finding such applications as patient stratification, drug regimen selection, toxicity avoidance, therapeutic monitoring, and detection of predisposition to disease. The issuance of pharmacogenomics guidance by the FDA and the introduction of the Genomics and Personalized Medicine Act of 2006 have been the basis for more extensive use of genetic testing in the development and administration of new therapeutics. Molecular diagnostics is becoming critical in enabling drug companies and doctors to use the advancements in pharmacogenomics to provide patients with better care. Molecular diagnostics is important to the clinical laboratory (Figure 2.5).

Figure 2.5: Clinical potential of molecular diagnostics



Source: Business Insights

Business Insights Ltd

Molecular diagnostics can become integral to the traditional laboratory, along with hematology and chemistry. It increases the value of the laboratory to an institution or healthcare system. It expands diagnostics to include a specific patient's response to a specific drug therapy and facilitates individualized therapy based on an individual's specific drug metabolism.

Improved assay/test efficiencies

Molecular biology revolutionized the diagnosis of diseases. Modern analyses based on the detection of nucleic acids - DNA and RNA - offer considerable advantages over traditional methods of pathogen detection in humans. These procedures detect viruses, bacteria, and parasites more rapidly and with far greater sensitivity and specificity than do traditional diagnostics. The cause of a disease and the specific genetic makeup of individual patients can be determined more precisely on the genetic and protein level, enabling the most suitable therapy to be developed. Molecular technologies also enable the early identification of persons who are at risk of developing certain disorders, improving the efficiency of assays and prevention programs. In these ways, molecular diagnostics provides care givers with the necessary tools for developing completely new strategies in the battle against both infectious and chronic diseases.

Hospitals and diagnostic laboratories using molecular diagnostic techniques need products that guarantee the highest levels of reliability and the greatest speed. Reliability is essential, because an inaccurate or missed diagnosis can be a matter of life and death. Early detection may allow faster response with the appropriate therapy, even before the manifestation of symptoms. In emerging point-of-need testing applications such as emergency medicine, users additionally require highly portable solutions with an ultrafast time to results.

One example of an improved, more efficient assay involves Fragile X syndrome, which is the most common, recognized, inheritable cause of mental retardation. Widespread testing is warranted by the relatively high frequency of the disorder. There are benefits of early detection and the identification of related carriers whose offspring are at a one-

in-two risk of inheriting the expanded pathogenic mutation. However, cost-effective screening of mentally handicapped individuals has been impeded by the lack of a single, simple laboratory test. Currently, Fragile X syndrome can be determined in males and a majority of females using a simple high-throughput PCR test. Due to the limited sensitivity of the PCR test, scientists in Australia found in their diagnostic service that approximately 40% of females appear homozygous, and a labor intensive and expensive Southern blotting test is required to distinguish these from females carrying one normal allele and an expanded allele.

The Australian researchers set out to develop an improved PCR assay that would delineate cryptic heterozygous females and extend the repeat size range of alleles - different forms of a genetic locus. A locus is the specific location of a gene or DNA sequence on a chromosome. This would reduce the number of follow-up Southern blot tests required, improving result turnaround times and reduce costs of additional testing. The improved PCR test displays a high level of precision, making it possible to differentiate among alleles. Using the new assay, investigators detected 46 of 83 (53%) cryptic heterozygotes previously labeled as homozygotes. The assay also extended the range of repeats amplifiable, up to 170 CGG repeats in males and 130 CGG repeats in females. Combined with the high precision, the assay also improved discrimination of normal from grey zone alleles, and grey zone alleles from small permutations. This PCR test significantly improves the precision and amplification of longer alleles. The number of follow-up Southern blotting tests required was reduced - by up to 50% - with consequent improvement in turnaround time and cost. The other important improvement provided by the new assay was its ability to identify alleles with the potential to be unstable when transmitted to offspring. Use of this assay will result in improved turnaround times and cost advantages for diagnostic laboratories performing high numbers of Fragile X syndrome tests. The high precision provided will also be of value in ongoing research focusing on the biological interrelationships and clinical significance of normal, gray zone and small mutations of fragile X mental retardation 1 (FMR1) 14.

Targeting antibiotic resistance

Another issue driving the need for new molecular diagnostics involves the ability of microorganisms to evade and even inactivate potent antibiotics. In the face of newly emerging infectious organisms, the global crisis in antibiotic resistance, and the threat of bioterrorism, there is a need to invigorate basic anti-infective science. There are several indications that new approaches are required to combat emerging infections and the global spread of drug-resistant bacterial pathogens. One is the pattern in rates of death from infectious disease in the 20th century. From 1900-1980, the rate dropped from 797 per 100,000 people to 36 per 100,000 people, a reduction by a factor of more than 20 and a testament in part to the efficacy of antibiotics[15].

However, from 1980-2000, that rate doubled, largely because of HIV but also due to the spread of drug-resistant bacterial pathogens, such as MRSA, vancomycin-resistant enterococci, multiple-drug-resistant gram-negative bacteria, and multiple-drug-resistant tuberculosis[16]. While the rise in mortality is due partly to infection in more seriously ill or immunocompromized patients, there is a need for new strategies and new molecules to treat pathogens that are resistant to nearly the full array of contemporary antibiotics. Another indication of the need for novel antibacterial therapeutics is the almost 40-year innovation gap between introductions of new molecular classes of antibiotics: fluoroquinolones in 1962 and the oxazolidinone linezolid in 2000[17].

Detection of antibiotic resistance is mostly based on determining the potential for growth. In non-sterile sites, such as the skin and the gastrointestinal tract, identifying the specific agent causing a disease is difficult. Even in sterile tissues, such as blood, present-day detection methods are often not sensitive enough to detect disease-causing organisms. Improved diagnostics could have an important impact. For example, if a physician could know at the patient's bedside which organism is causing a particular infection and whether that organism is resistant to common antibiotics, a treatment could be tailored quickly. Consequently, antibiotics would be used in a specific fashion, selecting only those likely to be effective; this procedure of judicious and specific antibiotic use would thus help extend the useful lifetime of new antibiotics.

Diagnostics that are able to identify the etiology and antimicrobial susceptibility of all infections could target therapy precisely and eliminate the use of antibacterial agents in patients who do not even have a bacterial infection. If they are performed early, such tests could avoid untargeted therapy during the days needed by current diagnostics. In one study, PCR testing took six hours to identify the etiology of 76% of community-acquired pneumonia cases, while older tests took several days to identify 49.5%[18]. Research into diagnostic tests that can reliably and quickly identify pathogenic organisms and their resistance profiles should be encouraged. Development of such tests could lead to significant advancement in the treatment of infectious disease. To cause the greatest reduction in inappropriate antibiotic use, such tests would need to be so rapid and reliable that clinicians would be comfortable waiting for the results before beginning antibiotic treatment. The tests must not only lead to successful diagnosis of the pathogen, but also have the confidence of clinicians.

A major issue in resistance is that not only disease-causing organisms, but also other resident organisms and the host itself are exposed to an antibiotic. Minimizing exposure to a patient through precise choice of antibiotic is critical in preventing the emergence of resistance by reducing the selection in off-target organisms. That is, the use of a narrow-spectrum antimicrobial agent optimized for use against a specific disease-causing organism would be less likely to select for resistance in non-targeted microorganisms. Advanced molecular diagnostics will facilitate the tight targeting of pathogens and enable the productive exploration of target-specific antibiotics. The advances could include selective interruption of organism-specific processes, such as virulence mechanisms, adhesion of surface antigens, and resistance mechanisms. Enhancing the host response at the site of infection is a potential approach to activating toxic molecules where they are needed. New tissue-specific delivery vehicles would greatly help to decrease the exposure of non-target species to antibiotics[19].

Next generation ultrasensitive molecular diagnostics

Proteins drive most biological processes, but measuring their concentrations at low levels has been impeded by a lack of appropriately sensitive technology. Current diagnostic guidelines based on the quantification of protein-based biomarkers suffer from three issues. Firstly, assay sensitivity is often what determines the lower limit of the threshold and the diagnostic cut-off value. Secondly, the threshold system only reveals the tip of the iceberg when it involves disease states. As in the molecular protein biomarker cTnI, a potential gold mine of information lies beneath the 99th percentile threshold value for a clinically relevant biomarker. This valuable information, quantifiable by single molecule counting (SMC) technology in particular, could be used to diagnose, stratify, determine risk, or aid in disease prevention. Thirdly, development of a disease state is not an on-off proposition. Rather, there is a continuum of disease development which makes disease onset and diagnosis difficult to mark. The fuzzy line marking the onset of disease is a common cause of diagnostic failures.

An excellent example of prolonged disease onset leading towards diagnostic failure is Alzheimer's Disease (AD). The only definitive diagnosis of AD is a post-mortem examination of brain tissue for amyloidal plaques and neurofibrillary tangles. Currently, clinical diagnosis of this disease is made by ruling out other probable causes for the symptoms of AD, which are usually only apparent after significant disease progression has occurred. Thus there is no reliable way at this time to clinically define when this complex disease officially starts. An FDA approved molecular diagnostic for AD is needed.

The need for an early diagnosis for AD is especially important as new therapies for AD are developed, which provide better patient outcomes when administered early in the course of the disease. There is no FDA approved protein biomarker for clinical diagnosis of Alzheimer's disease, though there are some hopeful candidates: beta-amyloid and tau proteins. However, further clinical validation of this new diagnostic information will be necessary to define the disease state and set the guidelines for early

diagnosis and onset of AD. In this way, protein biomarker programs in AD and other disease areas can benefit immensely from the application of novel immunoassay technologies with ultra-sensitive detection.

One solution could involve integrating new technologies into next generation immunoassay systems. For example, Luminex's open-architecture xMap technology enables large numbers of biological tests – bioassays -- to be conducted and analyzed quickly and accurately. The technology integrates flow cytometry, microspheres, lasers, digital signal processing and traditional chemistry into a flexible immunoassay system that can be configured to perform a wide variety of bioassays. Luminex uses color coded microspheres, which can be combined into 100 distinct sets. Each set can be coated with a reagent specific to a particular bioassay, allowing the capture and detection of specific analytes from a sample. Within the Luminex compact analyzer, lasers excite the internal dyes that identify each microsphere particle, and also any reporter dye captured during the assay. In this way, xMap technology allows multiplexing of up to 100 assays within a single sample, both rapidly and precisely.

Another possibility: Singulex has developed a proprietary immunoassay technology, a next generation molecular diagnostic that is capable of quantifying biomarkers at the subpicogram level. The immunoassay technology uses paramagnetic microparticles as the solid phase for immune-capture and detection of analytes from complex biological samples, providing enhanced specificity, sensitivity and precision by one to three logs over existing plate-based methods. These types of immunoassays add value by increasing sensitivity to unprecedented levels of detection, some to below the femtomolar range. They are new tool kits for solving intractable problems in the biology of disease and can help scientists in clinical investigations which were previously considered untenable[20].

Platform variety

The variety of technologies used in molecular diagnostics has transformed clinical laboratory medicine. Novel platforms have become the basis for these tests, including

PCR and real-time quantitative PCR, as well as high-throughput sequencing. The development of different molecular platforms, especially those that are fully automated and integrated, can significantly increase successful implementation of these technologies in clinical practice.

PCR

PCR is a nucleic acid analysis technique that produces large amounts of a specific DNA fragment of a defined sequence and length from a small amount of a complex template. It can selectively amplify a single molecule of DNA or RNA several million-fold in a few hours. This technology makes possible the detection and analysis of specific gene sequences in a patient's sample. Analyses can be performed on even a few cells from body fluids or in a drop of blood. PCR eliminates the need to prepare large amounts of DNA from tissue samples. PCR has revolutionized molecular diagnostics.

PCR makes it possible to diagnose such diseases as leukemia and lymphomas. PCR assays can be performed directly on genomic DNA samples to detect translocation-specific malignant cells at a sensitivity which is at least 10,000 fold greater than other methods make possible. PCR also permits the identification of non-cultivatable or slow-growing microorganisms, such as mycobacteria, anaerobic bacteria, or viruses from tissue culture assays and animal models. The basis for PCR diagnostic applications in microbiology is the detection of infectious agents and the discrimination of non-pathogenic from pathogenic strains by virtue of specific genes. Viral DNA can be detected by PCR. The primers used must be specific to the targeted sequences in the DNA of a virus, and the PCR can be used for diagnostic analyses or DNA sequencing of the viral genome. The high sensitivity of PCR makes it possible to detect viruses soon after infection and even before the onset of disease. Such early detection may give physicians a significant lead in treatment.

Nucleic acid testing

An NAT, also known as a nucleic acid amplification test **(**NAAT), is a biochemical technique that detects a virus or a bacterium. These tests were developed

to shorten the window period, a time when a patient has been infected and when they show up as positive by antibody tests. The technology includes any test that directly detects the genetic material of the infecting organism or virus. There are several methods in this group, including:

- Methods based on PCR that use a primer to rapidly make copies of the genetic material;
- A reverse transcriptase PCR used for HIV and other RNA viruses;
- Transcription mediated amplification, which uses a slightly different molecular method than PCR but has the same basic principle;
- Branched DNA (quantiplex bDNA) tests that use a molecule that links to the specific genetic material.

A number of rapid methods can provide shorter analysis times in which there is a need for rapid results, including NAT based on specific genomic DNA and RNA amplification processes, such as PCR and transcription mediated amplification (TMA), which can provide fast results within a few hours. Such techniques are suited for detecting and identifying specific organisms or pathogenic species. NAT technology has fueled the growth of molecular diagnostics, the fastest-expanding IVD industry segment. NAT is a leading molecular diagnostics technology. The PCR is one of the most common methods in the NAT toolbox used to discover new biomarkers and develop diagnostics tests. Conventional diagnostic techniques, such as cell culture and antibody testing, consume considerable time compared to NAT. A PCR test using NAT only takes about 30 minutes to deliver results. It also requires minimal staff training and expertise due to its simple operations. Advances in technology have made NAT comparable to dipstick assays in terms of the time needed to obtain results.

In May 2010, EraGen Biosciences, Madison WI, received FDA 510(k) market clearance for its MultiCode-RTx HSV 1&2 Kit. It is a cleared molecular test for the herpes simplex virus. EraGen's testing kit is an in vitro diagnostic test for DNA

detection and typing for herpes simplex virus 1 and 2. Clinical laboratories can provide PCR-based, qualitative detection of HSV types 1 or 2 in approximately four hours utilizing a common nucleic acid extraction system and real-time PCR instrument.

Also in May 2010, IQuum, Marlborough, MA, received an Emergency Use Authorization (EUA) from the FDA for its Liat Influenza A/2009 H1N1 Assay. The assay detects and differentiates 2009 H1N1 influenza viral RNA starting from collected nasopharyngeal swab samples in less than 30 minutes. The entire NAT process is automated on the Liat Analyzer. The authorization allows the assay to be used in laboratories certified under the CLIA to perform moderate complexity (not waived) tests, enabling use in hospital near-patient settings. This approval is a stepping stone for the company to seek 510(k) approval for an H1N1 test on its platform; to tackle the point-of-care diagnostic market; and to further develop tests for other infectious diseases.

Microfluidics

Microfluidics involves the behavior, control and manipulation of fluids that are constrained at the sub-millimeter scale. It makes possible the processing of minute volumes of liquids to perform chemical, biochemical, or enzymatic analyzes of samples. Microfluidics emerged in the beginning of the 1980s and is used in DNA lab-on-a-chip technology, among other industrial applications. To date, the most successful commercial application of microfluidics is inkjet printing. But advances in microfluidics are revolutionizing molecular biology techniques for enzymatic analysis (glucose and lactate assays), DNA analysis, such as with PCR and high-throughput sequencing, and proteomics. Microfluidics and lab-on-a-chip methodologies are helping to make point-of-care diagnostics precise and more valuable, as it is helping to move testing away from the centralized laboratory and into doctors' practices, clinics and the home, from where results can be transmitted electronically to doctors.

Biochips/microarrays

Microfluidics find use in microarray technologies. A DNA microarray consists of an arrayed series of thousands of microscopic spots of DNA oligonucleotides, called features, each containing picomoles of a specific DNA sequence, known as probes. A probe can be a short section of a gene or other DNA element used to hybridize a target DNA or RNA sample. Probe-target hybridization is usually detected and quantified by detection of fluorophore-, silver-, or chemiluminescence-labeled targets to determine relative abundance of nucleic acid sequences in the target. Since an array can contain tens of thousands of probes, a microarray experiment can accomplish many genetic tests at the same time. These arrays have dramatically accelerated many types of investigation.

The purpose of microfluidic-based biochips is to integrate assay operations, such as detection, sample pre-treatment and sample preparation, onto a chip, or substrate. An emerging application for biochips is clinical pathology, especially the immediate point-of-care diagnosis of diseases. Biochips have been based on the concept of a DNA microarray, such as the GeneChip DNAarray from Affymetrix. This system consists of a piece of glass, plastic or silicon substrate on which pieces of DNA - probes - are affixed in a microscopic array. The system includes disposable DNA probe arrays (chips) consisting of nucleic acid sequences set out in an ordered, high density pattern; certain reagents for use with the probe arrays, a scanner and other instruments used to process the probe arrays; and software to analyze and manage genomic or genetic information obtained from the probe arrays. Similar to a DNA microarray, a protein array is a miniature array on which a number of different capture agents, most frequently monoclonal antibodies, are deposited onto a chip's surface. They can determine the presence or amount of proteins in blood. A microfluidic system can perform microarray hybridization on glass slides for molecular diagnostics and gene profiling.

Others

Gene expression profiling

Gene expression profiling involves measuring the activity - or expression - of thousands of genes at once, to create an overall picture of cellular function. These profiles can, for example, distinguish between cells that are actively dividing, or show how the cells react to a particular treatment. Many experiments measure an entire genome simultaneously. Sequence based techniques, like serial analysis of gene expression (Sage and SuperSage) are used for gene expression profiling. SuperSage is highly accurate and can measure any active gene, not just a predefined set. The advent of next-generation sequencing has made sequence based expression analysis an increasingly popular, digital alternative to microarrays. However, microarrays are far more common, accounting for 17,000 PubMed articles by 2006[21].

Scientists at Japan's Osaka Medical Center for Cancer and Cardiovascular Diseases have constructed a clinically useful molecular diagnostic system based on gene expression profiling. The expression of 3,456 genes in 32 patients, 12 and 20 of whom had prognostically distinct anaplastic oligodendroglioma and glioblastoma, respectively, was measured using a PCR array. The researchers undertook a supervised analysis using a weighted voting algorithm to construct a diagnostic system discriminating anaplastic oligodendroglioma from glioblastoma. The diagnostic accuracy of this system was evaluated by cross-validation. The clinical utility was tested on a microarray-based data set of 50 malignant gliomas.

Unsupervised analysis showed divergent global gene expression patterns between the two tumor classes. A supervised binary classification model showed 100% diagnostic accuracy by cross-validation using 168 diagnostic genes. Applied to a gene expression data set from a previous study, the model correlated better with outcome than histologic diagnosis, and also displayed 96.6% (28 of 29) consistency with the molecular classification scheme used for these histological gliomas. The molecular diagnostic system showed reproducible clinical utility and prognostic ability superior to traditional histopathologic diagnosis for malignant glioma[22].

Meanwhile, in April 2010, Caliper Life Sciences inked an OEM agreement with Access Genetics, Minneapolis, MN, to market its LabChip GX microfluidic system for molecular diagnostic applications. Under the agreement, Access Genetics will incorporate web-based software, materials, and protocols that it developed specifically for use with the LabChip GX and market the combined platform to clinicians, pathologists and physicians. Caliper sells the LabChip GX system, which uses microfluidic chip-based technology for nucleic acid analysis, for molecular diagnostic research applications. The firm aims to further the LabChip GX's use in the molecular diagnostics field. Access Genetics has developed the TeleGene web-based software for molecular diagnostic applications. The firm also runs a CLIA and CAP-certified high complexity clinical laboratory.

On another front, microRNAs (miRNAs) are small RNAs that act as regulators of protein synthesis. They are highly effective biomarkers. MicroRNAs' advantage as biomarkers lies in their high tissue specificity, and their exceptional stability in routine preservation methods for biopsies, including Formalin-Fixed, Paraffin-Embedded blocks of tissue. It has been suggested that their small size (19 to 21 nucleotides) enables them to remain intact in formalin fixed paraffin embedded (FFPE) blocks, as opposed to messenger RNA (mRNA), which tend to degrade rapidly in samples preserved by this method. In addition, early preclinical data have shown that by controlling the levels of specific microRNAs, cancer cell growth may be reduced.

Rosetta Genomics is developing microRNA-based molecular diagnostics. The company's research platform combining bioinformatics and laboratory processes has led to the discovery of hundreds of biologically validated novel human microRNAs. The company is building upon its scientific and clinical data to further validate the strength of its microRNA platform technologies and to develop microRNA-based diagnostics. Also involved in microRNA research is TrovaGene, where scientists are developing a microRNA isolation kit from urine, and several disease- and organ-specific microRNA detection kits.

Meanwhile, Biocartis has acquired Royal Philips Electronics' technology platform for fully-automated DNA/RNA molecular diagnostic testing designed for applications in patient sample testing, including oncology and infectious disease applications. Biocartis will develop, commercialize and finalize validation of the platform at its Dutch subsidiary Biocartis BV, Eindhoven, the Netherlands. On yet another front, cytomegalovirus, Epstein Barr virus, and BK virus, a polyoma virus, are among the most frequently diagnosed post-transplant viral infections. Infection with one or more of these viruses may play a significant role in organ rejection, graft dysfunction and other complications. PrimeraDx has created an automated platform, IcePlex, which allows quantitative multiplexing of dozens of nucleic acid targets in a single reaction. Primera's first quantitative multiplex assay, ViraQuant, is designed to detect and quantify CMV, EBV, BK, HHV-6 and HHV-7 using plasma and whole blood.

Challenges and issues

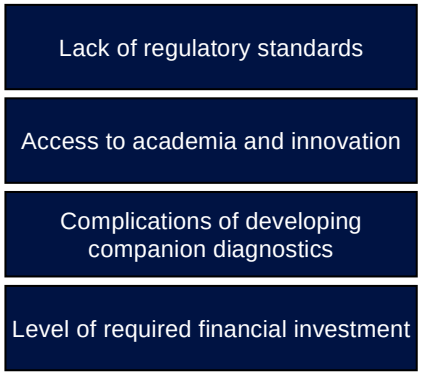
There are a variety of challenges facing the molecular diagnostics industry - not only manufacturers of these tests, but also users. With pharmacogenomics, the healthcare paradigm is shifting from being reactive towards proactive or preventive. This poses a major challenge to IVD manufacturers as this involves educating the medical community. Manufacturers might coordinate with makers of health care policy to solve reimbursement issues involving molecular diagnostic tests. Molecular diagnostics manufacturers should communicate the value of their technologies to healthcare regulators, payors, providers, and even patients for a timely acceptance. Meanwhile, clinical laboratories need qualified technical staff. The lack of technical expertise makes it difficult for laboratories to utilize molecular diagnostics. The complexity involved in training staff is a major concern, which is why manufacturers are being pushed to further automate their product offerings.

The growing trend of clinical lab automation is challenging the financial capabilities of laboratories as it becomes necessary to justify making investments in automated techniques. High-throughput, accuracy, speed and flexibility are the main reasons for

the success of automated instrumentation. The human genome project demanded improvements in testing methods, and researchers responded, surpassing objectives with amazing speed. Sequencing methods improved, and the genome was mapped. Some of the data yielded information with clinical relevance. Advances in processes and menus continue. New molecular diagnostic methods are faster and less complex. Many established high clinical utility, and many others, such as genomics, continue to hold great promise. Still, there exist many different types of biological tests - some protein, some gene, some sequencing, each is different. The challenge is comparing them and determining which is more reliable, specific or sensitive. Another challenge lies in trying to standardize tests. Yet another issue occurs when a health care provider does not have the molecular expertise to interpret test results, he might have to contact the lab if the results are not understood.

Essentially, to facilitate the development of molecular diagnostics, developers need to make themselves attractive enough for financial investment, and they need access to innovation, which often occurs at the university level. For the best success, they should partner with drug companies to develop companion diagnostics. But they face a variety of regulations and standards worldwide (Figure 2.6).

Figure 2.6: Molecular diagnostics: challenges for developers



Source: Business Insights

Business Insights Ltd

The value of diagnostics needs to be further understood outside of the IVD industry and better understood by insurance payors. It is particularly important for manufacturers of diagnostic tests to demonstrate the clinical utility and impact of IVDs on health economics so that payors will be motivated to reimburse at the value the test provides to doctors and patients.

Re-emergence of infectious diseases and other threats

More than 50 emerging and reemerging pathogens have been identified during the last 40 years. Until 1992 when the Institute of Medicine, Washington DC, issued a report that defined emerging infectious diseases, medicine had been complacent about such infectious diseases. Molecular tools have proven useful in discovering and characterizing emerging viruses and bacteria, such as Sin Nombre virus (hantaviral pulmonary syndrome), hepatitis C virus, *Bartonella henselae* (cat scratch disease, bacillary angiomatosis), and *Anaplasma phagocytophilum* (human granulocytotropic anaplasmosis). Other new or re-emerging threats include multidrug-resistant tuberculosis (TB); antibiotic-resistant bacteria that cause ear infections; pneumonia; meningitis; rabies; and diarrheal diseases caused by the parasite *Cryptosporidium parvum* and by certain toxigenic strains of *Escherichia coli*. Applying molecular diagnostics to test for dangerous, fastidious, and uncultivated agents for which

conventional tests do not yield timely diagnoses has been achieved for many agents. But widespread use of cost-effective, validated commercial assays has yet to occur. The ongoing challenge to the field of molecular diagnostics is to apply contemporary knowledge to facilitate agent diagnosis as well as to further discoveries of novel pathogens[23].

Several decades ago, the threat of infectious diseases appeared to be receding. Modern scientific advances, including antibiotic drugs, vaccines against childhood diseases, and improved technology for sanitation, helped control or prevent many infectious diseases, particularly in industrialized nations. The incidence of childhood diseases, such as polio, whooping cough, and diphtheria, was declining due to vaccines. Fast-acting, effective antibiotics fought off often fatal bacterial diseases, such as meningitis and pneumonia. Deaths from infection, commonplace at the beginning of the twentieth century, were no longer a frequent occurrence in the US. Meanwhile, in other parts of the world, chemical pesticides, such as DDT, were lowering the incidence of malaria, a major killer of children, by controlling populations of parasite-carrying mosquitoes. But the scientific community did not take into account the resilience of infectious microbes, which evolve, adapt, and develop resistance to drugs in an unpredictable and dynamic fashion. It also did not take into account the accelerating spread of human populations into tropical forests and overcrowded mega-cities where people are exposed to a variety of emerging infectious agents.

The reasons for the sharp increase in incidence of many infectious diseases are many. Population shifts and population growth; changes in human behavior; urbanization, poverty, and crowding; changes in ecology and climate; the evolution of microbes; inadequacy of public health infrastructures; and modern travel and trade have contributed. For example, the ease of modern travel creates many opportunities for a disease outbreak in remote areas to spread to a crowded urban area. Human behavioral factors, such as dietary habits and food handling, personal hygiene, risky sexual behavior, and intravenous drug use, can contribute to disease emergence. In several parts of the world, human encroachment on tropical forests has brought populations with little or no disease resistance into close proximity with insects that carry malaria

and yellow fever and other, sometimes unknown, infectious diseases. In addition, local fluctuations in temperature and rainfall affect the number of microbe-carrying rodents in some areas. In many countries, there has been a deterioration in the local public health infrastructures that monitor and respond to disease outbreaks.

Establishing accepted regulatory processes

The regulatory process involving approval of molecular assays and tests is often slow with the complexity of these types of tests often a challenge. Molecular diagnostics and genomic testing are challenging sciences to understand. Clinicians may underestimate the technology of the assay, which is biologically complex. In addition, new regulations may add to the cost of developing similar tests in the future. There is need for a standardization of regulations and the approval process involved, not only among different countries, but even within the same country.

Under the regulatory process of the FDA, there are two types of in vitro diagnostic tests: those that are developed by device manufacturers and sold as diagnostic test kits, and those developed by clinical laboratories for use within the laboratory (in-house tests). The FDA has regulated the former, while it has not regulated the latter. In late 2008, Genentech filed a Citizen Petition with the FDA urging the agency to take on greater oversight of diagnostic tests that are intended to guide therapeutic decisions and to regulate all laboratory developed tests. The biopharmaceutical firm addressed a concern of many in the field. Molecular diagnostic manufacturers are waiting for the FDA's final guidance on IVDMIAs - tests that use biomarkers for diagnosis of genetic diseases. The FDA issued draft guidance on IVDMIAs in September 2006. The agency said at that time that such tests, ordinarily overseen by clinical laboratory improvement amendments, must instead be cleared by the agency due to their complexity.

Genentech said in its petition that while the FDA took a step in the direction of regulating all such tests, it would like the agency to expand and strengthen its regulatory oversight. According to Genentech, pharmacogenomic information is contained on the label of around 10% of all FDA-approved drugs. Included among

those are Genentech's trastuzumab (Herceptin), which requires that patients be tested for particular genetic characteristics and the results be considered before the drug is administered. Danish diagnostics firm Dako makes the HercepTest, the first FDA-approved clinical test to determine HER2 protein overexpression in breast cancer tissues from patients for whom Herceptin treatment is being considered. But, Genentech points out, several other firms, including CombiMatrix Molecular Diagnostics and Monogram Biosciences, are selling HER-2 laboratory developed tests that have not been approved by the FDA.

Genentech also lists a number of other firms as selling laboratory-based tests that make claims that have not been verified by FDA. Meanwhile, it points to several instances where "FDA has shown a willingness to regulate some high risk LDTs (laboratory diagnostic tests) based on concerns about patient safety." Among the examples it cited was FDA's determination that LabCorp.'s OvaSure ovarian cancer test was misbranded and is "not within the scope of laboratory-developed tests over which the agency has traditionally exercised enforcement discretion." LabCorp subsequently decided to remove OvaSure from the market and seek a meeting with FDA officials to discuss its testing service and associated regulatory issues, although the lab did not agree with the agency's decision. Genentech said "it is simply unknown whether (lab developed tests) are supported by sufficient analytical and clinical evidence[24]. OvaSure remains off the market.

Molecular diagnostics are subject to the same regulations as medical devices. The level of potential harm to users drives the FDA's pre-marketing approval requirements. The regulatory environment is already complex and the FDA is growing increasingly cautious as diagnostics are becoming more relied on for critical medical decisions. The FDA is attempting to increase regulation of homebrew tests, which currently fall under the Centers for Medicare and Medicaid Services (CMS) CLIA. FDA regulates the components of homebrew tests but not the tests themselves. ASRs are subject to regulation as medical devices when they are purchased by clinical laboratories for use in homebrews or certain diagnostics. Most ASRs are classified as Class I. As diagnostics drive more treatment decisions, the FDA is increasing its role in enforcing

the safety of assays available on the market. The FDA is increasingly declaring complex diagnostics as Class II and III devices.

In September 2006, the FDA introduced a new class of diagnostics, IVDMIAs, which are tests that use biomarkers for diagnosis of genetic diseases. The agency has proposed applying standards to homebrew assays that fall under IVDMIA classification. Products already on the market may also be required to go through FDA's IVDMIA pre-marketing approval process. Successful molecular diagnostics companies will closely engage with the FDA and will invest in regulatory operations and the supporting research and risk management functions. Typical regulatory operations include submission of new product applications, promotion and labeling, and adverse events monitoring. Analytical instrument companies will need to adopt standardized, repeatable, adaptable, and auditable processes and technology. Rigorous and expensive clinical trials may be required to demonstrate safety. Planning for a changing regulatory environment and engaging with the FDA may prevent potentially damaging scrutiny following the commercialization of a diagnostic test[25].

Reimbursement

In 2000, the Institute of Medicine published a comprehensive report: "Medicare Laboratory Payment Policy, Now and in the Future." This report described a number of substantial difficulties created by the legacy US system for coding and payment of laboratory tests in an era of substantial advances for test technology. Few of these difficulties have been resolved. However, the pace of technologic change has risen and complex gene panel tests for cancer and other sophisticated diagnostics are becoming reality. Usually, the development of new medical technology proceeds through stages that are deliberately designed to reduce uncertainty, allowing rational investment in the next stage of research for the product. Innovation is discouraged if innovators perceive that a high and irreducible level of uncertainty is caused by payor issues, unrelated to the actual clinical value of the product, which will occur at the final stage of product development during market entry. It follows that more transparency and rationality in payor processes will encourage cost-effective innovation in molecular diagnostics.

In June 2008, the US Department of Health and Human Services commissioned a white paper to overview the current status of payor systems for coverage and reimbursement of complex molecular tests, and brought together an expert panel to discuss present difficulties and possibilities for change. The workshop focused on benefit classification, billing processes, coding systems, payment systems, and coverage decision processes. The goal of the workshop was not to choose single solutions, but to articulate the most pressing issues and discuss options for system change. Participants felt that the legacy coding system was the most pressing problem in the overall reimbursement system[26].

In the US, all in vitro diagnostics must be assigned a Current Procedural Terminology code in order to be reimbursed. Unfortunately these codes have not kept up with developments in molecular diagnostic technology. If a new diagnostic is "shoehorned" into an existing code, it may be reimbursed at a lower rate that does not reflect its cost of development, clinical benefit or medical economic value. Applying for a new code can take up to two decades and is a resource-intensive process. As patients and providers become increasingly cost sensitive, a diagnostic's reimbursement status largely determines its success in the market. A company must have a broad understanding of the reimbursement criteria for molecular diagnostics, and it is imperative to understand whether to use existing Current Procedural Terminology codes or apply for new codes that reflect a test's value in use. Reimbursement outside the US is driven primarily by single-payor systems. European countries, which, although operating under a more or less common regulatory regime, vary significantly in their reimbursement processes and criteria for molecular diagnostics. Successful firms in these markets have sought either local alliances or advisors with deep understanding of the idiosyncrasies unique to each country.

Medicare coverage

The full promise of molecular diagnostics and personalized medicine might not be realized because of Medicare reimbursement policies that were devised for diagnostics technologies in the early 1980s. Clinical laboratory tests influence as much as 70% of

health care decisions, yet they account for less than 2% of Medicare spending. The Medicare reimbursement system has focused on the treatment of acute conditions instead of the prevention and management of chronic diseases. What can be lost in the Medicare reimbursement process is an understanding that clinical laboratory tests provide physicians with greater information to make smarter, customized healthcare decisions and help prevent deaths, adverse events, and additional costs.

The Institute of Medicine in 2000 and the Lewin Group in 2005 both found that the current Medicare Clinical Lab Fee Schedule is flawed, complex, lacks transparency, and does not efficiently incorporate new technologies. The Lewin study also found the fee schedule has no way to account for the value of diagnostics to health care and provides few incentives for new test development. Specifically, the study found that Medicare payment policies for new diagnostic laboratory tests are "archaic, impractical and severely flawed." Lewin noted that Medicare often pays substantially less for a new test that offers greater benefits to patients and the health care system than an older test, providing little incentive for the development and adoption of new diagnostic tests.

Most recently, in March 2010, Vermillion Inc., Fremont, CA, announced that Medicare will cover its OVA1, a test to help assess the likelihood that an ovarian mass is benign or malignant. OVA1 is the first protein-based in vitro diagnostic IVDMIA, a new class of diagnostic. The test utilizes five well-established biomarkers - transthyretin (TT or prealbumin), apolipoprotein A-1 (Apo A-1), beta2-microglobulin (Beta2M), transferrin (Tfr) and cancer antigen 125 (CA 125 II) - and proprietary software to determine the likelihood of malignancy in women with ovarian mass for whom surgery is planned.

CHAPTER 3

Market developments

Chapter 3 Market developments

Summary

- MicroRNAs are a growing class of small, noncoding RNAs (17-27 nucleotides) that regulate gene expression by targeting mRNAs for translational repression, degradation, or both. These molecules are emerging as important modulators in cellular pathways such as growth and proliferation, apoptosis, and developmental timing.
- In November 2009, Ionian Technologies Inc. and Roche Diagnostics Corp. entered into a collaborative agreement based on Ionian's rapid isothermal nucleic acid amplification technology. Under this agreement, Roche will identify new applications and customers for the technology and will bring these opportunities to Ionian.
- British scientists have developed the first blood test for lung cancer. EarlyCDT-Lung measures a panel of six autoantibodies each selected for their involvement in the development of lung cancer. The test detects the body's immune response in the form of antibodies to antigens, which are produced by solid-tumor cancer cells.
- In early 2009, Sequenom Inc., San Diego, CA, signed an exclusive worldwide licensing agreement with Optherion Inc., New Haven, CT. Under the agreement, Sequenom's CAP accredited and CLIA-certified laboratory, Sequenom Center for Molecular Medicine, obtained the rights to develop and commercialize diagnostic tests to predict genetic predisposition to late stage age-related macular degeneration (AMD).
- Qiagen’s wholly owned subsidiary, DxS, has acquired the global and exclusive license for biomarker PI3K - phosphoinositide 3-kinase - from Johns Hopkins University, Baltimore, MD, to develop real-time-PCR and endpoint PCR assays.

Extracting microRNAs from tissue

MicroRNAs are a growing class of small, noncoding RNAs (17-27 nucleotides) that regulate gene expression by targeting mRNAs for translational repression, degradation, or both. These molecules are emerging as important modulators in cellular pathways such as growth and proliferation, apoptosis, and developmental timing. Researchers led by Dr. Soheil Dadras at the Stanford University Medical Center, Stanford, CA, have developed a novel methodology for extracting microRNAs from cancer tissues. The related report by Ma et al, "Profiling and discovery of novel miRNAs from formalin-fixed paraffin-embedded melanoma and nodal specimens," appeared in the September 2009 issue of the *Journal of Molecular Diagnostics*. Cancer tissues from patients are often stored by a method that involves formalin fixation and paraffin embedding, which retains retain morphological definition for later identification. However, this approach frequently prevents further molecular analysis of the tissue because of mRNA degradation. Even so, these tissues contain high numbers of microRNAs (miRNAs), which are short enough, about 22 nucleotides each, to not be broken down during the fixation process.

In this study, Dr. Dadras and colleagues optimized a new protocol for extracting miRNAs from FFPE tissues. Using their new procedure, they identified 17 new and 53 known miRNAs from normal skin, melanoma and sentinel lymph nodes. These miRNAs were well preserved in a 10-year-old specimen. This new technique will make it possible to identify novel miRNAs that may differ in cancerous and healthy tissue, even from long-preserved tissue, leading to improved disease prognosis and treatment response. The researchers suggest that their "cloning strategy has the advantage of not only discovering novel and known miRNA sequence identity but also providing an estimate of relative expression level. This methodology may provide a more robust strategy to obtain an accurate expression profile for novel or previously characterized small RNAs from clinically defined (formalin-fixed paraffin-embedded) tumor specimens, facilitating the discovery of oncomirs -- microRNAs with a role in cancer -- as biomarkers[27].

Cystic fibrosis genetic screening

Three reports describing advances in cystic fibrosis genetic testing appeared in the May 2009 issue of The *Journal of Molecular Diagnostics*. Cystic fibrosis is a hereditary disease that affects mucus secretions in the lungs, liver, pancreas and intestines. Approximately one in 4,000 children born in the US is affected with cystic fibrosis. Cystic fibrosis is an autosomal recessive disease caused by mutations in the *CFTR* gene. Cystic fibrosis patients must inherit a mutated gene from each parent.

Genetic screening for cystic fibrosis carrier mutations, involving one copy of a mutated gene, is universally recommended for the reproductive-age population. Current professional guidelines call for screening a panel of 23 common mutations in *CFTR*. However, many laboratories screen for an expanded panel of mutations. In the May 2009 issue of The *Journal of Molecular Diagnostics*, in Pratt et al., researchers describe a project coordinated by the US Centers for Disease Control and Prevention's Genetic Testing Reference Material (GeT-RM) Program to develop a set of reference materials for the expanded cystic fibrosis panel of mutations. The public availability of these materials will help to ensure the accuracy of cystic fibrosis genetic testing.

The reports by Schwartz et al. and Hantash et al. identify mutations that may lead to false screening results, either due to a large deletion in *CFTR* or because of mutations that interfere with laboratory screening methods.

> *"Taken together, these three papers demonstrate how the widespread experience with (cystic fibrosis) mutation testing and screening continues to reveal new insights about the mutational alleles of the CFTR gene and further refinements in how best to detect them and assure appropriate quality control while doing so[28]."*
>
> *Professor Wayne Grody, Departments of Pathology and Laboratory Medicine, Pediatrics, and Human Genetics at the UCLA School of Medicine, Los Angeles, CA*

PET scanning

A rapid decline in metabolic activity on a PET scan after radiation therapy for non-small cell lung cancer is correlated with good local tumor control, according to a study presented by researchers at Thomas Jefferson University Hospital at the 51st American Society for Radiation Oncology Annual Meeting in 2009. In addition, the researchers also found that the higher the metabolic activity and tumor size on a PET molecular scan before treatment, the more likely a patient is to die from lung cancer.

> *"PET scanning is an emerging tool of molecular imaging in lung cancer, in contrast to CT scans and MRI scans which are anatomic imaging,"*
>
> *"It has become an important tool in the evaluation of lung cancer staging and evaluation of treatment response."*
>
> *Professor Maria Werner-Wasik, Jefferson Medical College of Thomas Jefferson University*

Dr. Werner-Wasik and colleagues conducted a retrospective analysis of 50 patients with lung cancer who received PET imaging before and after radiation therapy. They analyzed the prognostic factors for tumor local failure. They measured the metabolic activity using the maximum standardized uptake value (mSUV). They also measured the tumor size -- metabolic tumor volume. The risk of local failure decreased for each unit decline in mSUV by the first post-therapy scan. When compared to the pre-therapy PET scan, the mSUV of the primary tumor declined by 72% in the by the first post-therapy scan, 76% by the second scan and 77% by the third scan. Nineteen patients achieved a metabolic complete response at the median time of 10.6 months. Eight patients suffered local failure. Other factors significantly associated with increased local failure included female gender, stage IV disease and large tumor size[29].

Expanded Medicare coverage

In late 2009, the US CMS decided to expand coverage of FDG PET for the initial staging of cervical cancer without previously imposed restrictions. CMS' decision to expand coverage of FDG-PET for the initial treatment strategy evaluation of cervical cancer is important for patient care, says Michael M. Graham, Ph.D., M.D., president of SNM, formerly the Society for Nuclear Medicine. Over the years, the body of scientific evidence has proven the value of molecular imaging scans for diagnosing, staging, restaging and monitoring treatment for many cancers."

CMS was encouraged to end the prospective data collection requirements for FDG-PET for the initial staging of some patients with cervical cancer. Previously, patients requiring PET for the initial staging of cervical cancer had to have this molecular diagnostic performed under the CMS coverage with evidence development policy, if the patient had not first had CT or MRI performed, or if other imaging was done but showed evidence of metastatic disease outside of the pelvis. Based on the strong body of evidence, the CMS concluded that FDG-PET can provide physicians with important information for how to treat patients with cervical cancer without the need for these restrictions.

Under the decision, the CMS will cover one FDG PET scan for the staging of cervical cancer. In these cases, physicians can determine the precise location of the tumor and identify the extent to which the tumor has grown. Physicians can then use this information to determine the optimum initial treatment strategy for each individual patient. Additionally, this can help physicians determine whether or not the patient would benefit from further diagnostic tests or therapeutic procedures. Through expanded coverage, physicians can provide patients with an individualized course of therapy meaning the right treatment at the right time. The decision from CMS derives in part from data collected by the National Oncologic PET Registry (NOPR), a comprehensive study that assessed the value of FDG PET for the initial diagnosis,

staging and treatment of many common types of cancer. In April 2009, the CMS made a decision to expand coverage of FDG PET for breast, cervical, colorectal, esophageal, head and neck, lymphoma, melanoma, non-small cell lung and thyroid cancers[30].

Ionian Technologies-Roche collaboration

In November 2009, Ionian Technologies Inc. and Roche Diagnostics Corp. entered into a collaborative agreement based on Ionian's rapid isothermal nucleic acid amplification technology. Under this agreement, Roche will identify new applications and customers for the technology and will bring these opportunities to Ionian. Roche will have exclusive manufacturing rights for these specific opportunities upon commercialization. This collaboration allows Ionian to continue to focus on its core strengths, including technology and assay development, while leveraging the business development, sales, and manufacturing expertise of Roche.

Ionian's isothermal amplification technology, the Near Assay, detects both DNA and RNA from bacterial or viral pathogens in less than 10 minutes. The technology is amenable to raw or unpurified samples, obviating the need for complex sample processing and purification steps. Ionian's technology is good for point-of-care and point-of-use settings[31].

Leukemia diagnostic kit cleared

China Medical Technologies, Beijing, China, received Chinese regulatory approval for its leukemia BCR/ABL fusion gene detection Fish probe in November 2009. The molecular diagnostic test kit is used to detect the Philadelphia translocation genetic defect associated with chronic myeloid leukemia, acute lymphoblastic leukemia, and acute myeloid leukemia.

China Medical develops, manufactures, and markets IVD products using fluorescent in situ hybridization (Fish), enhanced chemiluminescence, and surface plasmon resonance (SPR) technologies. In October 2009, Chinese regulatory authorities approved the company's SPR-based analysis system, for which an HPV-DNA biosensor chip is available. The company already offers a range of Fish probes for diseases including breast cancer, bladder cancer, and cervical cancer. Additional Fish probes are in clinical development or under regulatory review in China[32].

New lung cancer test

British scientists have developed a blood test for lung cancer. EarlyCDT-Lung measures a panel of six autoantibodies, each selected for their involvement in the development of lung cancer. The test detects the body's immune response in the form of antibodies to antigens, which are produced by solid-tumor cancer cells. These autoantibodies will appear long before tumors develop, meaning investigations in the form of scans and biopsies could be started at a much earlier stage. This will greatly improve survival rates because lung cancer is typically discovered late when tumors are relatively advanced. The new test was developed by researchers at the University of Nottingham, who set up the commercial company Oncimmune (USA) LLC, De Soto, KS, to develop the test. It launched in the US in May 2009.

Lung cancer is currently diagnosed only after a sample of lung tissue is collected during an invasive biopsy procedure and then analyzed. Nearly 40,000 people in the UK are diagnosed with the disease every year. It is one of the country's biggest killers - on average someone dies from it every 15 minutes - and only 10% of patients will still be alive five years after diagnosis. The new test involves obtaining a conventional blood sample from patients and could become a routine part of care for people considered most at risk, such as smokers, those with respiratory diseases and those with a family history of the disease. The antibodies produced by the body in response to the presence of cancer cells are different for each type of disease. Oncimmune has identified the antibodies specific to breast cancer and is in the final stages of

developing a test for the disease, which will launch in 2011. The company hopes that a single blood test, which would be able to identify any cancer type, will be available within five years[33].

AMD diagnostic

In early 2009, Sequenom Inc., San Diego, CA, signed an exclusive worldwide licensing agreement with Optherion Inc., New Haven, CT, under which Sequenom's CAP accredited and CLIA-certified laboratory, the Sequenom Center for Molecular Medicine, obtained the rights to develop and commercialize diagnostic tests to predict genetic predisposition to late stage age-related macular degeneration (AMD). The license agreement covers extensive intellectual property rights for the most significant AMD-related genetic variants that have been confirmed in multiple clinical studies around the world. The portfolio of intellectual property being licensed has been consolidated from major US universities which spearheaded genetic and clinical AMD research during the last decade.

Upon successful development of the test, Sequenom intends to market a laboratory developed test under its SensiGene brand name for genetic tests. The laboratory anticipates launching the new test early in 2011. The format of the assay that the company plans to develop is optimal for its MassArray technology. That platform has already been used in several of the key published studies that have validated the link between AMD and the genetic variants that are expected to form the basis of its planned test.

AMD is an insidious progressive eye disorder that starts with relatively harmless tiny yellow deposits on the retina and increases in severity with age. The end stage of this condition, called neovascular or wet AMD, develops in 10% to 20% of all cases, causes profound loss of central vision and is the leading source of legal blindness in people over the age of 50 in the developed world. It is caused by abnormal growth of fragile and leaky blood vessels (choroidal neovascularization or CNV) in the macula, a

small area where vision is keenest at the center of the retina, in response to chronic inflammatory stress.

Although no curative therapies for AMD exist, treatments are available that help to slow the progression or even partially reverse vision loss, provided diagnosis is made in the initial stages of wet AMD. Since loss of visual acuity in one eye is compensated by the fellow eye, patients with advanced AMD run the risk of not being diagnosed until they develop irreversible loss of central vision. A predictive test that identifies patients at higher than average risk to progress to wet AMD, should improve clinical management by transforming surveillance protocols and improve therapeutic decision-making. Approximately 75% of disease risk is inherited and predominantly caused by variations in a handful of genes discovered over the last five years. Most of the affected genes have been identified in regulatory proteins contained within the alternative complement system involved in innate immunity.

Sequenom's goal is to develop a simple non-invasive DNA test to be performed once, that will provide a clinician with genetic information specific to an individual's risk of progression to late stage CNV in order to optimize patient management to preserve vision. AMD affects 15 million to 20 million people in the US, more than 2.5 million people in Canada, and more than 50 million worldwide. In North America there are 2 million people with vision loss and more than 600,000 that are legally blind due to the disease. The worldwide incidence of the disease increases from 1 in 10 people over the age of 60 to more than 1 in 4 people over the age of 75[34].

Key biomarker gene

Qiagen’s wholly owned subsidiary, DxS, has acquired the global and exclusive license for biomarker PI3K - phosphoinositide 3-kinase - from Johns Hopkins University, Baltimore, MD, to develop real-time-PCR and endpoint PCR assays. Research has shown that variation in the PI3K gene could be a key biomarker for use as a companion diagnostic with certain cancer treatments. Mutations in the PI3K oncogene may be

predictive for the success of certain treatments of patients suffering from lung, breast, colorectal and other cancers. The company has an active PI3K assay development and partnering program with pharmaceutical companies to develop and market tests for new cancer drug candidates.

Qiagen already markets a PI3K test for research use. This test is based on real-time PCR. The assay, which uses technology that allows a very significant sensitivity, detects mutations frequently missed by sequencing methods. The patent for PI3K mutations in human cancers was initially filed by researchers at Johns Hopkins who assessed the biomarker during their evaluation of tyrosine kinase inhibitors targeting the EGFR (epidermal growth factor receptor) pathway. Qiagen already markets several tests determining the mutation status in oncogenes. This portfolio includes tests for mutations of K-RAS and B-RAF, which are indicative for metastatic colorectal, lung and other cancers. The K-RAS test is CE-marked for companion diagnostic use with epidermal growth factor receptor inhibitors Vectibix and Erbitux and is expected to be submitted for FDA approval. By testing for specific genetic variations related to certain biomarkers, health professionals can customize their treatments to achieve the best possible therapeutic results and avoid unnecessary treatments[35].

Point of care instrumentation

The Tecan Group, Männedorf, Switzerland, a provider of laboratory instruments and products, solutions, and Enigma Diagnostics Ltd., Salisbury, Wiltshire, UK, a point-of-care molecular diagnostics company, have signed a manufacturing and supply agreement for Enigma's mini laboratory (ML) instruments. The Enigma ML delivers fully-automated results from swab samples in less than 60 minutes at the point of care and to the same accuracy standards as reference laboratories. Under the agreement, Tecan will deliver commercially manufactured ML instruments for Enigma's global market supplies and will also manage the ML instrument's supply chain. The first ML demonstration instruments have been delivered for Enigma's GlaxoSmithKline-delivery commitments for point-of-care molecular diagnostic influenza tests. The launch of

Enigma ML and supply of commercial series systems for its initial use to identify specific influenza virus strains is anticipated in late 2010, subject to successful clinical trials and regulatory approval. Additional tests will be added for other areas, such as infectious disease management, to the ML system test menu in the future[36].

Genotyping test launch

Sequenom Inc., San Diego, CA, has launched its SensiGene Fetal RHD Genotyping test, developed by the Sequenom Center for Molecular Medicine. This is the company's first laboratory developed test powered by its SeQureDx technology, which isolates and analyzes circulating fetal nucleic acid from a maternal blood sample. People have one of four blood types, A, B, AB or O. Each of these is further classified according to the presence or absence of Rh factor proteins on the surface of red blood cells, which carry the Rhesus antigens. One of the main antigens is D. Those positive for the D protein are called RhD positive. Absent the D protein, a person is RhD negative. About 85% of Caucasians are RhD positive, while 92% to 98% of African American and Hispanic populations and 98% to 99% of Asian and Native American populations are RhD positive. Between half and all of the children born to an RhD negative mother and RhD positive father will be RhD positive.

RhD incompatibility in pregnancy occurs when the mother is negative for the Rhesus D factor, and the baby is positive. During pregnancy the baby's blood cells may enter the mother's bloodstream causing the mother to produce antibodies that destroy and eliminate the baby's red blood cells. This immune response may lead to RhD disease for the baby. RhD disease can result in jaundice, anemia, brain damage, heart failure or even fetal death. Without treatment, severe cases may result in stillborn deliveries.

The new fetal test is designed to detect circulating cell-free fetal (ccff) DNA from maternal blood and examine multiple regions of the gene that are known to be the most common genetic basis of RhD negative phenotypes. The test interrogates four targets within three exons located on the RHD gene on chromosome one. The test also

incorporates male-specific targets on the Y chromosome, because it has been demonstrated that Rh alloimmunization occurs more frequently in male fetuses. A quality control metric is also included to ensure detection of DNA. A fetal identifier control is a reflex control assay that detects fetal DNA in a sample within a large background of maternal DNA. The test is performed on Sequenom's proprietary MassArray system, which allows direct mass measurement of nucleic acids.

Fetal RHD genotyping utilizing real-time PCR has been widely used in Europe for more than a decade, and has led to better patient management and is even considered for reduction of unnecessary treatment with anti-D immune globulin. Based upon Sequenom's validation study, the SensiGene Fetal RHD Genotyping test appears to offer a higher level of sensitivity and specificity compared with the real-time PCR methodology. In the US, there are approximately 528,000 pregnancies in RhD negative women every year, and almost all of these women could benefit from an assessment of the RhD type of the fetus. RhD type can be determined by an invasive procedure, such as amniocentesis or chorionic villus sampling, but both procedures involve risk to the fetus. Currently in the US, most RhD negative women are managed without knowing the fetal RHD status[37].

Innovative colon cancer diagnostic

Health Discovery Corp., Savannah, GA, in February 2010 entered into an exclusive agreement with the Pancreas, Biliary and Liver Surgery Center of New York at Saint Vincent Catholic Medical Centers, New York, NY, to provide clinical specimens to be utilized to complete the final validation of the company’s molecular diagnostic test for colon cancer. This test demonstrated a 93% sensitivity and a 93% specificity in a previous validation study. Under the terms of the agreement, the Pancreas, Biliary and Liver Surgery Center of New York will provide specimens from their collected specimen banks, as well as blood and tissue specimens on all new patients along with all associated clinical and outcomes data.

Health Discovery owns all of the intellectual property and commercialization rights to this molecular diagnostic test for colon cancer and intends to partner with a large clinical laboratory for development, marketing and commercialization of this new colon cancer test. In developing this new molecular diagnostic test for colon cancer, the company employed the same discovery process that led to the urine-based prostate cancer test that is licensed for development and commercialization to Quest Diagnostics, Madison, NJ, on a royalty-based, world-wide co-exclusive basis. There are an estimated 1.2 million new cases of colorectal cancer worldwide and approximately 637,000 deaths from the disease[38].

Innovative pancreatic cancer diagnostic

Health Discovery Corp. entered into another exclusive agreement with the Pancreas, Biliary and Liver Surgery Center of New York at Saint Vincent Catholic Medical Centers to develop new molecular diagnostic tests for the early detection of pancreatic cancer. The center will provide all specimens from their collected specimen banks, specimens on all new patients and all associated clinical and outcomes data. The specimens will include tissue, blood and urine. The company will use its patent protected SVM (support vector machine)-based discovery technology to develop these new molecular diagnostic tests for pancreatic cancer in a similar fashion to the urine-based prostate cancer test that the company developed and licensed.

Health Discovery's SVM technology is an artificial intelligence and machine learning technology that enables the development of algorithms and techniques that allow computers to learn. Health Discovery will own all of the intellectual property and commercialization rights to these tests for pancreatic cancer and intends to immediately partner with a large clinical laboratory for development, marketing and commercialization of the tests[39].

Brain cancer companion diagnostic

Pfizer Inc., New York, NY, and DxS, a wholly owned subsidiary of Qiagen, in February 2010 entered into an agreement to develop a companion diagnostic test kit for PF-04948568 (CDX-110), an immunotherapy vaccine in development for the treatment of glioblastoma multiforme (GBM). In April 2008, Pfizer and Celldex Therapeutics Inc., Needham, MA, entered into an agreement to grant Pfizer an exclusive worldwide license to PF-04948568 (CDX-110) which is in Phase II clinical development for the treatment of newly diagnosed GBM.

GBM is the most common malignant primary brain tumor in adults and occurs in around 25,000 patients worldwide each year. Pfizer's investigational drug PF-04948568 (CDX-110) is a peptide vaccine which targets the tumor-specific epidermal growth factor receptor variant III (EGFRvIII), a mutated form of the epidermal growth factor receptor that is only present in cancer cells and occurs in 25% to 40% of GBM tumors. The Qiagen assay is designed to identify those patients whose tumors express the EGFRvIII mutation, allowing for the possibility of more targeted and personalized treatment. The EGFRvIII companion diagnostic will be developed and manufactured at Qiagen's Center of Excellence for Companion Diagnostics, Manchester, UK. The diagnostic will be a real-time PCR assay used to detect EGFRvIII RNA in tumor tissue[40].

Rapid thermocycling

Micronics Inc., Redmond, WA, has been issued a US patent for an integrated heat exchange system on a disposable, plastic cartridge. The new patent has broad utility across the life sciences sector with particular application in point of care molecular diagnostics. The patent, entitled "*System and method for heating, cooling and heat cycling on a microfluidic device*," is US Patent No. 7,648,835 (the '835 case). The patent identifies the use of exothermic or endothermic material in reservoirs that are contained within an integrated disposable plastic cartridge. Once the chemical process of the reservoir material is activated, the reservoir provides heating or cooling to specific locations on the cartridge. Multiple reservoirs may be included in a cartridge to provide varying temperatures. A complete PCR temperature cycle can occur in less than 15 seconds.

This is related to an earlier patent, U.S. Patent No. 7,544,506, also issued to Micronics. The devices related to these patents make it possible to perform PCR or real time PCR in a fraction of the time of commercial systems in use today. In Micronics' molecular diagnostic devices, all reagents required for a diagnostic test are incorporated into the disposable cartridge. Micronics is promoting a point of care molecular diagnostic platform, the PanNat system that employs disposable cartridges and a small, lightweight, easy to operate instrument. Using microfluidics, the company is able to substantially reduce the volumes of sample and reagents required to produce a test result, generally within a fraction of the time and cost that traditional reference lab and bench top methods require[41].

Acquisition of AcroMetrix

Life Technologies Corp., Carlsbad, CA, in January 2010, agreed to acquire AcroMetrix, Benicia, CA, a provider of molecular and serological diagnostic quality control products to clinical laboratories, blood screening centers and IVD manufacturers. Diagnostic controls allow a laboratory to achieve better standardization across systems and are more economically efficient to use than homebrew control reagents. There is a growing need for quality, independently provided controls to ensure the accuracy and integrity of laboratory test results.

Life Technologies holds a significant portfolio of molecular diagnostics products that comprise more than $300 million of the company's revenue, including magnetic beads, fluorescent dyes and specific antibodies, which can be custom designed for diagnostics manufacturers. The company also provides the Spot-Light HER2 Cish Kit for assessment of breast cancer patients; the Dynachip System for automated HLA antibody screening; and molecular diagnostic instruments, such as the 3500 Dx Series Genetic Analyzer, cleared for diagnostic use in certain European countries, and the 7500 Fast Dx Real-Time PCR instrument. The 7500 Fast and 7500 Fast Dx instruments have received Emergency Use Authorization from the FDA for surveillance of the Influenza A (H1N1) virus and have been used by public health agencies[42].

Real-time PCR

In April 2010, Life Technologies also expanded its family of real-time PCR systems with the introduction of a new high-productivity instrument. The Applied Biosystems ViiA 7 Real-Time PCR System seamlessly integrates a variety of quantitative PCR (qPCR) and genotyping applications. The ViiA 7 has been designed to improve productivity for research that includes how gene expression changes in response to pharmacological agents, and how genetic variation influences response to treatments

for disease. The system optimizes and simplifies several real-time PCR applications. A patent-pending OptiFlex System within the ViiA 7 provides the sensitivity to detect a single copy of starting genetic material and improves multiplexing flexibility[43].

APiX detection kit

Gentel Biosciences, Madison, WI, a developer of proteomics discovery tools, in April 2010 made available its APiX View Detection Kits for ultra-sensitive chromogenic detection of protein microarrays, including reverse phase protein. This launch expands the applications of APiX technology to include not only antibody and protein arrays on clear glass slides, but also tumor lysate arrays on porous nitrocellulose surfaces. APiX chromogenic technology makes it possible to detect any biotinylated molecule, generating light grey-to-black spots that are visible to the naked eye. APiX is also compatible with a variety of secondary antibodies such as anti-mouse and anti-rabbit[44].

Biomarker analysis

A research team has reported the clinical results of a new method for analyzing the molecular activity of cancer drugs for solid tumors using skin biopsies. The approach was made possible by Cambridge Research and Instrumentation Inc. imaging and analysis systems. The study relied on the ability of the company's multispectral imaging and analysis systems, Nuance and inForm, to discriminate between multiple, co-localized markers in intact tissue.

The study was a Phase Ib trial to assess whether increased levels of a protein called pCDC2 could serve as a biomarker for molecular target engagement for inhibitors of a cell division cycle-related protein called Wee kinases, especially used in combination with DNA damaging agents. The researchers, from Merck Research Laboratories, the New York University Cancer Institute and Mosaic Laboratories, collected biopsies from 32 patients at three time points before and after infusions of chemotherapy

regimens containing gemcitabine, cisplatin or carboplatin. The researchers used the CRi Nuance FX system to conduct multiplex analyses of phosphorylated CDC2 and total CDC2 protein. The analyses were conducted on cells of the epidermis, hair follicle and hair bulb. All three pre-specified primary analysis parameters detected significant induction of CDC2 phosphorylation in response to chemotherapy. The epidermis was most consistently evaluable across the skin biopsies and demonstrated strong induction of CDC2 phosphorylation. Increases in pCDC2 occurred in hair follicles and bulbs, but these tissues were present in fewer biopsies than epidermis, limiting the number of informative specimens. The company's systems enable researchers and clinicians to quantitate several disease and drug response markers in intact tissue samples[45].

Genetic dermatology

Genetic tests in key areas of dermatology have been brought under one roof by molecular dermatology research and development company DermaGenoma, Inc., Irvine, CA. DermaGenoma is developing new diagnostics and prescription based therapies for skin conditions tailored to an individual's genetic makeup. The diagnostic genetic tests that are part of the company include: HairDX, a genetic screening test for female and male pattern baldness (Androgenetic Alopecia); and the HairDX (RxR) Genetic Test for Finasteride Response. In addition to predicting Finasteride response for the treatment of common hair loss, the test helps doctors assess if a patient has an increased risk of developing benign prostatic hyperplasia. The company's portfolio also includes the PsoriasisDX Genetic Test, which helps identify those at high risk for developing psoriatic arthritis before they experience arthritic symptoms; and the HerpesDX Genetic Test for Frequent Genital Herpes, which helps doctors assess patients' risk for developing frequent Genital Herpes (HSV-2) outbreaks. The product lines will benefit from a large international distribution network in over 20 countries and six continents. DermaGenoma genetic tests are available through physician's offices and are administered using a simple cheek swab[46].

Genome sequencing agreement

bioMerieux, Marcy l’Etoile, France, and Knome, Cambridge, MA, are collaborating on the development of next-generation, sequence-based in vitro diagnostics. bioMerieux has exclusive rights to license Knome's proprietary genome analysis platform for use in the IVD market. Knome will gain access to bioMerieux's intellectual property in DNA extraction and sample preparation. bioMerieux has also purchased a $5 million equity stake in Knome. Knome provides genome sequencing and analysis services for those seeking to understand the genetics of human disease.

Multiplex DNA sequencing for molecular diagnostics development is part of bioMerieux's 2015 strategic road map. bioMerieux intends to develop molecular cancer and infectious disease diagnostics using Knome's proprietary sequence analysis technology and bioinformatic tools. In connection with the purchase, bioMerieux has the right to designate one director for election to the Knome board[47].

CHAPTER 4

Markets

Chapter 4 Markets

Summary

- To facilitate routine testing across a wider range of hospitals and reference laboratories, the market is demanding cost effective and simple-to-perform tests that have cleared the many regulatory hurdles. Automation is playing a key role in the development of tests that are easier and less expensive to operate.
- Infectious disease testing represents a large portion of the current market, given the re-emergence of infectious threats, including multidrug-resistant TB, new strains of HIV, and H1N1.
- Pharmacogenomics may be the most immediate new opportunity in the field.
- Many drug companies are investing significantly in pharmacogenomics in anticipation of shaving years off the drug discovery and approval process, bringing potentially lucrative drugs to market much sooner.
- Also in the future, the molecular oncology diagnostics sector will grow at a CAGR of 18%.
- The traditional trial-and-error practice of medicine is eroding progressively in favor of more precise molecular biomarker-assisted diagnosis and safer and more effective molecularly guided treatments. For the pharmaceutical industry, the outcome of this approach means increased efficiency, productivity, and novel product lines. The diagnostics industry has an opportunity for integration, increased value, and commercial opportunities for molecularly derived tests.
- Through 2015, the molecular diagnostics market will grow at double-digit pace, achieving an overall 14% compound annual growth rate to meet increasing demand for personalized medicine.
- Key areas of growth include infectious diseases, oncology, genetic testing and blood banking. A wide variety of drugs in late preclinical and early clinical development are being targeted to disease-specific gene and protein defects that will require coapproval of diagnostic and therapeutic products by regulatory agencies.

Overview

The molecular diagnostics industry represents a relatively new era in medicine that offers much promise for detecting disease and illness at a very early stage and for implementing personalized patient care. Molecular diagnostics offers a number of benefits, including the ability to perform rapid analysis, achieve high sensitivity and provide detailed information useful for the diagnosis of disease and the personalized treatment of individual patients. This new and expanding part of the in-vitro diagnostics market has emerged in response to a need for more rapid, sensitive and specific diagnostic tests than those that were available using only traditional techniques, such as growth-based tests, biochemical tests or immunoassays. Several factors will contribute to further significant growth of this market, including the decentralization of testing and advances in personalized medicine.

Traditionally, the market for molecular diagnostics has been dominated by testing techniques that rely on optical or fluorescence technologies and complex research instruments adapted to meet the demands of the clinical environment. These technologies are expensive to operate and require specialized facilities and highly-trained personnel. In addition, the devices that utilize these technologies are sensitive to dust, debris and movement and require specialized care and maintenance. To facilitate routine testing across a wider range of hospitals and reference laboratories, the market is demanding cost effective and simpler tests that have cleared regulatory hurdles. Automation is playing a key role in the development of tests that are easier and less expensive to operate. The market for molecular diagnostics is dynamic with significant competition from large, well-entrenched players, including Roche Diagnostics, Gen-Probe, Celera and Abbott Laboratories. The largest volume of patient samples is concentrated among a small number of large commercial laboratories, which confers strategic advantages to any player in the field that can offer products competitively – be they large or small companies.

Automation makes it possible for virtually anyone to collect a sample and carry out a molecular reaction. Under development is a new generation of automated laboratory

analyzers that will meet the growing demand for moderately complex molecular diagnostic tests. They will be able to reduce the complexity of these tests to the point where they can be run by less experienced lab staff.

Growth drivers

Two important growth drivers in the clinical setting for molecular diagnostics include the need for new biomarker assays as well as for techniques that lower the cost per test, and which improve ease of use, data quality and turnaround time. For example, ultra-high throughput, low-cost sequencing could potentially be a comprehensive diagnostic tool for every person, creating a significant market opportunity in early disease prognosis, diagnosis, optimal treatment and continuous monitoring - personalized medicine.

On one front, molecular diagnostic tests for infectious disease have been one of the highest-growing segments of the in vitro diagnostics market. But there is still some room for market growth for molecular diagnostics for blood banking, pharmacogenetics, predisposition diagnostics and cancer diagnostics. Infectious disease testing represents a large portion of the current market, given the re-emergence of infectious threats, including multidrug-resistant TB, new strains of HIV and H1N1. For example, in May 2010, Quest Diagnostics' Simplexa Influenza A H1N1 test received 510(k) clearance, making it the first test to receive clearance from the agency for the virus. While H1N1 has not become a widespread public health problem, reliable detection is needed to help manage high-risk patients, such as expectant mothers who have flu-like symptoms. This test will be the only one allowed to be marketed in the US after late June 2010. Previously, tests for the 2009 H1N1 influenza were available only through Emergency Use Authorization, which allows the FDA to authorize unapproved or uncleared medical products, or unapproved or uncleared uses of approved or cleared medical products, while a medical emergency is in effect.

Companies that develop or market molecular diagnostics must understand that their participation in the infectious disease testing sector could well drive their success.

Some segments of the infectious disease molecular diagnostics market are already well established and do not offer much of an opportunity for new market entrants. It is important that companies understand where the true opportunities remain, such as with the onset of new infectious threats. And they must be quick to respond to such changes in the marketplace if they expect to succeed.

A more general driver of the molecular diagnostics market is the aging population, which will require more testing for diseases that evolve with increasing age. According to information gathered by the United Nations, the US Census Bureau and other agencies, the median age of the world's population is increasing because of a decline in fertility and a 20-year increase in the average life span during the second half of the 20th century. These factors, combined with previously elevated fertility levels in many countries during the two decades after World War II, will result in increased numbers of persons more than 65 years of age between 2010 and 2030. Worldwide, the average life span is expected to extend another 10 years by 2050.

Other drivers for this market include the need for advances in genomics that drive the development of companion diagnostics. Drug and diagnostics companies could benefit from new pharmacogenomic diagnostics, such as the AmpliChip test. In December 2004, the FDA approved Roche Diagnostics' AmpliChip CYP450 diagnostic, the first pharmacogenomic diagnostics product. This test identifies mutations in two genes and determines whether a patient is a fast, normal, or slow metabolizer of drugs metabolized by the CYP2d6 and CYP2c19 gene products, which make up about one-fourth of all prescribed drugs. This information can help care givers determine safe and effective dosages for patient administration, and can help them avoid the traditional trial and error approach, which can be costly, time-consuming, and risky.

Future opportunities

Opportunities are many in the molecular diagnostics field - in the development of pharmacogenomics, panels and arrays. The first step in the genetic detection of disease involves a better understanding and characterization of the pathogens that impact

human health. Researchers are just beginning to understand the complex interplay between exogenous factors such as pathogens and environmental exposures, and their implications in the development of both acute and chronic disease. The more they understand the underlying pathology and pathophysiology of disease, the more effectively they can identify the therapeutic targets and biological markers necessary to diagnose, monitor, and treat disease. Some believe it is essential for clinical labs not only to be able to provide detection but also to take some responsibility and to provide treatment guidance. And keeping the cost per test low would facilitate market growth. The cost for a molecular diagnostic can range from less than $100 to $150 for a simple test, to up to $3,000 or so for a complex genomic test.

Pharmacogenomics may be the most immediate new opportunity in the field. Response to therapeutic drugs by an individual is partially a function of that individual's genetic makeup. The ability or inability to metabolize a drug is genetically determined. While a specific therapy may be safe and effective in one individual, the same drug can cause a severe adverse effect in another. When a patient has certain signs and symptoms, usually the physician prescribes a particular drug that clinical medicine has determined to be of value. Sometimes drug therapy fails, possibly because of genetic variations in metabolism of that drug. Laboratories will be able to test an individual for variations in particular drug response genes. The test results would help the physician prescribe the right drug at the right dose in a regimen specifically tailored to that individual, maximizing the chances of therapeutic success. Pharmacogenomics offers the potential for reducing the average cost of developing a new drug, now well over $1bn.

Many drug companies are investing significantly in pharmacogenomics in anticipation of cutting time off the drug discovery and approval process, bringing potentially lucrative drugs to market much sooner. Applying pharmacogenomics also has the potential for rescuing drugs that failed in early trials by ensuring that these drugs are prescribed only to that portion of the population for whom the drugs will be safe and efficacious from a genetic viewpoint. Pharmacogenetic testing will need to be done before prescriptions are written. It is possible that regulatory bodies will require a diagnostic test for pharmacogenetic signatures before a prescription may be written for

a patient. The best possible way to take full advantage of pharmacogenomics would be at the point of care, in the physician's office before the prescription is written. A care giver could take a blood specimen in his office, which would then be checked for DNA. The DNA would be analyzed in an instrument that assesses the patient's DNA for key genetic markers to inform the physician that one drug is a better choice for therapy than another because the patient is incapable of metabolizing another drug into its active therapeutic form[48].

Also in the future, the molecular oncology diagnostics sector will grow. Cancer involves a number of diseases with vast unmet clinical need for improved diagnostics and therapeutics. Cancer has about a 1% to 1.5% prevalence in developed western countries, which translates into a significant market opportunity for diagnostics companies. Any increase in the number diseases that could rely on molecular diagnostics for their early detection, such as breast cancer, is expected to drive procedure volume and the demand for the tests. As people age, they become more susceptible to illness, including breast cancer. The American Cancer Society's most recent estimates for breast cancer in the US for 2009 are:

- About 192,370 new cases of invasive breast cancer will be diagnosed in women;
- About 62,280 new cases of carcinoma in situ (CIS) will be diagnosed (CIS is non-invasive and is the earliest form of breast cancer);
- About 40,170 women will die from breast cancer.

A growing opportunity involves HER2, which is also called HER2/neu, and HER-2, referring to human epidermal growth factor receptor 2. Knowing one's HER2 status is an important part of a woman's health diagnosis. The R2 is a gene that sends control signals to cells, telling them to grow, divide and make repairs. A healthy breast cell has two copies of the HER2 gene. Some types of breast cancer initiate when a breast cell has more than two copies of that gene, and those copies start over-producing the HER2 protein. As a result, the affected cells grow and divide much too quickly, and can create a cancer.

The HER-2/neu diagnostic identifies those breast cancer patients, approximately 25% of all such patients, who express extra copies of the HER-2 gene. If tested for HER2 status, the results will be graded as positive or negative. If the results are graded as HER2 positive, that means that a woman's HER2 genes are over-producing the HER2 protein, and that those cells are growing rapidly and creating cancer. If one's results are graded HER2 negative, then the HER2 protein is not causing the cancer. For positive patients, the targeted cancer therapy drug Herceptin can be a highly effective treatment, and should also be considered as personalized medicine.

A number of other types of cancer, including prostate, stomach and lung cancers, also express HER-2/neu, and these represent growth opportunities for companion diagnostics. In April 2010, Roche's Genentech submitted a supplemental Biologics License Application to the FDA for Herceptin (trastuzumab) plus chemotherapy in people with advanced, HER2-positive adenocarcinoma of the stomach, including gastroesophageal junction cancer. The application was based on positive results from a Phase III study, known as ToGA, which showed that people who received Herceptin plus chemotherapy lived longer compared to people who received chemotherapy alone. The company will use diagnostics to help identify the right patients for its medicines. According to the American Cancer Society, an estimated 21,130 Americans were diagnosed with stomach cancer and more than 10,600 Americans died from the disease in 2009.

Other cancers, such as leukemia, are being explored in large-scale, international studies to investigate gene expression patterns and how they correlate with disease classification and treatment responses. Microarray-based testing is also being used to study the clinical implications of p53 gene mutations in a variety of cancers such as bladder cancer and breast cancer. Because p53 gene mutations are found in most tumor types, such tests may one day help doctors choose the anticancer therapies that are best suited to their patients' needs. There also is considerable evidence that microarray-based analyses of gene expression patterns can play an important role in subclassifying breast cancers and certain non-Hodgkin's lymphomas into aggressive and less-aggressive subtypes that require different types of treatment. A better classification of

human cancers is expected, which will be based on molecular signatures that ill accurately guide subsequent treatment.

World market forecasts

Optimized instrumentation and novel chemistries have enabled molecular diagnostics to evolve into a rapidly growing commercial field. Demand for these tests is high. There is an unmet need for robust, reproducible tests that provide consistent results within a lab as well as across many labs. Molecular diagnostics has taken off as an industry as a result of major advances in automation, integration, throughput, and the ability to use instrumentation in a random access mode.

After more than a decade of using molecular methods to diagnose important diseases, there is still an unmet need for reproducible, quality molecular diagnostic tests whose results are consistent not only within a lab but between labs. The industry is growing on the path of continuous innovation and changing technological base and is generating new applications. The way is paved by infectious disease testing and blood banking applications, but pharmacogenetic, predisposition diagnostics and molecular cancer diagnostics applications will grow in the years to come, all benefiting from from the advantages of molecular technologies: sensitivity, specificity and speed. A number of companies have not established positions in the market place. They are still honing their focus. Some companies have already determined their focus (Table 4.1).

Table 4.1: Key players in molecular diagnostics

Company	Key areas of focus
Abbott	HIV, HPV, oncology
Becton Dickinson	Healthcare-associated infections, toxins
Celera	HIV, cystic fibrosis, respiratory pathogens
Cytocell	Genetic diseases; breast cancer, lymphoma
Gen-Probe	Viruses, infectious diseases
IntelligentMDx	Infectious disease, influenza
Novartis	Allograft rejection, rheumatoid arthritis
OncoVista	Circulating tumor cells
Qiagen	HPV, HIV, genotyping, gene silencing, next generation sequencing
Roche	Virology, genomics, oncology, blood screening
TrovaGene (Xenomics)	Transreal DNA and RNA testing for infectious disease, tumor testing

Source: Business insights

Business Insights Ltd

Through 2015, the molecular diagnostics market will grow at a double-digit pace, achieving an overall 14% compound annual growth rate (Table 4.2) to meet increasing demand for personalized medicine. Key areas of growth include infectious diseases, oncology, genetic testing and blood banking. A wide variety of drugs in late preclinical and early clinical development are being targeted to disease-specific gene and protein defects that will require coapproval of diagnostic and therapeutic products by regulatory agencies. Educated patients will demand more information about their predisposition to serious diseases, and how these possible illnesses can be detected in an early stage, and then slowed or cured with new therapies specifically designed for their individual clinical status. Major drug makers will partner with diagnostics companies or develop their own in-house technologies that will enable them to offer more effective and less toxic integrated personalized drugs and diagnostics. Clinical laboratories will have a new opportunity, with the integration of diagnostics and therapeutics, to emerge as pacesetters of new medicine, guiding the selection, dosage, route of administration, and drug combinations in an effort to increase efficiency and reduce the toxicity of drug products.

The traditional trial-and-error practice of medicine is eroding progressively in favor of more precise molecular marker-assisted diagnosis and safer and more effective molecularly guided treatments. For the pharmaceutical industry, the outcome of the

molecular approach means increased efficiency, productivity, and novel product lines. The diagnostics industry has an unprecedented opportunity for integration, increased value, and commercial opportunities for molecularly derived tests.

Table 4.2: World market for molecular diagnostics, 2009-2015, ($m)

	2009	2010	2011	2012	2013	2014	2015
Blood screening	695	799	918	1,056	1,215	1,397	1,606
HIV/HCV testing	726	784	847	915	988	1,067	1,152
STD testing	435	487	546	611	685	767	859
Oncology testing	351	414	488	576	680	802	947
HPV testing	267	307	353	406	467	537	617
Hospital acquired infections	86	99	116	136	159	186	217
Genetic testing	357	414	480	557	647	750	870
Total	**2,917**	**3,304**	**3,748**	**4,257**	**4,841**	**5,506**	**6,268**

Source: Business Insights

Business Insights Ltd

Geographical segmentation

By far, most of the established market for molecular diagnostics lies in the North American region. The market is building in Europe, but is still at relatively an early stage in the rest of the world (Table 4.3) and (Figure 4.7). Geographically, the US and European markets are the most advanced in terms of adoption of molecular testing and make up the majority of the existing market. With the exception of blood screening, adoption of molecular diagnostics by the rest of world and Japan is limited to the infectious disease segment (e.g., HIV, hepatitis, tuberculosis) and is heavily contingent on price reductions. Among clinical applications, blood screening and HIV/HCV testing garner the greatest share of the market, followed by STD testing and other sectors (Table 4.4) and (Figure 4.8).

Table 4.3: World market for molecular diagnostics by geography, 2010, ($m)

Region	Market share	Sales
US/NA	60%	1,982.40
Europe	20%	660.80
Japan	7%	231.28
ROW	13%	429.52

Source: Business Insights

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Table 4.4: World market for molecular diagnostics by application, 2010, ($m)

Application	Market share	Sales
Blood screening	24.18%	799
HIV/HCV testing	23.72%	784
STD testing	14.74%	487
Oncology testing	12.53%	414
Genetic testing	12.53%	414
HPV testing	9.30%	307
Hospital acquired infections	3.00%	99

Source: Business Insights

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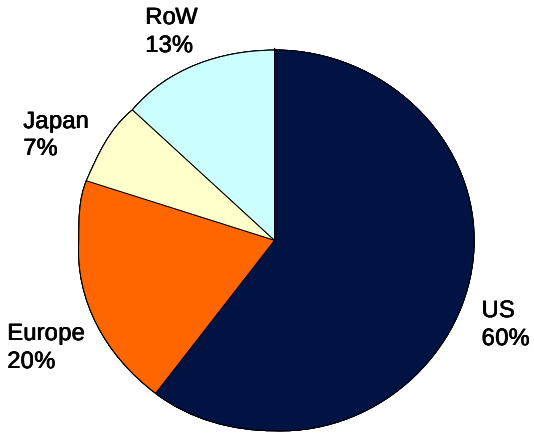
Figure 4.7: World market for molecular diagnostics by geography, 2010



Source: Business Insights

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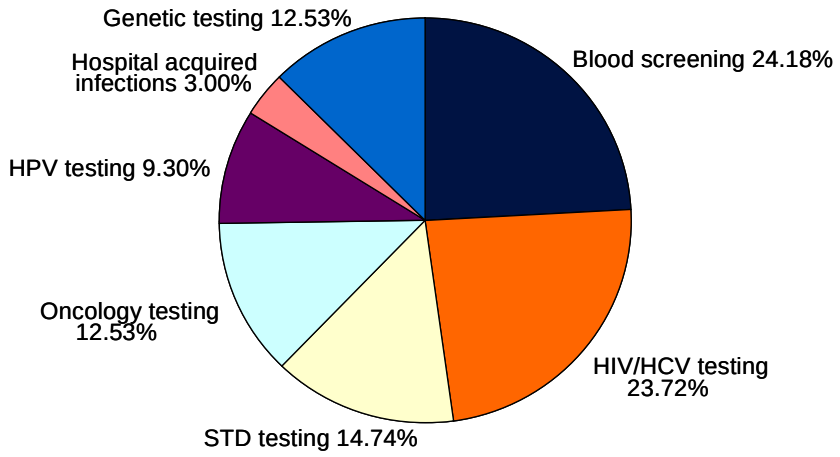
Figure 4.8: World market for molecular diagnostics by application, 2010



Source: Business Insights

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Type of testing

Blood screening

In blood screening, blood is scanned to test for a particular disease or condition. Although this procedure may be done for variety of reasons, the most common include HIV screenings, pregnancy screenings, and blood type screenings. The use of

a blood screening may also be needed to check for general infections and cancer. Additionally, all blood is carefully screened for serious diseases when it is donated to a blood bank.

Globally, the WHO estimates that more than 81m units of whole blood are collected annually[49]. About 14.5m units of blood are donated in the US[50], with a similar amount in Europe, and 7m units in Japan. Before entering the blood supply, donations are tested for evidence of exposure to blood borne viruses, including:

- Human immunodeficiency virus (HIV-1 and HIV-2); HIV-1 is common in the US and Europe, while HIV-2 is prevalent in West Africa countries such as Senegal, Nigeria, Ghana and the Ivory Coast;
- Hepatitis C virus (HCV);
- Hepatitis B virus (HBV);
- Human T-lymphotropic virus (HTLV-1 and HTLV-2), which is relatively uncommon in the US and Europe.

Several NATs are approved for screening donor blood. These were first introduced in the late 1990s initially for HIV and HCV, and were followed more recently by HBV and West Nile Virus. Prior to the introduction of NATs, blood centers used immunoassays to detect viral antigens or antibodies formed by the body in response to the virus. As this response may take some time, known as the seronegative or preseroconversion window, infected donors who have not developed detectable antibodies or viral antigens at the time of the donation expose blood recipients to infection. Because NATs directly detect the genetic material of viruses instead of waiting for the formation of antibodies, they reduce the seronegative window during which an infecting agent is undetectable.

The major companies in the infectious blood screening market are Gen-Probe/Chiron and Roche, which market NAT based tests and Abbott, which markets immunoassay

systems. Gen-Probe should retain most of the share of this market segment with its Procleix assay, followed by Roche and Abbott products. Gen-Probe developed and manufactures the Procleix assay, which is used to detect HIV-1 and the hepatitis C virus (HCV) in donated human blood; the Procleix Ultrio assay, which detects the hepatitis B virus in addition to HIV-1 and HCV; and the Procleix WNV (West Nile virus) assay. Gen-Probe's blood screening products are marketed worldwide by Chiron, a unit of Novartis Vaccines and Diagnostics Inc. Overall, this segment, which makes up more than 24% of the overall molecular diagnostics market, will experience a 15% compound annual growth rate (CAGR) through 2015 (Table 4.5).

Table 4.5: Global molecular diagnostics blood screening market, ($m)

	2009	2010	2011	2012	2013	2014	2015
Procrelix assay (Gen-Probe)	208.4	239.6	293.9	306.3	352.3	405.1	465.9
Cobas (Roche)	187.5	199.7	211.3	242.9	279.4	321.3	369.5
m2000 (Abbott)	173.6	199.7	220.4	253.5	291.5	335.3	385.5
Others	125.0	160.0	193.0	254.0	292.0	335.0	386.0
Total	**694.5**	**799.0**	**918.6**	**1,056.7**	**1,215.2**	**1,396.7**	**1,606.9**

Source: Business Insights

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HPV testing

The human papillomavirus (HPV) is a member of the papillomavirus family of viruses capable of infecting humans. HPVs establish productive infections only in the stratified epithelium of the skin or mucous membranes. While the majority of the nearly 200 known types of HPV cause no symptoms in most people, some types can cause warts. Others have the potential, in a minority of cases, to lead to the onset of cancers of the cervix, vulva, vagina, and anus in women or cancers of the anus and penis in men. HPV is probably the most common sexually transmitted infection in the US. Most sexually active men and women will probably acquire a genital HPV infection at some point in their lives. The American Social Health Association reported estimates that about 80% of sexually active Americans will be infected with HPV at some point in

their lifetime[51]. By the age of 50 more than 80% of American women will have contracted at least one strain of genital HPV.

The HPV testing market has been a significant sector of the molecular diagnostics market. According to the CDC, about 20m Americans are infected with HPV. There are about 6.2m new cases each year. About 80% of women will have acquired sexually transmitted HPV by age 50. While many of these cases resolve spontaneously, about one-third of the 30 currently identified sexually transmitted subtypes can, in rare cases, cause cervical cancer, which leads to death in approximately 5,000 US women annually. If clinicians combine HPV screening with a Pap smear, they can say with greater than 99% certainty that a woman does not have cervical cancer if both tests are negative.

In the current market for HPV, only about 20% of women over the age of 30 are screened for HPV using DNA-based tests in conjunction with a standard Pap smear, which leaves a lot of room for market growth. To capitalize on the growing market, some IVD companies are seeking to obtain FDA approval for positive-negative diagnostics that indicate whether a woman is infected with HPV, and for follow-up genotyping tests. If the first test is positive, genotyping tests can help to determine the specific strain, and whether it is one of those more highly implicated in cervical cancer. Most of the positive-negative screens under development test for 13 to 14 high-risk HPV strains. Roche Diagnostics is marketing the Amplicor HPV Test (CE-IVD), a PCR-based test for detection of 13 high-risk HPV genotypes. It is registered for use in the European Union and other countries that accept CE Mark certification. It also is approved in Canada and Japan.

Recently identified molecular pathways that are involved in cervical cancer are offering helpful information about novel bio- or oncogenic markers that will make it possible to monitor of essential molecular events in cytological smears, histological or cytological specimens. These markers are likely to improve the detection of lesions that have a high risk of progression in both primary screening and triage settings. E6 and E7 mRNA detection PreTect HPV-Proofer or p16 cell-cycle protein levels are examples of

such molecular markers. These markers, which are highly sensitive and specific, will allow the identification of cells undergoing malignant transformation.

Recently on the market, in March 2009, Third Wave Technologies, Madison, WI, a unit of Hologic Inc., received FDA approval for both the Cervista HPV HR (high risk) and the Cervista HPV 16/18 tests. Cervista HPV HR is designed to detect the 14 high-risk types of HPV known to cause cervical cancer. Cervista HPV 16/18 was the first HPV test approved for genotyping for HPV types 16 and 18, known to be associated with approximately 70% of all cervical cancers in the US. In January 2009, Sequenom, San Diego, CA, purchased SensiGen's AttoSense portfolio of tests along with certain other assets in a transaction worth $8.7m. Sequenom acquired all of SensiGen's assays, including the AttoSense HPV-G and HPV-Q tests for cervical cancer, AttoSense HPV-C for head and neck cancer, the AttoSense Kidney Test, and the EpiSense Lupus Panel. SensiGen has been developing this portfolio under a partnership agreement with Sequenom, and all tests utilize Sequenom's MassArray platform. AttoSense assays identify minute quantities, and identify nucleic acid targets that are difficult to detect accurately by current hybridization methods or which are found in extremely small quantities. In addition, Gen-Probe is developing a NAT to detect high-risk strains of the human papillomavirus, which causes cervical cancer.

The HPV testing segment makes up more than 9% of the overall molecular diagnostics market. It will experience about a 15% CAGR through 2015 (Table 4.6).

Table 4.6: Molecular diagnostics HPV testing market, breakup by competition, ($m)

	2009	2010	2011	2012	2013	2014	2015
Digene HPV (Quigen)	240.1	260.8	282.3	284.0	280.0	268.3	277.7
Aptima Assay (Gen-Probe)	0.0	10.0	15.0	40.6	70.0	107.3	154.3
Quest HPV test	13.3	14.7	16.1	17.8	19.5	21.5	23.6
Cervista	13.3	12.0	24.7	32.5	42.0	53.7	74.1
Others	0.0	9.3	14.7	30.9	55.1	85.8	87.4
Total	**266.7**	**306.8**	**352.8**	**405.8**	**466.6**	**536.6**	**617.1**

Source: Business Insights

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Hospital acquired infections

A hospital-acquired infection is also called a nosocomial infection. It initially appears between 48 hours and four days after a patient is admitted to a hospital or health care facility. About 5% to 10% of patients admitted to acute care hospitals and long-term care facilities in the US develop a hospital-acquired, or nosocomial, infection, with an annual total of more than one million people. Hospital-acquired infections are usually related to a procedure or treatment used to diagnose or treat the patient's initial illness or injury. The US CDC has shown that about 36% of these infections are preventable through the adherence to strict guidelines by health care workers when caring for patients. What can make these infections so troublesome is that they occur in people whose health is already compromised by the condition for which they were first hospitalized.

Hospital-acquired infections can be caused by bacteria, viruses, fungi or parasites. These microorganisms may already be present in the patient's body or may come from the environment, contaminated hospital equipment, health care workers, or other patients. Depending on the causal agents involved, an infection may start in any part of the body. A urinary tract infection is the most common type of hospital-acquired infection and has been shown to occur after urinary catheterization. The market for testing for this type of infection is still good. According to the 2009 National

Healthcare Quality Report and National Healthcare Disparities Report issued by the US Department of Health and Human Services' Agency for Healthcare Research and Quality, little progress has been made on eliminating health care-associated infections. For example, of the five types of hospital acquired infections in adult patients who are tracked in the report,

- Rates of postoperative sepsis, or bloodstream infections, increased by 8%;
- Postoperative catheter-associated urinary tract infections increased by 3.6%;
- Rates of selected infections due to medical care increased by 1.6%;
- There was no change in the number of bloodstream infections associated with central venous catheter placements;
- Rates of postoperative pneumonia improved by 12%.

Hospital acquired infections testing makes up 3% of the molecular diagnostics market. This segment is expected to experience a 17% CAGR through 2015, with Cephid retaining leadership in this segment (Table 4.7).

Table 4.7: Molecular diagnostics hospital acquired infections testing market, breakup by competition, ($m)

	2009	2010	2011	2012	2013	2014	2015
GenXpert (Cephid)	25.9	29.8	34.8	40.7	47.7	55.8	65.2
Luminex	4.3	5.0	10.0	12.0	20.0	30.0	40.0
Others	56.1	64.4	71.2	83.0	91.2	100.1	112.2
Total	**86.3**	**99.2**	**116.0**	**135.7**	**158.9**	**185.9**	**217.4**

Source: Business Insights

Business Insights Ltd

HIV/HCV testing

The human immunodeficiency virus (HIV) is a lentivirus that causes acquired immunodeficiency syndrome (AIDS), a condition in which the immune system begins to fail, leading to life-threatening opportunistic infections. Infection with HIV occurs by the transfer of blood, semen, vaginal fluid, pre-ejaculate, or breast milk. Within these bodily fluids, HIV is present as both free virus particles and virus within infected immune cells. The four major routes of transmission are unsafe sex, contaminated needles, breast milk, and transmission from an infected mother to her baby at birth (vertical transmission). Screening of blood products for HIV has largely eliminated transmission through blood transfusions or infected blood products in the developed world. From its discovery in 1981 until 2006, AIDS has killed more than 25m people. HIV infects about 0.6% of the world's population. In 2005 alone, AIDS claimed an estimated 2.4m to 3.3m lives, of which more than 570,000 were children.

HIV primarily infects vital cells in the human immune system, such as helper T cells, namely CD4+ T cells; macrophages; and dendritic cells. HIV infection leads to low levels of CD4+ T cells. When CD4+ T cell numbers decline below a critical level, cell-mediated immunity is lost, and the body becomes more susceptible to opportunistic infections. Hepatitis C is an infectious disease affecting the liver, caused by the hepatitis C virus (HCV). The infection is often asymptomatic, but once established, chronic infection can progress to scarring of the liver (fibrosis), and advanced scarring (cirrhosis) which is generally apparent after many years. In some cases, those with cirrhosis will develop liver failure or other complications of cirrhosis, including liver cancer or life threatening esophageal varices and gastric varices. HCV is spread by blood-to-blood contact. Most people have few, if any symptoms after the initial infection. Yet the virus persists in the liver in about 85% of those infected.

Persistent infection can be treated with medication. Peginterferon and ribavirin are the standard-of-care therapy. About 51% of those infected are cured. Those who develop cirrhosis or liver cancer may require a liver transplant, and the virus universally recurs

after transplantation. An estimated 270m to 300m people worldwide are infected with HCV. Coinfection with HIV and HCV can change the prognosis and disease progression of both.

- Chronic HCV infection develops in 75% to 85% of infected persons and leads to chronic liver disease in 70% of these chronically infected people;
- HIV and HCV co-infection has been associated with higher blood levels of HCV, more rapid progression to HCV-related liver disease, and an increased risk for HCV-related cirrhosis of the liver;
- HCV infection has been viewed as an opportunistic infection in HIV infected people since 1999. It is not, however, considered an AIDS-defining illness;
- As HIV medications and prophylaxis of opportunistic infections increase the life span of persons living with HIV. HCV-related liver disease has become a major cause of hospital admissions and deaths among HIV-infected persons;
- Patients who are coinfected with HIV and HCV have a markedly increased risk for stroke.

Molecular based technologies enable the sensitive identification of pathogens within a few hours, and quantitative techniques are particularly valuable in the management of chronic viral infections caused by HCV and HIV, when an assessment of viral load can be used to guide therapy and prognosis. Diagnostic tests for viruses include clinical tests for viral load monitoring (quantitative), detection (qualitative) and genotyping. The market is driven in part by HIV and HCV testing. Key players in this market segment include Roche, whose virology product portfolio is based on the company's real-time PCR technology. The company markets quantitative tests for HIV-1, hepatitis B * and C, and cytomegalovirus. The company’s Cobas AmpliPrep/Cobas TaqMan System is a fully automated real-time, continuous load IVD platform. The HIV-1, HCV, and HBV tests on this platform have been available in Europe since 2005. The HIV-1 test was approved for use in the US in May of 2007. Abbott markets its m2000 system, an automated instrument for DNA and RNA testing in molecular laboratories.

The system is based on real-time PCR technology and consists of *the m*2000sp for automated sample preparation and the*m*2000rt for real-time PCR detection and analysis. Outside the US, an extensive menu for infectious disease testing is available that includes HIV-1 viral load and hepatitis C (HCV) viral load. Except for the RealTime HIV-1 and the RealTime CT/NG, no other tests are currently available on the *m*2000 in the US.

In May 2009, Virco BVBA, Mechelen, Belgium, signed a global research and development, non-exclusive licensing agreement with Siemens Healthcare Diagnostics. Siemens is providing Virco a license which will enable Virco to develop and commercialize a new hepatitis C research service testing platform. This platform will initially be utilized by pharmaceutical companies for drug development support of new HCV antivirals. The platform will have the potential to provide HCV clinical diagnostic testing services in the future.

The HIV/HCV testing segment represents nearly 24% of the molecular diagnostics market. This segment is expected to have an 8% CAGR overall through 2015 (Table 4.8).

Table 4.8: Molecular diagnostics HIV/HCV testing market, breakup by competition, ($m)

	2009	2010	2011	2012	2013	2014	2015
Roche	290.4	321.5	330.3	356.7	385.2	416.0	449.3
Gen-Probe	210.5	235.2	237.1	256.1	276.6	298.7	322.6
Abbott	203.3	172.5	211.7	228.6	246.9	266.7	288.0
Becton Dickinson	14.5	23.5	42.3	45.7	49.4	$53.3	57.6
Others	7.3	31.4	25.4	27.4	29.6	$32.0	34.6
Total	**726.0**	**784.1**	**846.8**	**914.5**	**987.7**	**1,066.7**	**1,152.1**

Source: Business Insights

Business Insights Ltd

Genetic testing

Medical tests used to identify changes in chromosomes, genes, or proteins are genetic tests. Genetic testing identifies those at risk for a specific genetic disease, predicts the possibility of future genetic disease, or determines the risk for transmitting such a disease to their offspring. Testing may also be used as part of the process to identify, confirm, or predict the possibility of a specific medical condition occurring and to develop a treatment plan. Genetic tests, also called DNA tests, are the most sophisticated of techniques used to test for genetic disorders. These involve direct examination of the DNA itself. Genetic tests are used for several reasons:

- Carrier screening, which involves identifying unaffected individuals who carry one copy of a gene for a disease that requires two copies for the disease to be expressed;
- Preimplantation genetic diagnosis - screening embryos for disease;
- Prenatal diagnostic testing;
- Newborn screening;
- Presymptomatic testing for predicting adult-onset disorders, such as Huntington's disease;
- Presymptomatic testing for estimating the risk of developing adult-onset cancers and Alzheimer's disease;
- Confirmational diagnosis of a symptomatic individual.

Genetic testing makes it possible to determine vulnerabilities to inherited diseases. It can also be used to determine a child's paternity or a person's ancestry. Normally, every person carries two copies of every gene, one inherited from the mother, one inherited from the father. The human genome is believed to contain around 20,000 to 25,000 genes. Genetic testing in a broader sense includes biochemical tests for determining the presence of genetic diseases, or mutant forms of genes associated with increased risk of developing genetic disorders. Genetic testing identifies changes in chromosomes,

genes, or proteins. Most testing is used to find changes that are associated with inherited disorders. The early detection of genetic disorders would significantly reduce morbidity as well mortality rates. The results of a genetic test can confirm or rule out a suspected genetic condition or help determine a person's chance of developing or passing on a genetic disorder.

However, there are coverage and payment issues regarding genetic testing that are driven by the lack of appropriate coding. There is no effective way to identify these tests through the current claims process. CPT (current procedural terminology) codes are numbers assigned to every task and service a medical practitioner provides to a patient including medical, surgical and diagnostic services. They are used by insurers to determine the amount of reimbursement that a practitioner will receive by an insurer. When everyone uses the same codes to mean the same thing, they ensure uniformity. But CPT codes for genetic testing are not specific to the purpose for the test. Health plans do not have the appropriate data to understand how many and what kinds of molecular and genetic tests they have paid for, or should have paid for. This situation is common because the CPT codes being used today do not accurately reflect what new genetic tests are actually being done, nor do they link to specific types of results. Plans do not know how many or what kinds of tests they are paying for, and they do not have the data nor the guidelines to determine test appropriateness or connect them to outcomes. Reimbursement problems often result. As new tests continue to emerge, physicians are finding it difficult to remain educated about medical necessity and test efficacy. Moreover, physicians who graduated from medical school before 2005 or so received minimal or no education on molecular diagnostic testing in their curriculum.

Still, the molecular genetic testing market continues to grow. Genetic tests that assess a person’s risk of getting various diseases may someday be found at the corner drug store. In May 2010, Pathway Genomics, a start-up based in San Diego, CA, was supposed to make its personal genetic testing kits available at many Walgreen’s drug stores, of which there are 7,500 across the US. The Pathway Genomics Insight Saliva Collection Kit was to be sold nationwide. The company’s Insight Saliva Collection Kit was to retail in the $20 to $30 price range. The test examines specific variations in a

person’s DNA to derive information about their risk of getting diseases, such as diabetes, heart disease and various forms of cancer. But Walgreen’s decided not to carry the test kit after the FDA released an enforcement letter it had sent to Pathway Genomics requesting information regarding the product. The FDA believes it has regulatory authority over these laboratory-developed tests, but it has not always used this authority. Pathway's planned retail sale of the test has attracted FDA attention. The agency is asking the company to tell it why it does not think it needs FDA approval to sell the test. The FDA does not have any record of this test being submitted for approval or clearance.

Overall, about 900 genetic tests are available, and more are under development. Molecular and genetic test volumes have reached about 40m annual tests in the US and are expected to double to 80m by 2012. The US represents about half of the worldwide market for these tests, which for the most part cost from $300 to $3,000 per test. Almost 5% of the US population has had some type of genetic test already. In addition, 70% of people believe that they will have a genetic test by 2015. An increasing emphasis on the need to develop new and more effective testing methods is projected to further propel the growth in the genetic testing segment. The genetic testing segment, which totals more than 12.% of the molecular diagnostics market, should experience a 16% CAGR through 2015 (Table 4.9).

Sequenom, with its SNP genotyping and molecular typing technologies, is expected to be a leader in this segment. In May 2011, the company raised $51.6 million in a private placement, an important step toward regaining the confidence of investors. The funds will go toward R&D, product commercialization and general corporate purposes, The announcement came after Sequenom disclosed that it was resuming development of its prenatal test for Down syndrome. In April 2009, Sequenom abruptly delayed launch of the test because of what it described as employee mishandling of R&D test data and results, which brought inquiries from the Justice Department, the Securities and Exchange Commission, and cost several executives their jobs. Sequenom has agreed to pay $14m to settle a shareholder suit over the matter.

Table 4.9: Molecular diagnostics genetic testing market, breakup by competition, ($m)

	2009	2010	2011	2012	2013	2014	2015
Sequenom	167.8	178.1	206.6	245.2	284.5	330.0	382.8
Biomeriux	71.4	91.1	105.7	133.8	155.2	180.0	208.8
Luminex	53.6	70.4	81.7	94.8	109.9	127.5	147.9
Others	64.3	74.6	86.5	83.6	96.9	112.5	130.5
Total	**357.1**	**414.2**	**480.5**	**557.4**	**646.5**	**750.0**	**870.0**

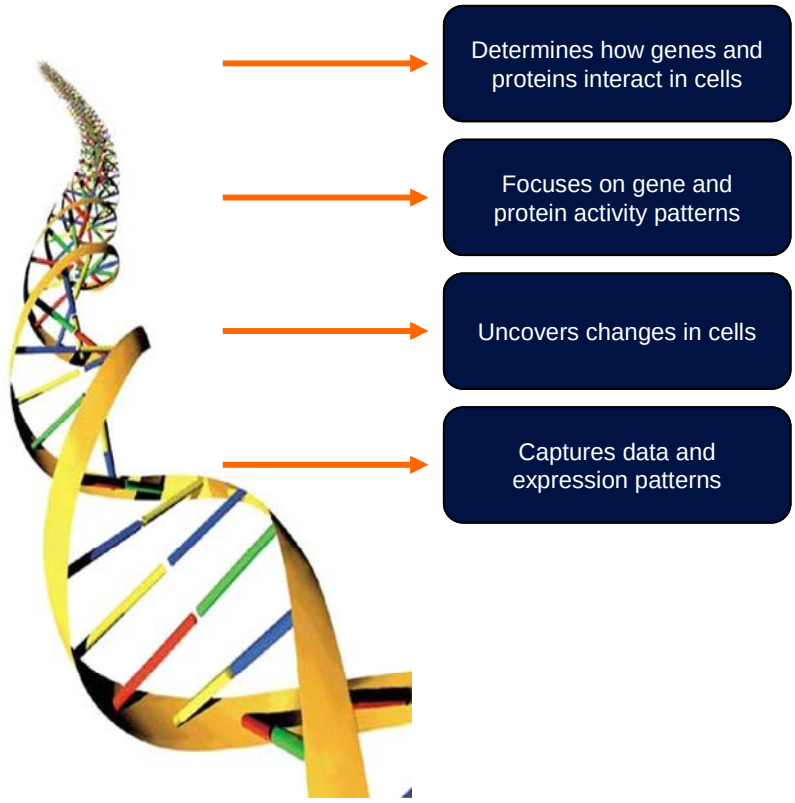
Source: Business Insights

Business Insights Ltd

Oncology

Although the use of molecular diagnostics will grow in such markets as infectious disease testing and blood banking, much of its future growth lies in oncology diagnostics. Key to this growth is how molecular diagnostics can diagnose cancer (Figure 4.9). Cancer involves a number of diseases with vast unmet clinical need for improved diagnostics and therapeutics. Cancer has about a 1%-1.5% prevalence in developed western countries, which translates into a significant market opportunity for molecular diagnostics. The cancer testing segment, while small in comparison to the other molecular diagnostic sectors in 2010, will experience solid growth with the continued emergence of pharmacogenetic and companion diagnostic tests for use in patient stratification and therapy selection. These tests are also likely to command premium pricing because of their high clinical value.

Figure 4.9: Molecular diagnostics diagnosing cancer



Source: Business Insights

Business Insights Ltd

Dako, Glostrup, Denmark, makes the HercepTest, which determines HER-2 protein overexpression in breast cancer tissues from patients for whom Herceptin treatment is being considered. The FDA has also approved a HER-2 test from Invitrogen, Carlsbad, CA, called Spot-Light that can be used to identify breast cancer patients who are candidates for Herceptin treatment. llumina is in the market with products for use in cancer studies, including technologies for microarray and sequencing. In Europe, Gen-Probe's Progensa PCA3 assay received marketing clearance in 2006. The assay detects the overexpression of the PCA3 gene in urine. PCA3 is highly over-expressed in the vast majority of prostate cancers, indicating that PCA3 may be a useful biomarker for the disease. The incidence of cancer and the number of cancer deaths remain high, but new molecular diagnostics are helping care givers more accurately diagnose cancers, identify a patient’s predisposition to the disease, and select individualized treatment

plans. There continues to be an emphasis on biomarker discovery and diagnostic-drug codevelopment. While the traditional pathological examination of cancer remains key, newer technologies such as microarrays, real time-PCR, mass spectrometric proteomic analyses, and protein chips are finding use in the development of new cancer molecular diagnostics. The oncology segment, which comprises more than 12.5% of the overall molecular diagnostics market, will experience an 18% CAGR through 2015 (Table 4.10).

Table 4.10: Molecular diagnostics oncology testing market, breakup by competition, ($m)

	2009	2010	2011	2012	2013	2014	2015
Illumina	112.2	132.4	156.3	184.4	217.6	256.8	303.0
Thinprep (Hologic)	105.2	124.2	146.5	172.9	204.0	240.7	284.1
Quest	70.2	82.8	97.7	115.3	136.0	160.5	189.4
Gen-Probe	0.00	20.7	29.3	40.0	60.0	80.0	100.0
Others	63.1	53.8	58.6	63.7	62.4	64.4	70.4
Total	**350.7**	**413.9**	**488.4**	**576.3**	**680**	**802.4**	**946.9**

Source: Business Insights

Business Insights Ltd

STD testing

Sexually transmitted infections are infections spread primarily through person-to-person sexual contact. Sexually transmitted disease (STD) is not only a cause of acute morbidity in adults but may result in complications with sequelae, such as infertility in both men and women, ectopic pregnancy, cervical cancer, premature mortality, congenital syphilis and fetal wastage, low birth weight, and prematurity and ophthalmia neonatorum. The STDs caused by bacterial, mycological and protozoal agents have been curable by appropriate antibiotics and chemotherapeutic agents for more than 40 years. In spite of this, STDs have continued to be a public health problem in both industrialized and developing countries.

An equilibrium has been reached, however, in most industrialized countries where there are low and often still falling rates of infection. In contrast, the equilibrium

reached in many developing countries has been with highly endemic levels of disease. In many developing countries, STDs have for several decades ranked among the top five diseases for which adults seek health care services. Reliable surveillance is rarely in place and the exact magnitude of the problem is frequently unknown. There are more than 30 different sexually transmissible bacteria, viruses and parasites. Several, in particular HIV and syphilis, can also be transmitted from mother to child during pregnancy and childbirth, and through blood products and tissue transfer. Some common sexually transmitted pathogens include:

- Neisseria gonorrhoeae (causes gonorrhoea or gonococcal infection);
- Chlamydia trachomatis (causes chlamydial infections);
- Treponema pallidum (causes syphilis);
- Human immunodeficiency virus (causes AIDS);
- Herpes simplex virus type 2 (causes genital herpes);
- Human papillomavirus (causes genital warts, and certain subtypes lead to cervical cancer in women);
- Hepatitis B virus (causes hepatitis and chronic cases may lead to cancer of the liver);
- Cytomegalovirus (causes inflammation in a number of organs including the brain, the eye, and the bowel);
- Trichomonas vaginalis (causes vaginal trichomoniasis).

The market for STD testing is significant. The World Health Organization (WHO) estimates that more than 340m new cases of curable sexually transmitted infections, namely those due to *Treponema pallidum* (syphilis), *Neisseria gonorrhoeae*, *Chlamydia trachomatis* and *Trichomonas vaginalis*, occur every year worldwide in men and women aged 15 to 49 years, with the largest proportion in the region of south and south-east Asia, followed by sub-Saharan Africa, Latin American and the

Caribbean. Millions of viral sexually transmitted infections also occur annually, attributable mainly to HIV, human herpes viruses, HPV and hepatitis B virus. Globally, these infections constitute a huge health and economic burden, especially for developing countries where they account for 17% of economic losses caused by poor health.

The herpes simplex virus type 2 infection is the leading cause of genital ulcer disease in developing countries. Data from sub-Saharan Africa show that 30% to 80% of women and 10% to 50% of men are infected. Among women in central and south America, prevalence ranges from 20% to 40%. In the developing Asian countries, its prevalence in the general population ranges from 10% to 30%. In the US, the prevalence of the viral infection among 14 to 49 year olds is 19%, and throughout the world, seropositivity rates are uniformly higher in women than in men and increase with age. HPV causes about 500,000 cases of cervical cancer annually with 240,000 deaths, mainly in resource-poor countries. HBV, which may be transmitted sexually and through needle sharing, blood transfusion and from mother to child, results in an estimated 350m cases of chronic hepatitis and at least one million deaths each year from liver cirrhosis and liver cancer.

Syphilis remains a global problem with an estimated 12m people infected each year, despite the existence of effective prevention measures, such as condoms, and effective and relatively inexpensive treatment options. Given social, demographic and migratory trends, the population at risk for sexually transmitted infections will continue to grow dramatically. The burden is greatest in the developing world, but industrialized nations can also be expected to experience an increased burden of disease because of the prevalence of non-curable viral infections, trends in sexual behavior and increased travel. The socioeconomic costs of these infections and their complications are substantial, ranking among the top 10 reasons for health-care visits in most developing countries, and substantially drain both national health budgets and household income[52].

In the US, the CDC estimates that there are 19m new STD infections every year, making STDs the most commonly reported infectious diseases in the US. STDs are

estimated to cost the US health care system about $16bn annually, and can cause serious long-term health consequences. Left untreated, STDs, such as chlamydia and gonorrhea can lead to infertility, and many STDs increase the risk of HIV infection.

Genital HPV is the most common sexually transmitted infection. There are more than 40 types of HPV that can infect the genital areas of males and females. These can also infect the mouth and throat. Most people who become infected with HPV do not even know they have it. Approximately 20m Americans are currently infected with HPV. Another 6m people become newly infected each year. HPV is so common that at least 50% of sexually active men and women get it at some point in their lives. Each year, about 12,000 women get cervical cancer in the U.S.

About one in six Americans (16.2%) between the ages of 14 and 49 is infected with herpes simplex virus type 2 (HSV-2), according to a National Health and Nutrition Examination Survey released by the CDC in April 2010. HSV-2 is a lifelong and incurable infection that can cause recurrent and painful genital sores. The findings indicate that herpes remains one of the most common STDs in the US.

The study finds that women and blacks were most likely to be infected. HSV-2 prevalence was nearly twice as high among women (20.9%) than men (11.5%), and was more than three times higher among blacks (39.2%) than whites (12.3%). The most affected group was black women, with a prevalence rate of 48%. As with other STDs, biological factors may make women more susceptible to HSV-2 infection. Additionally, racial disparities in HSV-2 infection are likely perpetuated because of the higher prevalence of infection within African-American communities, placing African-Americans at greater risk of being exposed to herpes with any given sexual encounter. People with herpes are two to three times more likely to acquire HIV, and that herpes can also make HIV-infected individuals more likely to transmit HIV to others. CDC estimates that over 80% of those with HSV-2 are unaware of their infection. Symptoms may be absent, mild, or mistaken for another condition. And people with HSV-2 can transmit the virus even when they have no visible sores or other symptoms.

The STD segment, which represents almost 15% of the molecular diagnostics market, will experience a 12% CAGR through 2015 (Table 4.11). Gen-Probe continues to take a healthy share of this market segment with its NAT-based tests for STD. Gen-Probe's key clinical diagnostics products include the Aptima Combo 2 and Pace assays, which are used to detect the Chlamydia and gonorrhea. Hologic is in the market with its Cervista HPV family of tests. While Becton Dickinson is in this market, it faces stiff competition from Gen-Probe and others in its STD testing franchise, and from Cepheid in hospital-acquired infections testing.

Table 4.11: Molecular diagnostics STD testing market, breakup by company, ($m)

	2009	2010	2011	2012	2013	2014	2015
Aptima Combo (GenProbe)	217.5	238.8	240.1	268.9	301.2	337.4	377.8
Hologic	108.8	107.2	130.9	146.7	164.3	184.0	206.1
Becton Dickinson	65.3	82.8	103.7	116.1	130.1	145.7	163.2
Others	43.5	58.5	70.9	79.5	89.0	99.7	111.6
Total	**435.1**	**487.3**	**545.6**	**611.2**	**684.6**	**766.8**	**858.7**

Source: Business Insights

Business Insights Ltd

CHAPTER 5

Corporate profiles

Chapter 5 Corporate profiles

Abbott Molecular

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Company description

Abbott's molecular diagnostics business includes instruments and reagents used to conduct analysis of patient DNA and RNA. The company’s products provide information based on the early detection of pathogens and subtle changes in patients' genes and chromosomes. Abbott markets molecular tests based on PCR and Fish technologies. The company offers genomic tests for chromosome changes associated with congenital disorders and cancer, including the Vysis PathVysion HER-2 DNA Probe kit to identify women with metastatic breast cancer who could benefit from Herceptin therapy. UroVysion detects genetic changes in bladder cells for monitoring for bladder cancer recurrence and for use as an aid in the initial diagnosis of bladder cancer in patients with hematuria (blood in urine).

In September 2009, Abbott entered into an agreement with Pfizer Inc to develop a molecular diagnostic test intended to screen non-small cell lung cancer (NSCLC) tumors for the presence of gene rearrangements. Pfizer has an investigational agent that selectively targets cancer-causing genes implicated in the progress of many cancers. To be eligible to receive Pfizer's oral therapy, a particular genetic translocation (rearrangement) known to be found in NSCLC tumors and a wide variety of other cancers, but not in normal cells, must be present.

AcroMetrix

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Company description

Acrometrix markets a line of molecular and serological diagnostic quality control products that help laboratories meet quality requirements. In December 2009, the company launched its OptiQuant BKV Quantification Panel. Designed to help laboratories assess the performance of molecular diagnostic test procedures for the BK virus, this panel plays an important role in the management of transplant patients.

In November 2009, the company launched its OptiQual HPV Genotype Panel. It is designed to help clinical laboratories comply with CLIA guidelines for qualitative molecular assays that detect HPV. This product can assist lab personnel with the validation and verification of their molecular HPV tests. Panel members include HPV-16, 18, 68, and a negative, and are offered individually allowing users to customize their own HPV genotyping panel. In July 2009, Acrometrix released the first standardized quality control for molecular Group B Streptococcus (GBS) testing, the OptiQual GBS Positive Control, is designed to help clinical laboratories comply with CLIA guidelines.

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Company description

Adnavance is a developer of direct detection molecular diagnostic tests. The company's patented and ultra-sensitive metalized-DNA (M-DNA) technology may eliminate the need for amplification for a large number of these tests.

The company's M-DNA platform is based on the conducting properties of hybridized DNA. Under strict reaction conditions, certain metal ions can enter the central core of hybridized DNA and displace the hydrogen bonds, enhancing the conductive properties of DNA. The result is a new confirmation of DNA that is highly conductive. The company uses a microarray of micron-sized electrodes to detect M-DNA. The inherent ultra-sensitivity arises from the differential measurement in conductivity between hybridized DNA (B-DNA) and metalized-DNA. This change in conductivity is so large that it may eliminate the need for the amplification used in current molecular-based tests.

The company's initial M-DNA diagnostic product will detect MRSA. Management expects to launch that product in 2010, targeting sales in the US, Canada and Europe.

Affymetrix

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Company description

Affymetrix introduced highly parallel genetic assays to the marketplace by commercializing the first DNA microarray in the late 1980s. The company's products and services include microarrays, instrumentation, reagents and assays, software and high-throughput services. Affymetrix is adding new genetic analysis technologies to streamline workflows.

The company is evolving into a provider of scalable genomic analysis tools and reagents for discovery, exploration, validation, and genetic testing. The acquisitions of biology company Panomics and USB, a developer, manufacturer and supplier of enzymes, reagents and kits for life science research and industrial applications, bring high-throughput, multi- to single-gene assays and molecular biology reagents to customers. Affymetrix's GeneChip microarray technology is a standard tool for analyzing complex genetic information. After inventing the technology in the late 1980s, Affymetrix scientists have been developing products that accelerate genetic research and allow physicians to develop diagnostics and tailor treatments for individual patients by identifying and measuring the genetic information associated with complex diseases. Affymetrix has installed almost 1,950 systems worldwide, and more than 21,000 peer-reviewed papers have been published using its microarray technology.

Asuragen Inc.

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Company description

Asuragen is focused on molecular oncology and genetic diseases, with an emphasis on microRNA (miRNA) technology. Asuragen's diagnostic portfolio consists of Signature Genetic Testing and Oncology Testing products as well as controls and standards engineered using its patented Armored RNA technology, including custom Armored RNA constructs for licensees of its Armored RNA technology. Asuragen offers a full range of contract manufacturing services for RNA and provides GMP contract manufacturing for *in vitro* synthesized RNA for use in vaccines.

Signature technology is optimized for the rapid multiplex analysis of nucleic acid sequences. Up to 100 DNA or RNA targets can be detected in a single reaction. Armored RNA is based on bacteriophage coated protein encapsulation of specific RNA targets to form pseudo-viral particles. The bacteriophage coated protein protects RNA transcripts from nuclease degradation and can stabilize RNA sequences. Armored RNA is designed for use as a standard and control in assays, in particular for use as positive controls or quantitative internal spiked controls for amplification and detection using real time-PCR. Asuragen is developing and manufacturing RNA Control Kits for Affymetrix.

AutoGenomics Inc.

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Company description

AutoGenomics has developed an automated microarray based multiplexing molecular diagnostic platform that can be used to assess disease signatures with genomic and proteomic markers for genetic disorders, infectious diseases, cancer and pharmacogenetics. The company’s Infiniti Analyzer is a fully automated, multiplexing, molecular diagnostics platform that uses BioFilmChip Microarrays for determination of a wide range of genetic applications.

The system is designed specifically for processing AutoGenomics' proprietary BioFilmChip microarrays that can be multiplexed and configured with biomarkers to assess disease signatures from a single sample specimen. In January 2010, American International Biotechnology Services established a partnership with AutoGenomics to utilize the automated analyzer. The company provides drug discovery and diagnostic development organizations a broad range of laboratory services, including services for molecular biology, microbiology, virology, immuno peptide, bioorganic, and protein chemistries.

Beckman Coulter Inc.

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Company description

Beckman Coulter develops, manufactures and markets products that automate complex biomedical tests. From medical research and clinical trials to laboratory diagnostics and point-of-care testing, Beckman Coulter's 200,000 installed systems provide biomedical information. The company reported 2009 revenue of $3.26bn.

Among the company’s products are the Vidiera NsP nucleic acid sample preparation instrument and Vidiera NsD nucleic acid sample detection instrument - specifically for the hospital and reference laboratory.

Becton Dickinson

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Company description

Becton Dickinson's operations consist of three worldwide business segments: BD Medical, BD Diagnostics and BD Biosciences. Corporate wide revenue in 2009 reached $2.226bn. Diagnostics revenues in 2009 of $2.2bn increased $66m, or 3%, over 2008. The Diagnostics Systems unit experienced growth in worldwide sales of its automated diagnostic platforms, including the molecular BD ProbeTec, BD Viper and BD Affirm systems. Research and development expenses increased $10m, or 7%, reflecting continued investment in the development of new products and platforms with emphasis on the company's molecular platforms.

In November 2009, Becton Dickinson closed its acquisition of HandyLab Inc., an Ann Arbor, MI-based company that develops and manufactures molecular diagnostic assays and automation platforms. In January 2009, the Diagnostics unit received clearance from the FDA to market the BD GeneOhm Cdiff molecular assay for the rapid detection of the toxin B gene found in toxigenic Clostridium difficile, the bacterial pathogen responsible for Clostridium difficile infection (CDI). In June 2010, the company received 510(k) clearance from the FDA to market its BD Max GBS Assay for Group B Streptococcus on the BD Max System.

Biocartis SA

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Company description

Biocartis is a privately owned biotech company that was founded in 2007. It develops molecular diagnostics platforms for low to highly multiplexed detection of molecular-based biomarkers. Biocartis is developing two diagnostic platforms:

- A molecular diagnostics platform that fully integrates any sample preparation of nucleic acids, amplification, detection, and the generation of a result without user intervention;
- A multiplex detection platform that includes encoded microcarriers, a micofluidic cartridge, and an instrument for low-to-high multiplexing detection of biomarkers.

Early 2010, Biocartis acquired Philips' technology platform for rapid fully-automated DNA/RNA molecular diagnostic testing. The platform has been designed for applications in a wide range of patient sample testing, including oncology and infectious diseases.

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Company description

BioHelix is developing a portfolio of technologies for nucleic acid analysis and molecular diagnostics through internal research and in-licensing of technology. The company has two isothermal amplification platforms: the target based-Helicase Dependant Amplification platform (HDA) and the primase-based Whole Genome Amplification platform (pWGA). In addition, BioHelix has developed a series of amplification enhancer reagents targeted to improve all types of nucleic acid amplification reactions.

The company initially aims to commercialize assays that target the infectious disease market. With new biomarkers fueling the growth of the personalized medicine field, BioHelix's technology platforms are positioned to capture these emerging markets with simple, rapid screening tests capable of being performed at the point-of-care (POC) and potentially in the home. In October 2009, BioHelix and Quidel Corp. San Diego, CA, a provider of rapid point-of-care diagnostic tests, entered into a joint development and commercialization agreement focusing on the development and commercialization of in vitro molecular diagnostic tests utilizing BioHelix's isothermal amplification technology.

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Company description

bioMérieux, specializes in the in vitro diagnostics sector, designing, developing, producing and marketing reagents, instruments and software for medical or industrial applications. The company had consolidated sales of about $1.37bn in 2008 and employs more than 5,800.

Among its molecular diagnostics products, the company offers nucleic acid extraction and testing products as well as microbial genotyping. Applications include MRSA screening, cervical cancer surveillance, HIV, lower respiratory tract infection, and central nervous system infections. In November 2009, the company launched NucliSens EasyQ MRSA, an automated test for MRSA. The product is CE marked, and bioMérieux will be submitting it for 510(k) approval with the FDA.

Bio-Rad Laboratories Inc.

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Company description

Bio-Rad provides products and services to the life science research and clinical diagnostics markets. The company employs 6,500 and serves more than 85,000 customers. Its technology is used in genomics, proteomics, drug discovery, medical diagnostics and other markets.

Bio-Rad's Life Science Group develops, manufactures, and markets a range of laboratory instruments, apparatus, and consumables used for research in functional genomics, proteomics and other areas. Bio-Rad's life science products are based on technologies used to separate, purify, analyze, identify, and amplify biological materials such as proteins and nucleic acids. Some of these technologies include electrophoresis, imaging, multiplex immunoassay, chromatography, microbiology, bioinformatics, protein function analysis, transfection, amplification, and real-time PCR.

The Clinical Diagnostics group develops, manufactures, sells and supports products for medical screening and diagnostics. The company is also known for its blood virus testing and detection, blood typing, autoimmune and genetic disorders testing, and internet-based software products.

Celera

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Company description

Celera develops and manufactures molecular diagnostic products that are used by hospitals and other clinical laboratories to detect, characterize, monitor and select treatment for disease. The company has a distribution agreement with Abbott, through which Celera develops and commercializes molecular diagnostics, with Abbott serving as the distribution partner.

Its services business, Berkeley HeartLab Inc, is a high complexity CLIA certified laboratory that offers more than 25 clinical diagnostic tests, including assays that determine lipoprotein particle size and density based on the company's segmented gradient gel electrophoresis technology. The company also performs genetic testing. These tests identify and characterize risk for cardiovascular disease and help physicians recommend treatment.

Celera's ViroSeq HIV-1 Genotyping System has been cleared by the FDA and is CE Marked for use in detecting HIV genomic mutations that confer resistance to specific types of antiretroviral drugs, as an aid in monitoring and treating HIV infection. The Cystic Fibrosis Genotyping Assay is a qualitative in vitro diagnostic device used to genotype a panel of mutations and variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene in genomic DNA isolated from human whole blood specimens. In February 2010, it was announced that Qiagen would distribute a Celera molecular multiplex assay. The assay is the next generation version of Qiagen's ResPlex II assay for detection of respiratory pathogens.

Cepheid

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Company description

Cepheid develops, manufactures and markets fully integrated systems and tests for genetic analysis in the clinical, industrial and biothreat markets. For 2009, the company reported revenue of $170.6m. The company markets tests in the areas of health care acquired infections, critical infectious disease and women's health.

The company expects to continue with the development of products for the immunocompromised, oncology and genetic disease. In January 2010, Cepheid received FDA approval to market Xpert vanA, a rapid test for vanA, the antimicrobial resistance gene most commonly associated with vancomycin-resistant enterococci, a healthcare associated infection.

CombiMatrix Corp.

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Company description

CombiMatrix is a biotechnology company with a subsidiary, CombiMatrix Molecular Diagnostics, whose patented electrochemical manufacturing process utilizes standard semiconductor technology, proprietary software and chemistry to build arrays of materials molecule by molecule. The company's CustomArray products are DNA microarrays, which have uses in the pharmaceutical, biotech, and agrochemical industries as well as in research and government markets. The company also uses its technology in internal programs for diagnostics development, drug development and biodefense applications in addition to partnerships for nanomaterials development. CombiMatrix also has bacterial artificial chromosome arrays (BAC arrays), which enable researchers to perform comparative genomic hybridization studies. Utilizing these array technologies, CombiMatrix is engaged in three business areas: the development of services and products for molecular diagnostics; the development, manufacture and sale of research tools and services to life sciences researchers; and the development, manufacture and sale of biosensor systems and technology for national defense. The company’s primary product for genetic studies is CustomArray, which includes a highly flexible oligonucleotide array that can interrogate small sets of target genes or whole genomes.

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Company description

Cytocell is a provider of DNA screening products - Fish probes - for the detection of human genetic diseases in the areas of cytogenetics and cancer. OncoSight is Cytocell's new Fish probe collection product, which can detect a range of amplifications, deletions and other chromosome aberrations in different tumor types.

In May 2009, Cytocell added eight hematology probes to its existing leukemia and lymphoma collection. The addition of these eight probes took the company's total oncology offering to 31 FISH probes.

DiagnoCure Inc.

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Company description

DiagnoCure is commercializing cancer diagnostic tests. The company's DiagnoCure Oncology Laboratories in 2008 launched the Previstage 2 GCC Colorectal Cancer Staging Test, a GCC-based molecular test for the management of colorectal cancer. The guanylyl cyclase C (GCC) is a marker for identifying colorectal cancer cells, for which DiagnoCure owns exclusive worldwide diagnostic rights. The company has an alliance with Gen-Probe for the development and commercialization of a second-generation prostate cancer test using PCA3, DiagnoCure's proprietary molecular marker. This test is available through laboratories in the US using PCA3 ASRs from Gen-Probe, in Europe as the CE-marked Progensa PCA3 in vitro assay, and in Canada.

Founded in 1994, DiagnoCure commercialized its first diagnostic test, ImmunoCyt/ uCyt+ for bladder cancer, in Europe in 1998. The product obtained clearance from the FDA for commercialization in the US in 2000. Diagnocure entered into a product divestment agreement for ImmunoCyt/uCyt+ with Scimedx Corp., Denville, NJ, a diagnostics manufacturer. In December 2006, the company, refocused all of its efforts and resources on molecular diagnostics development.

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Company description

For the past 40 years, the Diasorin Group has been an international player in the IVD market. The Diasorin Group comprises 15 companies based in Europe, the US, Central and South America, and Asia. It has more than 1000 employees. For 2009, consolidated net revenues rise to about $382m, or 24.3% more than in 2008. The Group generates less than 23% of its revenues in Italy and considers the US and the rest of Europe (about 23% and 37% of 2006 consolidated revenues, respectively) its primary markets.

The company has signed a non-exclusive licensing agreement with Japan's Eiken Chemical Co. Ltd. for the use of its Lamp (loop-mediated isothermal amplification) technology in connection with research in molecular diagnostics. With access to Lmp technology and focusing initially on infectious disease testing, Diasorin plans to develop a fully automated platform for molecular diagnostic tests by 2011.

Dx Assays

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Company description

In September 2008, Dx Assays Pte Ltd., a commercial developer of molecular diagnostic assays officially started operations. The company was established as a joint venture between Qiagen, and BioOne Capital, the biomedical science investment company of EDB Investments. Dx Assays is developing and validating molecular diagnostic assays for biotech and pharmaceutical companies, which can be used in drug discovery and development. The company also supports clinical development activities by designing and developing companion diagnostics for drug candidates targeted at specific patient populations.

EliTech Group

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Company description

The EliTech Group is a privately held group of companies and worldwide manufacturer and distributor of in vitro diagnostic equipment and reagents. The Group includes Vital Scientific and Seppim, which manufacture clinical chemistry analyzers and reagents; EliTech Microbio (formerly International Microbio and Serfib) which manufactures microbiology and immunology kits; Wescor, which makes laboratory instruments, such as strainers and sweat test devices; inoDiag which manufactures multiplex serology devices; Nanogen Advanced Diagnostics, which makes molecular biology kits; and Epoch Biosciences, which manufactures real-time PCR detection reagents.

In January 2010, the EliTech Group, announced that its Epoch Bioscience division of Wescor sold the intellectual property and assets of its electronic microarray technology, previously acquired as part of the Nanogen purchase. The sale was to the Gamida For Life Group. The microarray technology includes all properties associated with the NC400 electronic microarray product line, which is a nucleic acid profiling platform with applications in single nucleotide polymorphism applications. The microarray technology will be developed by Gamidor Diagnostics, Oxfordshire, UK, and Savyon Diagnostics, Ashdod, Israel. Gamida has developed applications for the NC400. The

asset sale allowed EliTech to enhance its presence in molecular diagnostics and real-time PCR.

Enzo Biochem

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Company description

Enzo Biochem uses genetic processes to develop research tools, diagnostics and therapeutics, and provides reference laboratory services. Founded in 1976, management is using the company's technologies as a platform for entry into the clinical diagnostics market. The business of Enzo Biochem is performed by three subsidiaries: Enzo Life Sciences, Enzo Therapeutics and Enzo Clinical Labs.

The company's Enzo Clinical Labs unit is using its position as a CLIA certified, New York State-licensed laboratory. It is bringing in house increasing numbers of tests that will individualize its lab, and is venturing more deeply into molecular diagnostics. Towards that end, there are companies that developed unique gene-based assays including, for example, those that predict recurrence of a specific type of cancer, or how a patient may react to a specific chemotherapeutic regimen - with which Enzo can link and materially assist in the commercialization of these technologies. In 2007, Enzo Life Sciences and Abbott Molecular. entered into a multi-year agreement covering the supply of Enzo Life Science's products to Abbott Molecular for use in its Fish product line. Both companies have also entered into a limited non-exclusive royalty bearing cross-licensing agreement of patents for Fish systems, comparative genomic hybridization analysis, and labeling and detection technologies.

EraGen Biosciences

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Company description

EraGen develops, manufactures, and markets molecular reagent products and software for the research and clinical testing markets. The company's marketed and pipeline products, based on its patented MultiCode platform chemistry, are nucleic acid-based testing products for the early detection and monitoring of cancer, genetic and infectious diseases. The MultiCode chemistry is a flexible platform for both real-time PCR and multiplex PCR-based assays.

In May 2010, the FDA granted 510(k) market clearance for EraGen’s MultiCode-RTx HSV 1&2 Kit. EraGen’s HSV 1&2 Kit is the first FDA-cleared, molecular test for the herpes simplex virus. It is an in vitro diagnostic test for the detection and typing of the DNA of herpes simplex virus 1 and 2. In September 2008, the company received Health Canada approval to market molecular testing products as in vitro diagnostics in the Canadian market. The approved tests are performed on the MultiCode real-time PCR system. The tests are for Bordetella pertussis and parapertussis, the cause of whooping cough and related disease; Enterovirus, which causes meningitis; Influenza types A and B; HSV 1 and 2; and Cytomegalovirus (CMV), the most common infectious agent present at birth and a major threat to solid-organ transplant patients

Fujirebio Diagnostics Inc.

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Company description

Fujirebio Diagnostics specializes in the development, manufacturing and commercialization of in-vitro diagnostic products, with an emphasis in oncology. Fujirebio Diagnostics is a subsidiary of Fujirebio Inc., a Japanese healthcare company with a focus on diagnostics.

In January 2009, Fujirebio Diagnostics and Abbott signed a license agreement to develop a new ovarian cancer test for use on Abbott's automated Architect diagnostic analyzers. Under the agreement, Fujirebio will develop and manufacture for Abbott the HE4 biomarker, a blood test that may help in the risk stratification of women at high risk for ovarian cancer, which is difficult to detect at an early stage. HE4 in a manual format is currently FDA-cleared for monitoring recurrent or progressive disease in patients with epithelial ovarian cancer (EOC), and is CE-marked in Europe as an aid in estimating the risk of EOC in premenopausal or postmenopausal women presenting with a pelvic mass.

Gen-Probe Inc.

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Company description

Gen-Probe manufactures and markets NATs used primarily to diagnose human diseases and screen donated human blood. The company markets a portfolio of products that use its patented technologies to detect infectious microorganisms, including those causing STDs, tuberculosis, strep throat, pneumonia and fungal infections. Gen-Probe's key clinical diagnostics products include the Aptima Combo 2 and Pace assays, which detect Chlamydia and gonorrhea. In blood screening, Gen-Probe developed and manufactures the Procleix assay, which detects HIV-1 and HCV in donated human blood; the Procleix Ultrio assay, which detects the hepatitis B virus in addition to HIV-1 and HCV; and the Procleix WNV (West Nile virus) assay. Gen-Probe's blood screening products are marketed worldwide by Chiron, a business unit of Novartis Vaccines and Diagnostics Inc.

Gen-Probe is developing NATs for detecting prostate cancer, drug-resistant hospital infections, and HPV. In addition, Gen-Probe is working with General Electric and Millipore to develop NATs that detect microorganisms that contaminate industrial processes.

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Company description

Gene Express develops patented Standardized Mixtures of Internal Standards (SMIS) that can be incorporated into molecular diagnostic tests. Gene Express also has its own proprietary panel of molecular diagnostic tests in development. The inclusion of these standards provides inter- and intra- test comparability (across samples, time and users) and absolute quantification of transcript abundance results, known as gene expression measurement. This accelerates the development of new tests and subsequent regulatory approval of multi-gene diagnostic tests by providing standardized data that will meet not only FDA guidance but also global regulatory requirements.

In its pipeline, Gene Express has LungCentury Gx, a gene expression quantification test that identifies individuals with the highest risk of developing lung cancer. The StaRT-PCR LungCentury Gx test measures the 10-gene panel in normal bronchial epithelial cells obtained by cytology brush through a bronchoscope. Gene Express also has a BCR-ABL1 quantification test that is designed to help optimize outcomes in response to imatinib (Gleevec) treatment for Philadelphia chromosome positive chronic myelogenous leukemia (CML) patients. In order to have effective control of CML, the patient must maintain a three-log reduction in BCR-ABL1 mRNA levels.

GE Healthcare

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Company description

GE Healthcare is a $17bn unit of the General Electric Co. Worldwide, GE Healthcare employs more than 46,000 people in more than 100 countries. The business manufacturers, sells and services medical equipment, including MRI, CT, PET, x-ray, digital x-ray, diagnostic cardiology, and nuclear imaging systems. The company is developing in vivo markers and the systems and processes needed to produce them.

GE Healthcare markets molecular and nuclear imaging systems. These molecular imaging systems are a type of molecular diagnostic in that they identify disease at an early stage and can be used to establish imaging biomarkers of disease. The company markets imaging agents as well as PET/CT and SPECT/CT molecular systems. In May 2010, GE Healthcare and CardioDx Inc., a cardiovascular molecular diagnostics company based in Palo Alto, CA, entered into an alliance to co-develop diagnostic technologies for patients with cardiovascular disease. This is the first investment made by GE's Healthymagination Fund, which is geared toward making investments in external health care companies and technologies.

Genomic Health Inc.

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Company description

Genomic Health is marketing its Oncotype DX Breast Cancer Assay, which analyzes the expression level of 21 genes in a woman's breast tumor sample. It has demonstrated the ability to predict a patient's likelihood to benefit from chemotherapy as well as her risk of experiencing a disease recurrence. Oncotype DX is recommended in both the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) clinical practice guidelines, including it in the standard of care for the majority of early-stage breast cancer patients.

Genomic Health also is developing assays for colon, prostate, non-small cell lung and renal cancer, and melanoma.

IBT Laboratories

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Company description

IBT is a clinical diagnostic and research laboratory specializing in immunology and allergy testing. IBT provides diagnostic assays for physicians, hospitals, and commercial reference labs nationwide. In addition, the company develops and offers specialized biomarker and cell-based assays for contract research and clinical trial testing. The company provides services to pharmaceutical and biotech firms, contract research organizations and major universities.

In September 2009, IBT merged with ViraCor Laboratories, Lee's Summit, MO, a molecular diagnostic and research laboratory providing diagnostic testing to critical care patients and those with compromised immune systems. ViraCor has expertise in infectious diseases and related pathogens, including viruses, protozoa and fungi.

Illumina Inc.

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Company description

Illumina is a developer of array-based products for DNA, RNA, and protein analysis, facilitating the genetic analysis research of its customers. The company’s core technologies, assay chemistries, systems, and software support SNP genotyping; gene expression profiling; epigenetics, the process of profiling changes in genetic sequence function; and proteomics.

Illumina is gaining a foothold in the molecular diagnostics market by partnering with customers, opening a new CLIA lab, and launching a research project to study cancer genomes. In May 2010, the company received 510(k) clearance for the firm's BeadXpress multiplex system. The FDA cleared the system, which includes the BeadXpress Reader and VeraScan software, for in vitro diagnostic applications. Illumina can simultaneously detect multiple analytes in a DNA sample using the firm's VeraCode holographic microbead technology. The BeadXpress system was launched in 2007 with RUO kits for custom genotyping, gene expression, methylation and protein analysis. Also in May 2010, the company received 510(k) clearance from the FDA for its VeraCode Genotyping Test for Factor V mutation (Leiden) and Factor II mutation (prothrombin).

IntelligentMDx

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Company description

IntelligentMDx has molecular diagnostic product offerings for seasonal/pandemic influenza, Bordetella, immunocompromised patient care and infection control testing including antimicrobial resistance screening and detection. IntelligentMDx commercializes molecular diagnostic test solutions under FDA QSR, ISO 13485:2003 and IVDD regulations and guidance for use in clinical reference laboratories.

IMDx's current pipeline includes proprietary nucleic acid (DNA or RNA) tests for real-time PCR. IMDx has a pipeline of single test (singleplex) and multi-test (multiplex) diagnostic products for a wide range of human diseases.

InVivoScribe Technologies Inc.

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Company description

InVivoScribe Technologies provides products for molecular research, molecular diagnostics, and personalized molecular medicine, including general purpose reagents, PCR-based reagents and controls for gene rearrangement, chromosome translocation, and gene mutation testing. Customers include pharmaceutical and biotechnology companies, medical and cancer research centers and reference laboratories. The company's research and in vitro diagnostic products are used in more than 50 countries to identify, classify and monitor leukemias, lymphomas and other lymphoproliferative disease.

The company's CE-marked IVD products, which are available only outside of North America, target biomarkers that have clinical utility. These tests identify, stratify and monitor hematologic cancers. The company's companion diagnostic products facilitate the development of pharmaceutical agents and devices. InVivoScribe's subsidiary, the Laboratory for Personalized Molecular Medicine, is a CLIA- and CAP-accredited international reference laboratory focused on molecular diagnostics and personalized molecular medicine. The laboratory is licensed to perform testing for FLT3 and NPM1 mutations, the most important prognostic biomarkers for karyotype normal acute myeloid leukemia.

IRIS International Inc.

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Company description

IRIS International is an in vitro diagnostics company focused on products that analyze particles and living cell forms and structures, or morphology of a variety of body fluids. The company's products harness its expertise in flow imaging technology, particle recognition and automation for hospital and commercial laboratories. The initial applications for its technology have been in the urinalysis market. The company is a provider of automated urine microscopy and chemistry systems, with an installed base of more than 2,400 systems in more than 50 countries. The company is expanding its core imaging and morphology expertise into related markets and is developing applications in hematology and urinary tract infections.

IRIS is developing molecular diagnostic tests based on its Nucleic Acid Detection Immunoassay, or NADiA, platform, which have applications in oncology and infectious disease. The company’s first product under development, NADiA ProsVue, is an ultra-sensitive, blood-based test for monitoring residual amounts of prostate specific antigen in prostate cancer patients following radical prostatectomy. Upon completion of clinical studies, IRIS will file a 510(k) submission with the FDA. In addition, the company is designing an ultra-sensitive blood test for HIV viral load measurement and a blood-based test for identification of HER2/neu, an important biological marker in determining the aggressiveness of breast cancer tumors.

Kreatech Diagnostics

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Company description

Kreatech is developing and commercializing detection products used for diagnostic and research applications. These applications include cytogenetics, microarrays and proteomics. Kreatech has expertise in oncology, hematology and prenatal diagnostics. In 2007, Kreatech launched its range of Fish probes in the US in partnership with Immunicon. The company also offers repeat-free probes for cytogenetic analysis.

Luminex Molecular Diagnostics Inc.

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Company description

Luminex's open-architecture xMap technology enables large numbers of bioassays to be conducted and analyzed quickly. For 2010, the company reported revenue of $120.6m, a 16% increase over 2008. Assays sales revenue of $31.1m increased 66% from 2008. Genetic tests from Luminex are based on xTag technology, which utilizes a proprietary universal tag system that allows optimization, product development and expansion of molecular diagnostic assays. xTag products conducted on the Luminex xMap system. The system uses lasers to read color-coded microspheres that attach to specific nucleic acid sequences. A multiplexed PCR reaction is performed to amplify the regions of interest in the target human or infectious agent genes.

The company currently markets human genetic and infectious disease assays, and immunoassays. In September 2009, Luminex received 510(k) clearance for a cystic fibrosis (CF) test: the xTag Cystic Fibrosis 39 Kit v2. In March 2010, Luminex acquired BSD Robotics, which will provide it with technologies in automation and robotics in the field of dry sample handling. The privately held Australian firm operates in several markets including newborn screening, forensics and human identification, and molecular diagnostics.

Myriad Genetics Inc.

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Company description

Myriad has molecular diagnostic products on the market, including BracAnalysis, which assesses a woman's risk of developing breast or ovarian cancer based on detection of mutations in the Brca1 and Brca2 genes. Also on the market is Colaris, which assesses a person’s risk of developing colorectal and a woman's risk of developing uterine cancer. It detects disease-causing mutations in three genes - MLH1, MSH2 and MSH6 - which are responsible for the majority of hereditary nonpolyposis colorectal cancer.

Colaris AP assesses a person’s risk of developing hereditary colorectal polyps and cancer. The test detects mutations in the APC and MYH genes. Melaris assesses a persons risk of developing melanoma. This test detects inherited mutations in the p16 gene (also called CDKN2A or INK4A), which occur in up to 40% of families with hereditary melanoma. Prezeon assesses loss of phosphatase and tensin homolog function in cancer patients, which is associated with more aggressive disease progression and poorer survival. TheraGuide 5-FU assesses a person's risk of developing a severe toxic reaction to 5-FU-based chemotherapy.

Nanosphere Inc.

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Company description

Nanosphere Inc. is a nanotechnology-based healthcare company. Nanosphere develops, manufactures and markets an advanced molecular diagnostics platform, the Verigene System, that enables genomic and protein testing on a single platform. It is a benchtop molecular diagnostics workstation. Nanoparticles, as used in Nanosphere's Verigene System and tests, are typically 13-20 nanometers (nm) in diameter. Depending upon the application, each nanoparticle is functionalized with either a defined number of oligonucleotides, such as short pieces of DNA or RNA with sequences complementary to target sequences of clinical interest, or a defined number of antibodies that are specific to a particular protein of interest, such as prostate-specific antigen [PSA] or cardiac troponin I [cTnI]).

The company is commercializing or has in development several genomic and protein assays, including for hyper-coagulation (FDA clearance received); genetic mutation that could indicate increased risk of blood clots, stroke and pulmonary embolism by warfarin metabolism (FDA clearance received); cystic fibrosis; hemochromatosis de novo 510(k) filed with the FDA in February 2009; prostate specific antigen; and cardiac troponin I.

Norgen Biotek

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Company description

Norgen focuses on sample preparation. Norgen has developed a platform technology based on a proprietary resin/matrix with many applications, including the purification, concentration and cleanup of DNA, RNA and proteins from various specimen types. Norgen's ISO certification, coupled with its sample preparation kits to isolate nucleic acids and proteins from various bodily fluids, places it in a position to begin the development and launch of diagnostic kits. The transition of its sample preparation kits into diagnostics is a major objective of the company.

In February 2010, Norgen launched 10 kits for the isolation of nucleic acids from blood, plasma and serum, including circulating nucleic acids. In March 2010, the company launched more than 30 kits for nucleic-acid based diagnostics. Norgen's new diagnostics include kits for the diagnosis of human pathogens, such as: HPV, HIV, HCV-1 and 2, HBV, chlamydia, and gonorrhea., among others. Attention has been paid to the development of kits based on non-invasive sample preparation.

Novartis International AG

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Company description

Novartis Molecular Diagnostics is a separate unit from Novartis Vaccines and Diagnostics. Novartis Molecular Diagnostics is a business unit under the Novartis Pharma organization and is responsible for developing both companion diagnostics to support the Novartis drug portfolio, as well as well as stand-alone diagnostics. The unit has a number of different projects underway, at various stages of development, but does not have any tests on the market.

Novartis is focusing on building capabilities internally while looking at partnering on content, technology and distribution channels. The company works with external partners to leverage technologies and, as needed, will selectively acquire or in-license specific intellectual property and capabilities.

OncoVista Inc.

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Company description

OncoVista is using levels of biomarkers in CTCs to develop drugs. CTCs express biomarkers which may provide prognostic/predictive value for disease outcome and response to therapy; allow stratification of patients for enrollment in clinical trials based on levels of drug target; enable monitoring of patient response to therapy; and allow profiling of metastatic disease which is otherwise difficult to access.

OncoVista has a controlling interest in AdnaGen AG, Hanover, Germany, which offers diagnostic products for colon and breast cancer diagnosis with a specificity of greater than 95% at a sensitivity of two tumor cells per 10 million normal nucleated cells, enabling the reproducible detection of low levels of CTCs in the blood. In January 2010, AdnaGen entered into an agreement with TATAA Molecular Diagnostics, Göteborg
Sweden, for the exclusive use of its Adnatest BreastCancer assays in an international breast cancer Coherta project. The study's goal is to monitor CTCs with the Adnatest BreastCancer assay to identify the HER2 type of metastases. In August 2009, Lab21 Ltd., Cambridge, UK, and AdnaGen entered into an exclusive service and distribution agreement for Lab21 to market AdnaGen's CE-certified circulating tumor cell diagnostic assays in the United Kingdom and Ireland.

Pall Gene Systems

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Company description

Pall is a filtration, separation and purification company. Its GeneDisc Cycler is an automated, miniaturized real-time PCR system. It performs gene amplification in an original disposable device, the GeneDisc plate. This disc is preloaded with the reagents necessary for the reaction.

In September 2008, Pall purchased GeneSystems, which has developed a molecular diagnostics platform. The acquisition of GeneSystems, with its patented approach to rapid microbiological detection equipment and disposables, expands Pall's Total Fluid Management’s capabilities in the $1 billion biopharmaceuticals process monitoring market.

Pathwork Diagnostics

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Company description

Pathwork Diagnostics develops and commercializes molecular diagnostics for oncology. The company delivers microarray-based tests to clinical laboratories and also provides diagnostic tests through its CLIA-certified laboratory. The company's tests utilize its analytics and a companion Pathchip microarray, which runs on the Affymetrix GeneChip System. The company's first test - the Pathwork Tissue of Origin Test - is FDA-cleared as an in vitro diagnostic kit. A functionally equivalent version of the test is also available through Pathwork Diagnostics Laboratory. The test aids in determining a tumor's origin so that cancer-specific treatment can begin.

The Tissue of Origin test is a gene expression–based test that uses a tumor's own genomic information to aid in identifying challenging tumors, including poorly differentiated, undifferentiated, and metastatic cancer. The test provides clinical information previously unavailable to physicians for tissue of origin identification. Up to an estimated 200,000 newly diagnosed cancer patients annually in the US may have a tumor for which the site of origin is uncertain after the initial diagnostic workup

PrimeraDx

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Company description

PrimeraDx is developing multiplexed, quantitative assays using its Star technology implemented on the IcePlex instrument platform. Star combines quantitative PCR with the ability to multiplex up to 60 targets in a single sample. The company's initial products are for infectious disease management. PrimeraDx plans to extend its focus into oncology to support cancer therapy management through diagnostic, prognostic, staging and therapeutic monitoring.

Star technology uses sequential sampling of PCR and capillary electrophoresis detection to generate quantitative results with the ability to accurately measure up to 60 analytes in a single sample. The company's ICEPlex is an automated high throughput, high multiplex, molecular testing system based on Star technology. A stand-alone bench-top analyzer, it is capable of running up to 96 samples (including controls) and reporting on up to 60 targets in each in less than four hours.

Orion Genomics

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Company description

Orion Genomics develops oncology diagnostic products for cancer screening and therapy selection. It interprets normal and abnormal epigenetic patterns of DNA methylation, also known as DNA's Second Code. The company is identifying epigenetic biomarkers and employing them in the development of molecular diagnostic tests to find breast, lung, ovarian, colorectal and other cancers. Additionally, it is discovering biomarkers that can aid in the selection of best therapies for cancer patients.

Orion has developed and patented a group of DNA methylation analysis tools. New research shows that errors in DNA methylation, DNA's Second Code, are a major contributor to age-related diseases, such as cancer. Using these tools, the company is developing diagnostic kits that can detect widespread cancer, including breast, prostate, lung and colorectal cancers. In November 2009, Orion Genomics entered into a multi-year collaboration and license agreement with the molecular diagnostics unit of Novartis Pharma. AG. The companies will discover epigenetic biomarkers, and both have rights to independently develop and commercialize diagnostic products in their fields. Orion Genomics also granted Novartis non-exclusive world-wide rights to its MethylScreen clinical assay technology, which is Orion’s PCR-based clinical assay platform that quantitatively detects epigenetic biomarkers in patient samples.

Osmetech Molecular Diagnostics

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Company description

Osmetech was founded in 1993, developing electronic odor sensor technology. An IPO followed in 1994 and in 1999, and the company changed its name from Aromascan to Osmetech, refocusing the business on health care opportunities. With the acquisition of the OPTI blood gas product line from Roche Diagnostics in 2003, the Critical Care Diagnostic Division was formed.

The Osmetech Molecular Diagnostics division was created from acquisitions of Molecular Sensing plc in October 2004 and Clinical Micro Sensors Inc. from Motorola in July 2005. Osmetech divested its Critical Care Diagnostic Division and focused on accelerating the expansion and development of molecular diagnostics. Osmetech launched its first generation eSensor 4800 system, an electrochemistry-based array system, together with an FDA cleared in vitro diagnostic test for cystic fibrosis carrier detection. In July 2008, Osmetech received FDA clearance for its second generation eSensor XT-8 molecular diagnostics instrument and warfarin sensitivity test. The eSensor XT-8 system utilizes electrochemical detection technology to detect nucleic acids on a microarray. It is a benchtop system. The eSensor Warfarin Sensitivity Test is an in vitro diagnostic for detecting and genotyping the *2 and *3 alleles of the cytochrome P450 (CYP450) 2C9 gene locus and the vitamin K expoxide reductase C1 (VKORC1) gene promoter polymorphism (-1639G>A) from genomic DNA extracted from whole blood, as an aid in the identification of patients at risk for increased warfarin sensitivity.

Qiagen NV

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Company description

Qiagen is a provider of sample and assay technologies. Sample technologies isolate DNA, RNA and proteins from any biological sample. Assay technologies are used to make specific target biomolecules, such as the DNA of a specific virus, visible for subsequent analysis. The company has developed and marketed more than 500 consumable and automated products to molecular diagnostics laboratories, academic researchers, pharmaceutical and biotechnology companies.

The assay technologies include a broad panel of molecular diagnostic tests. This panel includes the digene HPV Test, which is regarded as a gold standard in testing for high-risk types of HPV, as well as products for infectious disease testing and companion diagnostics. In the US, the company's HPV test is approved for use in conjunction with the Pap smear for women 30 and older as well as for follow-up evaluation of women of all ages whose Pap results are inconclusive.

The company manufactures more than 100 molecular diagnostic tests. More than 40 of them are CE marked or have been legally registered for in-vitro diagnostic use in other countries. The company's portfolio consists of multiplexing assays which allow for testing several pathogens in one single run. In February 2010, Qiagen and Celera announced an agreement under which Qiagen is distributing a Celera molecular multiplex assay, the next generation version of Qiagen's ResPlex II assay for detection of respiratory pathogens.

RedPath Integrated Pathology Inc.

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Company description

RedPath Integrated Pathology is a cancer molecular diagnostics company. The company's CLIA-licensed, CAP-certified laboratory delivers diagnostic information to physicians. In April 2010, RedPath agreed to be acquired by ExonHit Therapeutics SA, a French diagnostics and therapeutics biotech company for an upfront payment of $12.5M in cash and $10M in stock, and starting in 2012, subsequent additional payment up to $9.5M dependent on the achievement of sales targets. As a result of the agreement, RedPath will become part of ExonHit's US operations.

RedPath’s DNA-based technology platform, the PathFinderTG, is a diagnostic that can improve the way physicians diagnose, manage and treat patients when traditional testing methods result in indeterminate or indefinite results. RedPath has successfully developed, launched and earned reimbursement for the PathFinderTG molecular diagnostic assay for pancreatic cancer. A second diagnostic assay to differentiate new primary cancer from metastatic tumors will be launched. The company also has two programs in late-stage development and several earlier stage development programs in oncology.

Roche Diagnostics

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Company description

Roche Molecular Diagnostics develops tools for molecular diagnostic profiling, and discovers and validates molecular markers used to identify patients with disease predisposition, conclusively identify disease or differentiate disease subtypes and prognosis, select best medicines, titrate dosage, and predict therapy response and monitor treatment efficacy. Among Roche's products are the Cobas AmpliPrep/Cobas TaqMan System, a fully automated real-time, continuous load IVD platform for automated sample preparation, amplification and quantitation of RNA or DNA. The HIV-1, HCV, and HBV tests on this platform have been available in Europe since 2005. The HIV-1 test was approved for use in the US in May 2007. For blood safety applications, Roche provides PCR- and real-time PCR-based NATs and automation systems. The company also markets the AmpliChip CYP450 test, a pharmacogenetic microarray-based test that detects gene variations - including deletions and duplications - for the CYP2D6 and CYP2C19 genes, which play a major role in the metabolism of about 25% of prescription drugs. The test can help clinicians determine therapeutic strategy and treatment dose for therapeutics metabolized by the CYP2D6 or CYP2C19 gene.

Rosetta Genomics Ltd.

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Company description

Rosetta Genomics develops microRNA-based diagnostic tests and therapeutic tools. MicroRNAs are a group of short, 21 to 23 nucleotides in length, non-coding genes which regulate the expression of other genes. MicroRNAs have varying expression levels across various pathological conditions, and represent a new class of highly sensitive and tissue specific biomarkers. Rosetta Genomics' scientists have developed platform technologies for the identification, extraction, quantification and analysis of microRNAs from a wide range of samples.

Rosetta Genomics is offering various tests: miRview – designed with cancer of unknown primary patients in mind, it can accurately identify the primary tumor site in patients presenting with metastatic cancer; miRview squamous – using a single microRNA, this test differentiates squamous from non-squamous non-small cell lung cancer; and miRview – uses microRNA's high specificity as biomarkers to differentiate mesothelioma, a cancer connected to asbestos exposure, from other carcinomas in the lung and pleura. Rosetta Genomics is developing the second generation of its commercially available miRview tests to include a larger panel of identifiable cancer origins. The company is developing a test to predict the risk of a superficial bladder cancer to become invasive; and another a test to differentiate small from NSCLC, as well as to further subclassify NSCLC into squmaous and non squmaomos versions.

Seegene

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Company description

.Seegene specializes in oligo technologies and two core oligo platforms named ACP (annealing control primer) and DPO (dual priming oligonucleotide), which maximize the sensitivity and specificity of PCR. These technologies have been applied in various fields of genomic research.

Seegene is marketing Seeplex, its multiplexing PCR technology platform, which enables simultaneous multi-pathogen detection. The Seeplex platform utilizes DPO and ACP to create multi-pathogen tests. Seeplex has applications for infectious pathogen detection, drug resistance detection, SNP detection and somatic mutation detection. Seegene is looking for molecular diagnostic companies or instrument companies for strategic partnerships. The company will consider OEM business opportunities for its Seeplex products.

Siemens Healthcare

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Company description

Siemens' Healthcare unit offers medical imaging products as well as in vitro diagnostics, interventional systems and clinical information technology systems. The company acquired Dade Behring in November 2007 to expand its position in the laboratory diagnostics market. It had acquired the diagnostics division of Bayer Aktiengesellschaft in January 2007, to expand its position in molecular diagnostics.

The Healthcare portfolio includes a range of diagnostic testing systems and consumables, including clinical chemistry and immunodiagnostics and molecular diagnostics - testing for nucleic acids. In molecular imaging/diagnostics, Siemens markets SPECT, SPECT/CT, and PET/CT systems that image the biology of disease. The SPECT systems measure cellular and molecular biochemical activity, and when combined with diagnostic multislice CT, the hybrid SPECT/CT and PET/CT systems pinpoint the exact location, size, nature and extent of disease.

Singulex

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Company description

Utilizing quantitative single molecule detection technology, Singulex develops biomarker diagnostic systems that can detect and quantify normal and abnormal protein biomarkers in a variety of biological samples. Singulex is conducting several pilot studies with academic and molecular diagnostic partners to validate the company's commercial digital molecule detection platform, the Erenna Immunoassay System.

The Erenna Immunoassay System, for research use only, is capable of quantifying biomarkers at the sub-picogram level. The system utilizes paramagnetic microparticles as the solid phase for capture and detection of analyte from a complex biological sample, providing enhanced specificity, sensitivity and precision by one to three logs over existing plate-based methods. Pharmaceutical companies are using this system to implement advanced biomarker monitoring programs that address drug safety and efficacy. The system offers high-resolution monitoring of key disease biomarkers.

Thorne Diagnostics Inc.

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Company description

Thorne Diagnostics is developing technologies for the detection and quantification of proteins and nucleic acids, with companion electronic automation for the location, detection and analysis of rare cells in clinical samples. Its single-temperature (isothermal) detection platform, the Ramification Amplification Method, can increase discrimination power up to 1,000 fold above current methods. It and its companion technology, the Hybridization Signal Amplification Method, have advantages in sensitivity, multiplexing, quantification, and dynamic range over older amplification methods and offer real-time, super-exponential amplification.

The company’s techniques provide repeatable DNA analysis. Early detection of cancer recurrence, monitoring response to therapy for immunocompromised patients, and prenatal testing of fetal cells from maternal peripheral blood are potential applications. The methods can be used for single nucleotide polymorphism genotyping, genomic analysis, proteomics and single cell analysis.

TrovaGene Inc.

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Company description

TrovaGene, formerly Xenomics Inc., is a developer of molecular diagnostics. Its patented technology uses urine collection and can be applied to a range of applications, including tumor detection and monitoring, infectious disease detection, prenatal testing, tissue transplantation, genetic testing for forensic identity determination, drug development and research to counter bioterrorism. The company's strategy is to develop transrenal DNA and RNA tests initially for infectious diseases and for early tumor detection and therapeutic monitoring. These efforts are to be followed by development of diagnostics for oncology, transplantation monitoring and prenatal genetic testing.

The company is developing a transrenal DNA assay to detect the K-ras mutations in solid cancer tumors. This assay will be useful as an aid in the personalized management of patients with colorectal, breast, lung and pancreatic tumors as it relates to anti-EGFR therapy. TrovaGene plans to develop a BRAF and PI3KCA assay in conjunction with the K-ras assay. These additional assays when used in combination with K-ras will provide information for the personalized management of patients with colorectal, lung, breast and pancreatic cancer. TrovaGene also is developing a test to aid in the diagnosis of Lyme disease. TrovaGene has completed a pilot clinical study

with a transrenal DNA test to detect HPV DNA in urine. It is seeking partners to complete development and optimization and to assist with clinical trial efforts.

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Web: www.veridex.com

Company description

Veridex is a unit of Johnson and Johnson, and develops and markets in vitro diagnostic oncology products. The company's CellSearch System assesses CTCs to determine the prognosis and overall survival of patients with metastatic breast, colorectal or prostate cancer at any time during the course of treatment. CellSearch works by using antibodies that are joined to microscopic ferrofluid iron particles. These antibody-ferrofluid combinations attach very specifically to CTCs. Powerful magnets then draw the CTCs out of the blood sample. They are stained with additional biomolecules and chemicals so that they can be positively identified as CTCs.

In addition, Veridex markets Poseidon Repeat-Free Fish probes with Kreatech Diagnostics. Developed with the use of Repeat-Free technology, the probes eliminate the use of Cot-1 or blocking DNA, providing a clearer background and a brighter signal. By eliminating repeat sequences, clinicians have brighter signals and a clearer background.

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Web: www.vitagenomics.com

Company description

Vita Genomics conducts pharmacogenomics research, in vitro diagnosis product development and specialty contract research services in both the genomics and pharmacogenomics fields. The company has initiated a drug rescue program designed to resurrect drugs that have failed in previous clinical trials owing to low efficacies. This program applies pharmacogenomics approaches using biomarkers to screen subsets of patients who may respond better or avoid adverse responses to the test drugs.

Affymetrix. and Vita Genomics have collaborated on in vitro diagnostic product development using microarray technology. The resulting microarray-based in vitro diagnostic products can be used to treat patients and manage specific diseases. As part of the Powered by Affymetrix program, Vita Genomics incorporates Affymetrix patented arrays into the molecular diagnostic assays it developed to predict drug efficacy prior to treatment, and to assess risks and facilitate disease prevention. Vita Genomics has developed six technological platforms including high throughput sequencing, STR genotyping, SNP genotyping, clinical genomics, functional genomics and bioinformatics.

CHAPTER 6

Appendix

Chapter 6 Appendix

Methodology

This report analyzes the current and potential world markets for molecular diagnostics, including advances in the field. This report generally forecasts future growth to 2015. Market segments covered include:

- Blood screening;
- HIV/HCV testing;
- Sexually transmitted disease (STD) testing;
- Oncology testing;
- HPV testing;
- Testing for hospital acquired infections;
- Genetic testing.

This report also reviews the nature and direction of research and trends, and gives insight into some issues facing the industry. The report profiles several companies involved in developing and marketing these tests, including Abbott; Affymetrix, Beckman Coulter, IntelligentMDx, Nanosphere, and many others. Market forecasts are based on an examination of current market conditions and on investigations into the development of new products by key companies. The market data are generated into multiple year forecasts for different product segments covered in the report. The information presented in this report is based on data gathered from company product literature and other corporate brochures and documents, as well as information found in the scientific and trade press. In addition, interviews were conducted with company executives and researchers.

Glossary

AD: Alzheimer’s disease

AIDS: Acquired immune deficiency syndrome

AMD: age related macular degeneration

ASR: analyte specific reagent

CLIA: clinical laboratory improvement amendments standards

CMS: Centers for Medicare and Medicaid Services

CPT: current procedural terminology

CTC: circulating tumor cells

DNA: deoxyribonucleic acid

EGFR: epidermal growth factor receptor

FDA: Food and Drug Administration

FFPE: formalin fixed paraffin embedded

Fish: fluorescent in situ hybridization

GBS: group B streptococcus

HCV: hepatitis c virus

HIV: human immunodeficiency virus

HPV: human papillomavirus

HSV: herpes simplex virus

IVD: in vitro diagnostic

IVDMIA: in vitro diagnostic multivariate index assay

mRNA: messenger RNA

miRNAs: microRNAs

MRSA: methicilin-resistant staphylococcus aureus

MSUV: maximum standardized uptake value

NAAT: nucleic acid amplification technology

NAT: nucleic acid testing

NOPR: National Oncologic PET Registry

NSCLC: non-small cell lung cancer

PCR: polymerase chain reaction

RNA: ribonucleic acid

RUO: research use only

Sage: serial analysis of gene expression (Sage and SuperSage)

SMC: single molecule counting

STD: sexually transmitted disease

TMA: transcription mediated amplification

Endnotes

[1]Market Insights 2009. Life Sciences: Molecular Diagnostics New Tools for Evidence-Based Medicine. MaRS Market Insights, Toronto, Ontario, Canada.

[2]http://www.genome.gov/25019926. Collins, F. S. et al. Genomics and the Future *Scientific American*, December 1999, 50-55.

[3]http://www.asianhhm.com/diagnostics/molecular-diagnostics-personalised-medicine.htm. Blair, E. Molecular Diagnostics and Personalized Medicine *Present and future.*

[4]http://www.cancer.gov/cancertopics/understandingcancer/moleculardiagnostics/allpages.

[5]http://www.medscape.com/viewarticle/712541_7. Lester. D. S. Will Personalized Medicine Help in 'Transforming' the Business of Healthcare?: Companion Diagnostic versus Molecular Diagnostic Business.

[6]http://blogs.kentlaw.edu/islat/2009/01/genentech-files-petition-with-fda-urging-regulation-over-all-in-vitro-diagnostic-tests-aimed-for-use.html. Welch, T. Genentech Files Petition with FDA Urging Regulation Over All In Vitro Diagnostic Tests Aimed for Use in Therapeutic Decision Making.

[7]http://www.glgroup.com/News/FDA-Regulation-of-Molecular-diagnostics-29010.html. Powell, K. FDA Regulation of molecular diagnostics.

[8]http://www.nytimes.com/2008/10/09/business/09cancer.html?fta=y. Pollack, A. F.D.A. Says Cancer Test Failed to Get Its Approval.

[9]Balais, E. A. et al. Managing Clinical Knowledge for Healthcare Improvement. Yearbook of Medical Informatics, 2000.

[9]http://www.managedcaremag.com/archives/0904/0904.moleculartesting.html. Rizk, E. Molecular Diagnostic Testing Presents $5 Billion Conundrum.

[10]http://www.ivdtechnology.com/article/trends-and-advances-molecular-diagnostics. PARK, R. Trends and advances in molecular diagnostics.

[11]http://www.genengnews.com/articles/chitem.aspx?aid=1981. Persing, D. Automated Molecular Diagnostics.

[12]http://www.thefreelibrary.com/MRSA:+a+crisis+that+touches+you:+how+automated+molecular+dx+will+help...-a0194717745. Ashton, R. MRSA: a crisis that touches you: how automated molecular dx will help relieve the time and cost crises facing hospital labs.

[13]http://www.ngpharma.com/article/ONE-HOUR-MOLECULAR-DIAGNOSTICS-AT-THE-BEDSIDE/. Chen, S. One hour molecular diagnostics at the bedside.

[14]http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2375882/. Khaniani, M. S., et al. An improved Diagnostic PCR Assay for identification of Cryptic Heterozygosity for CGG Triplet Repeat Alleles in the Fragile X Gene (FMR1).

[15]Armstrong G. L., et al. Trends in infectious disease mortality in the United States during the 20th century. *J. Am. Med. Assoc.* 1999; 281(1): 61–6.

[16]Cohen, M. L. Changing patterns of infectious disease. *Nature.* 2000; 406(6797): 762–7.

[17]Walsh, C. Where will new antibiotics come from? *Nat. Rev. Microbiol.* 2003a; 1: 65–70.

[18]Templeton, K. E., et al. Improved diagnosis of the etiology of community-acquired pneumonia with real-time polymerase chain reaction. *Clin. Infect. Dis.* 2005; 41(3): 345–51.

[19]http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=nap11471&part=a2000e16eddd00013#a2000e16errr00065. Challenges for the Development of New Antimicrobials—Rethinking the Approaches: Report of a Workshop Committee on New Directions in the Study of Antimicrobial Therapeutics: New Classes of Antimicrobials.

[20]http://ddw-online.com/screening/235097/ho_low_can_you_go.html. Todd, J. and Agee, S. J. Ho Low Can You Go?

[21]Kawasaki, E. S. The end of the microarray Tower of Babel: will universal standards lead the way? July 2006. *J. Biomol. Tech.* 17 (3): 200–206. PMID 16870711.

[22]http://clincancerres.aacrjournals.org/content/13/24/7341. Shirahata, M., et al. Gene Expression-Based Molecular Diagnostic System for Malignant Gliomas Is Superior to Histological Diagnosis.

[23]http://jmd.amjpathol.org/cgi/content/abstract/10/3/185. Dong, J. Emerging Pathogens: Challenges and Successes of Molecular Diagnostics.

[24]http://www.genomeweb.com/genentech-files-citizen-petition-urging-fda-regulate-all-lab-developed-tests. Genentech Files Citizen Petition Urging FDA to Regulate All Lab-Developed Tests.

[25]http://www.deloitte.com/assets/Dcom-UnitedStates/Local%20Assets/Documents/us_lshc_bench%20to%20bedside_040909.p

df. Goverman, I. L., et al. Bench to bedside: Formulating winning strategies in molecular diagnostics.

[26]http://www.foleyhoag.com/NewsCenter/Publications/eBooks/Coverage-and-Reimbursement.aspx. Quinn, B. Coverage and Reimbursement for Molecular Diagnostics: Current Issues and Options.

[27]http://www.eurekalert.org/pub_releases/2009-08/ajop pcp082709.php. Colmone, A. Predicting Cancer Prognosis.

[28]http://www.eurekalert.org/pub_releases/2009-04/ajop-cft042409.php. Colmone, A. Cystic fibrosis testing -- next steps.

[29]http://newswise.com/articles/pet-imaging-response-a-prognostic-factor-after-thoracic-radiation-therapy-for-lung-cancer. Anon. PET Imaging Response a Prognostic Factor After Thoracic Radiation Therapy for Lung Cancer.

[30]http://www.eurekalert.org/pub_releases/2009-11/sonm-sae111209.php. Shaw, A. SNM applauds expanded medicare coverage for cervical cancer.

[31]http://www.ionian-tech.com/News_111209.html. Anon. Ionian Technlogies, Inc. Signs Molecular Diagnostic Manufacturing Agreement with Roche Diagnostics.

[32]http://www.genengnews.com/news/bnitem.aspx?name=67960836. Anon. Chinese Authorities Clear China Medical's Leukemia Diagnostic Kit.

[33]http://www.dailymail.co.uk/news/article-1189790/New-test-lung-cancer-save-thousands.html. MacFarlane, J. New test for lung cancer could save thousands.

[34]http://www.prnewswire.com/news-releases/sequenom-licenses-worldwide-rights-to-develop-age-related-macular-degeneration-diagnostic-test-83877892.html. Anon. Sequenom Licenses Worldwide Rights to Develop Age-Related Macular Degeneration Diagnostic Test.

[35]http://www.prnewswire.com/news-releases/qiagen-acquires-exclusive-licence-for-key-pi3k-gene-83828497.html. Anon. Qiagen Acquires Exclusive Licence for Key PI3K gene.

[36]http://www.prnewswire.com/news-releases/tecan-and-enigma-diagnostics-sign-global-manufacturing-and-supply-agreement-for-point-of-care-molecular-diagnostics-instruments-83617747.html. Anon. Tecan and Enigma Diagnostics Sign Global Manufacturing and Supply Agreement for Point-of-Care Molecular Diagnostics Instruments.

[37]http://www.prnewswire.com/news-releases/sequenom-announces-launch-of-sensigene-fetal-rhd-genotyping-test-83537072.html. Anon. Sequenom Announces Launch of SensiGene Fetal RHD Genotyping Test.

[38]http://www.businesswire.com/portal/site/home/permalink/?ndmViewId=news_view&newsId=20100210005877&newsLang=en. Anon. Health Discovery Corporation Inks Deal for Final Validation of a New Molecular Diagnostic Test for Colon Cancer.

[39]http://www.businesswire.com/portal/site/home/permalink/?ndmViewId=news_view&newsId=20100205005198&newsLang=en. Anon. Health Discovery Corporation Partners with Major New York City Pancreatic Cancer Center to Develop a New Molecular Diagnostic Test for the Early Detection of Pancreatic Cancer.

[40]http://www.businesswire.com/portal/site/home/permalink/?ndmViewId=news_view&newsId=20100204006586&newsLang=en. Anon. QIAGEN Unit And Pfizer Enter Into An Agreement To Develop A Companion Diagnostic For Brain Tumor Patients.

[41]http://www.businesswire.com/portal/site/home/permalink/?ndmViewId=news_view&newsId=20100202005116&newsLang=en. Anon. Micronics Receives Second Patent on Rapid Thermocycling Methodology for Molecular Diagnostics.

[42]http://www.businesswire.com/portal/site/home/permalink/?ndmViewId=news_view&newsId=20100112005862&newsLang=en. Anon. Life Technologies Signs Definitive Agreement to Acquire AcroMetrix.

[43]http://www.lifetechnologies.com/news-gallery/press-releases/2010/life-technologies-introduces-new-real-time-pcr-system.html. Anon. Life Technologies Introduces New Real-Time PCR System.

[44]http://www.businesswire.com/portal/site/home/permalink/?ndmViewId=news_view&newsId=20100416006129&newsLang=en. Gentel Launches APiX View Detection Kit to Enable Sensitive Detection for Protein Biotechnologies SomaPlex and Other Reverse Phase Protein Microarrays.

[45]http://www.businesswire.com/portal/site/home/permalink/?ndmViewId=news_view&newsId=20100419005686&newsLang=en. Anon. CRi Imaging Technology Enables Biomarker Analysis of Cancer Drugs with Skin Biopsies.

[46]http://www.businesswire.com/portal/site/home/permalink/?ndmViewId=news_view&newsId=20100420006179&newsLang=en. Anon. Top Dermatology Genetic Tests Developers Merge With DermaGenoma, Inc.

[47]http://www.prnewswire.com/news-releases/biomerieux-and-knome-sign-strategic-partnership-91692354.html. Anon. bioMerieux and Knome Sign Strategic Partnership.

[48]http://www.biotechnologyhealthcare.com/journal/fulltext/1/2/BH0102046.pdf?CFID=53096623&CFTOKEN=58202601. Farkas, D. H. and Bernard, D. W. SWOT

Analysis for Molecular Diagnostics: Strengths, Weaknesses, Opportunities, and Threats.

[49]WHO. Blood safety and donation. Fact sheet N°279. June 2008.

[50]AABB. 2007 National Blood Collection and Utilization Report.

[51]American Social Health Association - National HPV and Cervical Cancer Prevention Resource Center. Retrieved July 1, 2008.

[52] http://whqlibdoc.who.int/publications/2007/9789241563475_eng.pdf. Anon. Global strategy for the prevention and control of sexually transmitted infections: 2006-2015.

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