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*Life Sciences Reports*

## Molecular Diagnostics:

### New Growth, New Markets

Author: Leslie A. Pray, PhD

# Molecular Diagnostics: New Growth, New Markets

*By Leslie A. Pray, PhD*

## About the Author

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# Executive Summary

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Historically, the diagnostics industry has been overshadowed by the larger, more lucrative pharmaceutical industry. Advancing knowledge and technologies are pushing the diagnostics industry to the fore, however, and the molecular diagnostics industry in particular is emerging as a powerful health care player with tremendous potential. Advances in PCR (polymerase chain reaction), multiplexing, sequencing, and other technologies are propelling both new and old companies forward with new capabilities. A growing understanding of the molecular basis of cancer and other chronic diseases is opening up new realms of medicine to the possibilities of molecular diagnostic testing. This report highlights current trends in the molecular diagnostic industry and the major opportunities and challenges ahead.

A dominant theme of this report is that the emergence and growth of the personalized, or pharmacogenomic, medicine model provide tremendous revenue opportunities for molecular diagnostics. Although we are still decades (if not longer) away from the personalized medicine vision of individuals having their genomes and other molecular information stored on a “smart card” or in an easily accessible central database, along with individualized information about disease risk and drug response, personalized medicine has in fact arrived, with a handful of population-specific drugs and companion diagnostics on the market. In fact, many would argue that pharmacogenomic medicine has existed for decades and that this smart card vision distracts from the truly revolutionary and more immediate consequences that personalized medicine will have: refining the drug development process so that more high-quality (*i.e.*, more effective and safer) drugs for a broader range of conditions are made available to consumers. The greater challenge for molecular diagnostics companies will be to position themselves so that they can generate profits while interacting with pharma, regulatory agencies, consumers, and other stakeholders in ways that facilitate drug-diagnostic co-development and end in a win-win-win situation (*i.e.*, win for the diagnostic company, win for pharma, win for

consumers). A major aspect of this will be education of consumers and health care providers, as many industry leaders interviewed for this report agreed.

Another major theme explored in this report is that, although molecular diagnostics stands to benefit tremendously from the growth of personalized medicine and although it is almost naïve to discuss molecular diagnostics outside of the context of the personalized medicine model, personalized medicine is not the industry's greatest foothold. The largest market share of molecular diagnostics—about 80%—continues to be in the infectious disease arena. Roche Diagnostics is the top-performing molecular diagnostics company, bringing in approximately \$870 million in revenues in 2004, more than 60% of which were attributed to sales of the company's Amplicor human immunodeficiency virus (HIV) and hepatitis viral load tests.

Although the infectious disease sector, particularly viral load testing, will continue to occupy the largest sector of the market and will continue to grow at a modest rate—approximately 8% to 10% annually—other areas of molecular diagnostics, particularly oncology, will see greater rates of growth in the near future. Indeed, at an annual growth rate of about 30% to 40%, the fastest-growing molecular diagnostic test today is the human papillomavirus (HPV) assay, which could appropriately fall within the realm of either infectious disease or oncology testing, because the purpose of the test is to evaluate a woman's risk of developing cervical cancer by virtue of the presence of certain types of HPV in her cervical cells. Within the next several years, cancer diagnostics, which occupies less than 3% to 5% of the molecular diagnostic market today, will grow to occupy 10% to 15%.

Another major theme explored in this report is that, although most molecular diagnostic testing conducted today relies on DNA analysis, and for good reason—DNA is more stable than other biomarkers, and it is the best-studied type of biomarker—knowledge about other types of biomarkers is fueling some very interesting and potentially very profitable endeavors that do not necessarily focus on the genome. (The genome is the entire sequence of DNA that comprises an individual's genetic makeup.) After all, very few human diseases are purely genetic. Most result from a complex interaction between genes and environment. Many companies worldwide are exploring a wide range of non-DNA content molecular diagnostic possibilities, demonstrating that the industry is highly diverse with a multitude of potential business opportunities. For example, methylation tests involve assaying patterns of methyl groups (–CH<sub>3</sub>) that line the DNA double helix, vary among

individuals, and play a crucial, environmentally sensitive role in tumorigenesis and other human disease disorders.

A final overarching theme of this report is that, as with content, the molecular diagnostic industry also relies on a very diverse, constantly changing technology base. Although PCR is, without question, the most important molecular diagnostic technology, other dominant technologies are generating considerable profits, and there is a tremendous opportunity in the marketplace for new, improved technologies, PCR-based or not.

### **Roadmap for this Report**

The first chapter includes a historical overview of molecular diagnostics, an analysis of the role of diagnostics in the growing field of personalized medicine, and a summary of major market trends and drivers. Chapter 2 presents an overview of dominant and emerging technologies in the molecular diagnostics industry. Chapter 3 provides a summary of dominant and emerging applications of molecular diagnostics, with a focus on major areas of robust growth. Chapter 4 presents an industry-landscape look at key nontechnological trends and challenges, with a focus on regulation, consumer and health care provider education and marketing, and reimbursement. Chapter 5 provides an overview of molecular diagnostic business models in the context of factors that are expected to drive the industry forward. Chapter 6 includes six transcribed expert interviews with industry leaders. Finally, Chapter 7 provides a select list and description of companies that have shown remarkable progress in the field, smaller companies that are expected to emerge as dominant players in particular content or technological areas, and companies that exemplify a noteworthy aspect of molecular diagnostic business.

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## 2.6. Gene Methylation, or Epigenetic, Technology

Epigenetics is the study of heritable alterations in gene expression that have nothing to do with DNA sequence but are caused by physical or chemical changes to the gene. The best-studied and most common epigenetic change is the covalent addition or deletion of one or more methyl groups ( $-CH_3$ ), which normally line the double helix by the thousands, with clumps of methyl markers acting like switches, governing gene expression, turning genes on and off. Abnormal methylation patterns have been shown to be causally linked to cancer and have been associated with diabetes, obesity, male infertility, autoimmune diseases, psychiatric diseases, autism, and more.

Although scientists have known about epigenetic change for half a century, the field has exploded in the last several years. Scientists are uncovering important information about the relationship between epigenetic change and cancer. A growing number of researchers are conducting epigenetic investigations, attending epigenetic conferences, and writing on the topic. At least three companies—Epigenomics (Berlin, Germany), OncoMethylome Sciences (Durham, NC), and Orion Genomics (St. Louis, MO)—are banking on the promise that epigenetic, or DNA methylation, technologies will become leading molecular diagnostic tools. As with other molecular diagnostic technologies, the basic procedure involves collecting the blood or tissue sample from the patient, analyzing it (in this case, analyzing its DNA methylation pattern), and comparing that pattern to a reference data set. The results are used to aid in diagnosis or to help evaluate whether a patient is responding effectively to therapy.

*Scientists are uncovering important information about the relationship between epigenetic change and cancer.*

Although no FDA-approved methylation tests are yet on the market, many diagnostic laboratories offer homebrew methylation testing for Prader-Willi syndrome (PWS), Angelman syndrome (AW), and Beckwith-Wiedemann syndrome (BWS). PWS and AW are neurologic disorders that result from epigenetic abnormalities on chromosome 15. PWS is caused by a deficiency of paternal gene expression, and AW results from a deficiency of maternal gene expression. BWS is associated with an increased risk for embryonal tumor development, particularly Wilms' tumor. It is caused by epigenetic abnormalities on chromosome 11.

According to GeneTests, a public database maintained by the National Institutes of Health, as of August 2005, approximately 65 clinical laboratories worldwide (throughout Canada, Europe, South America, and the United States, as well as in India, Korea, Singapore, and New

signatures, associated with certain disease states. In May 2005, SomaLogic announced that it had entered into a technology development agreement with Quest Diagnostics, Inc., whereby Quest will develop new diagnostic tests for use in oncology, as well as for cardiovascular, autoimmune, and infectious diseases, based on SomaLogic's aptamer technology and aptamer-based disease signatures.

## 2.8. Nanodiagnosics

In just a few years, nanotechnology has catapulted from being a specialty field in the physical sciences to a worldwide industrial enterprise. The U.S. government predicts that the global nanotechnology market will be worth \$1 trillion by 2012. Some analysts expect that the nanosensor-based diagnostic industry in particular will reach the \$1 billion mark within the next several years, although few, if any, products are actually on the market yet. Most of the near-future revenues will likely come from research, not clinical, sales.

Nanotechnology involves the manipulation of matter at the nanometer or nanoliter scale: a nanoliter (nL) is  $10^{-9}$  liters, or one billionth of a liter. Nanoscale devices are approximately 100 to 10,000 times smaller than human cells, making it easy for them to enter cells, enter and exit the bloodstream, and readily interact with cellular and cell surface molecules. Because they have such easy access to so many different parts of the human body, the hope is that nanoscale devices will be capable of detecting diseases, including cancer, in ways that no other molecular diagnostic can. Nanodevices could, in theory, be used to detect and pinpoint at the molecular level tumorigenic-related changes occurring in only a small percentage of cells in the body.

As an example of the type of nanodiagnostic research currently underway, in February 2005, in a paper published in *Proceedings of the National Academy of Science*, Northwestern University researchers described a nanoparticle-based assay for detecting the onset of Alzheimer's disease (Georganopoulou *et al.* 2005). The assay relies on the use of gold nanoparticle probes comprised of target-complementary DNA sequences. The nanoparticles, which are approximately 13 nm in diameter—one-ten thousandth the thickness of a human hair—are extremely sensitive (the signal of one nanoparticle is equivalent to  $5 \times 10^5$  fluorophores), resulting in minimal background noise and clear assay signals. Also in February 2005, an Illinois-based company, Nanosphere, Inc., announced plans to expand and market the application of the same technology—the Verigene platform—to a variety of other diseases, including cancer.

### 3.3. Oncology

Although oncology has traditionally comprised less than 3% to 5% of the molecular diagnostics industry, it is growing faster than any other sector. The last several decades have seen a rapid increase in our scientific understanding of the molecular biology of cancer, enabling the rapid expansion of cancer predisposition screening (e.g., HPV testing) and pharmacogenomic testing (e.g., *HER-2/neu* testing). HPV, *HER-2/neu*, and leukemia/lymphoma testing are the most commonly used and most profitable oncology molecular diagnostic assays on the market today.

Molecular diagnostic testing in oncology is made possible by virtue of the fact that cancer cells are characterized by a genetic defect(s) that makes them unable to stop reproducing. The cells of a single tumor, or cancer, are more or less all clones of each other, each containing the same genetic defect(s). Once identified, these genetic defects can be used as markers to aid in the diagnosis and treatment of cancer.

In addition to our growing scientific understanding of the molecular etiology of tumor development and growth, another major force driving the field of oncologic molecular diagnostics is the increasing incidence of cancer worldwide. According to the American Cancer Society, by the end of 2005, an estimated 1.4 million new cancer cases and more than 570,000 cancer deaths will have occurred in the United States, excluding basal and squamous cell skin cancers and *in situ* carcinomas except urinary bladder, and approximately 58,000 cases of carcinoma *in situ* of the breast and 46,000 cases of melanoma *in situ* will have been newly diagnosed. Nearly half of all men and more than a third of all women in the United States will develop cancer during their lifetimes.

The greater sensitivity and objectivity of molecular diagnostic techniques, compared to traditional cancer diagnostics, is another major driving factor. Traditional tissue-based, or morphology-based, cancer diagnostic techniques cannot be used to predict or assess treatment or drug response. Morphologic evaluation is relatively insensitive, and the presence of tumor cells can generally only be detected when their frequency is greater than 1% to 10%. Tissue-based diagnosis is also very subjective. Molecular-based tumor diagnostic assays are more sensitive and more objective.

***Leukemias and Lymphomas***

Molecular diagnostic tests for leukemias and lymphomas were among the first cancer molecular diagnostic tests used in the clinic, in the 1970s, and they are still among the most widely used oncologic products in the industry. Many leukemias and lymphomas are characterized by specific mutations, usually chromosomal translocations, that can be readily detected through molecular diagnostic testing. Early on, clinicians would look for characteristic chromosomal abnormalities through a microscope. Then came the advent of the more versatile *in situ* hybridization (ISH) and fluorescent *in situ* hybridization (FISH) technologies (see Chapter 2). Finally, PCR entered the arena. Two of the currently FDA-approved molecular diagnostic tests for leukemia and lymphoma are FISH based. The others are mostly PCR based (Table 3.5).

**Table 3.5. FDA-Approved Leukemia/Lymphoma Tests**

Test	Technology	Company	Test
B-cell chronic lymphocytic leukemia (B-CLL)	FISH	Vysis (Abbott)	CEP 12 DNA Probe Kit
Chromosome 8 enumeration (chronic myelogenous leukemia, acute myelogenous leukemia, myeloproliferative disorders, myelodysplastic syndrome, other hematologic disorders not specified)	FISH	Vysis (Abbott)	CEP 8 DNA Probe Kit
HLA typing (human leukocyte antigens)	PCR	Biotest Diagnostics	Biotest HLA SSP
	Nonamplified direct probe assay	Biotest Diagnostics	Biotest ELPHA System
	PCR	GTI	GTI PAT HPA-1 (P1) Genotyping Kit
	PCR	Invitrogen	PeI-Freeze HLA High-Resolution SSP UniTray

FISH, fluorescent *in situ* hybridization; PCR, polymerase chain reaction

**Source: Cambridge Healthtech Advisors**

# Chapter 5

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## THE BUSINESS OF MOLECULAR DIAGNOSTICS

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### 5.1. Introduction

The projected growth of the molecular diagnostics industry will create ample market opportunities for both established and emerging molecular diagnostic companies. However, the regulatory, reimbursement, and education challenges (as highlighted in Chapter 4), coupled with the complex technological nature of molecular diagnostic testing (as detailed in Chapter 2), make molecular diagnostics a very difficult business that requires patience and deep pockets. This is why, even as opportunities abound, only a small percentage of start-up diagnostic companies succeed, either by becoming major players or by building innovative technology or content platforms and then developing alliances or entering into an acquisition with major or well-established players with more marketing and sales strength.

Growing from a start-up into a major player, as Digene has done, requires substantial capital and the time and strength to simultaneously build and strengthen all of the other various regulatory, marketing, and reimbursement components that must be in place as a product approaches the phase at which it is ready to be introduced to the market. After approximately 15 years, 2004 was the first year that Digene reported a positive net income. A much more realistic strategy for most companies is to excel in one particular content or technological area, strengthening their expertise to the best of the industry's capabilities, with the intention of developing an alliance or entering into an acquisition with a more established company.

Given the competitive nature of the industry, finding that technological or patent-protected content edge is crucial to maintaining the exclusivity necessary for raising capital and recouping

one's investment. Unlike in pharma, diagnostic assays are not long-lived, with multiple competitors working on the same tests or platforms and constantly developing new, improved technologies.

Some companies, like Solexa, view the research sector of the molecular diagnostic industry as a sizable opportunity for initial product launch. Research products can generate significant revenue, and the client base is well-funded, knowledgeable, and ample. If a company can provide a product that satisfies an unmet research demand before it enters the clinical arena, it can (in theory) generate revenues without the need for market-building and then build on its success. Solexa aims to do this with its first product launch (see Chapter 2), a whole human genome sequencing instrument that will lower the cost of whole human genome sequencing to \$100,000, orders of magnitude less than the current price.

Most successful molecular diagnostic companies, particularly start-ups and smaller companies focused on a single content or technology product, rely on strong collaborative relationships with investigators in academia or research institutes who are knowledgeable about advancements in the field. Although some discoveries or assays are developed in-house, many originate in research laboratories, where the primary focus is on research and publication, not commercialization, and where the pursuit of novel ideas and projects is encouraged irrespective of the outcome. This strong industry-academia collaboration among smaller companies may explain why so many novel technologies are born and matured in the start-ups before commercialization and then transferred to larger players who have more marketing and sales strength. Interestingly, that is what one of Solexa's "\$1,000 genome start-up" competitors, 454 Life Sciences, has done. As mentioned in Chapter 2, 454's novel sequencing technology will soon be commercially available through Roche.

**David A. Okrongly, PhD**

*Senior Vice President of Global Research and Development  
Bayer HealthCare, LLC, Diagnostics Division*

**Cambridge Healthtech Advisors (CHA):** What is Bayer Diagnostics' strength as a molecular diagnostics company?

**David A. Okrongly (DAO):** Our strength is in delivering a very comprehensive set of tests that can be used to manage critical diseases such as HIV, HCV, and HBV—tests needed at all stages for a patient's disease management. For instance, with respect to HIV, we can provide a serology test to diagnose its presence, a viral load test to stage and monitor the disease, and HIV resistance testing that can be used to help guide physicians in making choices for therapy after treatment failure. We can pinpoint the resistance-inducing mutation with our sequencing technology and then provide guidance with an FDA-approved mutation and resistance report that will direct the physician to options for going forward with changes to that patient's triple therapy. Our strength is in being able to provide this comprehensive, disease management menu, empowering a laboratory to work with one supplier for all its needs.

**CHA:** What percentage of Bayer Diagnostics' revenues come from molecular diagnostics?

**DAO:** Bayer is number two, and we occupy approximately 10% of the total molecular diagnostics market (excluding blood screening).

**CHA:** What percentage of the company's R&D activity is focused on molecular diagnostics?

**DAO:** I usually talk about it as a percent of sales, so we are putting roughly 25% to 30% of our molecular sales back into R&D for molecular diagnostics. It is currently a high investment area for us due to the emerging technologies and tests that require investment now for the long run.

**CHA:** What kind of growth are the HIV and hepatitis testing markets experiencing?

**DAO:** It is steady growth, currently 10% to 12% annually. Asia is growing faster, which may change the rate in time and will undoubtedly influence the menu we develop as well. When you look at the difference in chronic infection rates in hepatitis B in Asia, compared to Europe and North America, it is a very different kind of market. The patient with chronic infection requires different management and different types of tests. We are actually looking at that more from our immunodiagnostic line of products.

That raises an important point: When we look at *in vitro* diagnostics, we tend to view molecular and immuno- as two different markets, and from a laboratory perspective, they really are not. Rather, they are part of the total package of management for a patient. As I mentioned with HIV, the initial diagnosis could come from a serology test that detects antibodies to HIV. That kind of sets the whole ball in motion for all of the molecular follow-up—CD4, viral load, and HIV genotyping—that is used afterward to fully characterize and monitor the disease.

**CHA:** To what extent is Bayer's molecular testing group focusing its R&D activity on improving existing HIV and hepatitis tests *versus* developing new products for other diseases?

**DAO:** I would guess that it is about 3:1: three parts focused on improving, one part developing new. With respect to improving existing assays, the challenge is that our current customers have changing demands with respect to productivity and ease of use, which require new investment in either platform or assay technology. Added to that is the burden of regulatory approvals for the changes that are going to be made to that product. In fact, that becomes a significant part of both the time and cost of doing the product development with existing assays.

We are very excited about some new genomic products that will be launched into the market next year. One is a cystic fibrosis test. Also in development is cytochrome P450 work, and we have active research efforts in pharmacogenomic tests that could be used for patient selection for certain types of therapy.

**CHA:** What parallels do you see between the way HIV is managed today and the way that cancer will be managed in the future?

*We have active research efforts in pharmacogenomic tests that could be used for patient selection for certain types of therapy.*

the white clover genome), the Donal Danforth Plant Science Center (to sequence the corn genome), and others. Orion continues to stay active in ag-biotech through its “Genomic Services” business, which has reportedly generated more than \$20 million in profits over the past couple of years.

### **SEQUENOM, Inc.**

#### **Vital Statistics:**

**Location:** 3595 John Hopkins Court, San Diego, CA 92121-1331

**Phone/Fax/Website:** 858-202-9000/858-202-9001/www.sequenom.com

**Founding Information:** SEQUENOM was founded in 1994.

**Selected Management:** Dr. Harry Stylli, President and Chief Executive Officer; Stephen L. Zaniboni, Chief Financial Officer; Charles R. Cantor, PhD, Chief Scientific Officer; Andreas Braun, MD, PhD, Chief Medical Officer

**Number of Employees:** 148

**Financial Information:** (NASDAQ: SQNM) The company’s reported total revenue for 2004 was \$21.8 million.

As first mentioned in Chapter 2 and elaborated on in an expert interview with SEQUENOM’s Chief Scientific Officer, Charles Cantor, the company is known for its proprietary MassARRAY system, a novel mass spectrometry–based DNA analysis platform that demonstrates exemplary multiplexing capabilities. Mass spectrometry is more typically in proteomic analysis, but the MassARRAY system is designed for use in single nucleotide polymorphism (SNP) genotyping, gene expression analyses, methylation analyses, and other types of nucleotide testing. In a recent study published in the *Proceedings of the National Academy of Science*, researchers from SEQUENOM showed that their MassARRAY HPV test was 1,000 times more sensitive than the current standard (*i.e.*, Digene’s Hybrid Capture), enabling a greater ability to detect associations between high-risk HPV variants and cervical cancer