

Molecular diagnostics is now used for a wide range of applications, including:

- Human clinical molecular diagnostic testing
- Veterinary molecular diagnostic testing
- Identity testing (paternity and other identity tests)
- Forensic testing
- Human leukocyte antigen (HLA) typing (histocompatibility testing, or immunogenetics)

1.2. Focus of This Report

The focus of this report is on human clinical molecular diagnostics. Even within this field, molecular diagnostics is being applied to a wide range of diseases and applications. As previously mentioned, the first molecular diagnostic tests to reach the market were for infectious diseases, and this remains the largest segment of the molecular diagnostics market. However, other applications of molecular diagnostics in the fields of oncology, personalized medicine, inherited disorders, and many other areas are rapidly growing.

This report focuses on these rapidly growing and emerging new applications of molecular diagnostics, as this field expands beyond infectious disease testing. Chapter 2 briefly discusses selected technologies that are being used by molecular diagnostic companies. Many examples of companies and commercial products either on the market or in development for noninfectious disease molecular diagnostic applications are discussed in Chapter 3. In addition to the wide range of tests described, clinical laboratories can also develop their own “laboratory-developed” or “home-brew” molecular diagnostic tests. No attempt has been made to try to include all of the activities on the part of clinical laboratories, although selected major tests that are only available as services from clinical laboratories are discussed in this report.

Molecular diagnostics has emerged as a significant segment of the overall clinical diagnostics market. Chapter 4 discusses the molecular diagnostics market, including many of the trends and factors that are driving its growth. Personalized medicine has become an important field that is already having a significant impact on patients and physicians, and also on the pharmaceutical industry. Section 4.3 discusses

Molecular diagnostics has emerged as a significant segment of the overall clinical diagnostics market.

target nucleic acid that was present in the sample. Thus, with real-time PCR, it is possible to perform quantitative PCR assays. Selected additional advantages of real-time PCR assays (compared to conventional PCR tests) include improved sensitivity and broader linear (and dynamic) range of the assay. This reduces the need for repeat testing and for dilutions of specimens in order to obtain quantitative results.

Additional modifications or different types of PCR reactions have also been developed. For example, with multiplex PCR, two or more sets of primers are used in one reaction. With PCR *in situ*, DNA in a tissue sample is amplified and then detected by ISH. (ISH is discussed in more detail in Section 2.2.) Several other types of PCR reactions have also been developed.

In addition to PCR, several additional amplification technologies have been developed and/or commercialized, selected examples of which are summarized in Table 2.1, including both probe and signal amplification technologies. These technologies also differ in other aspects. For example, PCR requires a heating step with each amplification cycle, while certain other technologies (including nucleic acid sequence-based amplification [NASBA] and strand displacement amplification [SDA]) are isothermal reactions. Also, the different amplification technologies vary in the number of steps and number of enzymes required, among others.

Table 2.1. Selected Nucleic Acid Amplification Technologies and Selected Companies that Use These Technologies

| Technology | Company | Comments |
|-----------------------------------|---------|---|
| Branched DNA amplification (bDNA) | Siemens | <ul style="list-style-type: none"> • Signal amplification technology • Uses 4 probes and produces branched oligodeoxyribonucleotides (bDNAs) as amplifiers. • The assay process involves: release of target RNA in sample, hybridization of target with CEs and LEs (binding target to bottom of microwell), hybridizing preamplifiers to LEs, hybridizing amplifiers to preamplifiers (resulting in branched oligodeoxyribonucleotides), hybridizing label probes to amplifiers, and addition of dioxetane substrate (which generates chemiluminescent signal). |

Continued

PCA3 is expressed by prostate cancer cells and is highly overexpressed by prostate cancer cells. Gen-Probe reports that this gene is 60- to 100-fold overexpressed in the cancer cells in more than 95% of cases of prostate cancer. Also, PCA3 is reportedly more specific to prostate cancer than is PSA, which is also elevated in certain noncancerous conditions of the prostate.

Gen-Probe has developed the PROGENSA PCA3 Assay, a test to detect overexpression of PCA3 mRNA in urine. This test is based on Gen-Probe's Transcription-Mediated Amplification (TMA) technology. In November 2006, the PROGENSA PCA3 Assay was CE marked in Europe, where it is now available. PCA3 antigen-specific receptors have been developed for the United States. In its Form 10-K for 2007, Gen-Probe reported that, as of December 31, 2007, five clinical laboratories in the US had validated TMA assays for PCA3 and PSA using Gen-Probe's ASRs and general-purpose reagents. Gen-Probe acquired exclusive rights to the PCA3 gene in November 2003, when the company signed a license agreement with DiagoCure.

Leukemias and Lymphomas

Leukemia and lymphoma are hematological cancers, meaning that they arise from blood-forming cells. The American Cancer Society estimated that, in 2008, there would be 44,270 new cases of leukemia and 74,340 new cases of lymphoma in the United States, and that 21,710 people would die from leukemia and 20,510 would die from lymphoma.¹

Leukemia can be classified as either lymphocytic or myelogenous (or myeloid) leukemia, and as either acute or chronic leukemia. The classification of lymphocytic versus myelogenous leukemia is based on the type of cell from which the leukemia originated. Lymphocytic leukemia is a cancer of lymphoblasts (immature lymphocytes) or lymphocytes in the bone marrow. There are two types of lymphocytes: B-lymphocytes are involved in humoral immunity (the production of antibodies) and T-lymphocytes have a role in cellular immunity. Myelogenous leukemia originates from myeloid cells in the bone marrow. The other major classification of leukemia is as either acute or chronic leukemia. Originally, this classification was based on the patient's life expectancy, as acute leukemias progress more rapidly than chronic leukemias. The differentiation between acute and chronic leukemia is now made based on the maturity of the leukemia cells, with acute leukemia cells originating from immature cells and chronic leukemia cells arising from more mature cells. Altogether, these two major classifications result in four major types of leukemia: acute lymphocytic leukemia (ALL), acute myelogenous leukemia (AML),

Gen-Probe has developed the PROGENSA PCA3 Assay, a test to detect overexpression of PCA3 mRNA in urine.

Growing Number of FDA-Cleared and Approved Tests

Major challenges for molecular diagnostic companies are the regulatory issues and hurdles that they face with new tests and technologies. The current and evolving regulatory climate is discussed in Section 4.4. As noted in that discussion, many molecular diagnostic companies initially marketed their products as ASRs, rather than developing full kits and going through the 510(k) or premarket approval (PMA) processes.

One of the major trends in the industry is the growing number of molecular diagnostic tests that are FDA cleared or approved. Several of these tests included in the tables and discussions in Chapter 3 were not FDA cleared or approved at the time of the previous Insight Pharma Report on this market (*Molecular Diagnostics: A Rapidly Shifting Commercial and Technology Landscape*, November 2007).

Consolidation (Acquisitions)

Within the field of molecular diagnostics, a number of acquisitions have occurred. Recent selected examples of acquisitions within the molecular diagnostics market are summarized in Table 4.1. These include acquisitions by other molecular diagnostic or IVD companies, or both. In addition, non-IVD companies are starting to enter this field. Two examples of non-IVD companies that have recently acquired molecular diagnostic companies are Hologic (Bedford, MA; which has focused on medical imaging systems and surgical products for women's healthcare) and the pharmaceutical company Solvay.

Table 4.1. Selected Recent Corporate Acquisitions in Molecular Diagnostics

| Parties | Date (or Date Announced) | Description |
|---|---|---|
| Solvay Pharmaceuticals acquired Innogenetics | Latest announcement 11/13/08 Successful acquisition announced 9/9/08 | 4/08: Solvay announced that it had launched a friendly bid to acquire Innogenetics in a cash offer that was valued at €5.75 per share. This offer was later increased. 9/08: Solvay announced that it had succeeded in the acquisition of Innogenetics in a cash transaction for €6.5 per share, which is €200.7 million for 100% of Innogenetics shares. Solvay announced that, after settlement of the offer, it would hold 84.3% of Innogenetics shares. 11/08: In a press release, Solvay announced that it would proceed with a squeeze-out of the remaining Innogenetics shares and request a delisting. Solvay reported that, after the closing of the offer, it would hold 95.33% of the Innogenetics shares. |

Continued

Oliver Schacht then gave an example of the impact of this change on his company (see the full expert interview in Chapter 5).

The above discussion of the FDA regulations is brief and does not include many of the details that diagnostic companies must face. Additional information can be found on the FDA Web site (www.fda.gov).

Regulatory Issues and Consideration for Pharmaceutical Companies Developing Pharmacogenomic Therapies

Pharmaceutical companies seeking to market a new therapy in the United States face a completely different set of FDA regulations. These regulations cannot be reviewed in detail within the scope of this report. However, it is important to note that regulations affecting pharmaceutical companies in the pharmacogenomics field are also evolving and changing.

If a healthcare provider is not reimbursed for a particular service, the market for products relating to that service will be very limited.

In March 2005, CDER, at the FDA (which regulates the pharmaceutical companies), issued guidelines entitled “Guidance for Industry. Pharmacogenomic Data Submissions.”⁵⁷ In addition, in August 2007, CDER issued a draft guidance entitled “Guidance for Industry. Pharmacogenomic Data Submissions—Companion Guidance.”⁵⁸ Subject areas covered in this companion topic include gene expression data from microarrays, genotyping, proficiency testing, and others. Thus, while CDRH is regulating diagnostic tests that are commercialized as companion tests with personalized medicine drugs, CDER is now also addressing issues related to test data that are submitted with applications for drug approvals.

Reimbursement of Molecular Diagnostics

Reimbursement is an important issue for all new healthcare products, not just diagnostics. If a healthcare provider is not reimbursed for a particular service, the market for products relating to that service will be very limited. Obtaining reimbursement, and especially adequate levels of reimbursement, can be challenging for all products, including molecular diagnostics products. The importance of reimbursement for the molecular diagnostics industry was demonstrated in the expert interviews (see Chapter 5), in which it was mentioned by several experts.

It is difficult to make general statements about the status of reimbursements in the molecular diagnostics field as a whole. Many molecular diagnostic tests are reimbursed, and the levels

You might see 80% compound annual growth rate in pharmacogenetics, but that is from such a small base that it is still relatively immaterial compared to the 15% that you might see from molecular diagnostics in infectious disease. So, my general thought is that a lot of the excitement is in personalized medicine but, for the near future, the money is going to be on infectious disease.

David Craford

Vice President, Commercial Operations, Pathwork Diagnostics, Sunnyvale, CA

***CHI:** To start, please give an overview of your company's technology (or technologies) in the field of molecular diagnostics, and the key or most significant current applications that your company is marketing and/or developing using this molecular technology.*

David Craford: Our core technology is informatics. We like to take very large, complex data sets and reduce them to useful clinical information. Today, we are using mRNA information and whole-genome expression array data. Although our capabilities can extend to other types of data, we have chosen at this time to focus. We believe that our niche is that, even when we reduce it, we do not need to get 5 or 10 genes. We feel that, for some of the questions that people ask, if you are able to look at hundreds, or even thousands, of genes, you can get better quality, more robust answers. Based on the studies that we have done for the Tissue of Origin Test, there is a real benefit in being able to look at 1,500 genes plus 100 controls, versus competitive tests that are looking at less than 100 genes. We would say that the same thing applies to many responses to therapy questions.

We also have a strong clinical development capability and operate under QSR [Quality System Regulations]. We have deep experience with producing and marketing IVD products, and we also operate a CLIA [Clinical Laboratory Improvement Amendments]-certified lab. So we have the ability to take these rich data sets, reduce them to clinical information, and offer them through our lab and then develop an IVD kit, which I think is unique right now in the molecular diagnostics industry.