

# ADVANCES

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*Life Sciences Reports*

## Cancer Diagnostics: Technology and Business Trends

Author: Lucy J. Sannes, PhD, Sannes & Associates, Inc.

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## Technology and Business Trends

*By Lucy J. Sannes, PhD, Sannes & Associates, Inc.*

### About the Author

*Lucy J. Sannes, PhD* is president of Sannes & Associates, Inc., a consulting firm specializing in evaluation and management of the biosciences. Before forming Sannes & Associates, she held management positions at Genetic Systems and Abbott Laboratories in product development, product support, and technical marketing. Dr. Sannes received her PhD in biological chemistry from the University of Michigan and her MBA from Seattle Pacific University.

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**Cambridge Healthtech Advisors**, 1000 Winter Street, Waltham, MA 02451  
Phone: 781-547-0200 • Fax: 781-547-0100 • [www.advancesreports.com](http://www.advancesreports.com)

# Executive Summary

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Cancer is a group of diseases that are characterized by abnormal cell growth. Cancers can originate from almost any part of the body. The American Cancer Society estimates that approximately 1,372,910 new cases of cancer will be diagnosed in the United States in 2005 and that about 570,280 Americans will die from cancer during this year. This estimate of new cases of cancer does not include carcinomas *in situ* (noninvasive cancers) for any site except the bladder or basal cell or squamous cell skin cancer. The American Cancer Society also expects that more than one million cases of basal cell and squamous cell skin cancer will be diagnosed in 2005.

Cancer diagnostic technologies and assays are essential for the detection, diagnosis, and management of cancer. For certain cancers, methods are available for screening apparently healthy (asymptomatic), average-risk individuals. Early detection and diagnosis of cancer significantly improve survival rates. In addition, some cancers (such as cervical and colorectal cancers) can be detected in an even earlier, precancerous stage of development (in which the cells are abnormal with dysplasia present but the cancer has not yet developed). For these cancers, screening for and removal of the abnormal precancer cells can reduce the incidence of new cases of that type of cancer. Applications of cancer diagnostic procedures and tests include:

- Identification of individuals at increased risk of developing cancer
- Screening asymptomatic individuals to identify cases of cancer at an early stage
- Diagnosis of the cancer
- Staging and location of primary and metastatic tumors
- Determining prognosis

- Predicting response to therapy (or identifying the optimal therapy for a patient)
- Monitoring response to therapy
- Early detection of recurrence of the cancer

These diverse applications require a broad range of cancer diagnostic technologies. Both *in vivo* imaging technologies and *in vitro* cancer diagnostic tests are routinely used. This report presents diverse examples of four *in vivo* imaging applications and four *in vitro* cancer diagnostic tests and profiles a number of companies in this market.

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For certain cancers, methods are available for screening apparently healthy (asymptomatic), average-risk individuals. The ideal cancer screening test would be for a disease that can be detected in either a precancer or early stage of development and that can be effectively treated if cancer is detected. A number of different organizations make recommendations regarding cancer screening; those from the American Cancer Society are summarized in Table 1.2.

**Table 1.2. American Cancer Society Recommendations for the Early Detection of Cancer in Average-Risk Asymptomatic People (2005)**

Cancer Site	Population	Test or Procedure	Frequency
Breast	Women, aged 20+	Breast self-examination (BSE)  Clinical breast examination (CBE)  Mammography	Beginning in their early 20s, women should be told about the benefits and limitations of breast self-examination (BSE). The importance of prompt reporting of any new breast symptoms to a health professional should be emphasized. Women who choose to do BSE should receive instruction and have their technique reviewed on the occasion of a periodic health examination. It is acceptable for women to choose not to do BSE or to do BSE irregularly.  For women in their 20s and 30s, it is recommended that clinical breast examination (CBE) be part of a periodic health examination, preferably at least every 3 years. Asymptomatic women aged 40 and over should continue to receive a CBE as part of a periodic health examination, preferably annually.  Begin annual mammography at age 40 <sup>a</sup>
Colorectal	Men and women, aged 50+	Fecal occult blood test (FOBT), or fecal immunochemical test (FIT) <sup>b</sup>  Flexible sigmoidoscopy  Fecal occult blood test (FOBT) <sup>b</sup> or fecal immunochemical test (FIT), and flexible sigmoidoscopy <sup>c</sup>  Colonoscopy  Double contrast barium enema	Annual, starting at age 50.  Every 5 years, starting at age 50.  Annual FOBT or FIT, and flexible sigmoidoscopy every 5 years, starting at age 50.  Every 10 years  Every 5 years, starting at age 50.
Prostate	Men, aged 50+	Digital rectal examination (DRE) and prostate-specific antigen test (PSA)	The PSA test and the DRE should be offered annually, starting at age 50, for men who have a life expectancy of at least 10 years. <sup>d</sup>

*Continued*

**Table 1.2. American Cancer Society Recommendations for the Early Detection of Cancer in Average-Risk Asymptomatic People (2005)**

Cervix	Women, aged 18+	Pap test	Cervical cancer screening should begin approximately 3 years after a woman begins having vaginal intercourse but no later than 21 years of age. Screening should be done every year with conventional Pap tests or every 2 years using liquid-based Pap tests. At or after age 30, women who have had three normal test results in a row may get screened every 2–3 years with cervical cytology (either conventional or liquid-based Pap test) alone, or every 3 years with an HPV DNA test plus cervical cytology. Women 70 years of age and older who have had three or more normal Pap tests and no abnormal Pap tests in the last 10 years and women who have had a total hysterectomy may choose to stop cervical cancer screening.
Endometrial	Women, at menopause	At the time of menopause, women at average risk should be informed about risks and symptoms of endometrial cancer and strongly encouraged to report any unexpected bleeding or spotting to their physicians.	
Cancer-related checkup	Men and women, aged 20+	On the occasion of a periodic health examination, the cancer-related checkup should include examination for cancers of the thyroid, testicles, ovaries, lymph nodes, oral cavity, and skin, as well as health counseling about tobacco, sun exposure, diet and nutrition, risk factors, sexual practices, and environmental and occupational exposures.	

<sup>a</sup>Beginning at age 40, annual clinical breast examination should be performed before mammography.

<sup>b</sup>FOBT for colorectal cancer screening, as it is sometimes done in physicians' offices with the single stool sample collected on a fingertip during a digital rectal examination, is not an adequate substitute for the recommended at-home procedure of collecting two samples from three consecutive bowel movements, and is not recommended. Toilet bowl FOBT tests also are not recommended. In comparison with guaiac-based tests for the detection of occult blood, immunochemical tests are more patient-friendly and are likely to be equal or better in sensitivity and specificity. There is no justification for repeating FOBT in response to an initial positive finding.

<sup>c</sup>Flexible sigmoidoscopy together with FOBT is preferred compared with FOBT of flexible sigmoidoscopy alone.

<sup>d</sup>Information should be provided to men about the benefits and limitations of testing so that an informed decision about testing can be made with the clinician's assistance.

**Source:** Reprinted from Smith RA, Cokkinides V, Eyre HJ. "American Cancer Society guidelines for the early detection of cancer, 2005." *CA: A Cancer Journal for Clinicians*. 2005;55(1):31–44, with permission.

### **Potential Impact**

The potential impact of CT colonography (or virtual colonoscopy) is significant. Development of a colorectal cancer screening test that is effective in the early identification of polyps and colorectal cancer and that overcomes some of the patient compliance issues that reduce the numbers of asymptomatic average-risk individuals who are screened could potentially significantly increase the use and effectiveness of colorectal cancer screening. This, in turn, could reduce both the numbers of patients who are diagnosed with colorectal cancer (as abnormalities are detected as precancerous lesions) and improve survival rates as more cancers are detected at an early (and treatable) stage.

One question for which the answer is not clear is the potential impact of CT colonography on the use of colonoscopy. Wider use of CT colonography for cancer screening may reduce the number of screening colonoscopy examinations that are performed. Patients with larger lesions (1 cm or more in size) would be given a colonoscopy examination and polypectomy (removal of the polyps). It is not yet clear how patients with smaller polyps will be managed, and thus it is not known whether CT colonography will increase or decrease the use of colonoscopy.

### **Competition**

CT colonography faces considerable competition from the other colorectal cancer screening technologies that have been used for many years. These include the *in vitro* diagnostic (IVD) FOBT, discussed in Section 3.2, plus three imaging procedures: flexible sigmoidoscopy, colonoscopy, and double-contrast barium enema. Each of the imaging options is discussed briefly in this section, followed by a discussion of the advantages and potential limitations of CT colonography.

Sigmoidoscopy is an imaging procedure in which either a flexible or a rigid endoscope is used to examine the sigmoid colon (the portion of the colon that is closest to the rectum). Although a randomized clinical trial has not been conducted to demonstrate the effectiveness of this screening procedure, some studies have shown that screening by sigmoidoscopy appears to reduce the mortality from colorectal cancer, and this procedure has been widely accepted and used for many years. The American Cancer Society recommends that, if flexible sigmoidoscopy is used to screen for colorectal cancer, the procedure should be performed every 5 years for average-risk adults aged 50 and above. An advantage of flexible sigmoidoscopy is that sedation is not

*CT colonography faces considerable competition from the established colorectal cancer screening technologies.*

### 2.3. Advances in Breast Cancer Imaging

According to the American Cancer Society, breast cancer is the leading cause of new cases of cancer among women in the United States and the second leading cause of cancer deaths. The American Cancer Society estimates that, in 2005, there will be 211,240 new cases of breast cancer and 40,410 deaths due to breast cancer among women in the United States. In addition, an estimated 1,690 men will be diagnosed with breast cancer this year, and 460 men will die of this disease.

Early detection of breast cancer is important. According to the American Cancer Society, if the cancer is detected at an early, localized stage, the 5-year relative survival rate is 97.5%. However, if breast cancer has already metastasized and spread to distant locations in the body, the 5-year relative survival rate is only 25.5%. Due to the widespread use of breast cancer screening, many cases are detected early, and the overall 5-year relative survival rate is 87.7% according to the American Cancer Society.

Breast cancer screening techniques include breast self-examination (BSE) by women, clinical breast examination (CBE) by health care professionals, and mammography. The American Cancer Society recommends that women be screened annually by mammography starting at age 40. There has been some discussion regarding how often women should be given mammograms to screen for breast cancer. For example, the U.S. Preventive Services Task Force recommends screening mammography, with or without clinical breast examination, every 1 to 2 years for women aged 40 and older. The National Cancer Institute recommends that women in their 40s and older be screened every 1 to 2 years and that women who are at higher risk of developing breast cancer seek expert medical advice about whether they should start screening before age 40 and about the frequency of screening.

Mammography has clearly been a significant advance that has detected many early-stage cancers before they would otherwise be discovered. However, it has limitations, and improved screening technologies have been developed. This section reviews current screening for breast cancer and advances in breast cancer imaging.

*Mammography has limitations and improved screening technologies have been developed.*

**Table 2.4. Selected Companies Marketing Imaging Systems for Detection and Diagnosis of Breast Cancer**

Company	Comment(s)
Gamma Medica	LumaGEM 3200S high-resolution gamma camera or scintamammography
GE Healthcare	Senographe family of mammography systems Digital mammography
Philips Medical Systems	
Siemens	Mammomat mammography systems Breast array coil for magnetic resonance imaging Acquired Acuson ultrasound product lines

Note: This table provides examples of major manufacturers and is not a list of all companies in this field.

*Source: Cambridge Healthtech Advisors*

## 2.4. Emerging Role of Positron Emission Tomography in Cancer Diagnostics

Structural imaging technologies such as x-rays (including mammography), CT, and MRI have proven to be valuable tools for cancer diagnostics. However, these technologies all share the limitation of not being able to detect cancer until tissue structural changes (due to the cancer) are large enough to be seen by the imaging technology. Molecular imaging offers the potential of detecting molecular and cellular changes that result from the disease process before the tumor is large enough to cause the structural changes detected by other imaging modalities. PET is a molecular imaging technique that has attracted considerable interest for cancer diagnostics.

### *Description and Status*

PET is an imaging technique that uses positron-emitting isotopes. Positrons travel only a short distance (about a millimeter) in the tissue before capturing an electron. The positron and electron are annihilated, creating two gamma-ray photons that travel in opposite directions. A ring of scintillation crystal detectors that surround the object being imaged can detect the pairs of gamma rays, allowing the location of the annihilation event to be traced. The principles of PET are demonstrated in Figure 2.2.

**Table 2.6. Companies Developing/Marketing *In Vivo* Diagnostic, Monoclonal Antibody–Based Imaging Agents**

Company	Product/Technology	Status	Comments
Immunomedics	MyelomaScan	Evaluated in preclinical ; discontinued	•For multiple myeloma
Intracel and KS Biotech (acquired by Xenova Group in 2003)	HumaSPECT (votumumab)	Approved in Europe in 1998; marketing authorization expired 2004	• <sup>99m</sup> Tc-labeled fully human mAb •For colorectal cancer
Neoprobe	RIGScan CR	Phase III	•RIGS system for colorectal cancer

AFP, alpha-fetoprotein; CEA, carcinoembryonic antigen; IgG, immunoglobulin G; <sup>111</sup>In, indium 111; mAb, monoclonal antibody; NHLs, non-Hodgkin's B-cell lymphomas; PSMA, prostate-specific membrane antigen; RIGS, radioimmunoguided surgery; TAG-72, tumor-associated glycoprotein-72; <sup>99m</sup>Tc, technetium 99m.

Source: Cambridge Healthtech Advisors

**OncoScint CR/OV.** The first monoclonal antibody–based *in vivo* diagnostic agent to reach the market was Cytogen's OncoScint CR/OV (satumomab pendetide), which is a <sup>111</sup>In-labeled murine monoclonal antibody directed against the tumor-associated glycogen-72 (TAG-72). OncoScint was approved in Europe in 1991 for colorectal cancer and in the United States in 1992. OncoScint CR/OV was Food and Drug Administration (FDA) approved for determining the extent and location of extrahepatic malignant disease in patients with colorectal or ovarian cancer. Sales of OncoScint were limited. In December 2002, Cytogen stopped marketing OncoScint because PET imaging demonstrated the same or better sensitivity.

**ProstaScint.** Cytogen's second monoclonal antibody–based imaging agent, ProstaScint (capromab pendetide), is a <sup>111</sup>In-labeled murine monoclonal antibody that is targeted against the glycoprotein prostate-specific membrane antigen (PSMA). ProstaScint is used to determine a cancer's location and the extent of spread (metastasis) of the disease. More specifically, it is FDA approved for use in newly diagnosed patients with biopsy-proven prostate cancer, thought to be clinically localized after standard diagnostic examination, who are at high risk for pelvic lymph node metastases. It is also indicated for use in postprostatectomy patients with a rising prostate-specific antigen

- Emerging molecular diagnostic technologies, including microarrays and other technologies being applied to the development of novel cancer diagnostic assays, for detection of genetic mutations, translocations, and so forth, associated with cancer

No single technology or assay can meet the needs of all *in vitro* cancer diagnostic applications. Cytologists and pathologists gain considerable information from viewing the abnormal cancer cells under a microscope. This information can be enhanced with the use of stains, antibodies, or fluorescent nucleic acid probes to evaluate the samples on the slides. Immunoassays can detect the presence of an abnormal protein, a tumor marker (antigen associated with cancer), or antibodies that are present as the result of elevated expression of cancer-related genes, and molecular assays can detect mutations or other changes (including changes in DNA methylation) that are associated with cancer.

*Assays to detect changes in proteins have proven to be valuable for certain applications.*

### ***Trends in Cancer In Vitro Diagnostics***

Although *in vitro* cancer diagnostics has been recognized as an important field for many years, progress in this area has been slow. Considerable effort has been made (on the part of academic researchers and diagnostic companies) to try to identify novel tumor markers that can be used for screening, diagnosis, or other applications of *in vitro* cancer diagnostics. However, identification of useful new markers has proved to be very difficult due to limitations in sensitivity and specificity with most protein tumor markers that have been identified. Researchers have examined the potential of using multiple tumor markers together to try to identify combinations that may be useful for applications such as cancer screening. However, this has not proven to be successful. To date, the only protein tumor marker that is used for cancer screening is the PSA test for prostate cancer.

Assays to detect changes in proteins have proven to be valuable for certain applications. One group of examples includes the traditional tumor markers (CEA, PSA, CA-125, *etc.*) that are discussed above. Another example is immunophenotyping of leukemias and lymphomas. This example is discussed in Section 3.4. Although immunophenotyping of leukemia and lymphoma is a well-established area of *in vitro* diagnostics that has provided valuable information to physicians for several years, this testing is becoming even more important with the development of targeted therapies (targeting the clusters of differentiation [CD] antigens and other targets) for these cancers.

### **3.3. Theranostic Applications of Cancer *In Vitro* Diagnostics: Erbitux and EGFR**

Erbitux (cetuximab) is a recombinant chimeric (human/mouse) monoclonal antibody that binds to the extracellular domain of the EGFR (Epidermal Growth Factor Receptor; also called *HER-1* or *ErbB-1*), which is overexpressed on the surface of many cancer cells. In February 2004, the FDA approved Erbitux for use (in combination with irinotecan) in treatment of EGFR-expressing metastatic colorectal carcinoma in patients who are refractory to irinotecan-based chemotherapy. Thus, in order to identify which patients are eligible for treatment with Erbitux, the patients' tumors must be tested for expression of EGFR. On the same day that Erbitux was approved, the FDA also approved a test kit for detection of EGFR in colon tissue.

Erbitux (cetuximab) was developed by ImClone Systems. It is co-promoted and distributed in the United States and Canada by Bristol-Myers Squibb. Merck KGaA distributes Erbitux outside of North America. DakoCytomation manufactures and markets EGFR PharmDx, the diagnostic kit (for detection of EGFR) that was approved by the FDA on the same day that Erbitux was approved.

#### ***Description and Status***

The EGFR (HER-1, ErbB-1) is a transmembrane glycoprotein that is a member of the ErbB family of proteins. Other members of this family include HER-2 (ErbB-2), HER-3 (ErbB-3), and HER-4 (ErbB-4). The EGFR protein consists of three domains: (1) an extracellular, ligand-binding domain that can bind to regulatory factors such as EGF and transforming growth factor-alpha (TGF-alpha), (2) a hydrophobic transmembrane domain, and (3) an intracellular cytoplasmic domain with tyrosine kinase activity. EGFR is expressed in many normal epithelial tissues and has a role in signaling and the regulation of cell proliferation, differentiation, and survival. EGFR is overexpressed in a number of cancers, including colorectal, lung, head and neck, breast, and prostate cancers; glioblastomas; and others. Overexpression of EGFR is associated with a poorer prognosis (compared to cancers that do not overexpress EGFR), resistance to chemotherapy, and shorter disease-free survival time.

EGFR is being targeted by a number of pharmaceutical companies that are developing new cancer therapies. Approaches pursued by these companies can be divided into two different strategies: development of monoclonal antibodies that block binding of extracellular ligands to the receptor and development of small-molecule inhibitors of the

Soon to be acquired by Siemens, CTI Molecular Imaging offers microPET; microCAT; image fusion, analysis and custom software; biomarker delivery and labeling; Eclipse cyclotrons and chemistry, and precursors; and site planning.

It also offers PET radiopharmaceuticals and the PET.CONNECT suite of IT products. The PET technology was developed in collaboration with Siemens.

## **DAKOCYTOMATION**

### **Vital Statistics:**

**Location:** Produktionsvej 42, DK-2600 Glostrup, Denmark

**Phone Number/Fax Number/Web Site:** +45-44 85 95 00/+45-44 85 95 95/ [www.dakocytomation.com](http://www.dakocytomation.com)

**Year Founded:** 1966

**Selected Management:** Jes Østergaard, President and Chief Executive Officer; Erik Winther, Corporate Vice President, Finance and Chief Financial Officer; Else Beth Trautner, Corporate Vice President, Sales

**Number of Employees:** Approximately 1,381

**Recent Financial Information:** 2004 sales: \$1,518.8 million. Net operating profit: \$43 million

**Partners:** Clariant, ViroNovative BV, Corixa Corporation, Cytyc, Roche, Pathogenesis, AstraZeneca, Targeted Molecular Diagnostics, Human Genome Sciences

DakoCytomation uses pharmacodiagnostic tests such as HercepTest for identifying women who would benefit from Herceptin therapy. Herceptin is a humanized monoclonal antibody targeted against HER-2 protein overexpression.