1.5. Research Areas

Cancer biomarker research embraces many areas of study, including tumorigenesis, metastasis, clinical trial and surrogate endpoints, cell isolation, target identification, drug resistance, apoptosis, signaling pathways, post-transcriptional factors, microRNA, and others.

The importance of cancer biomarkers is now increasingly recognized and acted on by regulatory organizations, healthcare providers (from reimbursement through to practicing clinicians), cancer organizations, research institutes, and charities. For example, the American Joint Committee on Cancer (AJCC) states in the opening of its mission statement, “The purpose and scope of the AJCC is to create and promote a taxonomy of cancer patient groups that accurately predicts outcomes by incorporating traditional (TNM) and newer data in a timely and dynamic process.” Here, newer data embrace the burgeoning cancer biomarker field.

Despite significant research on cancer biomarkers to date, only a few examples have been incorporated into the TNM system by the AJCC, reflecting the need for validation and the complexity of adopting alternative diagnostic systems that must run alongside the existing practices. It is still uncertain which new biomarkers will be included in the next (2009) revision of the TNM system, reflecting the need for adequate clinical trials and validation (AJCC, personal communication).

1.6. Treatment Selection

Biomarkers have already established important applications in the selection of therapies. Here, the drug targets are also the biomarkers and are therefore therapy-directing. Examples include:

- CD20 positivity for treatment of lymphomas with rituximab
- HER2/neu positivity for treatment of breast cancer with trastuzumab
- BCR-ABL translocation for treatment of chronic myelogenous leukemia (CML) with imatinib
- KIT or platelet-derived growth factor receptor-alpha (PDGFRA) positivity for treatment of gastrointestinal stromal tumors (GIST) with imatinib
Fluorescent In Situ Hybridization (FISH)

Fluorescent in situ hybridization (FISH) is a fluorescence probe technique that is used to detect specific DNA sequences or DNA features. It is a cytogenetic method and can be used both to detect and localize specific DNA sequences on chromosomes. Using fluorescence microscopy, the localization of fluorescently labeled probes can be determined. FISH has been used to screen individuals for chronic myelogenous leukemia (CML) and acute lymphoblastic leukemia (ALL).16

In ALL, a variety of clinical and laboratory features allow clinicians to predict whether or not a patient will remain in remission. These prognostic factors include age, sex, hemoglobin level, and other features. The detection of certain genetic abnormalities is also important, and it is here that FISH offers more advanced approaches over some conventional cytogenetic analyses.16

In most cases of CML, the leukemic cells exhibit an abnormality, not found in nonleukemic white blood cells or other cells, that is due to a reciprocal translocation between one chromosome 9 and one chromosome 22. This produces one chromosome 9 longer than normal and one chromosome 22 shorter than normal. The latter has been named the Philadelphia chromosome.17 As such, FISH provides an important tool in the cancer biomarker armory.

2.2. Protein Methods

Enzyme-linked immunosorbent assays (ELISAs) are broadly and commonly used in the study of cancer biomarkers, both as single-antibody techniques and double-antibody sandwich-based methods. To cite one of many examples in the literature, Barbara Zehentner, PhD, and colleagues used an ELISA sandwich assay for the mammaglobin biomarker in the study of breast cancer.18

Immunohistochemistry

Immunohistochemical methods, which use antibodies to identify and locate specific protein molecules in cells or tissue sections (e.g., using a microscope), are also commonly used in the study of cancer biomarkers. These techniques involve the use of antibodies against biomarkers on cancerous cells and tissues.
3.4. Breast Cancer

Breast cancer is the most common cancer in women worldwide and accounts for more than 25% of all female malignancies. Incidence has been rising in many parts of the world, including the United States, Canada, Europe, the Nordic countries, Singapore, and Japan. According to Globocan 2000, more than one million new cases occur each year worldwide.

Much of the study of breast cancer has focused on the genetics of familial cancers and the identification of the associated BRCA1 and BRCA2 genes; however, these genes are uncommon, and interest has also focused on lower-risk genes (Table 3.4). For example, CHEK2 is associated with a doubling of the risk of developing breast cancer in women who carry this gene.

Table 3.4. Breast Cancer Biomarkers

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSCs</td>
<td>Proteins</td>
<td>CD44/CD24 markers are indicative of breast cancer stem cells (tumorigenic) and differentiate them from nontumorigenic breast cancer cells. These 2 markers have been used to monitor the destruction of CSCs by GSK’s drug Tykerb (lapatinib). The CD44/CD24 population of breast cancer cells are putatively associated with metastasis.</td>
</tr>
<tr>
<td>BRCA1/2 mutation</td>
<td>Genes</td>
<td>Women found to have the BRCA1/2 mutations have a higher risk of developing breast cancer, but this is reported to be highly variable.</td>
</tr>
<tr>
<td>HER2/neu</td>
<td>Protein</td>
<td>A protein in the breast tumor determined by immunohistochemistry for the prognosis of breast cancer and therapy selection. This test is on the FDA-approved list.</td>
</tr>
<tr>
<td>HER2/neu</td>
<td>Protein</td>
<td>Measurement of the protein in the patient’s serum for the monitoring of breast cancer. This test is on the FDA-approved list.</td>
</tr>
<tr>
<td>HER2/neu</td>
<td>Protein</td>
<td>Determination of DNA by FISH in the breast tumor, for prognosis and therapy selection. This test is on the FDA-approved list.</td>
</tr>
<tr>
<td>Cytokeratins</td>
<td>Protein</td>
<td>Protein in the breast tumor determined by immunohistochemistry for prognosis. This test is on the FDA-approved list.</td>
</tr>
</tbody>
</table>

Continued
Important Cancer Biomarkers

Growth Factors and Receptors

The EGFR is one of a group of related membrane receptors that includes HER2. The overexpression of the \textit{HER2/neu} gene and \textit{HER2/neu} protein has been found in 10\% to 34\% of invasive breast cancers and is so far the only breast cancer biomarker to enter standard screening practice in the clinic. Kits available for the screening of this biomarker include the Dako HercepTest (DakoCytomation, Denmark) and the Ventana Pathway (Ventana Medical Systems, Tucson, AZ), which are used to assess the eligibility of patients to receive Herceptin (trastuzumab; Genentech, South San Francisco, CA).

Genetic Markers

A number of genetic markers are associated with breast cancer susceptibility. These include \textit{BRCA1/BRCA2}, \textit{p53}, \textit{ras (K-ras)} \textit{PTEN}, and \textit{MDM2}.

3.5. Ovarian Cancer

Ovarian cancer is the fifth leading cause of female cancer-related deaths in the United States, and more than 60\% of women who develop it will die from the disease. Ovarian cancer is commonly described as the “silent killer,” often only being detected when it has reached an advanced stage. This reflects the lack of reliable screening methods. This cancer also exhibits resistance to drug therapy.

CA125

Serum CA125 (a mucinous glycoprotein) is routinely monitored when ovarian cancer is detected, but has limited value as a predictor of the disease (Table 3.5). Ultrasound is also routinely used to investigate and diagnose this cancer. A number of studies have confirmed the poor reliability of CA125. For example, in one study, 220,000 	extbf{women tested} for CA125, and those with concentrations equal to or greater than 30 U/ml, were further examined using ultrasonography, which showed that only 11 of the 19 individuals with ovarian cancer were detected based on CA125, and there were three times as many false-positives as true positives.
**Figure 3.1. Classification of Cancer Biomarkers by Type**

<table>
<thead>
<tr>
<th>Biomarker Type</th>
<th>Number of Biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prediction</td>
<td>3</td>
</tr>
<tr>
<td>Early detection</td>
<td>5</td>
</tr>
<tr>
<td>Detection</td>
<td>27</td>
</tr>
<tr>
<td>Cancer type/staging</td>
<td>4</td>
</tr>
<tr>
<td>Therapy selection</td>
<td>7</td>
</tr>
<tr>
<td>Metastasis</td>
<td>3</td>
</tr>
<tr>
<td>Monitoring</td>
<td>14</td>
</tr>
<tr>
<td>Prognosis</td>
<td>10</td>
</tr>
</tbody>
</table>

*Note: Independent evaluation.*

*Source: Insight Pharma Reports*
Competitive Opportunities

Immediate opportunities for improving competitive position are most likely to be seen in established therapy areas, where biomarkers aid patient stratification and the development of personalized therapies. Biomarkers clearly offer competitive opportunity at all stages of drug and diagnostic research and development (R&D) through to the clinic. Some may immediately offer more appropriate drug targets.

It is likely, however, that the risk attached to biomarkers will be higher when they are selected earlier in development than when they are paired later. Biomarkers have opened up opportunities in development and in the global market, and, although this offers considerably more opportunity for some companies, it will also lead to promising early developments losing their value later in the pipeline, as new later-stage biomarker-therapy paired developments compete for position. For example, a relatively simple biomarker that supports the use of a cancer blockbuster over another drug may have huge commercial value over a biomarker that represents a promising paradigm shift in cancer therapy but that is much earlier in development.

Cost Saving

The extent to which biomarkers offer cost savings is yet to be established. In principle, biomarkers reduce risk and increase success rates at all points in drug and diagnostic development through to the clinic.

In practice, biomarker development demands substantial investment, and expensive clinical-economic studies will need to be carried out to prove economic value.
In other cases, a number of more recent biomarkers are not extensively tested and proven. Inevitably, all of these species will require evaluation over time before the statistics are proven. This equally applies to the commercial case for these species and the need to recoup development costs.

### 5.3. Opportunities

Cancer biomarkers have enormous potential at many levels of cancer research, R&D, and clinical oncology. While the full value of cancer biomarkers is far from being realized, these species empower scientists and physicians by supporting better and more informed decision-making.

As summarized in Section 5.1 (Strengths), these opportunities apply to patients, healthcare payers and reimbursement authorities, healthcare providers, drug and diagnostic development companies, and governments.

**Patients**

Cancer biomarkers allow greater awareness of earlier and better diagnosis and its impact on success rates and prognosis. Through screening, genetic cancer biomarkers offer individuals the ability to assess their risk of developing cancer at some time in the future. This applies to all individuals, but has particular relevance to patients who are known to be at greater risk, such as those with increased family risk, smokers, reformed smokers, and others.

Prior knowledge or the identification of risk factors will allow individuals to take greater control of their personal circumstances, such as by seeking regular screening.

**Healthcare Payers/Reimbursers**

Cancer biomarkers offer payers and reimbursement organizations improved guidelines on which treatments are covered.

**Healthcare Providers**

For healthcare providers, cancer biomarkers provide opportunities to improve screening programs and the more efficient identification of patients at risk or those who have cancer.
Of the respondents to the question concerning their organization’s view toward collaborative biomarker development, approximately 70% indicated that they support precommercial development (Figure 6.6).

**Figure 6.6. Views on Collaborative Biomarker Development**

What is your organization’s view(s) toward collaborative biomarker development?

- Supports precommercial, collaborative biomarker development/validation: 48
- Expects to be a member of the NIH/FDA/PhRMA Biomarkers Consortium: 17
- Does not expect to be a member: 18
- Does not support precommercial, collaborative biomarker development/validation: 4

n = 69

Source: Insight Pharma Reports Cancer Biomarkers Survey—February 2008

Answers to the question concerning their organization’s experience with novel cancer biomarkers indicate that more than three-fourths of respondents have discovered or worked on cancer biomarkers (Figure 6.7).