

Executive Summary

New laboratory methods, improvements in the tools available to scientists, and an overriding need to improve cancer therapies are driving current efforts to map cancer-related changes in the body. These changes encompass predisposition or risk factors associated with cancer and subsequent developments of the disease.

The need to identify and understand cancer biomarkers is being driven by a number of factors. These include requirements to improve screening and early detection, to provide better guidance on therapy, and to avoid therapy resistance attributes, for understanding cancer staging, response to treatment, and prognosis. Cancer biomarkers can also provide important clinical endpoints or surrogate endpoints and assist in the decision-making of healthcare providers on reimbursement. The latter is important in ensuring selection of the most appropriate therapy for patients, in cost-saving, and, to drug development companies, in competitive differentiation.

The assessment and understanding of cancer is predominantly based on the long-established TNM (tumor, node, metastases) system, which has evolved to reflect increasing knowledge and improving practice. Developments in the cancer biomarker field offer major advances in the detection and assessment of cancer and subsequent decision-making on therapy. While these developments are potentially highly complementary to and synergistic with the TNM system, the adoption of cancer biomarkers in the clinic has, to date, been slow, and only a limited number are currently in routine use. This largely reflects the need for validation and assessment alongside the TNM system.

The translation of developments on cancer biomarkers is an area of high priority at the government level in many countries. This reflects the need to improve therapy for the patient and to take full advantage of current developments and knowledge of cancer, which

have grown substantially in the postgenomic era. For example, the American Association for Cancer Research (AACR)/Food and Drug Administration (FDA)/National Cancer Institute (NCI) Cancer Biomarkers Collaborative (CBC) was announced in April 2007 to “speed translation of promising laboratory discoveries into new medical treatments...” Cancer biomarkers are an important area in this respect.

Cancer biomarkers have the potential to extend substantially the capabilities of established cancer diagnostics, many of which have been limited to detecting cancer before treatment. Cancer diagnostics now offers advances in establishing disease predisposition, early detection, cancer staging, therapy selection, identifying whether or not a cancer is metastatic, therapy monitoring, assessing prognosis, and improvements in the adjuvant setting.

Genetics is providing some of the most important and fundamental advances in the cancer biomarker field, in particular relating to oncogenes and mutated tumor suppressors. Important areas include single nucleotide polymorphisms (SNPs), chromosomal aberrations (e.g., BCR-ABL translocation), changes in DNA copy number, promoter region methylation, and microRNAs.

A number of current cancer therapy selections are based on specific cancer biomarkers. These 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, and others. The number of selections is set to increase substantially in the next decade.

Recent years have seen increasing interest in the isolation of rare circulating cells, such as tumor cells. Further evidence is emerging of a distinct subpopulation of cancer cells within tumors that are thought to be tumorigenic, in contrast to the bulk of cancer cells, which are believed to be nontumorigenic. If these findings are confirmed in the clinic, these cells and the biomarkers that they express will establish an important position in the biomarker field.

Cancer biomarkers are becoming more important in the drug approval process and in decision-making by healthcare providers in terms of therapy options. On one level, these areas have become significant because tests for indicative biomarkers can now be performed, when previously they could not. However, there is increasing pressure to make the best decisions, for the patient and for economic reasons.

Cancer biomarkers increasingly enable healthcare providers to identify the best treatments, while avoiding others that may be less promising. In an age in which some targeted cancer therapies can cost as much as \$50,000 per year, the need to select the most appropriate drug for a specific patient has perhaps never been more important. Ultimately, this also comes back to providing the highest levels of patient care and best use of resources.

It is suggested that fewer than 10% of cancers can be linked to Mendelian inheritance of genetic traits. Nevertheless, genetics is fundamentally linked to cancer, through the changes that take place during the lifetime of an individual. These alterations include the activation of oncogenes and the inactivation of tumor-suppressor or DNA repair genes.

Post-transcriptional processes are important, such as epigenetic post-translational modifications that affect protein expression levels. All of these areas offer new biomarker capabilities.

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 CML with imatinib
- KIT or platelet-derived growth factor receptor-alpha (PDGFRA) positivity for treatment of gastrointestinal stromal tumors (GIST) with imatinib
- Estrogen receptor (ER) or progesterone receptor (PR) positivity, which is a prerequisite for treatment with tamoxifen or aromatase inhibitors
- Somatic mutations in the tyrosine-kinase domain of the epidermal growth factor receptor (EGFR), which have recently been shown to predict a greater efficacy of gefitinib

Genomic and proteomic technologies continue to develop increasing volumes of data on potential DNA, RNA, and protein biomarkers under study. Examples include:

- Oncogenes; for example, mutations in *K-ras* are linked to metastatic spread
- Mutations in tumor-suppressor genes, for example, *p53*
- Germline inheritance (e.g., TP53 [tumor protein 53] mutation, Li-Fraumeni syndrome), which increases the risk of developing cancers
- Mutations in drug targets; for example, the efficacy of anti-EGFR drugs such as gefitinib might depend on specific EGFR mutations
- Epigenetic changes
- MicroRNAs
- SNPs
- Mitochondrial DNA markers

Broadly, methods used to detect and study cancer biomarkers fall into four distinct areas: genetics (e.g., microarrays), proteins (e.g., immunohistochemistry), imaging (e.g., positron emission tomography), and general physical techniques (e.g., mass spectrometry).

Cancer biomarkers are important in a number of different ways. In addition to assisting in the detection of cancer, these species may provide important insights into the development and progression of the disease (guiding drug and diagnostic development), give endpoints or surrogate endpoints in clinical development, and provide guidance as to the choice of therapy and in prognosis.

An important attribute of cancer biomarkers is their use as clinical endpoints or surrogate endpoints. Surrogate endpoints are measures of clinical outcome that may not in themselves be of direct practical or clinical importance, but that correlate directly with desired clinical outcome (e.g., cure).

By their nature, cancer biomarkers also have limitations, however. For example, few, if any, of these species give a definitive guidance on diagnosis, an unambiguous yes or no. This applies to cancer detection as well as the many other associations that they can provide, for example, choice of therapy options, prognosis, and so forth.

Cancer biomarkers offer commercial opportunities in diagnostics and drug development, from early discovery through to the clinic. Nevertheless, the discovery of cancer biomarkers and the development and validation of assays are both complex and expensive, with no guarantee that these investments will see a commercial return.

The incentive to develop biomarker methods is uncertain in many areas of development, in particular where these species are not already linked to existing developments (e.g., as a clinical endpoint). Biomarkers that extend or support established research areas carry the least risk, whereas biomarkers that “stand alone” or represent a change of paradigm present the greatest.

Another challenging aspect to the cancer biomarker field concerns ownership. This is a crucial question, since it will determine the extent to which a company is able to invest in biomarker studies and subsequent development, in the hope of financial returns further down the line. Many molecular species that subsequently become labeled as biomarkers are researched for some years, particularly in academic laboratories, before there are sufficient data to justify their being labeled or classified as cancer biomarkers.

Cancer biomarkers that influence diagnostics, drug R&D, or clinical decision-making are establishing economic value. In many cases, this is hard to differentiate from other factors (e.g., from therapeutics molecules), to determine their independent value in commercial terms.

One case is seen with trastuzumab (Herceptin), for the treatment of breast cancer. In 2005, US sales of Herceptin increased 56% to \$747.2 million, from \$479.0 million in 2004. Since the HER2 biomarker test may be required by payers to demonstrate the need for Herceptin, it is clear that the test holds substantial value and is integral to sales. Where this test is a mandatory part of the decision to reimburse the drug, the interdependence of the biomarker and drug might imply a comparable value of the two.

The heterogeneous nature of cancer and patient-to-patient variability have long promoted discussions on evidence-based personalized therapies. Today, personalized cancer medicine is being brought closer to reality, a trend that is set to continue in the years ahead. This is being driven by a better understanding of cancer at the molecular level. The study of cancer biomarkers is at the heart of these developments, and new findings are driving a revolution in the ways that cancers are detected, diagnosed, and treated. This revolution is bringing to an end an era in which “one drug fits all” and is ushering in a new age in which diagnosis and treatment are more interdependent and selected therapies reflect the best evidence of how a particular patient will respond to one specific drug over another.

Drug development and drug costs have never been higher than they are today. This particularly applies to the cancer field, with the advent of targeted cancer drugs. Many of these new-generation drug costs run into the tens of thousands of dollars per patient. With increasing pressure on healthcare budgets, emphasis is being placed on drug selection, to maximize the benefits to the patient.

More stringent and rigorous approaches are being taken to identify the best drugs available for the treatment of specific cancers. It is here that biomarkers offer hope: They reveal a picture of what is happening at the molecular level and how this is linked both to the disease and its origins, and provide evidence-based guidance on choice of therapy. For the latter, cancer biomarkers also allow decisions to be made in terms of which drugs might be avoided, for example, in the case of drug resistance attributes. Toxicity-indicating biomarkers are also being evaluated. These considerations are now part of the scope and application for understanding cancer and finding better therapy solutions.

For many biomarker species, the commercial model has yet to be established. Given that much of this investment will need to be made in advance of clinical evidence, the study of biomarkers also carries high levels of risk, with no guarantees of commercial returns.